Medical University of South Carolina

Protocol

Study Title: Dyadic-Based Diagnosis, Care & Prevention for HIV Discordant Couples in Tanzania

NCT03098693

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A. SPECIFIC AIMS

Our primary goal for the proposed study is to examine the feasibility, safety, and impact on improved care and prevention of novel strategies to identify and engage HIV serodiscordant couples in an integrated prevention and treatment intervention. The study design is a prospective observational study of Dyadic-based Diagnosis, Care, & Prevention (DDCP) in a well characterized community in Kisarawe District, Tanzania. Valuable data from Project Accept, and clinical data from the National "CTC2" system facilitates analytic comparisons, and study efficiency. The DDCP intervention is grounded in important lessons from our extensive experience in Tanzania: (1) HIV testing is a critical precursor to the vast majority of combination prevention interventions, (2) a large attributable risk of HIV infection occurs within stable couples, yet engaging couples in prevention and care is rarely done, (3) health systems in the heavily affected countries cannot manage the burden of universal strategies promoted with combination prevention (4) targeting programs to high incidence populations is avoided due to fear of stigmatizing clients, and a lack of strategies to identify risk, and (5) a lack of measurement specificity for client's risk reduction strategies and service utilization - due, respectively, to the dynamic multivalent options people use to mitigate risk, and the inability to track clients over time and space in a manner that preserves their privacy when they access services.

For the first part of the study we propose to conduct a prospective observational study of between approximately 442 couples (884 individuals) to 1000 couples (2000 individuals) aged 18 years and above in Kisarawe, Tanzania who will be provided: (1) household-based self-testing education and HIV self-testing kits, (2) linkage to a post-test referral & counseling center for those who test positive, (3) facilitated enrollment to care and treatment for those couples with confirmed HIV infection; and (4) access to PrEP for the negative partner in a HIV serodiscordant couple. A baseline survey, and a follow-up survey approximately 2 weeks later and HIV test, will be administered to all enrolled couples. At six months, a subset of participants will be randomly selected to complete a brief follow-up survey. The subset will consist of 50% of participants who were confirmed HIV positive (but no less than 20) and 5% of participants who tested negative (but no less than 10).

In the second part of the study we will enroll from 60 to 70 serodiscordant couples. All HIV serodiscordant couples entering the second part of the study will be administered a baseline, 6-, 12-, and 18-month survey. We will collect ongoing clinical data from each clinic visit, and from the larger clinic population for comparison. Positive partners engaged in care as a dyad will have a viral load test at 18-months. Biometric data (fingerprint) will be collected at study and intervention encounters to link utilization of services with survey data. We will also enroll serodiscordant couples from patients already receiving care from the Kisarawe Care and Treatment Center (CTC). To ensure serodiscordant couples who participated in the self-testing phase have an opportunity to enroll in the second part of the study, we will keep enrollment open until approximately 1-month after the target enrollment for the second part of the study is reached. Based on historical rates of serodiscordant status among couples we estimate that we will need to enroll approximately 442 couples to identify 60 couples for the second part of the study, however, it may take up 1000 couples in the first part of the study to find this many serodiscordant couples. Additionally, since we will be conducting the HIV self-testing by geographic cluster, we will offer HIV self-testing to all eligible persons in each cluster that we start to avoid denying people in the geographic clusters access to HIV self-testing and also biasing our sample. This may result in us completing the enrollment of the 60 couples for the second stage of the project while still providing HIV self-testing in the first stage of the study. Thus, we may need to exceed the N of 60 as we complete the final geographic cluster with HIV self-testing to assure that those found to be discordant through self-testing have an opportunity to engage in the second part of the study. We thus may have up to 70 couples enrolled in the second part of the study. Because of the diversity in recruitment strategies, we will be able to track uptake of care between those newly diagnosed with HIV and those with previous diagnoses who have already begun receiving care.

This is an ideal study setting. The intervention strategy we propose is based on our extensive experience conducting large-scale HIV prevention trials in Tanzania for over 17 years in collaboration with Muhimbili University. Over the past 8 years we have collected extensive data on HIV risk and

household characteristics from NIMH Project Accept – a multi-site community randomized Phase III trial assessing the efficacy of community-based HIV voluntary counseling and testing. We have mapped and enumerated all households in the district, done qualitative research, characterized HIV risk factors (behavioral and biologic), done cost-analyses, worked successfully with the local communities and health system, established a collaboration with the PEPFAR-funded AIDS treatment centers, and established a rural research infrastructure with experienced intervention and research staff. Our specific AIMS evaluate 4 key strategic goals, including:

1. HIV Self-Testing for Stable Couples: (a) assess the acceptability, safety, and factors associated with uptake of HIV self-testing; and (b) determine the proportion of clients testing positive for HIV via self-testing who engage in care.

2. Dyadic Engagement of Serodiscordant Couples in Care & Prevention: (a) establish the proportion of serodiscordant couples who will enroll in HIV care as a dyad, (b) determine the effect of dyadic care enrollment on retention and adherence, and (c) assess reduction in risk of acquiring HIV infection for the negative partner.

3. Pre-Exposure Prophylaxis (PrEP): (a) establish the proportion and characteristics of HIV negative clients in a serodiscordant relationship who opt to take PrEP, (b) determine how engaging in ARV treatment by the positive partner affects PrEP utilization by the negative partner, and vice versa, and (c) Identify patterns and correlates of risk reduction strategies that couples in care utilize over time (abstinence, ARV for positive partner, PrEP for negative partner, condom use).

4. Operational: (a) determine Dyadic-based Diagnosis, Care, & Prevention (DDCP) program cost and economic efficiency, (b) compare DDCP to clinic-based and mobile VCT with regard to cost and efficiency for testing and linkage to care, and (c) assess the feasibility, acceptability, safety, and utility of using biometric data to track service utilization.

B. BACKGROUND AND SIGNIFICANCE

Significance: Despite 20 years of considerable HIV prevention efforts in Sub Saharan Africa the epidemic continues to have devastating impacts [1]. The expansion of treatment and care for AIDS in the region has provided important and lifesaving services but has also added complexity to coordination and service delivery across prevention and care efforts. There has been a growing recognition in the field of HIV prevention of the potential for improved program effectiveness by strategically combining HIV interventions.[2] NIAID and USAID have targeted funding for studies and interventions using combination HIV prevention strategies [3,4] and UNAIDS has recently stressed the potential benefits of carefully combined interventions.[5] A key recurring theme in these efforts is that no one strategy can carry the weight of reducing HIV incidence – there is no one “magic bullet” to stop an AIDS epidemic. What is less clear from the discourse on the topic is what exactly is the best strategy to combine interventions. One paradigm of combination prevention that has emerged might be termed the brute force strategy - that to control epidemics you need nearly universal coverage of component interventions (UNIVERSAL: HIV testing; linkage / engagement / adherence / retention in care & treatment; all negative males circumcised; etcetera). The nexus of this view can be found in a 2009 paper by Reuben Granich and colleagues published in The Lancet[6] which modeled the potential impact in South Africa of "universal voluntary HIV testing with immediate ARV therapy". The modeled analysis showed impressive results, with some scenarios indicating an extinction of the epidemic. However, the model assumptions required, as the title suggests, universal coverage and near perfect uptake of nearly all intervention components. Following this trajectory, the US Office of Global AIDS Coordinator has funded several very large HIV Combination Prevention studies,[7] notably: (1) the PopART trial,[8] a $37M project in Zambia and South Africa testing universal HIV testing with immediate access to ARV for those with HIV, and (2) a $20M CDC/Harvard study[9] in Botswana studying testing and circumcision of 70% of adults, engaging 90% of HIV-infected adults on ARV, and identifying and targeting individuals

Why Is This Study Important?

• Descriptive information on safety, acceptability, and uptake of couples-based self-testing is not available, despite the critical role sero-discordant couples play in the epidemic.

• It is critical that combination prevention programs identify lower cost methods of testing large numbers of people for HIV. Self-testing for HIV could be a vitally important innovation.

• Engaging couples in care as a dyad holds promise of improving entry, adherence, and retention in care programs.

•Despite its efficacy, PrEP has not been adopted widely. Understanding who would accept PrEP and how they would use it is critical to advancing integration of PrEP in combination prevention.

• Assessing the cost and efficiency of these interventions is critical for policy decisions.

with high viral loads for treatment. Against the backdrop of these important and ambitious trials is a declining level of donor support for HIV prevention. For example, in Botswana, home of the CDC trial, US PEPFAR funding for HIV is anticipated to decline from $75M in 2012 to $35M in 2016.[10] Moreover, the health systems in the most heavily affected countries are extremely weak and poorly resourced. The level of financial investment that would be required to implement these large-scale interventions with near perfect utilization is staggering. There are shortages of trained staff and poor infrastructure, and even with the substantial resources now dedicated to HIV treatment, results are disappointing. As noted by Rosen and Fox [11] in their systematic review of retention in care from testing to treatment in Sub-Saharan Africa, there is a "substantial loss of patients at every step, starting with patients who do not return for their initial CD4 count results and ending with those who do not initiate ART despite eligibility". While we fully support these important scientific studies, we believe it is also prudent to conduct studies on combination prevention strategies that target services to those most likely to transmit and acquire HIV. But how should such targeting be accomplished in a manner that would have a meaningful impact on HIV epidemics? There are several factors which help prioritized a more highly targeted strategy: (1) HIV testing is critical to many other typical components of combination prevention, including individual risk reduction, treatment, circumcision, and prevention of mother to child transmission - yet we need a lower cost strategy to reach large numbers of people with testing; (2) a large attributable risk of HIV transmission occurs in stable serodiscordant couples - yet engaging couples in prevention and care is rarely attempted; (3) treatment programs process clients as individuals, yet the preventative benefits of treatment accrue to the partners of clients, and familial support in treatment is critical to success in maintaining retention and adherence; (4) pre-exposure prophylaxis (PrEP) has been proven to be effective - yet PrEP is not being widely utilized to strategically reduce new infections, and (5) to fully understand the potential of novel programs to work we must better understand the nuances of risk reduction within couples, how clients utilize services over time, and how such programs compare with regard to cost and efficiency to alternatives models. Thus, we propose several innovative strategies to address these issues.

HIV self-testing - In a systematic review covering 21 studies from a host of countries, HIV self-testing has been found to be highly acceptable, typically preferred over clinic-based testing for HIV, and has a high degree of accuracy. [12] Regardless, we are aware of the potential safety and privacy concerns with its use and have made these a key focus of the proposed research. As noted by Walensky in a commentary on HIV self-testing, "...*to ensure investments are well-targeted in the scale up of self-testing programs, linkage to care is a critical evaluation measure. How to conduct those linkage-to-care studies, while maintaining the privacy that self-testing demands, will be among the next phase of self-testing implementation challenges*." [13]

Engaging serodiscordant couples in prevention and care as a dyad - When couples receive HIV counseling and testing together there is superior behavioral risk reduction than with individual VCT.[14-16] Our experience in conducting large-scale VCT programs is that couples rarely test together, and often present sequentially for HIV testing, not in parallel. Those testing sequentially for HIV within a partnership frequently do not disclose their results to their partner. What is more, we believe that engaging the couple together in care will likely enhance retention and adherence.

PrEP for negative partners in a serodiscordant couple - despite strong evidence of the efficacy of PrEP in reducing incidence, its implementation has not been supported. Indeed, the original efficacy trial that showed the strongest effect was conducted among serodiscordant couples, [17] and WHO has called for demonstration projects of PrEP with serodiscordant couples.

Theoretical Foundations / Social Action Theory - Social action theory informs our theoretical perspective. It is especially apt as it explains health protective behavior as an interaction among three domains which are in a state of reciprocal determinism - each affecting the other, including: (1) the self-regulatory capabilities of the individual, (2) the environmental context, and (3) responses to internal affective states.[18] Self-regulatory factors for risk reduction related to the proposed intervention include enhanced technical skills (ability to self-identify HIV infection, enhanced risk reduction options with PrEP), social skills (enhanced trust within relationship based on shared knowledge of HIV status), and interpersonal problem-solving skills (partner negotiation with dual HIV testing within couple). Environmental forces that the intervention addresses include lowering opportunity costs for HIV testing, privacy in HIV testing with self-test kits, and facilitated access to treatment via the intervention referral liaison. Management of internal affective states (fear, depression, anxiety) should be improved through the social support that comes with enlisting the couple in the testing, care, and treatment process; and by providing an additional risk reduction strategy (PrEP) that can be controlled by the negative partner. Consistent with previous research, we believe that improvements in self-regulatory capabilities can reduce the likelihood of sexual transmission acts[19,20] and that counseling available from our study referral liaison will help to build these capabilities. Negative affective and arousal states have been associated with decreased self-regulation of sexual behavior in both HIV-infected men and women.[21] Previous intervention research[22,23] shows that social support is effective at increasing coping skills (self-regulatory capabilities) as well as decreasing depression and anxiety (negative affective states) for people living with HIV, particularly if structured around issues likely to be confronted in the local culture (environmental context).

Innovation: We believe this is a bold intervention that challenges multiple widely held assumptions in the field of HIV prevention, and offers both theoretical and operational innovations, which include:

(1) Testing a novel targeted combination prevention package that is based on 8-years of field experience in the project setting, and which has been designed to be low-cost and replicable in low-income countries.

(2) Biometric Data to Assess Intervention Utilization will allow for the capacity to generate real time assessment of the timing, location, sequencing, and combination of services, for individuals & across couples.

(3) Self-testing will be explored as a method to decrease cost of testing large numbers of clients, and to engage couples to test for HIV as a dyad. Moreover, this study will quantify the potential to link HIV positive clients identified through self-testing to care and treatment which has not been done to date.

(4) Patterns of Risk Reduction Strategies will be carefully identified to better understand how abstinence, ARV for prevention, PrEP, and condom use interact as risk reductions strategies within couples over time.

