Kyaterekera Project: A Combination Intervention Addressing Sexual Risk-Taking Behaviors Among Vulnerable Women in Uganda

National Clinical Trial (NCT) Identified Number:
NCT03583541

Multiple Principal Investigators:
Fred M. Ssewamala, PhD
Susan Witte, PhD

Sponsor:
Washington University in St. Louis

Grant Title:
Kyaterekera Project: A Combination Intervention Addressing Sexual Risk-Taking Behaviors Among Vulnerable Women in Uganda

Grant Number:
R01MH116768

Funded by:
National Institute of Mental Health

Version Number: V.2.0
20181029

Approvals:
Original Approval: October 29, 2018
Subsequent Approval: October 29, 2023

TABLE OF CONTENTS

SPECIFIC AIMS

This is a resubmission responding to PA-17-106 calling for studies to advance combination behavioral, social and biomedical intervention approaches and to enhance prevention efforts targeting populations highly impacted by HIV. Proposed is a 3-arm randomized controlled trial (RCT), "*Kyaterekera Project: A Combination Intervention Addressing Sexual Risk-Taking Behaviors Among Vulnerable Women in Uganda*" that tests the impact of adding economic empowerment components to traditional HIV risk reduction (HIVRR) to reduce new incidence of sexually transmitted infections (STIs) and of HIV among female sex workers (FSWs) in Rakai and the greater Masaka regions in Uganda. The highest number of people living with HIV/AIDS (24.7 million) is in sub-Saharan Africa, with Nigeria, South Africa and Uganda accounting for 48% of new infections.[1] In Uganda, the HIV prevalence among 15-49 year olds is 7.2%, with Rakai (9.3%) and Masaka (12%)[2] districts above the national average.[1] Overall HIV prevalence is 12 times higher among FSWs, than the rest of the adult population, with 37% sero-prevalence among FSW in Kampala,[3] and 77% of FSWs reporting new STIs in the past year.[4] HIV prevalence among FSWs in Rakai and Masaka regions is as high as 61%.[5] While FSWs in Uganda have long been the subject of surveillance studies, few have been targeted for prevention efforts informed by insights from behavioral economics (BE) and empowerment strategies, despite calls from scientists for innovative structural interventions.[6-9] This application responds to this urgent need by examining outcomes and processes required for uptake and sustainability.[10] The investigative team completed an R34 testing a financial savings-led microfinance intervention for HIV prevention among 107 FSWs in Mongolia[11] and a pilot study on the proposed intervention's acceptability in Uganda among 31 FSWs, both of which inform the proposed study's intervention components, feasibility, effect size, and lessons learned about implementation, recruitment, and retention.

Guided by Social Cognitive[12-14]and Asset theories[15; 16] as well as BE principles,[17-22] the proposed RCT is carefully designed to test the additive contributions of savings-led microfinance beyond traditional HIV risk reduction (HIVRR) alone in decreasing biologically confirmed STIs, including HIV, improving high risk-behavioral outcomes, while concurrently reducing income from sex work. Working within established health care- and outreach-based settings, we will randomly assign 990 FSWs to one of three study arms (11 town centers each): (1) a control arm comprising treatment as usual (TAU) for FSWs (quarterly 2-3 hour health education sessions, HIV testing services, and STI screening), bolstered with 4 evidence-based sessions of HIVRR provided by local providers (n=330); or (2) a treatment arm including TAU, 4 sessions of HIVRR, combined with receipt of a matched savings account (HIVRR+S) to be used on short-term and/or long term consumption and skills development per a participant's discretion/choice (n=330); or (3) a treatment arm including TAU, 4 sessions of HIVRR, combined with a matched savings account for short-term and/or long term consumption and skills development, plus 6 sessions of financial literacy with integrated Behavioral Economics principles (e.g., delay discounting, economic utility, information salience, and loss aversion), and 8 mentoring sessions for supportive transition to options for alternative income (HIVRR+S+FLM) (n=330). The intervention will be delivered by Rakai Health Sciences Program (RHSP) and Reach the Youth-Uganda (RTY), a local community outreach non-governmental organization. We hypothesize that using local agencies to provide HIV prevention, matched savings accounts to invest in financial assets (including vocational training and business development), and financial education with integrated BE principles and mentorship will additively lead to significant and sustained reductions in study outcomes compared to HIVRR alone. Specifically, we hypothesize that the post-intervention odds of having STIs and HIV risk behaviors will be lower in the two treatment arms vs. the control arm, and lowest in the HIVRR+S+FLM arm. The specific study aims are:

Aim 1: To examine the impact of a financial savings-led microfinance intervention using HIVRR+S and HIVRR+S+FLM on HIV biological and behavioral outcomes in FSWs using a RCT. The primary outcomes will be: women's 1) cumulative incidence of biologically-confirmed STIs (Gonorrhea, Trichomonas, Chlamydia); and 2) reported number and proportion of unprotected sexual acts with regular and paying partners. Secondary outcomes will be: women's 3) rate of new HIV cases; 4) proportion of monthly income from sex and non-sex work; 5) reported number and proportion on preventive behaviors (condom purchasing, HIV testing, partner discussions); and 6) for HIV+ women only, viral load as a marker of ART adherence.

Aim 2: To examine intervention mediation and effect modification. We will statistically assess whether the primary outcomes are mediated or moderated by participant characteristics; and whether key theory-driven variables and BE measures mediate or moderate intervention outcomes.

Aim 3: To qualitatively and quantitatively examine implementation in each study condition. We will investigate participants' interventional experiences (satisfaction, facilitators, barriers, recommendations); factors influencing participation, sexual decisions, financial behaviors; and perceptions on programmatic sustainability.

Aim 4: Assess the cost and cost-effectiveness of the HIVRR+S and HIVRR+S+FLM intervention compared with traditional HIVRR in terms of cumulative number of STI and HIV cases averted over the 24-month period.

RESEARCH STRATEGY

3.1. Significance

3.1. A. FSWs and their partners are key bridge populations in Uganda and should be targeted in prevention interventions. A systematic review of the HIV burden among FSWs in 50 low and middle-income countries[23] found that FSWs had increased odds of HIV infection (OR 13.5, 95% CI 10.0–18.1) relative to the general female population. A study among FSWs in Kampala, Uganda, found HIV prevalence to be as high as 37%, with significant presence of other STIs including Gonorrhea (13%); Chlamydia (9%); Trichomonas (17%); and bacterial vaginosis (56%).[24] In more rural regions and HIV "hot spots" including those targeted by the proposed study, the prevalence of HIV among FSWs is as high as 61%.[5] STIs and alcohol use are co-factors for HIV risk globally, but also in Uganda[25; 26] where problem drinking rates among FSWs are as high as 54%,[25; 27] and STI rates[27] and lifetime IPV[28] is significantly higher among FSWs compared to the general population. While FSWs in Uganda have long been the subject of surveillance studies, few have been targeted for innovative and sustainable prevention intervention approaches despite calls from scientists in the region.[6]

3.1.B. Social structural factors play a crucial part in shaping risks of STI/HIV infection among FSWs and their clients in Uganda including their work environment, violence, stigma, cultural issues,[29-33] and criminalization of sex work.[34] Poverty is the most commonly cited reason for involvement in commercial sex work in Sub Saharan Africa (SSA).[35-38]In Uganda, with disproportionately higher rates of poverty and unemployment among women[39], transactional sex is a survival strategy.[40; 41] A growing body of evidence suggests that HIV prevention interventions must address risk factors beyond the individual level to be effective.[42; 43] Gender inequalities in particular have affected women's social, economic and political opportunities, keeping them significantly more disadvantaged than their male counterparts.[29; 30; 44; 45] Females engage in high-risk sex for economic survival, and perceive their acts as a strategy to improve their socio-economic well-being.[46] As in other locations, in Uganda FSWs are offered at least twice as much money for unprotected sex.[47; 48] The economic advantage of higher risk sex in the face of high HIV prevalence and public health imperative suggests a need for structural interventions offering alternative forms of income for FSWs.