(5) Enhanced understanding and use of existing data from Project Accept, and the Kisarawe HIV Treatment Center will be achieved through comparisons to the cost and efficiency of competing HIV testing methodologies (Project Accept), and data from the Tanzanian Care and Treatment Center's "CTC2 Database" on retention and adherence (available from Government Care and Treatment Clinic).

(6) Enrolling couples as a Dyad in the HIV Testing and Care Continuum. We will examine a novel strategy to stimulate couple testing in parallel, engage the couple in care as a unit, and to enhance risk reduction options within couples with PrEP.

C. PRELIMINARY STUDIES

VCT Efficacy Trial - In 1994 Dr. Sweat established research collaboration with the Muhimbili University Department of Psychiatry to conduct the Voluntary HIV Counseling and Testing Efficacy Study. With support from USAID and the World Health Organization we developed a randomized clinical trial in Tanzania, Kenya and Trinidad. A total of 3120 individuals and 586 couples were enrolled in the three countries, randomized to receive VCT or health education (couples were randomized as a unit), and followed for an average of 7.3 months for the first follow-up and 13.9 months for the second follow-up with retention rates >70% for all groups. There was a 35% reduction in the percentage of males reporting any unprotected sex with non-primary partners from baseline to follow up for men receiving VCT versus a 13% reduction in the comparison group ($p<0.001$) [24]. For females there was a 39% reduction in the percentage reporting any unprotected sex with non-primary partners from baseline to follow up for males receiving VCT versus a 17% reduction in the comparison group. Dr. Sweat also conducted a cost-effectiveness analysis, published as a companion paper to the main study report in The Lancet, showing that VCT is cost-effective [25].

Project Accept –This was a multisite community-based randomized controlled trial developed in direct response to our experiences in the VCT Efficacy Trial. Key goals were to test large percentages of the population, especially young people who have the highest incidence rate, and to do this within the communities where people live in order to destigmatize and normalize HIV testing. Project Accept had 5 sites: Kisarawe, Tanzania; Kwa Zulu Natal, South Africa; Soweto, South Africa; Mutoko, Zimbabwe; and Northern Thailand. The Project Accept intervention was designed to: (1) increase availability of VCT in community settings, (2) engage the community with mobilization activities, and (3) provide posttest psychosocial support. Intervention teams rotated through villages (activities were delivered in tents). The primary study endpoint was HIV incidence, measured in a post-intervention cross-sectional probability-based sample of all persons aged 18-32 years using an algorithm based on the BED assay, avidity index, and CD4+ T-cell count. Additional detailed information on the study design and assessment of the study design and endpoints can be found in the study protocol, which is registered with ClinicalTrials.Gov (identifier # NCT00203749). Project Accept has published 41 papers in peer-reviewed journals [26-63] as of May 2014. The project has been highly successful in generating uptake of HIV testing and Post-Test Support Services. In a paper Dr. Sweat recently published in Lancet Infectious Diseases[46] we reported that a significantly higher percentage of 16-32-year-olds were tested in intervention communities than in control communities. The mean difference in the proportion of clients receiving HIV testing between CBVCT and SVCT communities was 40.2% (95% CI 15.8–64.7; p=0•019). The overall estimated reduction in incidence in intervention vs. control communities was published in Lancet Global Health in 2014 [64], and was 13.9% (RR = 0.861, 95% CI for RR = 0.725–1.023; p = .08). This trend was also seen in a preplanned subgroup analysis with a reduction in incidence for 25-32-year-olds of 25.4% (RR = 0.746, 95% CI for RR= 0.536–1.038; p = .08), and was significant with a 30.2% reduction in incidence (RR = 0.698, 95% CI for RR =0.543–0.898; p = .009) for young women 25-32 years old.

The Triage Project - In Kisarawe district we have recently initiated a two-arm Phase II community randomized controlled trial (N=355 per arm) in two matched rural communities (different communities from those proposed herein). The primary endpoint is HIV and STI incidence. The intervention components include: community mobilization, community-based VCT at a community prevention center, enhanced counseling for high risk and HIV-infected clients, and incentives for uptake of VCT by sex partners of high risk and HIV-infected clients. For clients who test positive for HIV there is posttest psychosocial support, income generation activities, assisted and active referral to treatment, and adherence support for treatment. Formative work has y been completed, and the study plans is currently enrolling participants.

Our research experience, infrastructure and staff capacity in Tanzania are excellent. Our team has the following accomplishments with Project Accept: (1) created detailed physical maps of this rural district, (2) mapped every household in the entire district with a population of approximately 160,000 using GPS technology at baseline and again recently at follow up, (3) conducted 3,065 baseline field interviews, (2) 463 serial qualitative interviews over 30-months, (3) 20 key informant qualitative interviews, (5) 7,196 HIV tests with counseling, (4) 9,772 post test support visits, (5) 4,197 community mobilization activities and events reaching 103,870 persons, and (6) trained and supported 74 part time community outreach volunteers. For our recent post-intervention assessment, we have had the following success: (1) response rate for household enumeration of 98.4%, (2) consent rate for individual interviews of 96.8%, (3) consent rate for post-intervention blood collection in household of 82.7%, and (4) completed survey response of 96.1%. We have also conducted detailed costing of all intervention components at two time points, collected detailed individual intervention utilization data on all clients, held regular community advisory board meetings, and have had regular external intervention quality control assessments.

How will we do the work?

- **Enumerate, and enroll approximately 442 (and up to 1000) couples aged 18+. Obtain individual informed consent.**
- **Baseline interview administered and biometric data (fingerprint) collected.**
- **Distribution of 2 HIV Self-test kits provided with instructions to go to study center if either partner tests HIV positive.**
- **Those presenting at study center will have confirmatory rapid HIV test (blood) and if infected referred and escorted to adjacent collaborating government HIV Care and Treatment Center (CTC).**
- **For the estimated 60 sero-discordant couples presenting, immediate access to ARV for positive partner, and access to PrEP for negative partner.**
- **Biometric data collected at each clinical visit for 60 sero-discordant couples, & 6-, 12-, & 18- month survey.**
- **Follow up interview with couples sampled at baseline and confirmatory rapid (blood) HIV test**
- **Clinical data on retention, adherence, client characteristics on existing patient population enrolled in HIV care at CTC collected for comparison.**
- **Detailed costing of all intervention components.**

Experience of Investigators – **Dr. Michael Sweat** is a tenured Professor of Psychiatry and Behavioral Sciences at the Medical University of South Carolina and Director of the MUSC Center for Global Health. Prior to joining MUSC in 2007 he was an Associate Professor and Director of the Social and Behavioral Interventions Program in the Department of International Health in the Bloomberg School of Public Health at The Johns Hopkins University and is Adjunct Professor there now. He was PI for the Tanzania site of NIMH-Project Accept, is currently PI of an NIMH R01 conducting systematic reviews of the effectiveness of HIV behavioral interventions in developing countries (The Evidence Project); PI on a NIMH Challenge Grant for comparative cost-effectiveness analysis of a variety of HIV interventions; PI on a USAID-funded project developing policy guidance on HIV behavioral interventions; and he collaborates with numerous other projects. **Dr. Jessie Mbwambo** is a member of the faculty in the Department of Psychiatry at Muhimbili University of Health and Allied Sciences in Dar es Salaam, the leading national research university in Tanzania. Dr. Mbwambo earner her medical degree from the University of Dar es Salaam, did post-doctoral fellowships at The University of Manchester and Harvard. She was Tanzanian PI for Project Accept, is Tanzanian PI for the Triage Project, and she is the PI on numerous other HIV studies. She is also an international expert on interpersonal violence related to HIV.[65-71] **Dr. Theonest Rutayuga** is a psychiatrist at Muhimbili, and has significant experience working with HIV-infected clients. His expertise with providing clinical medical care in Tanzania for those with HIV and AIDS, and his psychiatry training make him an excellent candidate for leading the clinical field operations. **Dr. Kevin O'Reilly** is an internationally recognized expert in HIV/AIDS prevention (formerly at the WHO), and Adjunct Professor at MUSC. He has led WHO's PrEP working group and worked closely with multiple international PrEP projects. Dr. O'Reilly will join the study as a consultant, both a clinical psychologist and biostatistician, and has led the statistical analysis on over 30 NIH-funded trials. **Ginny Fonner** works in Tanzania as the project coordinator for Dr. Sweat for the Triage Project. She is a former Peace Corps volunteer in Zambia and obtained her PhD in International Health at Johns Hopkins School of Public Health. She is fluent in Kiswahili and is conducting her dissertation work in Kisarawe. **Dr. Basant Singh** has his PhD in Psychology and has

worked with Dr. Sweat since 2002 as data manager on multiple projects and operates a data management center in India for Dr. Sweat. He has vast expertise in data management, computer programming, information systems, and statistical analysis. He was the data manager for all 5 sites (4 countries) for Project Accept.

Given that the CITI training program is not available in the language of the local staff in Tanzania, and since they do not have access to and facility with computers and internet linkages, the CITI training program is not a viable option to assure rigorous ethical training for these staff. Ethics training will be conducted using a set of material modeled after the CITI program. Tests to assure mastery of the material will also be administered in this manner. Careful documentation in the study records will be maintained. This training program has been used in the previous studies conducted in Tanzania by our investigators with the approval of the IRB of record.

D. RESEARCH DESIGN AND METHODS (including data analysis) _____

Study Design

Overview: This is a prospective observational cohort study of Dyadic-based Diagnosis, Care, & Prevention (DDCP). Consistent with studies focused on methodological development and formative work we will provide proof of concept for the intervention, identify descriptive statistics for the intervention outcomes, and examine the acceptability, feasibility, cost, and safety of the intervention.

Community Selection - The study will be located in Kisarawe, a rural district in the Coastal Region adjacent to a major transit route and approximately 75 km from Dar es Salaam. The economy in Kisarawe is agricultural, and it is located on a major east-west transit route. The study population will be drawn from Kisarawe Ward, which contains urban and peri-urban villages in and around Kisarawe town. The District Hospital and District Care and Treatment Center (CTC) are also located in Kisarawe town. The director of District CTC in the study setting is highly supportive of the project and has pledged to work closely with us and allow access to clinical data of existing patients. Based on the 2012 census in Tanzania, in Kisarawe Ward there are 3,101 households and 11,838 individuals.

Preparedness - Prior to initiating the study we will establish a Community Advisory Board (CAB). The CAB will have representatives from the community, and will include village leaders, representatives from civic groups, Mosques, health care providers, and other interested parties. We will convene meetings of the CAB every 6-months to seek advice, provide information, and solicit feedback on the safety and acceptability of the intervention. In our previous work the CABs have been invaluable to our study operations and in generating partnerships with communities.

Why Is There No Control Group?

- **This is an exploratory study primarily investigating operational research issues: safety, acceptability, retention, adherence, uptake of intervention components, and cost. Randomization to a control condition would not significantly enhance the knowledge gained from the study for these questions.**
- **Measuring differences in HIV incidence across arms would be desirable. However, to measure HIV incidence would require that we test participants for HIV at baseline. It is unethical to withhold the HIV test results, and providing HIV testing at baseline would contaminate the control group, as they would receive a key element of the experimental intervention.**
- **For research questions requiring comparative data (e.g. retention in care, adherence to treatment) we will have access to blinded clinical data from the Care and Treatment Center for clients not enrolled in the study for comparison.**
- **For costing, economic efficiency, safety and acceptability we have excellent and recently collected data from the same geographic area from Project Accept for comparisons.**

Sampling of Households –Based on data from the 2012 census, Kisarawe Ward will be divided into sections by village and sub-village. To begin sampling, one village/sub-village will be selected. Once selected, data collectors will visit every household in the selected area. Once an entire section has been covered, data collectors will select a new section of the ward to sample. This process will continue until approximately 442 couples have been enrolled, although we may need to enroll up to 1000 couples as described earlier. To recruit for the second component of the study we will approach couples who participated in self-testing and are found to be serodiscordant. We will also recruit the serodiscordant cohort from patients already enrolled in care at the Kisarawe CTC. We will continue recruiting using both methods until 60 serodiscordant couples (but up to 70 as described earlier) have enrolled in the second part of the study. We may recruit more than 442 couples—but no more than 1,000 couples—in the self-testing component of the study in order to enroll 60 serodiscordant couples in the second part of the study. As well, we may enroll up to 70 serodiscordant couples in the second part of the study if we are continuing to finish out a geographic cluster with provision of HIV self-testing.

Enumeration of Household Members – When a household is approached for potential participation in the study, data collectors will explain the study, and with verbal consent of the head of household, establish if there are eligible couples within the household. Recruitment and Data Collection - Couples selected for inclusion will be invited to participate in the study. Couples are defined as two persons in an ongoing sexual relationship of at least 6-months, and each of these persons considers the other to be a "partner" in the relationship. To be eligible for participation, each individual has to be 18 years or older, live in the household regularly (thus, we are focused on cohabitating couples), and with no plans for moving from the area before the follow up period. Both members of the couple need to be aged 18 years or above, and at least one member of the couple must be aged 55 years or below. Additionally, each member of the couple must be willing to disclose their HIV status to their partner following self-testing, either facilitated by a counselor by the couples themselves. Before beginning the consent process, the interviewer will verify eligibility with the individual with respect to residency and age information. If the selected individual is not available during the household visit, the interviewer will be required to return to the household a minimum of two times (on different days/times of day) to locate the selected individual, request consent, and conduct the interview. Each member of eligible couples will be consented separately and in private, and consent of both members is required for entry into the study. Privacy will be ensured by having the consent and interview take place in a location where conversations cannot be overheard and the participant feels comfortable. If a couple declines to participate, they will be asked if they would be willing to tell us why. They will be consented for this process. At two weeks after leaving the self-testing kits with couples, data collectors shall return to study cohort members and repeat data collection (survey & blood for follow up interview). At this time, data collectors will collect any unused test kits and will also collect used test kits (sealable envelopes will be provided to participants to keep test kits after use). All collected test kits will be taken to the Study Center and kept in designated biohazard bins before being incinerated at the collaborating government health facility adjacent to the Study Center. At six months, a subset of participants will be approached to complete a follow up survey. The subset will consist of 50% of participants who were confirmed HIV positive (but no less than 20) and 5% of participants who tested negative (but no less than 10). For recruitment at the CTC, we will raise awareness about the study with existing CTC patients. If interested, these patients will be provided a card they can give to their partners to come and receive HIV testing through the study. The patients themselves will not have to retest for HIV since they are already receiving HIV-related care. The negative partner will receive HIV confirmatory testing at the Study Center. Serodiscordant couples in the area found through this recruitment strategy will be offered participation in the study. Similar eligibility criteria and definition of a "couple" used for the self-testing recruitment will also be used for the CTC-based recruitment (with the addition of residing near or within Kisarawe Ward). For CTC-based recruitment, written informed consent from both partners, completed individually and in private, will be required for entry into the study.