3.1.C. Evidence-based microfinance for enhancing HIV prevention may better address structural factors that hinder traditional prevention efforts for FSWs. Microfinance (MF) programs constitute one of the fastest growing anti-poverty strategies in developing countries.[49] MF interventions lead to reductions in sexual risk behaviors among poor women and those engaged in sex work.[41; 50-52,53,54] MF interventions in Kenya and South Africa report reductions in the numbers of sex partners and higher consistency in condom use,[55] improved HIV-related communication, increased voluntary counseling and testing and a decrease in unprotected sex.[56] Similar findings were reported from a study in Baltimore[53], and India[54]. There are important limitations to a MF approach that focuses specifically on microloans, particularly for poor women who experience intersectional marginalization due to their sex work.[57-59] We innovate by proposing interventions that use a savings-led approach, which has the benefit of enabling participants to accumulate assets faster and pay for life-cycle events without accumulating debt and an over-reliance on borrowing.[60] Savings-led approaches have demonstrated efficacy in reducing sexual risk behaviors among young women in Uganda;[61; 62] and among FSWs in Mongolia (see preliminary studies).[63-65] Savings-led MF approaches for economic empowerment (EE) are in line with Ugandan Government's vision 2040 that calls for investment in financial inclusion for the most vulnerable groups. Thus, such approaches should be a priority for testing among poor vulnerable groups, including FSWs, before being taken to scale.

3.1.D. Supporting FSWs in a financial savings-led structural intervention. Uganda has a large and growing number of FSWs, yet access to targeted EE opportunities, including skill-based HIV prevention strategies for FSWs, is limited. Informed by theory, evidence-based interventions, pilot work and protocols with FSWs for feasibility and safety (see preliminary studies)[11; 64; 65] we will offer all participants access to an evidence-based HIV prevention intervention with a savings and a skills-based FLM components. In addition to asset-theory, these components will be informed by BE principles (i.e., delay discounting, information salience, economic utility, and loss aversion [see 3.3.C.2b]) that target economic motivations of sexual risk behaviors. At the intersection of psychology and economics, BE examines decision-making in contexts of time and resource constraints.[21; 22] BE has been used to understand and improve decision-making in drug adherence and addiction.[66-73] Yet, few studies have used BE principles in HIV prevention interventions with low-income FSWs. In addition, the proposed intervention targets FSWs at greatest STI risk -those who operate at the low end of the market, most often street-based, and typically poorer than FSWs based in the capital city.[39] Our target population may benefit more from alternative income sources that offer equal reimbursement with lowered risk and stigma compared to sex work.[74-76] FSWs in Rakai and Masaka—our target districts, may typically earn the

equivalent of $50-$100 USD per month depending on their status. With financial and skills-based assets gained through the study intervention(s) women may decide to pursue vocational training to earn a comparable income ($50-$100 USD). Local vocational training options provided by study partners, including chicken rearing and sewing, offer incomes within the national median income range. Given the challenges FSWs face (e.g. partner violence, stigma and discrimination), we are mindful of the structural- and individual-level challenges women may encounter while participating in the study. Partnering with local health care and community organizations providing partners familiar with the FSW population assures a stronger social safety net for participants, and supports capacity for program sustainability.

3.2. Innovation.

The study includes a number of innovative characteristics: 1) it integrates social cognitive and asset-building theories combined with BE principles in the testing of a combination of evidence EE components (matched savings and financial literacy with mentoring) that will promote women's HIV risk reduction and economic self-sufficiency; 2) it incorporates existing local service structures (health promotion staff and outreach workers), and collaboration of local vocational training and small business development institutions, which may provide more rapid and sustainable dissemination of findings; 3) it tests an EE model that is tailored to the unique needs of FSWs by 3a) ensuring sensitivity training for staff - including local police-[74] regarding barriers presented to women with a history of IPV and/or active alcohol use to build support and a safe participation environment; 3b) provides matched savings to build assets towards making a transition from sex work to another vocation/skills development; 3c) it provides training in personal financial literacy before matching savings[77; 78] so the women may understand the risks of credit in advance of their accessing loan programs, obtain concrete information on how to budget and save to support both short-term and long term investments in educational and vocational training; 3d) empowers FSWs to make informed decisions on spending, recognizing a woman's need to spend savings on short-term consumption as well as long-term investments (e.g., vocational training and/or skills development); 3e) additionally empowers FSWs to understand their delay discounting tendencies to prefer small rewards immediately (such as receiving higher pay for condomless sex) over larger rewards available at some later time (such as benefits to sexual health) in order to maximize uptake of safe sex practices and long term health benefits; 3f) makes more salient the economic utility of maintaining good sexual health goals and share positive experiences of avoiding unsafe sexual triggers; 3g) examines how women choose to spend accumulated assets as opposed to restricting them via a "conditional" cash transfer approach to spend only on a specific goal; and 3h) actively builds on literature showing that having safe, alternative forms of employment may reinforce motivation among vulnerable women to live a more future focused and productive life; and 4) it includes a 24-month follow up to test long term impact, costs and cost-effectiveness of the intervention to inform scale-up and sustainability, and an integrated qualitative component to examine multilevel implementation factors and increase our understanding of the active ingredients of the intervention, including how women make financial choices and spend their savings. Matching will not be conditioned on the usual expenditures and/or savings goals dictated by programs.[79-82] The unconditional study design recognizes that women engaged in sex work face competing demands (child care, school fees, food, etc.), and that a conditional transfer may prohibit these vital expenditures. Lessons from our matched savings studies for AIDS-affected children and their families in Rakai and Masaka indicate that when given a list of options, including education and training, the majority (over 95%) of families opt for education related expenses.[80; 83; 84] Moreover, there are no reports of matched savings being misused. Families believe that education and training are true long term investments.[85] As proposed in this study, increasing employability and access to income via marketable skills in safe, alternative forms of employment may be an additional incentive that allows FSWs to be more competitive in the formal job market.[86] Our study is supported by extant literature on contingency management, contracting, and voucher systems for vulnerable and stigmatized populations, which increases access to income and participation in treatment services and promotes engagement in safe and empowering forms of employment among individuals.[87; 88] Our study follows the same underlying premise that when FSWs have access to alternative forms of employment and start earning formal income, they may become motivated to improve their skills and employability for professional advancement. The study findings may advance our understanding of how best to implement gender-specific HIV prevention globally, [50; 56] engaging women across the HIV treatment cascade (from negative to positive). Further, results will inform intervention's efficacy to reduce STIs and implementation sustainability, including cost effectiveness.

3.2.A. Theoretical Framework: The study is guided by social cognitive[14; 89], and asset theories.[15; 16]

Social Cognitive Theory[14] (SCT) has guided many HIV prevention studies and includes social cognitive mediators listed below (see figure 1). The central tenets of SCT, including self-efficacy and outcome

expectancies, are measured in this study for both paying and intimate partners. Self-efficacy, for example, have been found to affect whether people consider changing their behavior, the degree of effort they invest in changing, and long-term maintenance of behavior change.[12] Self-efficacy with respect to negotiating and using condoms with partners –intimate or paying– has been found to be a strong predictor of condom use[90; 91] and is often found in conjunction with empowerment in sexual relationship decision making.[92] The EE components for the proposed study have been adapted to integrate self-efficacy with outcome expectancies related to building financial literacy, vocational knowledge, and business development skills. For example, participatory sessions, characterized by lecture, discussion, modeling and role plays, include information on financial literacy skills and emphasize realistic goal-setting and ongoing savings to generalize lessons into daily life.