Intervention

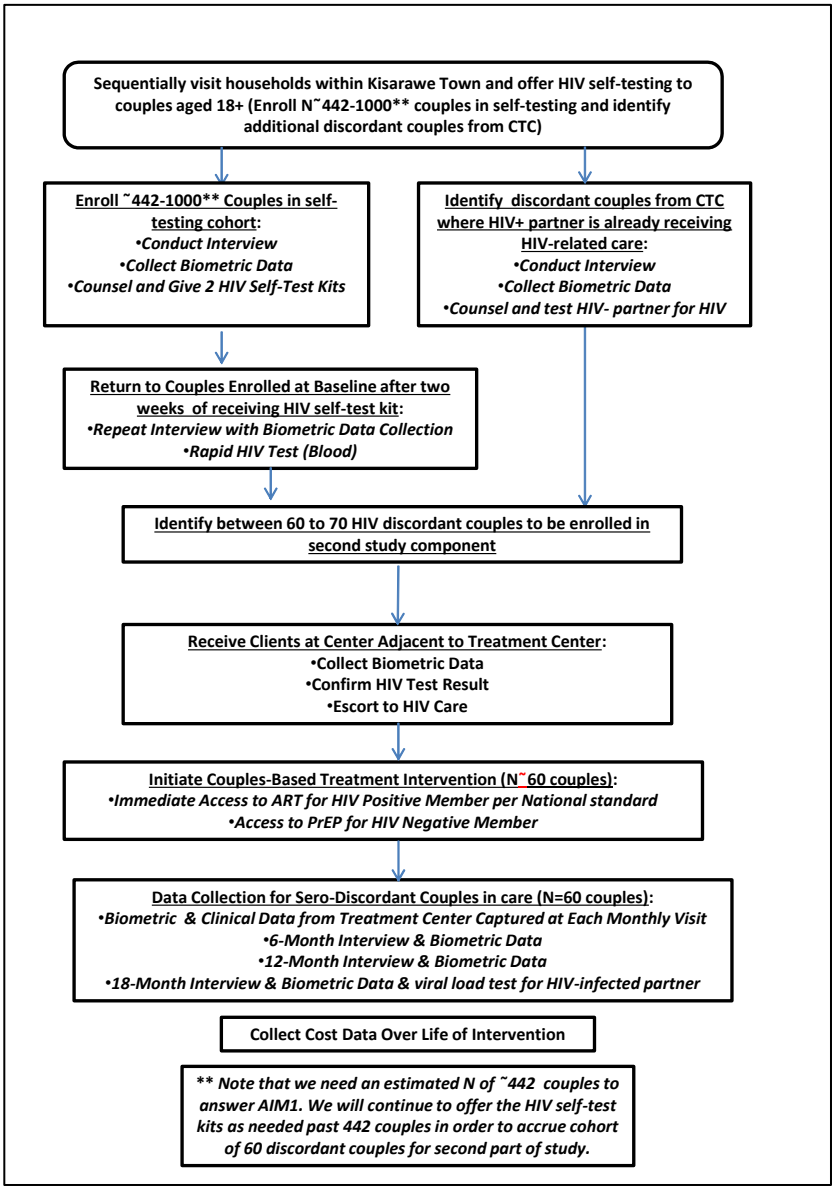
The following key intervention components will be implemented: An orientation of how to use the HIV self-test kit will be provided, with printed instructions left with two self-test kits. Self-testing kits will NOT

be provided to a couple if only one member of the couple agrees to the test and to disclosure. This measure will be employed to protect the safety of clients and avoid potential coercive testing. We will utilize the OraSure OraQuick® Rapid HIV-1/2 test kit for self-testing. Couples will also be instructed on how to take universal precautions when handling the test (latex gloves will be provided) and what to do with the test once it is used (either by disposing of it themselves, returning it to the Study Center during confirmatory testing for later incineration, or placing it in a sealed envelope to be collected by data collectors who will return two weeks following self-test kit provision). The couple will be instructed that if either of the couple members has a positive HIV test that they should go to the ***Study Center*** we establish, together as a couple if possible. The couple will also be instructed to come to the Study Center if they receive an equivocal test result or have trouble interpreting the results (standard testing using the Tanzanian National Testing Algorithm will be conducted). We will also give them the phone number of the center, so they can also call or text if they have questions. Following self-testing, counselors will be available to participants at the Study Center. Participants can also reach counselors by phone during operating hours (a phone number will be provided to them prior to self-testing). This service will be provided in additional to the standard counseling that will be available once participants report to the Study Center. No personal information will be divulged via phone when calls are made. For participants who contact the center, have had a positive test, but are unable to come to the center we will offer to come back to their house to consult with them. If only one member of the couple presents at the center, they will be offered services, but we will seek permission to contact the other member of the couple for follow up. The Study Center will be located within walking distance to the Kisarawe Care and Treatment Center (CTC), which is centrally located in the study area, and fairly easy for participants to access either by walking or bicycle. The CTC is operated by the District Health System, is located in the Kisarawe District Hospital, and is funded with support from PEPFAR.
Confirmatory HIV Voluntary Counseling and Testing Two weeks after the self-testing has been offered, we will return and offer confirmatory testing. Standard blood-based rapid tests will be offered to all participants who present with report of a positive HIV self-test result. A fingerprint scan will be taken, and a survey will be conducted. We will offer to provide HIV testing to both partners and will only do this jointly with the couple (sharing the results) with each member's consent. Individual HIV confirmatory testing will also be offered if preferred. We will utilize Tanzanian and WHO/CDC standards for provision of VCT, and have vast experience conducting VCT in the area, and in training and monitoring staff conducting VCT. If clients have trouble using the self-test kits, couples can come to the Study Center where they can receive standard HIV testing and counseling services with trained counselors.

Referral Counseling will be offered for any client with a confirmed positive HIV test result. Concordant seronegative couples will be advised to retest in 6-months, following national guidelines. Concordant seropositive couples will be counseled on the importance of HIV treatment and will be offered an escort to the CTC for services. Serodiscordant couples will be reminded of the option for them to enter care and treatment as a couple as part of the study intervention, and that the negative partner will have the opportunity to receive PrEP through the study. In addition, the counselor will review with the couple the clinical risks and benefits of PrEP and seek consent for them to be interviewed again in 6-months and 12-months (in addition to the 18-month scheduled interview). If the positive partner is not already enrolled in care, they will be offered an escort to the CTC to schedule an appointment.

Enrollment in HIV Care as a Couple. Consent will be confirmed to enter care as a study participant. The staff member will explain that the positive partner is eligible for HIV-related treatment regardless of their CD4 count and will remind the couple that the positive partner is eligible for care, according to the national guidelines, should they not want to enter the study. A Study Nurse will review again the benefits and risks associated with PrEP, and the preventative benefits of ARV use with regard to reduction in HIV transmission to the negative partner. In addition, a month's supply of condoms will be provided to the couple, and staff will inform them that they can return for more condoms as needed, and they will be counseled on the preventative benefits of condom use and sexual abstinence. The positive partner will then be referred to the CTC Medical Officer who will conduct a medical assessment and following national guidelines, establish a treatment regimen for the positive partner. In many cases, families share a cellphone. In order to be able to communicate with participants and add a layer of protection to confidentiality, we will provide an inexpensive cell phone to each participant. In

addition, both partners will be asked their preferred alternative communication methods in the event we are unable to reach them using the provided study phones or they are unable to make it to the study office for the 6-, 12-, and 18-month study visits.



The ***Negative Partner will be Offered PrEP.*** This will be in the form of Truvada (TM) which is a fixed-dose combination tablet combining 200mg FTC (emtricitabine) and 300mg TDF (tenofovir disoproxil fumarate). It is manufactured by Gilead Sciences, and Gilead has offered to donate the full supply of Truvada needed for the study. FTC is a nucleoside reverse transcriptase inhibitor (NRTI) and tenofovir is a nucleotide reverse transcriptase inhibitor (NtRTI). One pill is taken daily. In the Partners in Prevention trial there was an observed 75% (95% CI: 55-87%, P<.0001) reduction in incidence with this regimen in Kenya and Uganda.[17] Clients will be advised that they need to have an HIV test conducted regularly to assure that there is no breakthrough infection of HIV, and to promptly report any adverse events or side-effects. All participants eligible for PrEP with have their blood drawn for Creatinine testing to ascertain kidney function. We will also screen PrEP candidates for Hepatitis B prior to starting PrEP. If participants test Hepatitis B positive, they will be provided an additional test (for ALT) to ascertain liver function. If kidney or liver function is poor, the participant will not be eligible for PrEP. For those who test Hepatitis B negative, the vaccination will be offered. Follow up visits will be scheduled at the CTC for the positive partner as per standard of care in Tanzania and the Study Center for the negative partner for a clinical assessment and renewal of prescriptions of ARV (and PrEP as indicated). With consent we shall also track the clinical records of study participants to assess the uptake of ARV & PrEP, and the refilling of prescriptions, clinical signs and symptoms, regular CD4 counts, and HIV test results of the negative clients. At each entry to the clinic a data collector will take a fingerprint scan of study participants and indicate in the records (via tablet) the reason for the visit, and at each visit participants will be assessed for any negative social, psychological, or physical events. All adverse events and unintended consequences will be promptly reported to the study PI for follow up. All pregnancy-related adverse events will be reported to the Antenatal Pregnancy Registry. As PrEP is a relatively new HIV prevention tool, information about PrEP, such as best practices for monitoring safety and adherence, is constantly being updated as data emerges from other studies. We plan to monitor this information and update the study protocol accordingly. We will submit amendments to the IRB for any protocol changes that occur.

Clinical Data from Care and Treatment Center – Tanzania, with support from the Clinton Foundation, has implemented a medical records data information system in Care and Treatment Centers called the CTC2. This system records data on patient characteristics, enrollment, pharmacy data, retention, adherence, complications, and CD4 count (and we will add viral load to assess viral suppression at the 18-month follow-up study visit). We will have access to these data, and will, with participant consent, link biometric data for study participants to their clinical data. In addition, the CTC in Kisarawe will provide blinded CTC2 data on other clinic patients enrolled in the program to allow for comparison of client characteristics, retention, adherence, and viral suppression.

Quality Assurance & Quality Control – We will employ a number of strategies to minimize bias and maintain quality during data collection procedures. Field supervisors will revisit a sample of households that interviewers were assigned to visit and for which they reported the structure as non-residential or as a non-existent household, to verify the household status. In order to minimize selection bias in our sample, interviewers will visit an assigned household a minimum of three times, on different days and at different times, in order to establish contact with either the head of household (or other responsible adult), or the selected individual for study participation. Each interviewer will review each form for errors before leaving. Field supervisors will monitor interviewer progress with households and review data from every interview.

Protocol for Mitigating Risks – Importantly, there are some key safety considerations associated with the use of HIV self-test kits and the collection of biometric data. Prior to commencing study enrollment, we will develop a detailed safety protocol. Fortunately, multiple members of the research team (Drs. Sweat and Mbwambo) have extensive experience managing safety risks in research, and Dr. Mbwambo,[65-71] is an expert in the study of interpersonal violence. Specific to the provision of HIV self-test kits, there is the possibility that one partner might attempt to coerce the other partner to take the test. There is also the possibility for a loss of confidentiality of individual's HIV status. Finally, there is the potential for psychological distress or intimate partner violence if an individual's HIV status becomes known. Several strategies will be used to reduce these risks. To minimize risk for partner coercion, members of each couple will be consented separately in private. Further, when training research staff in the consenting procedures, it will be emphasized that under no circumstances should they or any household member attempt to influence an individual's participation. Prior to distributing test kits to a consented couple, staff will provide counseling to the couple to ensure both members are comfortable receiving the test and to develop an agreement regarding shared confidentiality. Finally, all study participants will be provided access to the study counselor located in the community.