Figure 1: Conceptual Framework

Asset theory[15; 16] posits that economic assets may yield a range of outcomes, including increased economic stability. These, in turn, may mutually reinforce non-economic assets, including psychological, behavioral, and social assets.[15; 16] For low-income women, assets gained from EE are rich and complex, and have been operationalized to include economic, health, gender-based and psychological empowerment.[93; 94] For FSWs intersectional stigma and oppression increases the interpersonal and structural barriers to achieve such gains. In the current study asset theory recognizes that there may be psychological, behavioral and social asset improvements in mediators for the three study arms, e.g. condom negotiation self-efficacy, social support, access to services, as illustrated in figure 1. While all the groups may receive psychological, behavioral and social benefits, the HIVRR+S and HIVRR+S+FLM groups include planned accumulation of monetary and financial assets (e.g. personal savings and personal savings plus financial literacy training and mentorship) which we hypothesize will reinforce their psychological and behavioral mediators in a mutual manner yielding risk reduction increases above and beyond that of the HIVRR condition. Asset theory has been successfully applied in EE interventions in Uganda,[49; 95; 96] resulting in sexual risk reduction among Ugandan adolescents,[96; 97] HIV risk reduction among FSWs in Baltimore, Kenya, South Africa and Mongolia.[51; 53; 55]

3.2.B. Study Team and Formative Research Guiding Proposed Study. The proposed study will be led by Drs. Fred Ssewamala (Washington University; WUSTL) and Susan Witte (Columbia University) (Multiple PIs [MPI]). Dr. Ssewamala is Professor of Social Work and Public Health at WUSTL, and Director of the International Center for Child Health and Development (ICHAD). He has 15+ years of experience designing and conducting randomized control trials in SSA, and has published over 60 articles detailing these results.[62; 80; 84; 96-98] Ssewamala and Witte collaborated on the two pilot studies informing this proposal.[11] Witte is an Associate Professor of Social Work at Columbia University and a faculty affiliate Global Health Research Center of Central Asia (GHRCCA) and Social Intervention Group (SIG). Witte led the pilot studies informing this proposal and has over 24 years of experience conducting HIV prevention intervention research with sex workers and other vulnerable populations. Both MPIs will be responsible for the conduct and management of the research (see MPI leadership plan). The team has assembled a cadre of co-investigators (Co-Is) and consultants who will work on the study. At WUSTL, Ssewamala will be joined by Drs. Sensoy Bahar, Guo, and McKay. Specifically, Guo (Co-I), an expert in advanced statistical methods, will work with Ssewamala and Dr. Bellamy (lead biostastician) on research design and primary biological and behavioral data analyses (Aims 1 and 2). Sensoy Bahar's (Co-I) expertise in the use of qualitative methods will be harnessed for Aim 3, with support from Dr. Nakigudde (Makerere University), while McKay will provide her expertise in regard to HIV intervention research and implementation science. At Columbia University, Witte will be joined by Dr. Garfinkel (Co-I), with strong Economics and Social Work training, to lead and guide the cost and cost-effectiveness component of the study (AIM 4), working closely with Drs. Tozan (Consultant), and Ssewamala (PI). Ssewamala and Garfinkel have collaborated on multiple studies focused on cost and cost-effectiveness.[99-102] In addition, the team includes Dr. Jennings (Co-I, Johns Hopkins University) whose expertise in behavioral economics (BE) will be harnessed during the integration of BE principles throughout the study. Jennings is the PI of a RCT that incorporates a microenterprise intervention with BE principles, specifically for HIV prevention

in African-American young adults, on which Ssewamala is also Co-I. At RHSP, Dr. Kagaayi, a medical Doctor by training with strong methods and statistical analysis training will direct analyses conducted at RHSP. Ssewamala, McKay and Sensoy Bahar have worked with the RSHP team on multiple NIH funded studies[103; 104] and Suubi4Her (R01MH113486). In addition, Dr. Riedel (Consultant) will work with the MPIs to provide training on the HIVRR and FLM components. These combined teams will be joined by local NGO partners, including vocational training/skills development sites in Uganda (see letters of support). To maximize cultural relevance, feasibility, and adherence to ethical issues,[105] we have secured members of the existing RHSP FSW program community advisory board (CAB) that includes FSWs, NGOs, local police, government, training centers, and banks. The CAB will meet quarterly to provide feedback on study protocols and to guide study implementation.

3.2.B.1. Rakai Health Sciences Program (RHSP) (Dr. Kagaayi, Executive Director). RHSP is one of the oldest and most respected research institutions in SSA. Located in the Rakai district of Uganda, RHSP conducts innovative HIV prevention and treatment research while providing medical care to HIV positive individuals and families. Since 1988, RHSP has conducted many rigorous studies, including the Rakai Community Cohort Study (RCCS), an on-going annual HIV/STI surveillance study among 15,000 participants aged 15-49 years. The RCCS monitors incidence and prevalence of HIV, STIs and other diseases, provides a framework within which many intervention trials are conducted and through which HIV, demographic and behavioral trends are monitored.[106; 107] With funding from the President's Emergency Plan for AIDS Relief (PEPFAR), RHSP provides HIV prevention, care and treatment services to over 20,000 people regionally.[108] Special attention has been given to high risk populations including FSW, who receive routine HIV prevention education, condom distribution, STI screening and treatment, HIV testing, counseling and linkage to care.[5]

3.2.B.2. Undarga Project (Witte, PI, Ssewamala, co-I). Undarga (R34MH093227) was the first study to test preliminary effects, feasibility, and safety of a combined HIV prevention plus savings-led microfinance intervention (MF) on sexual risk reduction among 107 FSWs in Mongolia.[11] FSWs reporting unprotected sex were randomized to attend 4 sessions of HIVRR alone or 4 sessions of HIVRR plus a 34-session microfinance intervention, incorporating 12 sessions of financial literacy (FL), 12 sessions of business development skills, and 10 sessions of business mentorship, with corresponding weekly matched savings for asset-building. At 6 months post intervention women assigned to the HIVRR+MF condition reported significantly fewer paying sexual partners, fewer unprotected acts of vaginal sex, significantly lower income from sex work and increased financial literacy knowledge and skills compared to women assigned to HIVRR only.[11; 109] Undarga resulted in **Project NOVA (PI: Witte) (**R01DA036514**)** currently – in Year 4 – testing efficacy of HIV prevention plus vocational training and conditional matched savings on biological STI/HIV risk reduction outcomes among women reporting drug use and who engage in in sex trading in Kazakhstan. As indicated in Table 1, over 80% of FSWs attended 75% or more of 34 intervention sessions. Women report increased self-worth, confidence and self-efficacy for identifying alternative income sources to sex work post intervention.

3.2.B.3. Suubi and Bridges Studies (Ssewamala, PI). Ssewamala has led multiple EE studies, all Implemented in the study region: Rakai and Masaka, including Suubi-Uganda (R21MH076475), Suubi-Maka (R34MH081763), the Bridges study (R01HD070727), Suubi+Adherence (R01HD074949),[62; 79-81; 83; 96-98; 110-117] and Suubi4Girls (R01MH113486) whose findings and protocols inform the current proposal. These studies were among the first to rigorously test an asset based intervention using a savings-led approach in the care and support of youth (including women) affected by AIDS in Uganda.[62; 79; 81; 96-98; 110-115] Later studies have observed longer term psychosocial, behavioral and health outcomes for AIDS-affected youth via EE,[81; 99; 116] asset accumulation.[62; 79-81; 83; 84; 96-99; 110-117] and addressed the cost-effectiveness component.[101; 102; 118]

3.2.B.4 Emerge Project (Jennings, PI). The Emerge Study (K01MH107310) is an RCT testing the feasibility and longitudinal efficacy of a microenterprise intervention with behavioral economics (BE) in reducing self-reported sexual risk behaviors and economic outcomes in African-American young adults in Baltimore, 90% of whom lacked full-time employment (n=41 youth); 29% reported ever trading sex. The Emerge curriculum is among the first to draw upon BE principles relating to delay discounting, economic utility, loss aversion, and endowment effect to support economically-disadvantaged youth at risk for HIV. Youth are empowered in HIVRR-BE sessions to invest in immediate and long-term rewards of safe sexual and economic behaviors. These BE principles will inform the proposed study intervention.