Measures

We will adapt our core questionnaires from Project Accept and The Triage Project when relevant. These instruments have undergone extensive piloting and field application in the study setting. Instruments (attached as appendices) were developed in English then translated to Kiswahili, and then back-translated by an independent translator. **(1) HIV-related stigma** will be assessed using a scale developed by Project Accept investigators. Previously published items on stigma were compiled and reviewed by site teams and social scientists currently conducting international HIV/AIDS research. In Project Accept these measures resulted in an alpha of 0.62 at baseline. **(2) HIV risk behaviors** will be assessed using standardized items that have been used previously in international settings and successfully used in several multicenter trials supported by the NIH, including the HPTN family of studies (e.g., HIVNET 016A, HIVNET 009). Risks include recent (one-month), intermediate (six-month), and longer-term (lifetime) measures of sexual behavior (by partner gender, type of activity, condom use), using partner-by-partner elicitation (for up to the last 4 partners). We included measures of relationship type (spouse, friend, casual acquaintance, commercial, etc.). We have developed algorithms to produce easily understood outcome measures (e.g., frequency of unprotected intercourse; proportion of acts using a condom). **(3) Rates of HIV Testing**. We will include questions in the behavioral questionnaire on history of voluntary HIV testing (first time, last time, number of times total, location, cost, provision of counseling, review of counseling content, rate of returning for results). We also will collect ongoing client data on testing utilization. **(4) Social norms concerning HIV testing**

measures were developed for Project Accept and will be used in this study. We will inquire about behavioral intention to seek VCT, attitudes (fears, worries, resolve, anxiety), self-efficacy to seek VCT, perceptions of abilities to overcome barriers, norms regarding VCT in the community, and perceptions of support for intentions. Items were constructed, tested for meaning in pilot studies, revised and translated/back-translated for meaning in Project Accept. In Project Accept these measures resulted in an alpha of 0.81 at baseline. **(5) Discussions about HIV**. In the NIMH Collaborative HIV/STD Prevention Trial baseline questionnaire, questions were developed for a five-country community-randomized trial (Zimbabwe, Peru, China, India, and Russia) to capture key elements of community conversations about HIV/AIDS and the frequency of discussion with specific individuals (spouse, family, friends, key opinion leaders); we adapted these items for use. In Project Accept these measures resulted in an alpha of 0.76 at baseline. **(6) Disclosure of HIV status** will be measured as it was in earlier VCT research in Africa.[76] The instrument asks about the disclosure of serostatus to spouses, sexual partners, immediate family, other relatives, friends, religious leaders, health care professionals, and employers. The proportion of participants reporting each disclosure will be calculated after eliminating those who say the disclosure was not applicable to them. In Project Accept these measures resulted in an alpha of 0.83 at baseline. **(7) HIV-related negative life events** will be measured as they were in prior VCT research in Africa [76]. Negative HIV-related life events include breakup of a marriage or sexual relationship, physical abuse by a sexual partner, neglect by family, being disowned by family, rejection by peers, and being discriminated against by health care providers or employers. The proportion of participants reporting each life event is calculated after eliminating those who say the life event was not applicable to them. In Project Accept these measures resulted in an alpha of 0.74 at baseline. **(8) Safety Related to Intervention** measures will assess specifically whether any adverse events (such as those listed in item 7 above) were experienced as an outcome of receiving each specific intervention component from the study. We will especially assess consequences of HIV self-testing, disclosure of HIV test results, accessing treatment, and PrEP utilization. We will also ask whether there was any coercion, pressure, or sanction for experience for clients to receive services and the source of each. These detailed questions will be added to our utilization data collection forms for each service assessing negative life events experienced from previous services received from the project. **(9) Potential for Misrepresentation** will also be assessed with regard to whether clients indicate higher risk behaviors than are true. We will do this by comparing data across couples, and over time to establish whether there are inconsistent results emerging. **(10) Cost** - The PI has significant experience with costing and cost-effectiveness analysis and led the costing component of the previous multi-site study. Cost data will include a range of costs for each item, with high, low, and average costs recorded. Data to be collected include: (1) Conversion rate of local currency to US dollars at 6-month intervals over the life of the project; (2) buying power of the currency at the beginning, midpoint, and end of the project based on the World Bank's Purchasing Power Parity Index; (3) costs of all commodities used in the intervention; (4) labor costs for intervention workers; (5) promotional and advertising costs; (6) average time clients spent with intervention; (7) rent; (8) maintenance; (9) incentives to participants; (10) volunteer activities; (11) user fees; (12) value of donated goods and services; and (13) other relevant costs. An annuity function will be applied to startup costs and they will be distributed over the life of the intervention. Time preference will be taken into account by applying discounting to future benefits at 0%, 5% and 7% as recommended by the US Panel on Cost-Effectiveness in Health and Medicine[80]. **(12) Clinical** - for serodiscordant couples we will collect from the CTC: (1) date, time and reason for clinic visit, (2) results of CD4 and viral load tests (if any), (3) any reported medication side-effects, (4) medications prescribed, (5) pick up time and date of prescriptions, (6) HIV test results, (7) change or stop events for medications and associated reasons noted in record. These same results will be available in blinded format for other clients enrolled in the CTC and will be collected for comparison. In addition, for those in the cohort we shall conduct a HIV test at the follow up interview with counseling and referrals for care. For HIV positive members of serodiscordant couples followed in the cohort we will also collect blood for a viral load test at the time of the final interview to assess viral suppression.

Formative Research

Prior to conducting the intervention, we will conduct formative research to explore the knowledge, attitudes, and perceived benefits/concerns towards HIV self-testing, pre-exposure prophylaxis (PrEP) use, and early ART among people affected by HIV – both PLWH enrolled in care and seronegative (or unknown status) partners of PLWH – in Kisarawe. This will provide valuable information that will improve intervention implementation.
The specific aims of the formative research component include:

- To develop appropriate counseling tools and strategies regarding HIV self-testing, PrEP, and early ART for the Kisarawe community during the DDCP intervention
- To identify and address challenges/barriers to uptake of HIV self-testing, PrEP, and early ART so these can be addressed during counseling and while raising community awareness
- To use perceived concerns and benefits to improve intervention implementation

To evaluate these aims, we will conduct up to 45 qualitative, in-depth interviews (IDIs) with different target sub-populations recruited from the Kisarawe CTC, including people who are currently receiving ART (up to 15 interviews), people who are in care but not on ART (up to 15 interviews), and HIV-negative people whose partners are in care (up to 15 interviews). Participants will be selected by purposive sampling through the CTC in Kisarawe District Hospital, Kisarawe Town. We will target adult HIV-positive Kisarawe community members engaged in services at the CTC, stratifying by type of services received: either engaged in care (receiving monthly ART) or not in care (registered at CTC but not receiving monthly ART, likely waiting for CD4 count to drop below national guideline threshold). We will also try to sample approximately equal numbers of men and women, for equal gender representation. In addition, we will use chain/snowball sampling among CTC clients to reach our other target sub-group: HIV-negative members of couples engaged in CTC services. In addition, we will hold four focus groups (1 for males in care, 1 for females in care, 1 for males who are seronegative partners, and 1 for females who are seronegative partners) with 5-10 participants per group to understand social norms and confirm findings.

Candidates for interviews will be recruited via purposive sampling from the Kisarawe Care and Treatment Center to delve into personal experiences and hypothetical scenarios. Three groups of informants will be solicited, with fairly equal representation of males and females:

- Up to 15 people living with HIV who are currently receiving ART
- Up to 15 people living with HIV who are in care but not on treatment (connected to CTC, but getting their CD4 count checked / on waitlist for ART)
- Up to 15 HIV-negative people whose partners are in care (but they are not)

Each participant will be interviewed for approximately 60 minutes. A follow-up interview with some participants may be warranted. The focus groups will also last approximately 60 minutes. Trained data collectors will go through the informed consent process with each participant prior to commencing the interview or focus group. Willing participants will sign a written informed consent document, and with participants' permission, all interviews and focus groups will be audio-recorded.

Two qualitative interviewers will be hired. Interviewers will also serve as transcribers and will generate verbatim Swahili language transcripts from the digitally recorded interviews and focus groups as soon as possible after they are conducted. A trained translator, fluent in English and Swahili, will also be hired to create typed English language versions of the fully transcribed digital interviews as Microsoft Word documents.

All qualitative staff involved in human subjects research will undergo training on qualitative research ethics, methodology, and specific data collection expectations and methods for the DDCP study.

Participants will not be given transportation reimbursement. The site for interviews and focus groups will be at the Kisarawe Project Office, a five-minute walk from the Care and Treatment Center and

within 30 minutes walking distance from anywhere in Kisarawe Town. Refreshments will be provided for focus group participants. All interview informants will receive a small compensation for their time in the form of 10,000 Tsh in cash.

The purpose of the IDIs is to delve into what people think about three new HIV interventions: self-testing, PrEP, and early ART. The interviews will explore people's response to these intervention strategies, including perceived benefits and risks; capture contextual issues that may facilitate or become barriers to uptake, initiation, or adherence; elucidate social interactions (particularly at the dyadic level) that impact decision-making; and estimate acceptability and hypothetical usage. IDIs are an appropriate method to understand these issues because they enable researchers to elicit individual narratives, such that the interviewer can explore what is meaningful and relevant to individuals and couples targeted by the DDCP intervention. The purpose of the FGDs is to delve into what people think about three new HIV interventions: self-testing, PrEP, and early ART. The discussions will explore the acceptability of these interventions, as well as social norms. FGDs are an appropriate method to understand these issues because they enable researchers to elicit social/group norms and validate data generated in previous IDIs, such that the interviewer can explore what is meaningful, relevant, and acceptable within the community targeted by the DDCP intervention. They will also be used to discuss potential future interventions or solutions to concerns identified during interviews.

To analyze the qualitative data, verbatim Swahili transcripts will be generated from digital recordings of each interview immediately following the interview. Interviewers will transcribe their own interviews.. Transcripts will be spot checked for quality assurance to ensure that they are truly verbatim, either by the study coordinator or other Swahili-speaking members of the study team. Field notes will be coded on a regular basis, at least weekly, as they are uploaded into Atlas.ti, a qualitative data management software program. This will enable ongoing analysis and reflection on the purposes and findings of the formative work. At least two members of the study team will use thematic coding to ascertain themes present in the data. Transcripts will be coded line-by-line, and key ideas and themes will be developed by grouping codes. A coding template will be developed from a sample of the early transcripts and will be used to code later transcripts in an ongoing process as data is collected. As more transcripts are coded, the template will be refined to reflect any newly emerging ideas or themes. Ongoing analysis will involve frequent returns to the original transcripts to ensure text is coded within context. Coding will be carried out using a qualitative data analysis software program. After coding, memos will be written to summarize major themes based on the field notes and transcripts. This analytical process will strive to situate the current practices and initial perceptions of the planned Dyadic intervention in the Kisarawe context. Results will be used to develop counseling tools and strategies appropriate for the Kisarawe community when introducing the Dyadic study, to raise community awareness about the project, and to improve intervention implementation by being prepared to address concerns and challenges identified in the formative work.

Data Management - We have a well-established data processing center in New Delhi, India that has processed data for Project Accept and the Triage Project. Data will be collected using tablets programmed to store data in an encrypted format and transferred via wireless cell phone internet access at completion of the interview. The data are automatically erased from the tablet at this stage, and data are transferred to project servers for analysis. This allows real time monitoring of progress in the field, reported via automated Benchmark reporting tables on a password protected website, and facilitates monitoring of the status of data collection, and helps us make rapid corrections to assure timely adherence to the timeline. In addition, data are rapidly available for analysis. Fingerprint readers are linked to the Tablets using a USB connection, and biometric data are linked to the source survey or utilization forms. In preparation for this study we have developed the data entry systems and field tested the technology in Tanzania, and had excellent performance.

Utilization and Clinical Data Collection - Tablets will be provided to study staff collecting survey data, and to staff at the study referral center adjacent to the Care and Treatment Center (CCTC). Upon presentation at the CTC participants will first register with the study staff, have biometric data collected, and answer a few very short questions on why they are there. Clinical data from the CTC from each

visit (see measurement section) will later be abstracted and linked to the client by Patient ID number (obtained at first entry to the study, and linked by study staff to biometric identifier). Questions will also be posed to participants at each survey catchment to assess self-report utilization of services. These data will be used together with survey data in the following analyses.

Qualitative sub-study for the Dyadic Study

Based on finding a significant number of HIV serodiscordant couples in Kisarawe who were made aware of the DDCP study but chose not to participate (n≈40), we propose conducting a small qualitative sub-study to understand more about couples' decision-making to participate or not participate in dyadic-based research involving access to PrEP and ART. Given the new prevention and treatment landscape in the field of HIV involving PrEP and early ART, it is critical to understand how serodiscordant couples make decisions to protect their own health and that of their partner(s), and it is equally critical to understand how to honor and appropriately involve both members of a couple in research studies that directly affect them. The DDCP study will inform understanding of the uptake of dyadic PrEP and ART services among serodiscordant couples, as well as how dyadic care performs in regards to adherence and retention in care, and the proposed qualitative sub-study will enhance these aims by investigating how couples are making decisions about their health, including their decision to participate as research subjects and their uptake of interventions services, including ART and PrEP.
The specific aims of the qualitative sub-study include:

1. Understand and describe how relationship factors affect couples' rationale for participation in a research study as a couple.

2. Identify relationship factors that act as barriers and facilitators for utilization of intervention services (self-testing, PrEP, and ART).

To evaluate these aims, we will conduct up to 48 qualitative, semi-structured in-depth interviews (IDIs) with different target sub-populations, including (1) up to 24 individuals involved in serodiscordant relationships currently participating in the PrEP/ART cohort of the DDCP study and (2) up to 24 individuals involved in serodiscordant relationships who chose not to join the PrEP/ART cohort. The non-participants will be selected in ways that mirror the two methods of recruitment into the dyadic care portion of the study: (2a) up to 12 individuals involved in serodiscordant relationships who participated in the self-testing phase of the study, and (2b) up to 12 individuals involved in serodiscordant relationships who were identified through the Kisarawe CTC.

Sample size will be determined by data saturation. Interviewing up to 24 individuals currently participating in the study and up to 24 individuals not participating in the study, with both recruitment strategies represented (self-testing and existing serodiscordant couples at the CTC), should provide sufficient numbers to reach saturation as research has shown saturation is typically reached within 12 cases.[90] While interviewing both members of a couple would provide a unique ability to compare perspectives' within a dyad, participation in the qualitative sub-study will not be dependent upon a partner's willingness to participate; in other words, participation will be on an individual basis. If both members of a couple would like to participate in the sub-study, this will be encouraged and allowed, although members will be interviewed separately and no information about the other member's interview will be shared. It will also be acceptable if only one member of a couple would like to participate in the sub-study. An individual's decision to participate in the sub-study will be kept confidential and not shared with anyone, including with the participant's partner.

Participants will be purposively sampled, and interviews will be conducted individually with each member of a couple (if both members of a couple chose to participate; this is not a requirement for participation), with maximum variation sought for gender and HIV status. All participants will be aged 18 years of older. Inclusion criteria include being aged 18 years and older, involved in a serodiscordant relationship, and some exposure to the DDCP study prior to the time of interview (ranging from current participation to prior knowledge from previous recruitment efforts at CTC or from participating in self-testing phase of study). For current dyadic-care participants, existing participants will be approached

about sub-study participation immediately following their regularly scheduled parent study research appointment (e.g., either 6- or 12-months following enrollment). Participants who participated in self-testing but chose not to participate in dyadic care will be approached at their 6-month home-based post-self-testing follow-up visits. For known serodiscordant couples identified through the CTC, they will be approached at the CTC by study staff. Participation or non-participation in the sub-study will not affect current participants' standing in the parent study and for participants not currently part of the parent study, participation in the sub-study will not preclude from receiving their usual HIV care services or from joining the DDCP study in the future.

Each participant will be interviewed for approximately 60 minutes at the study office in Kisarawe, or another private location of the participant's choosing. The focus of the interview guides will be twofold: (1) Dyadic-based rationale for study participation or non-participation, including: a) participation in decision-making, b) couples' perceived benefits and risks of participation; c) primary motivations for joining/not joining, d) concerns/rewards regarding family and community perceptions of study involvement; and e) perceptions of the consent process (only for those who are current or former DDCP participations); and (2) Decision process for utilizing HIV-related services (PrEP/ART), including: a) partner influence on ART/PrEP uptake/discontinuation; b) family influence on PrEP/ART utilization (e.g., desire to conceive a child); and c) community influence on PrEP/ART (e.g., stigma).

Trained data collectors will go through the informed consent process with each participant prior to commencing the interview. Willing participants will sign a written informed consent document, and with participants' permission, interviews will be audio-recorded. To reduce bias, interviewers will be hired from outside the DDCP study for the qualitative sub-study. Interviewers will also serve as transcribers and will generate verbatim Swahili language transcripts from the digitally recorded interviews as soon as possible after they are conducted. Trained translators, fluent in English and Swahili, will also be hired to create typed English language versions of the fully transcribed digital interviews as Microsoft Word documents.

All qualitative staff involved in human subjects research will undergo training on qualitative research ethics, methodology, and specific data collection expectations and methods for the DDCP study. All qualitative data generated from the sub-study will kept and maintained in manners similar to the data collected from the parent study. All paper-based forms will be kept in a locked filing cabinet in a locked project office in Kisarawe. We will use MUSC's "Box" system to store electronic data, including voice recordings, transcriptions, and translations. These files will be password protected and only accessible to study investigators and interviewers. Signed consent forms will also be scanned and stored on Box. Participants will be assigned an ID number; no full names or other identifying information will be collected.

The site for interviews will be at the Kisarawe Project Office, a five-minute walk from the Care and Treatment Center and within 30 minutes walking distance from anywhere in Kisarawe Town, or at a private location of the participant's choosing. All interview informants will receive a small compensation for their time in the form of 10,000 Tsh in cash and up to 5,000 Tsh for transportation reimbursement.

To analyze the qualitative data, verbatim Swahili transcripts will be generated from digital recordings of each interview immediately following the interview. Interviewers will transcribe their own interviews. Transcripts will be spot checked for quality assurance to ensure that they are truly verbatim, either by the study coordinator or other Swahili-speaking members of the study team. Regular debriefing meetings will also take place with the team, which will enable ongoing analysis and reflection on the purposes and findings of the qualitative sub-study. Changes to questions and probes asked during the interviews may change as new themes emerge, but all questions will remain within the scope of the study aims. At least two members of the study team will use thematic coding to ascertain themes present in the data. Transcripts will be coded line-by-line, and key ideas and themes will be developed by grouping codes (axial coding). A code book will be developed from a sample of the early transcripts and will be used to code later transcripts in an ongoing process as data is collected. As more transcripts are coded, the codebook will be refined to reflect any newly emerging ideas or themes.

Ongoing analysis will involve frequent returns to the original transcripts to ensure text is coded within context. Coding will be carried out using a qualitative data analysis software program, such as Atlas.ti or Dedoose. For analysis, we will employ the constant comparative method, which is derived from Grounded Theory,[91] and involves conducting open and axial coding as mentioned above, and drawing comparisons on various axes, including from within the same interview, within the same sub-group (e.g., current participants), across sub-groups (e.g., current participants to those who chose not to participate), and across individuals of a couple, if both members of the couple are interviewed.

This research will help address the parent study's aims of understanding dyadic-based uptake and use of intervention services as well as provide understanding of dyadic-based rationales for joining or not joining a research study and perceptions of the consent process, which could help improve ethical considerations for dyadic-based research in the future.

Exit Interviews

At the end of their final interview, we will ask all Dyadic Care study participants to take a two-phase exit interview. The purpose of the exit interviews is to assess the participant's experiences with study operations and challenges that they experience in preventing HIV infection after study participation. The first phase of exit interviews will occur immediately after the 18-month study visit and will consist of asking a set of brief questions, taking approximately 15-minutes. The second phase of the exit interview will occur one month later and will consist of a set of brief questions. Following each of the two interviews, we will provide a risk mitigation counseling session to help participants navigate HIV risk reduction challenges.
In addition, we will invite a sample (up to 12 couples or 24 individuals) of study subjects to participate in a brief qualitative interview of approximately 1-hour duration to gather in-depth information in an open-ended format on the same topics. This will be targeted to study participants where one of the members of the couple was taking PrEP at the end of their study participation.

COVID-19 Safety Guidelines / Precautions

In January 2020, reports began surfacing about a novel coronavirus outbreak in Wuhan, China. In February 2020, the World Health Organization gave it the official name new coronavirus disease 2019, abbreviated as COVID-19. COVID-19 is caused by a coronavirus called SARS-CoV-2. Within a matter of weeks, COVID-19 began spreading via human-to-human transmission to other countries in East Asia, Europe, and North America, before being declared a global pandemic by the WHO on 11th March 2020.

The virus that causes COVID-19 is thought to spread mainly from person to person, mainly through respiratory droplets produced when an infected person coughs or sneezes. These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs. Spread is more likely when people are in close contact with one another (within about 2 meters). Recent studies have suggested that COVID-19 may be spread by people who are not showing symptoms. COVID-19 seems to be spreading easily and sustainably in the community ("community spread") in many affected geographic areas. Community spread means people have been infected with the virus in an area, including some who are not sure how or where they became infected.

Current symptoms reported for patients with COVID-19 have included mild to severe respiratory illness with fever, chills, cough, and difficulty breathing. These symptoms may appear 2-14 days after exposure to the virus. Older adults and people who have severe underlying medical conditions like heart or lung disease or diabetes seem to be at higher risk for developing more serious complications from COVID-19 illness.

Tanzania had its first confirmed case of COVID-19 reported on 16th March 2020. The number of cases rose to 480 as of 29th April 2020, with 16 confirmed deaths. However, a lack of testing availability

means that the actual number of cases is likely to be much greater than the official case count reported by the Ministry of Health.

There is currently no vaccine to prevent COVID-19; the best way to prevent illness is to avoid being exposed to this virus. Therefore, a series of precautions are essential to anyone coming into contact with other people. We have established safety guidelines to prevent exposure of both study staff and participants to COVID-19 while conducting study operations:

1. Wash hands often – Every staff member and participant should wash their hands often with soap and water for at least 20 seconds, especially after being in a public place, or after blowing their nose, coughing, or sneezing. Staff and participants should be made to wash their hands before entering and leaving the Study Center and CTC. If soap and water are not readily available, use a hand sanitizer that contains at least 60% alcohol. The person should cover all surfaces of their hands and rub them together until they feel dry.
2. Avoid touching eyes, nose, and mouth with unwashed hands.
3. Wear protective layers – Staff must cover their mouth and nose with an N95 mask (preferably) or a cloth face cover when in the Study Center or CTC. Staff must also wear latex gloves when handling tablets or other surfaces that may have been touched by other people. Discard the gloves after each encounter; do not reuse the same pair of gloves. Staff must continue to keep approximately 2 meters between themselves and participants or other healthcare workers. The cloth face cover and gloves are not a substitute for social distancing.
4. Clean and disinfect – Clean AND disinfect frequently touched surfaces daily. This includes tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks. If surfaces are dirty, clean them. Use detergent or soap and water prior to disinfection. Then, use a household disinfectant in the form of wipes and/or spray. Most common EPA-registered household disinfectants will work.
5. Avoid close contact – Remember that some people without symptoms may be able to spread virus. Keeping a 2-meter distance from others is especially important for people who are at higher risk of getting very sick.
6. Discontinue in-person study visits – (a) No hospital-based study activities – CTC2 card data extraction will pause beginning 1st May 2020. Additionally, no Data Collector will be stationed at the CTC for Monthly Clinical ART visits. (b) Only clinical PrEP visits will be conducted in-person – per guidance issued by MUSC IRB, NIMR, and MUHAS DRP, study visits should only continue if the withholding of medication would impose a greater risk to participants than potential exposure to COVID-19. Therefore, we will continue to provide PrEP medication to our HIV-negative participants. At the time of the first confirmed case in Tanzania, there were 13 seronegative participants who were still enrolled in the study and may come to the Study Center for PrEP through early August 2020. (c) Remainder of study surveys will be conducted over the phone – we already have IRB approval to conduct surveys over the phone with the participant's permission. The Nurse Supervisor, PrEP Nurse, and Interviewer Supervisor will attempt to call participants and record survey answers in the tablets. We will provide compensation money electronically via mobile money transfer (Halo-pesa). (d) No qualitative interviews – in-person qualitative exit interviews will pause beginning 1st May 2020.
7. Reduce staff load – In an effort to minimize exposure to staff and maintain social distance, only four technical staff (Study Coordinator, Nurse Supervisor, PrEP Nurse, Interviewer Supervisor), one driver, one cleaner, and one security guard will be on duty per week. The remaining field staff, drivers, cleaners, and security guards will be rotated out on a weekly basis.
8. Continued monitoring – The Principal Investigators, Co-Investigators, and Study Coordinators will continue to monitor the COVID-19 situation in Tanzania. The Tanzania-based team will provide regular updates to the South Carolina-based team to monitor the progress of the outbreak and community transmission within Tanzania and in Kisarawe District, specifically. We will update our procedures as necessary, maintaining the safety of staff and participants as the highest priority.

Analysis Plan

Data Structure: There are two key unique features of the primary data for this proposal. First, because couples are enrolled in the study, there is inherent nesting of two individuals within each couple. Second, the measurement design leads to repeated measurements outcomes for some of the aims. Given the aims of the study, many of the outcomes will be evaluated using descriptive statistics. However, issues such as nesting and repeated measurements will be carefully considered. For example, for the first aim, uptake will be reported by each individual within the couple, and the descriptive statistics will be reported both at the individual level within the couple and at the aggregate couple level. For the outcomes that will be evaluated using inferential statistical analyses, the nested data structures (e.g., repeated measurements within couples) will be addressed using mixed-effects regression models (MRMs; e.g.).[81] These highly flexible models accommodate variability in the number/spacing of outcome measurements, and they readily accommodate linear and non-linear outcome distributions (e.g., dichotomous, count). **Outcome Distributions & Individual Trajectories:** Prior to analysis, each outcome will be carefully inspected to determine the most appropriate distribution for modeling. Likewise, for outcomes with repeated measurements, the trajectory for each participant on each outcome will be plotted using "spaghetti plots".[82] These plots will illustrate the level of and variability in each outcome, along with patterns of change over time. **Model Building & Estimation:** Singer and Willett's (2003)[83] model building approach will be used to specify fixed and random effects. The MRMs will be performed using MLwiN software. [84] Due to the relatively modest sample size for some of the analyses, the models will also be performed using Bayesian MCMC-based estimation [85] in MLwiN. This simulation-based approach utilizes a large number of iterations – each informing the next – to produce an empirically-based sampling distribution for each parameter. For example, rather than a single point estimate of the parameter of interest, the MCMC-based provides the magnitude, precision, and variability of the parameter estimates. **Attrition & Missing Data:** Individuals or couples who drop out of clinic care will be retained, when possible, in ongoing research measurement according to Intention-to-treat principles.[86] Some research data will inevitably be missing, and the methods recommended by Schafer and Graham[87] will be used to evaluate missing data assumptions and guide the subsequent analyses. Given few missing data and evidence supporting a MAR mechanism, the procedures detailed above will be utilized with all available data. Given non-trivial missing data and evidence supporting MAR, multiple imputation for longitudinal data will be used to provide complete data.[88] Finally, given non-trivial missing data and evidence suggesting NMAR, pattern mixture models will be used to control the missing data .[82]

Evaluation of Specific Aims & Associated Hypotheses

AIM 1 - We hypothesize that the majority of couples (GT ~ 50%) will utilize the HIV self-test kits and share their results with their partner. To evaluate the factors associated with uptake of HIV self-testing, a single level logistic regression model with a logit link function will be performed. The outcome will be the HIV self-testing status (0 = did not use self-test, 1 = used self-test). Demographic variables (e.g., age & gender) will be evaluated as predictors of self-testing uptake, with results focusing on ORs, and corresponding 95% CIs.

AIM 2 - We hypothesize that a large proportion of serodiscordant couples who present to the study referral office (GT ~ 70%) will engage in care together, have higher rates of adherence and retention than individually enrolled clients, and have a reduction in risk behaviors for HIV transmission from baseline to 18-month follow up. For this aim, there are repeated measurements of retention in care and adherence (level-1) nested within positive partners (level-2). A dichotomous predictor variable at the individual level (i.e., level-2) will test for differences in the log-odds of treatment retention between those enrolled in care as a couple and those enrolled in routine clinic services. The adherence outcome will be analyzed in a similar manner. For this outcome, there are several indicators of medication adherence. First, for the positive member of the couples, self-reports of ARV adherence will be obtained at 6, 12, and 18 months. Second, individuals on ARV are expected to return to the clinic each month to have the prescription refilled. Third, for individuals in the study, viral load tests will be obtained at 18 months allowing us to assess viral suppression as a marker for medication adherence. For the

first outcome, self-reported ARV adherence, the three repeated measurements will be nested within the positive partners. The unconditional model will estimate the rate of, and variability in, ARV adherence across participants. Based on inspection of "spaghetti plots," subsequent level-1 growth models will be specified to test for change in the rate of ARV adherence over time. For the second outcome, each positive individual from the study and from the CTC will have 18 monthly measurements of ARV refill status (i.e., 0 = Not Refilled, 1 = Refilled). This will be modeled as described above, with the level-2 dichotomous indicator testing for a difference in the average log-odds of adherence for those enrolled as a couple and those enrolled in routine clinic care. Given the large number of measurements per individual, alternative specifications are possible, and this will be guided by inspection of the spaghetti plots. For the third outcome, CD4 counts at 18 months will be compared using a single-level regression model to test for differences between those enrolled as a couple and those enrolled in routine services. For the fourth outcome, sexual frequency, condom use, and sex in the context of ARV or PrEP will be estimated. Using a mixed-effects model, predictor variables related to risk will be added to the model. These variables will also be considered for entry as time-varying covariates (i.e., entry at level-1) or as aggregative, couple-specific predictors.