3.2.B.5 Reach the Youth (RTY) Microfinance Project: Pilot for Proposed Study (December 2015-March 2016). To test feasibility of proposed protocols and review relevance and cultural context of proposed intervention, together with our local partners led by RTY , we undertook a pilot initiative. First, in February 2016 a total of 30 women who identified as FSWs participated in 4 focus groups conducted in the greater Masaka

region. Groups were led by RTY. Women highlighted the challenges they face, and their interest in and capacity to engage in the proposed interventions. Women ranged in age from 22-39 (m=31 years). Mean age at which women entered sex work was 25 years (range19-36) and had been in sex work an average of 6 years (range 2-14). Most women reported working in bars or from the street, engaging clients with or without alcohol (no mention of drugs), roughly 75% fulltime and 25% part time. Sex work or 'hustling' paid the bills, including rent and school fees for children and allowed women to make ends meet. Women described payment of 3000 shillings per customer (~1 USD) for sex while using a condom, but up to 20,000 shillings (~ 6 USD) for unprotected sex. Many women borrowed from SACCOs, but most stated that these did not seem to help as the "pay back happens too quickly". Some already had small business venture experience but lacked capital to launch. Women expressed a wish to "*become a respectable person and to have a job.*" Other women were extremely motivated to learn financial literacy skills in "*order to take control over [their] economic situations*". The women cited retail kiosks, weaving, cosmetology and catering, as some of the vocations of interest -all of which are integrated into one of the treatment groups. Some women indicated that if they made about 100,000 Uganda shillings (~30 USD) per week, they would be transitioning out of sex work to other forms of income.

3.2.B.6. Preliminary studies. This study protocol is informed by pilot findings and lessons learned from Ssewamala, Witte, Jennings' studies to date (Suubi, Bridges, Undarga, Nova, Emerge, RTY Microfinance Project and RHSP's surveillance studies). To disentangle the role of financial assets and training in risk reduction we include 3 study arms. These examine the additive benefit of matched savings alone (to generate capital), as well as the additive benefit of matched savings plus financial literacy with integrated BE principles and mentoring combined above and beyond traditional HIV risk reduction. Some women feel that capital is all that is needed for them to shift income sources. Others feel that they need additional supports that consider social, psychological, and economic factors influencing sexual decision-making. Mentorship sessions provided following financial literacy are focused on exploring critical steps needed to support transition to vocational and training, employment or business development. Mentorship session outlines from Undarga will be augmented with lessons from the Suubi, Bridges, Suubi4Her and Emerge Project curricula. Both the Suubi and Bridges Mentorship Curricula have been implemented for the past 10 years in the study region among young people.[85; 117] Mentorship includes connection to in-country collaborators' (RTY and RHSP) training resource centers, which will refer/link participants to local and regional trainings including formal income generation approaches, model farmers, vocational (sewing) and educational trainings. This linkage to several highly marketable income generating activities or skills development at existing institutions further strengthens the structure, relevance and potential sustainability of the intervention for FSW should it demonstrate efficacy. Prior research[82; 119; 120], including our pilot work to demonstrate feasibility, provide important start up advantage for the proposed study. Included below is Table 1illustrating number of session and retention from the research team own studies.

Table 1. Preliminary Studies: Recruitment, Number of Training Sessions and Retention Rates.

Study	Study site	Sample size	Recruitment period	Retention rate	Intervention sessions
Suubi+Adherence (1R01HD074949)	Masaka, Uganda	702 dyads	3 wks	96% (4yrs.)	18
Bridges (1R01HD070727)	Masaka, Uganda	1410 dyads	6 wks	92.7% (5yrs.)	36
SMART Africa (U19MH110001)	Masaka, Uganda	2434 dyads	6 wks	On-going	16
Nova (R01DA036514)	Almaty, Kazakhstan	354 FSW	6 wks	90% (12m, on-going)	34
Undarga (R34MH093227)	Mongolia Ulaanbaatar	107 FSW	6 wks	84% (6m)	38
RHSP FSW	Masaka, Uganda	600 FSW	8wks	91-94%	

3.3. Study Design and Methods

We propose a three-arm RCT to evaluate the efficacy of adding savings and financial literacy and mentorship to traditional HIV risk reduction on reducing new incidence of STI infections among 990 FSWs. The three arms are: 1) bolstered treatment as usual (TAU) care for FSW receiving only HIV Risk Reduction (HIVRR) (n=330) versus 2): HIVRR plus Savings (HIVRR+S) (n=330); or 3) HIVRR plus Savings plus Financial Literacy (FL) plus Mentorship (M) (HIVRR+S + FLM) (n=330). There will be five assessment points: baseline (pre-test), 6, 12, 18 and 24-months post-intervention initiation (see Timeline below). The study is nested within existing RHSP supported service provision hubs for FSWs and will be conducted with 990 self-identified FSW recruited from 33 comparable town centers located in Rakai, the Greater Masaka, Lwengo and Mpigi districts. Stratified randomization of town centers to conditions will be used. The 33 towns will be matched based on whether they are predominantly rural or urban, and relative number of FSWs registered. The restricted randomization technique of Hayes and Moulton (2009) will be implemented within the four strata to assure overall group/ geographical balance across the three study groups. Following matching, towns will be randomized to one of the three study arms by town center, reducing likelihood of contamination. Each town's assignment to condition will remain blinded to staff until enrollment takes place (described below). Given the high HIV

prevalence in our proposed study sample, to ensure that HIV serostatus is balanced across interventions, HIV status will be used as a blocking factor during the cluster randomization process using the strategy outlined in Bellamy et al 2005, lead statistician on the study.[121; 122] This strategy was employed successfully in an HIV risk reduction trial of HIV sero-discordant couples on which Witte was Co-Investigator.[123] This study will use an embedded experimental mixed methods design[124] where qualitative data will be collected post-intervention across all three arms. The qualitative data will explore: a) participants' experiences with each of the study arms and their specific components, including how women make spending decisions; b) key multi-level factors that may have hindered and facilitated FSWs' participation in each intervention component (HIVRR, S, FLM); c) savings and risk-taking decisions and behaviors post-intervention (follow-up); d) FSW perceptions regarding economic costs and rewards, relevance of including salience of positive or negative feedback, relating to preventive sexual behaviors; and e) perceptions on sustainability of each intervention. Data integration will occur at the interpretation and discussion stages for complementarity and expansion.[125; 126]

3.3.A. Study Sites, Recruitment, Screening, Eligibility, Enrollment: There are roughly 1,895 registered women receiving services at RHSP and RTY-hubs within the 33 towns targeted for the study and for whom we have reliable contact information. Both RHSP and RTY staff will use their quarterly meetings with FSWs to recruit potential participants for the study. Based on demographic statistics from both institutions, we expect between 80-90% of women to meet study eligibility criteria. We further expect possible attrition from screening to enrollment of 10-20%. However, we use conservative estimates in anticipation of enrolling at least 990 women (minimum of 55% eligibility) into the study. Outreach will be made during quarterly visits to 5-6 towns per month, rolling out study start up over 6 months (see timeline- Figure 2). In the initial meeting in each town, RHSP and RTY outreach staff will provide information on study participation and screen women to determine eligibility. Women will be eligible if they: 1) are at least 18 years old. We believe minors below age 18 are at a different developmental stage and may require a different intervention; 2) report having engaged in vaginal or anal intercourse in the past 90 days in exchange for money, alcohol, or other goods; and 3) report at least one episode of unprotected sexual intercourse in the past 90 days with either a paying, casual, or regular sexual partner. Women are ineligible if they: 4) have a cognitive or severe psychiatric impairment that would prevent comprehension of study procedures as assessed during Informed Consent process (see E. Human Subjects); or 5) are unwilling or unable to commit to completing the study or 6) have previously been randomized. Following recruitment, participants meeting inclusion criteria will be consented to participate and scheduled to complete baseline interview (including bio-testing) within 14 days. Blood and vaginal swab specimens are collected and taken the same day to the reference laboratory at RHSP for testing. Results are reported to the study team; single dose treatment will be provided by RHSP through their medical clinic services upon receiving a positive test result for all STIs, consistent with government protocols. We will follow the procedures provided in the 2016 Uganda Clinical Guidelines to test for Chlamydia (CT) and Gonorrhea (GC). Specifically, ~~As recommended by the Centers for Disease Control (CDC),~~ we will use Rapid tests ~~the more sensitive Nucleic Acid Amplification Test (NAATs)~~ for Chlamydia (CT) and Gonorrhea (GC) testing, while Trichomoniasis will be tested using culture which is considered a current criterion standard. STI treatment is monitored to ensure that any STIs assessed at follow-up time points are accurately captured as new infections (see E. Human Subjects). we will use the Rapid tests for Chlamydia (CT) and Gonorrhea (GC) testing, while Trichomoniasis will be tested using culture which is considered a current criterion standard. STI treatment is monitored to ensure that any STIs assessed at follow-up time points are accurately captured as new infections (see E. Human Subjects). Women are eligible regardless of their current HIV serostatus; the intervention is beneficial as both primary and secondary prevention of new STIs and HIV. Following baseline in all towns, women will be scheduled for the four sessions of HIVRR to begin within 30 days; and completed within 30 days from the start date. Given the use of cluster randomization, all women from the same town will be assigned to the same study condition. Disclosure of condition will happen at the first intervention session. Intervention sessions will take place at our collaborating NGO premises/ community outreach posts used by the RHSP and RTY. Study activities will be scheduled at times when there are no other community activities at these hubs. Within each town, recruited women will be divided into groups of approximately 8-12 members, an ideal size to ensure interaction with facilitators and other group members. For towns randomized to either treatment condition: HIVRR+S or HIVRR+S+FLM, a single savings session will follow the last HIVRR session (described below). FLM sessions will follow the savings session in those towns randomized to HIVRR+S+FLM. According to RHSP and earlier studies in the region, women who attend the TAU services demonstrate attendance rates of 94% and women who attend multisession activities have slightly lower attendance rates by ~3 percentage points (91%).[5; 62; 96; 97; 112; 117; 127-129] Based on our prior and ongoing studies with FSWs, once women are meaningfully engaged, they continue to attend intervention sessions. Further, we acknowledge the

challenge of achieving retention in multisession interventions with vulnerable populations. However, a recent review of FSW interventions in sub-Saharan Africa shows that those with multiple components, of high intensity and coverage, yield more desired outcomes compared to those with a limited number of components.[186] We will use retention strategies currently utilized by RHSP and the Suubi+Adherence study to successfully follow participants. During consenting, we will ask participants to provide future contact information, including phone number(s), and list of the names, addresses, and contact information of three people who will always know how to reach them. Participants will be reminded that in any contact made, we will not discuss details about them or their study participation. To further reduce potential attrition, we will reimburse women for transport to sessions. Effective use of these procedures in our previous research studies has resulted in very low attrition rates (9.7% over 5 years).[116-118; 130; 131] We will keep drop-out records and test for attrition bias based on baseline data. If such bias is present, we will limit generalizations accordingly or, where possible, introduce statistical adjustments to address bias. Strategies outlined here follow the protocols used in the *Bridges* and *Suubi-Uganda* studies.[62; 110; 132]

3.3.B. Subject Participation: Progression through the study is illustrated in the timeline.

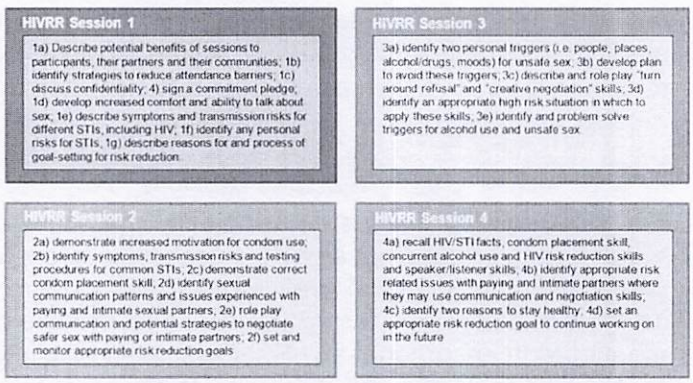
Figure 2. Study Timeline

Hire/train project staff, site prep, convene CAB, refine and adapt intervention and assessment protocol (as needed).	1-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54	55-60
	X									
Screen, recruit, consent participants		X								
Baseline Assessment, Randomization		X								
HIV Risk Reduction (HIVRR) Sessions		X	X							
Saving period begins; Deliver FL and M sessions			X	X						
Make-up Sessions				X						
6 month follow-up assessment; qualitative interviews				X						
12 month follow-up; biomarker collection; qualitative interviews				X	X					
18 month follow up assessment					X	X				
24 month follow-up; biomarker collection; qualitative interviews						X	X			
Data entry, cleaning, integration and data analysis	X	X	X	X	X	X	X	X	X	X
Manuscript preparation, dissemination of study findings.							X	X	X	X

3.3.C. Intervention Conditions

3.3.C.1. Women in the control condition (and in the treatment arms) will receive treatment as usual (TAU) for FSW in the study area. Provided by RHSP, TAU includes: *health education, HIV testing services, STI screening and treatment* in a session that lasts about 2 hours, provided on a quarterly basis. This will be bolstered with 4 sessions (see Figure 3) provided twice per week for 2 weeks of an evidence-based, HIV/STI risk reduction intervention tested in two previous studies by Witte (See E. Human Subjects). [11; 133] During session 3, linkage to PrEP and ART/ medication adherence skills will also be provided.

Figure 3 Control Condition HIVRR



3.3.C.2. Treatment Conditions

3.3.C.2a. HIVRR+S. Women in this arm will receive TAU for FSW and the 4 HIVRR sessions (described above) and a single session following HIVRR specifically describing bank account opening, the matching process, and how to interact with banks. In this session our partnering banks will open up matched savings accounts for women in the two treatment arms. Women in both arms will save money in their matched savings accounts over a 10-month period post HIVRR (described below). The study team will monitor the accounts using the statements received directly from the banks holding the accounts. Participants will receive monthly bank statements indicating their own savings and the associated match (1:1 match rate).

3.3.C.2b. HIVRR+S+FLM. Women in this arm will receive TAU and the 4 HIVRR sessions (as above). Next, they will receive the savings session (described above) and 6 financial literacy (FL) sessions provided twice a week for 3 weeks, followed by 8 mentorship (M) sessions supporting transition to vocational, educational training, employment or business development, and receipt of a matched savings account to be used on short-

term and/or long-term consumption and skills development per participants own discretion/choice.