AIM 3 - We hypothesize that a moderate proportion of HIV negative partners will utilize PrEP (~ 30%), that PrEP utilization among HIV negative partners will be associated with lack of ARV use by positive partners, and ARV use by positive partners will be associated with lack of PrEP use by negative partners. To evaluate the factors associated with uptake of PrEP, a single level logistic regression model with a logit link function will be performed. Demographic variables such as age and gender will be evaluated as predictors of PrEP uptake, with the results focusing on the odds ratios, and corresponding 95% confidence intervals, for these variables. To evaluate association between ARV and PrEP utilization within couples, two main models will be performed. For the first, the outcomes will be variables related to the use of PrEP. Likewise, for the second, the outcomes will be variables related to the use of ARV. These outcomes will be evaluated using MRMs as described above. Because each outcome is specific to one member of the couple (i.e., the negative partner for PrEP and the positive partner for ARV), the data will have a two level structure with repeated measurements (level-1) nested within couples (level-2). At the repeated measurements level of the model, the partner's ARV or PrEP status for the preceding time period will be entered as a time-varying covariate. For example, for the PrEP outcome, the positive partner's ARV status will be entered at level-1, and this will test for differences in the use of PrEP for negative partners whose positive partners were on ARV versus not on ARV. Similarly, for the ARV outcome, the negative partner's PrEP status will be entered at level-1, and this will test for differences in the use of ARV for positive partners whose negative partners were on PrEP versus not on PrEP. More tailored formulations are also possible. For example, introducing a lag between the predictor and outcome could test the extent to which PrEP and ARV status were associated with later initiation of ARV or PrEP. We hypothesize couples will alternate risk reduction strategies (abstinence, ARV treatment for the positive partner, PrEP for the negative partner, and condom use) but typically maintain at least one strategy. Each risk reduction strategy will be considered as a separate outcome, with repeated measurements of strategies (level-1) nested within couples (level-2). The model specification will be heavily informed by preliminary evaluation of the spaghetti plots, as described above. These plots will guide tests for patterns of change over time (e.g., linear), specific phases of change, or even invariance over time such that aggregation is justified. After building the mixed-effects model, predictor variables related to the use of abstinence, condoms, ARV, or PrEP will be added to the model. These variables will also be considered for entry as time-varying covariates (i.e., entry at level-1) or as aggregative, couple-specific predictors based on the findings of the previous models. Such a formulation will test for, for example, differences in the use of risk reduction strategies for time periods when the positive partner is on ART versus not on ART. Based on the descriptive statistics and the patterns of use of each individual strategy over time, supplemental analyses will be considered that simultaneously evaluate all of the strategies. For instance, cluster analyses could be used to identify groupings of individuals based on the combination of risk reduction strategies utilized.

AIM 4 - We hypothesize that the program cost per client served associated with HIV testing and case detection for Dyadic-based Diagnosis, Care and Prevention (DDCP) will be substantially (~30%-50%) lower than for either clinic-based VCT or community based VCT; that HIV case detection will be more

economically efficient (detect more cases at a lower cost); and, that DDCP will detect substantial more (GT ~ 80%) serodiscordant couples than the alternatives. For these analyses we will use standard procedures for estimation of the cost of interventions that adhere to the Panel on Cost-Effectiveness in Health and Medicine's guidelines.[80] This will include identification of the various types of resources consumed by the intervention, establishing a unit associated with each type of resource used, estimating the dollar value of each resource, calculating the number of units used, and multiplying the units of resources used by the dollar cost for each. These are summed to derive the cost of the intervention. Indirect costs will also be added to establish the gross cost. For each intervention and associated site we will estimate the total and average costs for the interventions. Startup costs will be annuitized over the life of the interventions using a standard annuity function. The discount rate utilized for the annunitization of one-time capital expenditures will be the same as that used in the overall analysis. We will estimate the full costs of the interventions, assuming no cost sharing, volunteer labor, or donated commodities. We will derive our cost estimates using a micro-costing methodology such that resource consumption is determined by identifying, measuring, and valuing all incremental costs needed to provide the interventions. These estimates will be compared with project budgets and reviewed with project staff to assure accuracy. These procedures were used for our costing of Project Accept interventions, and we have recently collected detailed costing estimates available for both clinic-based VCT and community-based VCT from the study area. In addition, we have highly detailed utilization data from Project Accept that specify associated rates of HIV case detection and rate of couple's HIV testing. These were recently published in Lancet Infectious Diseases.[46] Analysis for this aim involves direct comparison across program types (independent t-tests for mean differences, and non-parametric tests for counts) of differences in cost, efficiency, and number of serodiscordant couples detected.

Precision of Estimates and Statistical Power: The level of precision and statistical power is necessarily limited given the stage of the research and the sample size associated with many of the outcomes. For the descriptive statistics, the margin of error was computed as an indicator of the level of precision afforded by the sample.

For AIM 1 – Based on our review of available literature on the prevalence of HIV sero-discordancy in stable couples we estimate that we will need to enroll approximately 442 couples to yield enough serodiscordant couples (N=60) to enroll in the second phase of the study. However, this is an uncertain estimate, and it may require up to 1000 couples. The expected percentage of the sample that will opt to use the HIV self-test is 50%-70%. The widest margin occurs at the level of 50%; therefore, this value was selected. With a sample of 442 and self-test use of 50%, the 95% confidence interval for the true value of this estimate is 46% to 54%. With a sample of 1000 and self-test use of 50%, the 95% confidence interval for the true value of this estimate is 48% to 52%.

For AIM 2 - For the estimated sub-sample of 50 individuals for the PrEP use outcome, the 95% confidence interval for 50% PrEP use is 36% to 64%. If this percentage is as high as 75%, the confidence interval would be 63% to 87%. For the MRMs, this sample is sufficient for accurate estimates of fixed effects. [89] Although the point estimates of variance components and SEs could be biased, the proposed Bayesian MCMC-based analyses will provide increasingly valid estimates and will provide information about the variability and precision of the estimates. [85] Also of note, with the current design, the primary statistical test (i.e., that a time-varying correlation = 0) has a much smaller sample size requirement than does the primary statistical test for a traditional randomized design (i.e., between-group difference in slopes = 0). Statistical power was estimated using the method recommended by Maas and Hox [89] for a design with a level-1 predictor variable, a random intercept, and no other random effects. The lower limit on power is provided by the outcomes with 3 research measurement occasions, and outcomes utilizing clinic data and samples will offer much higher statistical power. With an estimated 50 individuals and 3 measurement occasions, the level-1 sample size is 150. Penalizing this sample for a nesting effect characteristic of repeated measurement data, ICC = .50, the effective level-1 sample size is 75 (i.e., given the dependence in the data, the level-1 sample of 150 offers the power of a sample of 75). For the dichotomous outcome and the dichotomous level-1 predictor, with an effective level-1 sample of 75, power is .80 to detect an event rate of 30%

(i.e., OR = 4.26). Assuming up to a 20% loss to follow-up rate, we will enroll 60 couples to ensure there are at least 150 measurements in total.

In sum, with between 442 and 1,000 couples in the HIV self-testing component of the study, and between 60-70 couples in the Dyadic Care component of the study we estimate that we will have adequate statistical precision and power to answer the requisite study questions.

TIMELINE – Based on experience working in the area we feel confident we can meet these goals:

Year 1: Obtain IRB approval from MUHAS and MUSC; finalize survey; hire and train data collection staff; conduct household mapping and validate GIS data; prepare communities for study. *Year 2*: Hire and train locally based intervention staff; Collect baseline data. *Year 3*: Implement Intervention. Track participants. Collect quality assurance data. Collect clinical and cost data. *Year 4*: Track participants. Collect quality assurance data. Collect clinical and cost data. Draft manuscripts for publication. *Year 5*: Track participants. Complete collection of behavioral, biological, clinical, and cost data. Complete quality assurance on data; conduct data analyses; draft manuscripts for publication.

E. PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement and Characteristics

An individual's decision to participate in the cohort will not affect his or her ability to utilize standard of care HIV prevention services or treatment offered in the area.
We will seek to enroll between 442 couples and 1,000 couples in the cohort to assess the study outcomes from a community with population of approximately 11,900. As noted earlier, we may need to recruit more than 442 couples, up to a maximum of 1,000 couples, in order to meet the enrollment criteria of 60 serodiscordant couples in the second portion of the study. In addition, we may enroll up to 70 couples for the second part of the study as we complete the provision of HIV self-testing in the final geographic cluster getting HIV self-testing (as we need to complete the entire cluster for the voracity of the study sampling). The cohort of this size is calibrated to meet our specific aims of determining the uptake of HIV self-testing, self-referral for care when infected, engagement in care, retention in care, and the safety and acceptability of the intervention. Pregnant women and children age 18-21 years will not be excluded from seeking HIV prevention services or from participating in the self-testing cohort. Pregnant or breast-feeding HIV-negative women who join the HIV serodiscordant couple component of the study will be allowed to take PrEP as Truvada has shown no increase in adverse effects related to fetal/infant health, both when used as PrEP[90] and when used as treatment for HIV. It will be a woman's choice whether to continue using PrEP during pregnancy and breast-feeding after discussing the risks and benefits with the clinical officer. Age does not impact potential risks to participants. However, at least one member of the couple should be aged 55 years or below to be eligible for participation. Other potentially vulnerable populations will not be included in the proposed clinical trial.

To help prevent lost to follow-up occurrences, serodiscordant couples recruited from the CTC must reside within or near Kisarawe Ward. Potential participants who do not reside within or near Kisarawe Ward will be excluded. The following towns are considered near Kisarawe Ward for the purposes of this study: Chanika, Masaki, Pugu, Minaku, Msimbu/Homboza, Kazimumbwi.

Due to the need to collect ongoing clinical data at the Kisarawe CTC, positive partners who choose to enroll into care at a CTC other than the Kisarawe CTC, will not be allowed to participate in the second phase of the study.

Age does not impact potential risks to participants. Other potentially vulnerable populations will not be included in the proposed clinical trial.

Individuals under the influence of drugs or alcohol and anyone presenting with mental disability that would preclude ability to understand study procedure, risks, and benefits will be excluded from participation.

All human subject data will be collected within the study communities by staff at Muhimbili University of Health and Allied Sciences (IRB FWA00004301), subcontractor to The Medical University of South Carolina (MUSC). Source documents will be stored securely at Muhimbili facilities and managed by Muhimbili and MUSC research personnel. Data will be collected using IRB approved data collection instruments.

Inclusion of Women and Minorities

1. All households within a certain geographic area will be approached to participate in the study. The distribution of men in women in the study communities is thought to be relatively equal, and the vast majority of men and women live jointly in mixed gender households. It is thus expected that the makeup of those invited to participate in the study will have no gender bias.

2. Moreover, the study and associated intervention is designed to target couples as a dyadic unit, and the vast majority of couples will be heterosexual and thus include a man and a woman. Both men and women will be recruited to participate in intervention services. All ethnic groups will be sampled for inclusion with no bias and should be proportional to their distribution in the population given the geographically based sampling being utilized.

3. HIV is highly prevalent among both men and women in the study communities. As such, the study intervention will offer Dyadic-based Diagnosis, Care, & Prevention (DDCP) services to members of both genders in an attempt to apply study findings to both males and females, and any minority groups present in the community.

4. No gender or ethnicity will be excluded from the trial.

5. The trial will seek to enroll members of both genders and individuals of any ethnicity residing in the study communities. The study team will assure that the Community Advisory Board has substantial members of both women and men, residing in the community.

Inclusion of Children

Children age 18-21 years (as defined by NIH guidelines) will be eligible to participate in the study. In Tanzania 18 years is the legal age at which an individual may independently consent to participate in clinical research. It is important that 18-21-year-olds are included in the proposed trial as young adults are the most at risk age group for contracting HIV. Our study personnel are experienced in conducting research with 18-21-year-olds as our previous and current studies have provided a host of HIV services, including HIV testing and counseling, to young adults and our staff are familiar with the specific risks affecting this age group in Tanzania.

Sources of Materials

Human subject materials will consist of demographic & behavioral survey data, and clinical data collected at the Care and Treatment Center (HIV test results, CD4 counts, medications prescribed and taken, and clinical observations) collected from subjects in the self-testing cohort, and at baseline, 6-months, 12-months, and 18-months for the approximately 120 individuals identified as being a member of a HIV serodiscordant couple), and from utilization data collected at each use of a service. In order to access this data, we will collect the Care and Treatment patient number of participants.

Human subject data collected for the proposed research will only be used for the purposes of the proposed study. The study will utilize handheld battery powered computer tablets for the collection of subject data. Identifying data will be limited to a fingerprint scan and contact information selected by the participant. These electronic data will be transmitted to MUSC subcontractor Basant Singh who will provide data management services. The tablets will be programmed such that data transmission occurs over wireless cellular internet connection, and data will be encrypted using high level encryption algorithms. Upon completion of collection of study data, it will be transmitted and automatically erased from the tablet device. Utilization data will also be collected using the Tablet / Fingerprint system to allow the study team to link service utilization to survey data. The advantage of the biometric of identification of participants is that this method of identification is extremely difficult to link to other individual identifiers. It is thus likely more private and less likely to compromise the identity of study participants as compared to other methods of identification used for matching data. Survey data entries and utilization data will not contain any other identifying information on study subjects. Separately, the study staff will collect tracing information from those who consent to enroll in the study.