Session#	Content
1	A recap on savings: Why Save and Set Savings Goals
2	Bank Services: Advantages of Using Banks; How to Use a Bank; Managing Risks of using ATM; BE Delay Discounting
3-4	Budgeting: Examine Money Management and Set Financial Goals; Describe Importance of Budgeting; Staying within budget; BE Economic Utility
5	Debt Management: My Money, Managing Loans; Costs of Borrowing; Delinquency: What Is It and How Does It Happen? The Dangers of Over-Indebtedness and Default; BE Salience
6	Savings: Increase Your Savings, Save for Emergencies and Make a Savings Plan; BE Loss Aversion

Figure 4. FL Intervention Content

Financial Literacy. Adapted for testing with FSWs in Undarga, this widely translated, evidence-based Financial Education Core Curriculum [134] addresses the importance of savings, banking services, budgeting (including household budget development) and debt management. Undarga adaptation for FSWs included shortening and simplifying sessions while retaining core elements; adding weekly check-ins due to safety concerns FSWs share related to intervention participation, and safety planning as needed. We will further adapt sessions in months 1-6 with the CAB to assure language and illustrative examples are culturally consonant, and to infuse BE principles consistent with HIVRR. Specifically, during sessions 1 & 2 we will include information on delay discounting, for example, learning to understand the tendency to prefer small immediate rewards (higher pay for condomless sex) over larger available at a later time (remaining HIV-negative or having high medication adherence);[69; 135-138] session 3 & 4 will include details on economic utility;[21; 139] sessions 5 will contain information on salience (e.g. understanding occasions when women may minimize triggers to unsafe sex, with the goal of making more salient in their minds opportunities to protect against HIV);[18; 19; 22; 140; 141] and session 6 will address loss aversion.[20; 69; 139; 142]

Mentorship. Mentorship to bridge the transition from FL and savings to a vocational change is a critical component of this intervention. These sessions are intended to support the transition –equipped with financial literacy and savings -- to vocational, educational, employment or small business development training using matched savings.[117] The mentorship sessions are adapted from the pilot study and integrate components (such as referral and linkage, coaching, exchange visits to model farmers) from income generating activities provided by our collaborating partner, RTY. All sessions include check-in and individual attention. The first 4 sessions focus on identifying options for vocational, educational, employment or business development training. The second 4 sessions include invited experts in identified areas of interest by group members for more intensive time and attention to individualized needs to make the transition.

A matched savings individual development account, (hereafter, IDA) is a savings account held at a local bank whereby deposits made by the woman are matched by the intervention to encourage savings and investment in skills and asset development. The accounts introduce women to financial management skills, introduce them to formal financial institutions, and by matching their deposits, incentivize women to save small amounts.[112; 143; 144; 146; 147] Each woman assigned to either treatment group will receive an IDA held in her own name. We have partnered with two national registered banks operating in the study area: Centenary Rural Development Bank and DTB Bank, to host these matched savings accounts (see letters of support). Women will be allowed and indeed encouraged to contribute up to 50,000 shillings (~15 USD) per month towards their IDAs. The maximum amount of women's contribution to be matched (the match cap) will be an equivalent of US$15 per month for 10 months' time. Women who save the maximum allowable amount (US$150) will have accumulated savings of US$300 over time (if they maintain saving the maximum matchable amount per month without dissaving) (US$150 in savings from their own contributions plus US$150 from the match: a 1:1 match). Each month during the intervention period an account statement will be generated for each woman to note her accumulated savings (own savings plus the match). Monthly statements act as "morale boosters". Unique to this study is our innovative spending model, which empowers women with agency to make informed financial decisions. During the intervention, women will have direct access to both their personal savings deposited in the accounts and the match provided by the study. This is different from our prior studies that required the participants' own savings and the match to be kept in separate accounts and to get approval by the research team to access the match.[62; 79-81; 83; 84; 96-99; 110-115] This added unconditional component provides women with a safety net to address short-term consumption needs and financial emergencies if they arise. With 14 sessions of FLM sessions tailored specifically to the needs of FSWs in Uganda, we expect women will be equipped with the knowledge to make well-informed investment decisions, but also feel supported in case of immediate consumption needs. The research team will monitor, but not restrict, how women spend their match via assessment questions and qualitative interview questions. Also, the study team will have access to and review participants' bank statements to ascertain deposit and withdrawal frequency.

3.3.D. Process Measures and Quality Assurance: We will adapt quality assurance (QA) procedures used

successfully in the team's ongoing HIV/STI intervention studies. We will provide comprehensive training prior to start up following detailed protocols for all procedures. We will audiotape all assessment interviews and randomly select 20% for fidelity review. We will use process measures to monitor the fidelity and quality control of intervention implementation. Specifically, we will capture: 1) Attendance/ dosage using a participant attendance form to monitor session attendance; and 2) Adherence and Contamination using a Session Adherence Checklist consisting of number, duration, and sequence of session activities and perceived quality of delivery, including potential contamination. Both will be used at the end of each session and facilitated by the study team. 3) Participant satisfaction using a questionnaire to assess attitudes towards and satisfaction with the HIVRR curriculum and each treatment component (savings, financial literacy, behavioral economics, and mentoring). All session data will be reviewed on an ongoing basis by the team led by the MPIs.

3.3.E. Procedures to maximize internal and external validity: Additional measures will be taken to monitor the following threats that may compromise internal validity. The control and treatment interventions are provided in distinctly different towns, per the randomization procedure, reducing the threat of contamination. Since these towns depend on the same economic activities, when migrations happen due to business seasonality, women tend to move to the capital city, Kampala, not within our targeted towns. However, as we will be monitoring all participants' attendance, we will also assess and monitor reports of any exposure to session content (through assessment survey, process measure and anecdotally among staff) inconsistent with a participant's random assignment. Staff will be trained on the experimental nature of the interventions and the importance of not introducing Saving and FLM content to the HIVRR participants. We will implement a rigorous quality assurance process throughout the study. If QA monitors discover contamination, they will identify how facilitators responded and address with staff; follow-up assessments will include a brief survey containing six items asking if they discussed any knowledge, skills or information that they learned in the sessions with other participants, and if so, what topics.

3.3.F. Assessment: Completed at baseline, 6,12,18 and 24 months post-intervention completion, assessments will include sociodemographic data, outcome measures, and putative moderators and mediators specified by our theoretical framework (see Table 1).[83; 106] Self-reported sexual risk outcome questions are used in the PIs current HIV prevention trials and ask specifically about the number and type of sexual acts in the past 90 days, as well as of protected sexual acts in the past 90 days with various partner types. They will be interviewer- administered, utilize a computer-assisted data entry system employed by the team in current clinical trials; and will be conducted in a private space at satellite field offices, typically in 60 minutes.
All female and male interviewers will minimize discomfort about potentially sensitive information. Participants will be compensated for each assessment. (Detailed in E. Human Subjects).

Table 2: Assessment Variables	Measurement	Relia-bility	Timepoint
Moderators			
Age, income, education, marital status, history of sex work	Sociodemographic Questionnaire		B, 6,12,18,24
Alcohol use, substance use, criminal justice history	Modified RBA[148]	.66-.83	B, 6,12,18,24
Mental health status	PTSD Checklist-Civilian (PCL-C),[149] BSI[150]	.97	B, 6,12,18,24
Partner violence history (paying and intimate)	Revised Conflict Tactics scale[151]	.80	B, 6,12,18,24
# and type of sexual partners (past year)	Modified RBA[148]	.66-.83	B, 6,12,18,24
Perceived stigma	Sex Worker Stigma (SWS) Index[152]	.87-.88	B, 6,12,18,24
Mediators			
HIV/STI knowledge	HIV/STI knowledge[153]	.80	B, 6,12,18,24
Condom Use Self-efficacy	Condom Use Self-Efficacy Scale[91]	.94	B, 6,12,18,24
Condom Use Outcome Expectancies	Condom Barriers Scale[154]	.82	B, 6,12,18,24
Condom Negotiation Self-efficacy	Condom Negotiation Self Efficacy [90]	.80	B, 6,12,18,24
Sexual Communication Skills	Sexual Communication Scale[155]	.80	B, 6,12,18,24
Social Support	MSPSS[156]	.84	B, 6,12,18,24
Current partner violence (paying and intimate)	Revised Conflict Tactics scale[151]	.80	B, 6,12,18,24
Attitudes towards gender roles; decision-making; communication	Gender Relations Scale[157]		B, 6,12,18,24
Access to services	RBA Services[148]	.66-.83	B, 6,12,18,24
Financial Literacy	Financial Literacy knowledge[134]	.80	B, 6,12,18,24
Savings Deposits	Bank Statements		B, 6,12,18,24
Behavioral economics measures	TBD		
Sexual Relationship Power Scale	SRPS[92; 158; 159]	.89	B, 6,12,18,24
Vocational, educational, or business development sessions attended			6,12,18,24
Outcomes			
STI (gonorrhea, Trichomonas, chlamydia) HIV status	Laboratory assays (see 3.3. F.1) & E.		B,12,24
STI testing and treatment	Chart Review		24
Sexual Risk: #,% of unprotected sexual acts by partner type; #, % protective practices; e.g. PrEP uptake, ART adherence, condom use	Modified RBA[148]	.66-.83	B, 6,12,18,24

Proportion of income from sex work, non-sex work, savings, debt	Economic Indicators Questionnaire		B, 6,12,18,24
Cost of staff time, supplies, overhead for HIVRR and for SMF	Project records; Admin. Review		ongoing
Viral load, CD4 count[#160; 161] (HIV positive women only)			B,12, 24

3.3.F.1. Biological assay: Collection, counseling, notification, referral for treatment, follow up and monitoring procedures for biological testing for HIV, Gonorrhea, Trichomonas, and Chlamydia – all used at RHSP and in current studies by the MPIs – will be completed at baseline,6,12,18 and 24 months post-intervention intervention completion. RHSP staff will also conduct chart review at 24 months for all participants to ensure that we identify any STI testing and treatment falling outside the study protocol. Details are provided in the Human Subjects section.

3.3.F.2. Qualitative component. Semi-structured in-depth interviews will be conducted at the end of the intervention, and at 6, 12 and 24-month follow-up for each study group. The first interview will focus on: 1) Participants' experiences with the respective intervention and its specific components (i.e., HIVRR, savings, financial literacy, and mentoring) and 2) Key multi-level (individual, economic, family, contextual, and programmatic) influences that affected their participation. The follow-up interviews will unpack the longer-term impact, including key multi-level factors affecting participants' savings and risk-taking decisions and sexual behaviors post-intervention. The follow-up interviews will also inquire into participants' perceptions of economic costs and rewards of preventive sexual behaviors and perceptions on program sustainability. A purposive criterion sampling strategy[162] will be used: Participants in the highest, mid (average) and lowest quartiles of number of attended sessions in each condition will be identified, and 30 participants (10 from each quartile) from **each** study condition will be randomly selected (n=90; this sample size will be sufficient for theoretical saturation).[163-165] This sampling method will ensure that participants with varying experiences are represented. This will allow us to identify common patterns and variations in participants' experiences. Interviews will be conducted in English or Luganda based on participants' preference. Questions will be translated (English to Luganda) and back-translated by two proficient team members. Each interview will last about 60 minutes and will be audio-taped. At the end of the intervention, all facilitators (about 9) will be interviewed to gain a deeper understanding of implementation patterns and processes, including their perceptions on sustainability.

3.3.G. Data Analysis:

Aim 1: Statistical Analysis of Intervention Efficacy. We will employ a logistic regression approach to evaluate Aim 1. Specifically, we will examine whether the presence of a biologically confirmed, incident STI post-randomization is associated with random intervention assignment. Our primary interest is to determine whether or not STI incidence differs for those randomized to (1) HIVRR+S or (2) to HIVRR+ S+FLM compared to HIVRR alone over the 24m follow-up period. Model estimates will be translated to estimates of incidence risk ratios or odds ratios and 95% confidence intervals (CI) and p-values will be calculated for inference. A logistic modeling strategy will also be implemented similarly for HIV incidence outcomes. Because behavioral outcomes of interest change over time and will be measured at multiple time-points, we will employ a similar logistic regression strategy, properly accounting for the repeated measures over time, via a generalized estimating equations (GEE) approach.[166] Specifically, when evaluating self-reported proportion of unprotected sexual acts with both regular and paying partners a logistic GEE will be employed specifying a logit link. We will be interested in estimating rate ratios or odds ratios comparing (1) HIVRR+S to HIVRR alone or (2) HIVRR+S+FLM to HIVRR alone. A Poisson GEE modeling strategy (e.g. GEE with specified log link) will be used to evaluate remaining secondary outcomes (1) self-reported number of unprotected sexual acts with both regular and paying partners. In sum, all models will assess intervention differences (HIVRR+S or HIVRR+S+ FLM versus HIVRR alone) in outcomes (STI incidence, unprotected sexual acts) longitudinally using a logistic regression strategy or the flexible GEE extension for repeated measures using an intent-to-treat approach.

Power Analysis for Aim 1 (1.1 and 1.2). Power and sample size considerations for this proposal prioritized the primary aim (Aim 1.1 and 1.2). Specifically, the study is powered to examine differences in STI incidence over 24 months post-randomization across interventions (HIVRR+S or HIVRR+S+FLM vs. HIVRR alone – 2 primary comparisons). Baseline prevalence estimates for this region and population are 77%, and 37% for STI and HIV respectively. We have assumed a range of plausible incidence measures that are a fraction of the prevalence estimates in order to estimate the sample size required for this study. Any women who test positive at baseline for an STI will be treated and therefore assumed STI free at randomization. Further, any subsequent positive STI results are considered incident cases. We determined that a sample of 330 FSWs per study arm in a cluster-randomized design would sufficiently detect a hypothesized odds ratio of 0.696-0.765 (where the STI incidence in the HIVRR alone ranges from 0.2-0.4 and the STI incidence in the HIVRR+S and HIVRR+S+FLM groups ranges from 0.15-0.35), adjusting for up to 20% attrition over follow-up with 80%

power. This estimate assumes (conservatively) both an intra-class coefficient equal to 0.01 and a Bonferroni correction of the 2-sided Type 1 error for the 2 primary comparisons. We have identified 33 total clusters/towns (11 per study arm) or ~30 FSWs per cluster, per intervention, so randomizing 330 women in equal proportions to each intervention, in a cluster-randomized design, to HIVRR+S to HIVRR+S+FLM to HIVRR alone, should provide sufficient power to test the 2 primary hypotheses. Sample size estimates were constructed assuming a cluster-randomized design using the algorithms outlined in Donner and Klar (2000).[167]

Aim 2. Statistical Analysis of Mediation and Effect Modification. We will explore whether key variables moderate the intervention's effect on primary outcomes. We will expand the modeling framework proposed for Aim 1 to include 'moderator X intervention' interaction terms along with the corresponding main effects. We will use contrasts to assess the magnitude and significance of each moderator on intervention effects through these interaction terms. SAS will be used to fit and evaluate potential moderators of any observed intervention effects. Similarly, we will examine whether key theory-driven variables mediate the intervention's effects on the primary outcomes, again we expand the modeling framework from Aim 1 to examine (a) whether the HIVRR+S or HIVRR+S+FLM improves the primary outcome compared to HIVRR alone (Aim 1); (b) whether the intervention improves each mediator; and (c) whether improvements in the mediator over time are associated with improvements in the primary outcome over time. This general approach to evaluating potential mediators of any observed intervention effects is easily implemented in the logistic and Poisson GEE modeling framework in SAS as recently illustrated in another HIV risk modification trial.[168]