Tracing data will only be made available on an as needed basis to study staff certified to have access to these data. These data are necessary to return to the participant following self-testing and for contacting participants in the Dyadic Care phase who have missed study visits. Which tracing data are collected will be at the discretion of each individual participant, but must be adequate to allow for reasonable capacity of the study staff to conduct follow up interviews (approximately 2 weeks for approximately 884 participants, and at 6-months, 12-months, and 18-months for the approximately 120 individuals identified as being a member of a HIV serodiscordant couple). Options for tracing data provided by the participant to choose from include (but are not limited to) name, address, GPS coordinates of household, second party contact information of a trusted friend or family member, and phone number. Access to the tracing data will be limited to when it is needed, such as when contacting participants to schedule follow-up interviews. Access to the tracing data will be restricted the Principal Investigator and delegated staff members. Strict procedures will be in place with regard to how participants are contacted, using only those allowed by the participant, and carefully worded scripts will be used in attempts to reach participants to avoid disclosure of their participation in the study. Our team has over 9 years of experience conducting research in the area and is well versed in privacy and confidentially procedures and has an excellent track record of tracing participants discretely and in a manner acceptable to study participants. Clinical data from the HIV Care and Treatment Center will also be collected with the consent of participant. While HIPAA guidelines are vague with regard to applicability in foreign sites, we will nonetheless adhere to HIPAA guidelines in this study.

Data Security and Encryption

We will employ the same data security and encryption measures as previously used for another study based in Tanzania, which were approved by the MUSC IRB (Application Number: Pro00014914). Using these encryption and safety measures, we have experienced no data breaches or lapses in data security. Therefore, we plan to continue using these robust measures, which are outlined below:

1. There are multiple levels of security measures and data encryption for the tablet computers. A password must be entered to activate the tablet and a second password must be entered to access the data capture software. There are different levels of access for interviewers, field supervisors, and system administrators.
2. The data captured on the device will be in a machine-readable (xml) format, which is not easy to interpret without using a computer program. To add another layer of security, once data have been transferred to the central server, it is removed from the device. There is also an option to store data on the device for certain duration; however, when at all possible data will not be stored on the tablets. In such a case, data stored on the device is archived in a separate directory and encrypted using 128 bit AES encryption. Thus, any data stored on the device is inaccessible unless decrypted. The decryption key is not stored on the device and is maintained by the central data management team.

3. As an additional security measure, lost or stolen tablets can be tracked and have their data erased remotely by data management staff when the lost or stolen tablet is connected to a Wi-Fi or cellular network. If an electronic tablet is lost or stolen, the user/custodian in charge of the device will immediately contact the Project Manager in Tanzania who will then contact MUSC's Computer Security Incident Response Team (CSIRT). The Project Manager will also immediately delete all data stored on the device remotely. All electronic tablets will be stored at the project office in a locked filing cabinet in a locked office at the end of each day.
4. All data captured by the tablets will be transmitted to the database server in India using HTTPS, which is a widely used communications protocol for secure electronic communication. HTTPS provides authentication of the web app and associated web server that one is communicating with, which protects against malicious attacks. Additionally, it provides bidirectional encryption of communications between a client and server, which protects against eavesdropping and tampering with the contents of the communication.
5. The Database server support RAID-1 storage in which a complete copy of the data is stored on multiple independent disk drives as a precaution against disk failure. The database is configured to make automated backups and logs of all modifications. Additional monthly backups of the database will be stored on external media such as DVD disks, which will be stored under lock and key. Access to the server and database are restricted to authorized personnel with a valid password.
6. Hard copies of the consent form and HIPPA authorization form will be stored in a locked filing cabinet in a locked office at project headquarters in a separate physical location from the electronic survey data.
7. Fingerprints will be scanned using a portable USB fingerprint scanner attached to the tablets. When a fingerprint is entered in to the system, a "template" of the fingerprint is stored in the database in encrypted format. A fingerprint template is a set of lines, angles and measurements (minutiae) based upon the unique characteristics of an individual’s fingerprint. These details from templates are later used for 1:1 or 1:n matching. No actual fingerprint images are stored, and templates cannot be reverse engineered to form a fingerprint image. This protects the user’s fingerprint data and prevents it from ever being compromised.
8. In order to share data between study partners, MUSC Box will be utilized. MUSC Box is cloud storage and will allow data to be shared for the purpose of analysis. The MUSC Box folder that contains our data will only be shared with those who are covered under an MUSC Business Associate Agreement, as this obligates them to follow US Federal Guidelines to protect patient privacy.
9. Utilization Data – All enrolled sero-discordant couples who come for HIV-related care and prevention at the Kisarawe CTC Center will be fingerprinted and administered a brief survey. Nurses at the CTC will be trained on how to collect this data, which will be uploaded weekly to the data management team in India. Information sheets about data collection will be available for all CTC patients.
10. Collecting digital fingerprint scans on the tablet computers of cohort members, participants accessing intervention services, and CTC patients will allow service utilization to be tracked throughout the study. Scanning fingerprints provides the most anonymous and secure tracking mechanism because there will be no way for community members to identify who has had their fingerprint scanned and therefore no way to identify who has participated in the study. In this intervention, the major risk to participants is a breach in confidentiality, and scanning fingerprints provides a way to minimize this risk while still enabling study objectives to be achieved. Cohort members will be made aware of the fingerprint scan during the informed consent process and individuals accessing services will be provided an information sheet explaining the purpose of the fingerprint scan.

Internal Data Monitoring Plan

To maintain assurances that data are transmitted and stored in compliance with HIPAA and the study protocol, the following plan will be implemented:

1. Monthly incremental data updates will be securely sent to the Principal Investigator from the Data Management Center in India. The Principal Investigator can also request data at any time throughout the project to ensure the database is being maintained.
2. All staff will be trained in research ethics, maintaining confidentiality, and data security policies, including data security breach protocols, prior to project implementation.
3. Access to all study databases will be password protected to ensure the confidentiality of study participants. All data collection instruments, utilization logs, consent forms, and adverse event reports will be stored in locked file cabinets, with access controlled by the Project Manager.
4. To ensure the Data Management Team complies with HIPAA rules and regulations, the Data Manager, Dr. Basant Singh, will sign a HIPAA Business Associate Agreement for the project.
5. Periodic audits of the Data Management Center in New Delhi, India will be conducted by an independent third party. The third party will be trained in research ethics and will have working knowledge of the data and data security measures included in the protocol. The auditor(s) will interview the Data Manager and will complete a data security checklist. Any data security risks identified during the audit will be brought to the Principal Investigator's attention within 24 hours. If security risks are found, the third party auditor will recheck the facility in one week to ensure risks have been eliminated and all systems are in compliance with the study protocol.

Potential Risks

Individual Psychosocial Risks

The primary risks to participants are social and/or psychological harm associated with HIV testing, through participation in the intervention and/or intervention assessments, including: disruption of family (e.g., breakup of couples following HIV disclosure); discrimination (e.g., loss of employment or status in the community); displacement (e.g., loss of housing as a result of HIV status); abuse (e.g., acts of violence directed at people who are diagnosed with HIV); anxiety about testing for HIV or the results of testing; and embarrassment (e.g., being questioned about sexual behavior). In addition, participation in the intervention assessments, and counseling related to HIV testing or HIV status involves the risk of anxiety, discomfort, and/or embarrassment in answering questions related to HIV risk behavior or discussing sexual issues or other personal matters. Participation in any component of the study involves risk of loss of privacy.

Individual Physical/Health Risks

Physical harm may result from abuse related to HIV disclosure as a result of participation in the intervention and/or pre/post-intervention assessment cohort components. In addition, there may be health consequences associated with loss of housing, employment, or resources caused by displacement or discrimination based on HIV status. Study participants may experience pain or discomfort associated with blood sample collection. Blood sample collection may also be associated with local infection in very rare instances. There are also known risks to taking ARVs and PrEP, such as drug toxicity, lactic acidosis, gastrointestinal effects (nausea and vomiting), and lipodytrophy. All medications used in the study are FDA approved and no off-label use of these medications will be made by the study. Clinical care will be provided in the government health clinics by trained and certified clinicians using standard protocols for care approved by the Ministry of Health in Tanzania, and the funding agency, PEPFAR.

Community Risks

Due to the fact that the study is geographically bound in its sampling of study participants, the community as a whole may experience stigma, misperceptions, and/or negative rumors. For example, the community may possibly be viewed as having a high prevalence of HIV as the reason for its inclusion in the study. The community may also be perceived to be receiving special benefits beyond those outlined above. All these may lead to ostracism of and discrimination toward the community and its members by neighboring communities.

Alternatives

Alternatives to the proposed research are limited. There are voluntary counseling and testing services for HIV offered through government health centers in the communities. However, services are limited and opportunity costs of travelling to seek testing may be high. PrEP is not available in Tanzania independent of research projects. ARV treatment is available in the area, although limited by access to HIV testing services.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Written informed consent will be obtained from each participant in the cohort prior to their participation in the assessment. The consent forms will be developed in accordance with the principles of informed consent as described in Title 45, Code of Federal Regulations (CFR), Part 46 and Title 21 CFR, Part 50, as well as in accordance with current community standards of practice in Tanzania, and will be approved by the IRB. We have significant prior experience in conducting the informed consent process for HIV prevention trials within the cultural context of Kisarawe District. The informed consent procedures for this study will be designed to maximize understanding of potential risks to participants. All consent forms will be translated into the local language and certified by a translator to ensure correct use of language. Consent forms will be read aloud to participants by study interviewers. After reading the consent forms, prior to seeking a signature, interviewers will ask participants to summarize the study and explain the reasons why they want to participate in order to ensure the participants' understanding. If there are cultural, literacy, or political reasons why a signature is not appropriate, individuals will be allowed to mark the consent form with an "X" or their thumb print, as approved by the IRB. Individuals will be provided with a signed copy of their consent form and information on how to contact the study staff to report adverse events associated with their participation in the research activities. A participant ID label will be placed on the consent form for identifying purposed. Due to the high illiteracy rate in the area we are conducting research, many participants will be signing the consent form with an X, a thumbprint, or their signature may be illegible. In order to keep track of the consent forms, a PtID label is necessary. Otherwise, we would not be able to determine which consent form belonged to a participant. Study staff will be trained on the importance of ensuring that individuals provide voluntary informed consent. If a participant wants to obtain the assent of others (for example their husband, father, or village leader) prior to giving informed consent, this will be permitted. Such assent, however, may not be substituted for her/his consent.

Verbal informed consent will be obtained from all individuals seeking to utilize intervention services. For Project Accept, the IRB granted a waiver of written informed consent for individuals seeking voluntary counseling and testing and post-test support services. We will seek a similar waiver of written informed consent for all individuals utilizing intervention services in the proposed study. IRB-approved information sheets on intervention services will be provided to prospective participants. All intervention services and procedures will be explained to participants and they will have the chance to ask questions before giving verbal consent. Verbal consent will be obtained from participants before they utilize any of the intervention services.

Couples will be asked to consent separately in private. Inclusion of a couple in the study requires independent consent of each member of the couple.

Protections Against Risk

Institutional Review

Prior to implementation of any study component, the protocol, informed consent forms, subject materials, and data collection instruments will be approved by the MUSC IRB. The Muhimbili University IRB and the Tanzania National Institute for Medical Research (NIMR) will also approve the study prior to its implementation. All changes to the study affecting the safety and welfare of study participants will be approved by the IRBs prior to implementation.

Confidentiality

Confidentiality of all study participants will be strictly maintained across all study components. One purpose of the intervention is to encourage discussion of HIV in communities, and thus de-stigmatize it.

Counselors, interviewers, support services facilitators, and all other relevant project staff, including nurses, will be trained on procedures for maintaining confidentiality and required to sign a pledge of confidentiality.

All study data, laboratory specimens, and forms will be identified by a coded participant ID number and encrypted biometric data only, to maintain participant confidentiality. Personal identifiers (such as informed consent forms or locator forms) will not be recorded on the same page as subject study data and will not be transmitted offsite. For the intervention component of the study, only the minimum amount of identifying information required to provide services will be maintained. Identifying information will not be recorded on utilization data collection instruments that are transmitted offsite for data processing and analysis.

After completion of the 18-month intervention component, identifying information for intervention participants that is not required for the study analysis will be destroyed.

Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate locked file at the study site headquarters, in an area accessible only to authorized study personnel. If participant names and corresponding participant IDs are entered into a computer database, this database will be password protected and maintained in a directory separate from any study-specific data. Files will be encrypted when technically possible.

Data Management Center Protections

Access to all study databases will be password protected to ensure the confidentiality of study participants. All data collection instruments, utilization logs, consent forms, and adverse event reports will be stored in locked file cabinets and/or password protected computers. The study investigators and research coordinators will control access to secure documents. Any breach in confidentiality will immediately be reported to the IRB. The databases will be stored electronically on secure computers protected by a firewall. More information is provided in the above section labeled “Data Security and Encryption.”

Research Ethics Training

All study personnel will complete training in the ethical conduct of human subject research prior to participating in any research activities, in accordance with NIH rules. The investigators, research coordinators, data manager, and senior research staff at Muhimbili University have completed the University of Miami Collaborative Institutional Training Initiative (CITI) course in research ethics and will maintain this training throughout the project period. Because the CITI course is not translated into Kiswahili and non-management level research staff in Tanzania lack regular internet access, these

individuals will participate in an alternative in-depth training program on the ethical conduct of human research that we have developed and that has been approved by the MUSC IRB. The course covers the history and principles of human subject research ethics, principles of ICH/GCP, principles of informed consent, and adverse event reporting.