Aim 3. Qualitative Component Analysis. Interviews will be transcribed and uploaded to QSR NVivo11 analytic software. Analytic induction techniques[169] will be used for coding. Initially,10 interview transcripts randomly selected across the three study groups will be read multiple times and independently coded by the team using sensitizing concepts and identifying emergent themes (open coding).[170] Broader themes will be broken down into smaller, more specific units until no further subcategory is necessary. Potential themes and subthemes include, barriers as well as facilitators at the individual-level (e.g., motivation, readiness to change, time constraints); economic-level (e.g., savings, sex and non-sex work earnings, condom purchasing, and related BE perspectives), family-level (e.g., competing demands, support); program-level (e.g., content relevance; interaction with other program participants, site-specific concerns); and macro-level (e.g., criminalization of sex work, cultural norms, stigma). In addition to implementation and sustainability, these findings will also shed light into potential mediators and moderators. For facilitator interviews, potential themes/ subthemes include facilitator-level (competency, motivation, training, supervisory support), participant-level (e.g., readiness for change, commitment), site/agency-level (readiness, buy-in, resources), macro-level (e.g., bank systems, cultural norms, stigma). Analytic memos will be written to further develop categories, themes, and subthemes, and to integrate the ideas that emerge from the data.[170; 171] Codes and the inclusion/exclusion criteria for assigning codes[172] will be discussed as a team to create the final codebook in NVivo. Each transcript will then be independently coded by two investigators using the codebook. Inter-coder reliability will be established. A level of agreement ranging from 66 to 97% based on level of coding indicates good reliability.[162] Disagreements will be resolved through team discussions. The secondary analysis will compare/ contrast themes and categories within and across the three groups to identify similarities, differences, and relationships among findings. Member checking, peer debriefing, and audit trail will be used to ensure rigor.[165]

Aim 4: Analysis of Cost and Cost-effectiveness. To assess cost-effectiveness of the intervention, we will develop a state-transition Markov model to simulate the risk of STI and HIV acquisition in a hypothetical cohort of 1,000 FSWs and estimate the clinical benefits (STI and HIV infections and Disability-adjusted life years) and costs over their lifetimes, comparing HIVRR-alone to HIVRR+S+FLM and HIVRR+S, from the health care perspective. The efficacy and costs of the interventions for reducing STI/HIV incidence among FSWs will be informed by the trial. Using a micro-costing approach, we will prospectively measure the actual use of resources associated with interventions and service provision in all three study arms. Costs will be drawn from project administrative records and routine program monitoring and evaluation data and collected from every organizational level that will be involved with interventions and service provision throughout the intervention period. There are mainly four main categories of costs: (1) Personnel costs will be calculated for staff administering and overseeing the interventions based on time spent and salaries; (2) Consumable costs include costs of all consumable items and equipment that have no resale value after one year. (3) Overheads include utilities (e.g. water, electricity, communication), rent, and recurrent maintenance costs of facilities and equipment. (4) Capital costs include equipment (e.g. laptops, printers, photocopiers) with an expected useful life of more than one year and will be annualized using a standard discount rate of 3%. We will add a start-up period, which will include activities conducted before the beginning of the RCT, such as planning and recruitment and training of staff. All these costs will be added to measure the overall resource use and the total

cost of intervention and service provision in the three study arms. Distinguishing between start-up costs and implementation costs is important to estimate the cost of scaling up an intervention. We will also distinguish between research costs and routine monitoring and evaluation costs. All research costs will be excluded; however, routine monitoring and evaluation costs will be included as it is expected that these costs will also be incurred in replication and scale up. All costs will be adjusted for inflation to facilitate comparison over time. Other clinical, epidemiological and cost input variables will be derived from the trial cohort or will be obtained from the published studies. Following the standard cost-effectiveness guidelines, future costs and health benefits will be discounted at annual rate of 3%. Strategies will be compared by calculating the incremental cost-effectiveness ratios (ICERs), defined as the additional cost of a specific strategy divided by its additional clinical benefit, compared with the next least expensive strategy. To assess the uncertainty in key variables and the robustness of the results to model assumptions, we will perform a probabilistic sensitivity analysis using a Monte Carlo simulation technique with 10,0000 iterations and the probability distributions based on data from the trial and the published literature:[173; 174] We will also compare the cost-effectiveness of HIVRR+S and HIVRR+S+FLM to other interventions targeted at FSWs in developing country settings.[177-179]

Data integration. The qualitative and quantitative data analyses will be done separately. Findings will be integrated at the interpretation and discussion stages[124] Conclusions and inferences will be synthesized for a more contextualized and thorough understanding of the impact of the additive components of the treatment interventions. The mixed methods design will serve two purposes: 1) *Complementarity;*[125; 126] and 2) *Expansion.*[125; 126] Qualitative findings will be connected to quantitative findings where the former will provide explanations and context for findings produced by the latter. More specifically, the qualitative data will potentially provide further explanation and context to the impact of the study [results in primary outcomes (e.g., risk taking) and mediators (e.g., social support; gender roles)] over time with questions focused on multi-level factors impacting decision-making and behavior. Moreover, the qualitative findings will complement our understanding of attendance and participant satisfaction (also measured quantitatively) for each study group.

3.3.I. Potential Challenges and Alternative Strategies: We do not anticipate major threats to study implementation, yet we recognize potential concerns. We have a stringent retention plan for session attendance. We expect to achieve enrollment goals and high retention (up to 90% at 24m post intervention, based on retention of registered clients recorded by RHSP staff and in our ongoing regional studies). Should recruitment, enrollment, or retention deviate from anticipated rates, we will schedule conference calls to enact solutions. A limitation of this intervention may be that it only appeals to poorer FSWs, who are at higher STI risk, for whom income from local vocations or small businesses are competitive. Reduced stigma and other asset gains, however, may yield broader appeal. While lack of condition on spending may lead some women to not spend on needed skills development (at least in the short-run), 14 sessions of FLM courses tailored specifically to FSWs, should equip women with knowledge to make well-informed investment decisions.

3.3.C. Dissemination and Sustainability: Findings will be disseminated through local, national, and global meetings and publications. There is substantial evidence, including recent public policy, for sustainability of the proposed treatment conditions—if proven effective. First, the policy environment in Uganda supports gender responsive development initiatives. Citing women's inadequate access to and control of assets, the GOU has committed to "reduce gender inequalities so that all women and men, girls and boys, are able to move out of poverty and achieve improved and sustainable livelihoods"[180] Similarly, Uganda's National Development Plan II (NDP) pairs women's gender equality and empowerment with "accelerated socioeconomic transformation." Aligning national goals with the UN 2030 Sustainable Development Goals (SDGs), Uganda policy makers stated their aim to give women equal rights to economic resources.[181] Further within the NDP II, the Social Development Sector is charged with increasing the percentage of women accessing economic empowerment initiatives to 30% by 2020.[182] In coordination with Ugandan stakeholders, USAID has also made recommendations to GOU in the context of the Country Development Cooperation Strategy, which emphasize an increase in women's asset ownership and expansion of their access to formalized bank accounts[183],and other formal financial services.[184] [185] In addition to financial services, skills development is of great interest to the GOU evidenced by its commitment to both formal and non-formal training for new entrants to the labor market in the Business, Technical, Vocational Education and Training (BTVET) Act of 2008 followed by the ten year BTVET strategic plan (2012-2022). The increasing demand for skills development, particularly among Ugandan youths, has resulted in government and Non-Governmental organizations' expansion of training opportunities and programs.[182] As these policies will likely evolve over the course of the study, our PIs, team and CAB members will remain current with efforts and pursue communication with key stakeholders so that study findings may inform and integrate into ongoing efforts.