Vulnerable Populations

Pregnant women and children age 18-21 years will not be excluded from the self-testing portion of the proposed study. For the prevention and care sub-cohort involving serodiscordant couples, pregnant women will be allowed to take PrEP for the duration of their pregnancy and breast-feeding. If an HIV-negative woman tests pregnant as baseline, she and her partner will be counseled about the possible risks of taking PrEP and will still be eligible to enroll in the sub-cohort, even if the HIV-negative woman chooses not to take PrEP. If an HIV-negative woman becomes pregnant while taking PrEP, she will be counseled about the possible effects of the medication during the duration of her pregnancy and breast-feeding period but will remain in the study.

Participation in the research will potentially be of direct benefit to these individuals. Human subject protections will meet the requirements of 45 CFR 46. Clinical care for the intervention components (ARVs and PrEP) will take into account pregnancy and follow standard clinical guidelines for administration of these medications accordingly.

Adverse Events and Linkage to Care

Subjects participating in all aspects of the research will be regularly monitored for adverse events. Staff will be trained to assess for possible adverse effects of the research on participants. Procedures for assessment, monitoring, and reporting of adverse events will be outlined in the data safety monitoring plan approved by the IRB.

All stages of this trial have been planned in the context of recognized ethical principles for protecting human participants in international research. The project involves a number of strategies to ensure that the trial reflects the needs and concerns of the participating communities and countries. To ensure that participants who test positive for HIV during the intervention and pre/post-intervention assessments can be linked to the highest quality treatment and care available, the study team will refer subjects to the Care and Treatment Centers (CTC's) at the district hospital in Kisarawe, and, if necessary, Muhimbili University hospital in Dar es Salaam. Since March 2006, the Kisarawe District Hospital has been actively dispensing ARVs to HIV-positive people in need of treatment. The study staff will work with subjects who accept referrals and treatment providers to facilitate care and support treatment adherence. Study participants will be told about the provision of ARVs at the Kisarawe District Hospital and the CTCs during every component of the intervention. Project staff will give ARV referrals to every HIV-positive individual who asks about treatment. This trial is designed to determine the impact of the Dyadic-based Diagnosis, Care, & Prevention intervention, which includes improving linkages to care, facilitating treatment access, and supporting treatment adherence for HIV positive individuals, but it will not take primary responsibility for providing treatment services for HIV-positive clients. We will refer HIV-positive clients to existing HIV clinical services. Participants are not obligated to receive a referral, and no copies of referrals issued will kept in order to protect participant confidentiality. Even if individuals choose not to access further care or prevention services after testing, HIV testing and ARV provision are widely accepted HIV prevention interventions, and the local government encourages and supports its provision in the host country. It is recognized that VCT, even in the absence of advanced HIV treatment regimens, does provide benefits to clients, and large proportions of populations in these settings wish to know their HIV infection status.

In order to track and facilitate access to care throughout the study, we will maintain contact with the health facilities in the town of Kisarawe to monitor which types of HIV-related prevention and treatment interventions are available in each facility. The study team will also coordinate with local health authorities and donors to enhance the quality of treatment and care to the best possible standard.

Potential Benefits of the Proposed Research to the Subjects and Others

Individual Benefits

Participation in the intervention and the cohort components of the study may provide the following benefits for individuals: (1) Participants can learn their HIV status. HIV testing outside this study may be difficult to access for some participants because of logistical issues (e.g., location and expense); (2) knowing one's HIV status may allow participants to plan for their future, particularly in terms of family responsibilities; (3) Knowing one's HIV status may afford participants the opportunity to live healthier lives in terms taking better care of themselves—either by staying HIV-negative, or if infected, seeking out available care and support services; (4) Knowing one's HIV status may cause behavior change that could give participants resolve to protect themselves or prevent HIV transmission to their sexual partners; (5) It should be noted that pre and post-test counseling is rarely offered in public VCT clinics and the quality of the counseling at public VCT sites may be of lower quality compared to the protocol standards; (6) In addition to enhancing availability and quality of VCT, the intervention offers individual and couples counseling, individualized risk assessment, and services depending on the needs and risks of the client; (7) Receiving pre and post-test counseling may answer participants' questions about HIV and its transmission, dispel inaccurate information/beliefs participants may hold, reduce participants' anxieties, and help participants to initiate and maintain behaviors to protect themselves and their partners; (8) Participants who access ARV and PrEP may receive medication, beneficial information, support, and/or referrals that assist them in staying HIV negative (if negative), staying as healthy as possible (if positive), protecting their partners, planning for their future, disclosing their status (if they choose to do so), and relieving stress and anxiety.

Community Benefits

Communities involved in the study receive free HIV prevention services throughout the intervention component. The community will receive high-quality, community-based distribution of free HIV self-test kits, standard counseling and testing services, as well as facilitated referral for HIV treatment, none of which would be otherwise available to the community. This study explores the preventative benefits of a comprehensive intervention designed to reduce the number of new infections in developing countries with high HIV prevalence, which, if successful, would have enormous social benefit. An intervention that is effective, cost-effective, sustainable, and easily disseminated in developing country settings is critically important, as at present there are no prevention interventions proven to be effective specifically for generalized epidemics (i.e., more than 5% of antenatal clinic women infected with HIV).

The communities involved in the proposed study and other communities with generalized epidemics would receive the most direct benefit of the research—not the U.S. or other industrialized countries with concentrated epidemics, where this intervention may not be effective, because HIV prevalence is too low and structural barriers to HIV prevention differ. Thus, this study also responds to the ethical principle of justice, as the group exposed to the research risks receives the potential benefit of the research.

The study team has extensive experience conducting community preparedness activities, including establishment of community advisory boards prior to community participation in a clinical trial. The proposed research will be conducted in consultation with and with the support of the participating communities.

Importance of the Knowledge to be Gained

This study is designed to answer important scientific questions about the acceptability, safety, and feasibility of self-testing for HIV, early ART and PrEP use among HIV serodiscordant couples in Tanzania. All medical technologies (e.g., self-testing) and drugs (PrEP and early ART) have been

approved by the FDA. Additionally, early ART and PrEP have been recommended as HIV prevention strategies by the World Health Organization for HIV serodiscordant couples. Therefore, this study does not aim to assess the efficacy of these interventions as their efficacy has already been demonstrated. Instead, the aim of this study is to assess the feasibility, safety, and impact on improved care and novel HIV prevention strategies for HIV serodiscordant couples in an integrated prevention and treatment intervention. The outcomes of this study could have significant public health impact in communities and developing countries around the world.

Subject Safety and Minimizing Risks (Data and Safety Monitoring Plan)

In accordance with NIH policy, a comprehensive Data Safety Monitoring Plan, outlined below, will be approved by the IRB prior to the start of any research activities. The PI will have overall responsibility for monitoring the safety of the trial. The PI, in consultation with the other key personnel and senior research staff, will routinely review study data, the implementation of study procedures, QA/QC results, and community feedback to assess the ongoing safety of the research.

Procedures for monitoring, assessing, and reporting adverse events will be implemented. All adverse events will be reported to the PI and to the IRB when required. Staff will be trained to assess for adverse events and other adverse effects of the research at all points of participant contact. All consent forms and information sheets given to participants will contain contact information for the study staff and instructions on reporting adverse events. Additionally, regular communication and consultation with community leaders, CTC staff, and other district health staff will be used to assess for adverse effects. The in-depth process tracking system and continuous QA/QC program developed for our current research project will be adapted and implemented for the proposed study. We have significant experience implementing rigorous QA/QC measures to ensure data accuracy and subject safety.

ClinicalTrials.gov Requirements

The proposed trial will be registered with ClinicalTrials.gov, even if not required by law, in accordance with NIH guidelines. The Principal Investigator will be the “responsible party.”

Types of Data and Events to be Captured

Assessing the safety of this intervention is one of the study’s main operational goals. As a result, we have built-in safety assessments to almost all data collection tools, including the follow-up assessment for all couples who self-tested for HIV and follow-up assessments for serodiscordant couples engaged in care. For self-testing, the following safety measures will be measured and tracked:

1. Coercion, pressure, or sanction to engage in HIV self-testing;
2. Loss of confidentiality over HIV test results as a result of self-testing;
3. Psychological distress as a result of self-testing;
4. Intimate partner violence as a result of self-testing.

These data will be collected when participants come to the study’s Referral Center for confirmatory HIV testing following self-testing and during the follow-up assessment on the participating couples occurring approximately two weeks following self-testing.

For serodiscordant couples engaged in care, the following psychological and physical outcomes will be assessed at every monthly clinic visit:

1. Coercion, pressure, or sanction to engage in project services (PrEP or early ART);
2. Loss of confidentiality over HIV status as a result of engaging in project services;
3. Psychological distress as a result of engaging in project services;
4. Intimate partner violence as a result of engaging in project services;

5. Medication side-effects from PrEP or ART.

Additionally, data on adverse events and unanticipated problems will be collected throughout the study. During the informed consent process, participants will be provided with information on how to contact study staff in the event of an adverse event. Staff will be trained to assess for possible adverse effects of the research on participants and how to report adverse events.

Roles and Responsibilities for Gathering, Evaluating, and Monitoring Data

The PI will have overall responsibility for monitoring the safety of the trial. The PI, in consultation with the other key personnel and senior research staff, will routinely review study data, the implementation of study procedures, QA/QC results, and community feedback to assess the ongoing safety of the research.

As part of their training, **staff** will be taught how to recognize any situation that occurs in the field that qualifies as an incident or adverse event (AE)/serious adverse event (SAE), as well as the necessity of immediately reporting their knowledge of the situation to their supervisors. To aid the field staff in the process of reporting, a simple reporting form is being developed. The staff will be trained on how to fill out this form, providing as much detail as possible in the narrative description of the AE/SAE or incident. It will be the field staff's responsibility to immediately inform his/her direct supervisor that an AE/SAE or incident occurred. The supervisor will immediately contact the **Project Manager**. Then, the **supervisor, field staff, and Project Manager** will have 24 hours to fill out and submit the form. The **Project Manager** will contact the **Principal Investigator** (Dr. Sweat) and **co-Investigator** (Dr. Mbwambo) once the form is complete. Copies of the form will be kept at the Kisarawe office to ensure that they are easily and readily available to anyone needing to make an AE/SAE or incident report.

As soon as the **Project Manager** receives the written report, he/she will verbally apprise the Principal Investigator of the AE/SAE or incident by phone and/or email. Once the **Principal Investigator** has given his final approval of the report, the **co-Investigator** (Dr. Mbwambo) will send the forms to the relevant **Tanzanian bodies – MUHAS IRB and the NIMR IRB**. **Dr. Sweat** will be responsible for submitting the forms to the MUSC IRB. The **Principal Investigator** will work with the **Project Manager** to ensure that the appropriate follow-up form the AE/SAE occurs.

All field-based staff who will be working with human subjects research, including the Tanzania-based project manager and data collectors, will be added to the MUSC IRB application once the staff have been hired, provided with MUSC NET-IDs, and have successfully completed the CITI-alternative ethics training course.

Timeline for Reporting Adverse Events and Unanticipated Problems

Once staff have been alerted to an adverse event or unanticipated problem, they will have 24 hours to complete an adverse event report and submit the report to the Principal Investigator. The Principal Investigator and Co-Investigator will submit the report to the necessary entities (MUSC and Muhimbili IRBs) within one week following receipt of the adverse event report.

Frequency of Monitoring

Safety data on self-testing and engagement in care will be monitored on a monthly basis during periods in the study when these activities are underway. Because utilization data will be collected on electronic tablets, the Principal Investigator will have real-time access to this information.

Procedures for Communication

Regular communication and consultation with community leaders, CTC staff, and other district health staff will be used to assess for adverse effects.

A phone/email tree will be established to link all study staff. The phone/email tree will be displayed prominently at all study-related locations.

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G. CONSULTANTS

Dr. Kevin O'Reilly is an internationally recognized expert in HIV/AIDS prevention (formerly at the WHO), and Adjunct Professor at MUSC. He has led WHO's PrEP working group and worked closely with multiple international PrEP projects. Dr. O'Reilly will join the study as a consultant, both a clinical psychologist and biostatistician, and has led the statistical analysis on over 30 NIH-funded trials.

H. FACILITES AVAILABLE

Family Services Research Center

A division of MUSC's Department of Psychiatry and Behavioral Sciences, the FSRC is directed by Michael D. Sweat, Ph.D., an established NIH-funded researcher. The FSRC has more than $5,000,000 per year in research grants and consultation and policy contracts. Multiple clinical trials have been directed from the FSRC, as have various dissemination and implementation research studies. The FSRC includes nearly 30 full-time employees who are fully supported by research grants, primarily from the National Institutes of Health, and by consultation contracts with state and private child serving agencies. Fourteen are Ph.D. or M.D. level faculty in the Department of Psychiatry and Behavioral Sciences. Other staff includes therapists, research assistants, data managers, and administrative assistants. The FSRC is located in 7,500 square feet of office space adjacent to the MUSC campus. Resources available within the FSRC include access to multiple large databases, data management experts, other statisticians, office space, computer linkages, and affiliation with doctoral level faculty pursuing careers in mental health services research through grant-funded investigations.

Muhimbili University, Department of Psychiatry - our project site in Tanzania is linked to the Department of Psychiatry at Muhimbili University, the leading University in the country. Project offices are housed on two air-conditioned floors of a new building located at the National Teaching Hospital built to house a regional center dedicated to service, research, and training on HIV VCT-related services. The Hospital has a stable power supply with backup generators. We maintain a computer facility with networked workstations, a data management center, secure storage facilities for project data, and administrative offices. We also currently will maintain a rented vehicle for Project Accept and have a 6-room field office in Kisarawe town. We also have excellent laboratory facilities at Muhimbili via a Memorandum of Agreement with a lab operated in conjunction with Harvard University. For the past 17 years Dr. Sweat has maintained a successful collaboration with Muhimbili, and we feel that resources are of the highest caliber to complete the proposed study. While Project Accept is ending in the coming months, we will be able to convey a host of resources to future studies such as this one, including project equipment, skilled staff, and access to office space and lab facilities.