ENHANCED HIV/STI AND PREGNANCY PREVENTION STUDY TO IMPROVE ADOLESCENT REPRODUCTIVE HEALTH SERVICES IN UGANDA

(“***H**ealth **I**mprovements-For-**T**een **U**gandans” or the **HI**-4-**TU** Study)*

MAKERERE UNIVERSITY– JOHNS HOPKINS UNIVERSITY (MU-JHU)
RESEARCH COLLABORATION
(MUJHU CARE LTD)
KAMPALA, UGANDA

NCT02845284

PROTOCOL VERSION 3.0
June 16, 2016

Protocol title: Enhanced HIV/STI and Pregnancy Prevention Study to Improve Adolescent Reproductive Health Services in Uganda

Short title: '*HI-4-TU Study*' which stands for **H**ealth **I**mprovements-For-**T**een **U**gandans

Sponsor: Eunice Kennedy Shriver National Institute of Allergy and Infectious Diseases (NIAID), Grant # **5UM1 AI 069530**

Principal Investigator:
Prof. Florence Mirembe M.MED, PhD
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail : flomir2002@yahoo.com

Program Director/Co-Principal Investigator:
Prof. Mary Glenn Fowler MD, MPH
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002 E-mail : mgfowler@mujhu.org

Co-Investigator:
Dr. Clemensia Nakabiito, MBChB, M.MED
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail: cnakabiito@mujhu.org

Co-Investigator:
Dr. Philippa Musoke, MBChB, PhD
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail: pmusoke@mujhu.org

Co-Investigator
Dr. Monica Nolan MBBS, MPH
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail : mnolan@mujhu.org

Project Coordinator
Dr. Carolyne Akello MBChB, MSc
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail: cakello@mujhu.org

Co-Investigator
Dr. Samuel Kabwigu MBChB, M.MED
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail : skabwigu@mujhu.org

Consultant/Adolescent Expert
Mr. Peter Mpinga
Naguru Teenage Information and Health Centre
P. O. Box 27572, Kampala, Uganda
Tel: +256-414-288304 Fax: +256-414-288305
E-mail: mpinga_peter@yahoo.com

Co-Investigator
Ms. Juliane Etima, MA Counselling Psychology
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail: jetima@mujhu.org

Social Scientist/Interviewer
Ms. Nabukeera Josephine B. A ,M.A Sociology
MU-JHU Care Ltd
Upper Mulago Hill Road
P.O. Box 23491, Kampala, Uganda
Tel:+ 256 414 541044 Fax: +256 414 543 002
E-mail: josephinenabukeera@yahoo.co.uk

Consultant/Statistician
Fredrick Edward Makumbi, MS, PHD
School of Public Health, College of Health Sciences
Makerere University
P. O. Box 7072, Kampala, Uganda
Tel: +256-414-543872, Fax +256-414-531807
E-mail: fmakumby@musph.ac.ug

Consultant/Obstetrician & Gynaecologist
Prof. Josaphat Byamugisha, M.MED, PHD
Head Dept of Obstetrics and Gynecology
Makerere University
P. O. Box 7072, Kampala, Uganda

Tel: +256-414-543872, Fax +256-414-531807 E-mail: byamugisha2001@yahoo.com

Table of Contents

LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	Audiovisual Computer Assisted Self Interview
ALHIV	Adolescents Living with HIV
ANC	Antenatal care
ANOVA	Analysis of Variance
AP	Ante partum
BP	Blood Pressure
CRF	Case Record Form
CRS	Clinical Research Site
CTU	Clinical Trials Unit
EBF	Exclusive Breastfeeding
FP	Family Planning
FGD	Focus Group Discussion
GCP	Good Clinical Practices
GPS	Group Peer Support
HEADDS	**H**ome & **E**nvironment, **E**ducation & **E**mployment, **A**ctivity, **D**rugs, **S**exuality, **S**uicide/**D**epression
HBM	Health Belief Model
Hb	Hemoglobin
hCG	Human Chorionic Gonadotropin

HI-4-TU	Health Improvement for Teen Ugandans (Study)
HIV	Human Immunodeficiency Virus
HSP	Human Subjects Protection
HTC	HIV testing and counseling
IDI	In-depth Interview
ICH	International Conference on Harmonization
IEC	Information Education and Communication
IMPAACT	International Maternal Pediatric and Adolescent AIDS Clinical Trials Network
IRB	Institutional Review Board
ITN	Insecticide Treated Nets
IPS	Individual Peer Support
JCRC	Joint Clinical Research Centre
JHU	Johns Hopkins University
KAP	Knowledge, Attitudes and Practices
KII	Key Informant Interview
MICH	Maternal, Infant and Child Health
MOH	Ministry Of Health
MTCT	Mother-To-Child (HIV) Transmission
MU-JHU	Makerere University – Johns Hopkins University Research Collaboration
NIH	National Institute of Health
PEPFAR	Presidents Emergency Plan For AIDS Relief
PNC	Post Natal Care
PP	Postpartum
PMTCT	Prevention of Mother-To-Child (HIV) Transmission
RCG	Routine Care Group
RH	Reproductive Health
RPR	Rapid Plasma Reagent
SES	Socioeconomic status
SIDI	Serial In-depth Interview
SOP	Standard Operating Procedures
STI	Sexually Transmitted Infection
STD	Sexually Transmitted Disease
T&C	(HIV) Testing and Counseling
TOT	Trainer of Trainers
TPHA	Treponema Pallidum Hemagglutination Assay
UNCST	Uganda National Council for Science and Technology
WHO	World Health Organization

PROTOCOL SUMMARY

Background

Supporting pregnant adolescents and teen mothers to improve uptake of health services for themselves and their infants is a critical public health issue in Uganda. These health services include support during pregnancy and lactation to promote maternal and infant health and uptake of dual protection methods which both prevent HIV and other STIs and promote planning and spacing of subsequent pregnancies. Barriers to be overcome include negative and discriminatory attitudes among both health care providers and the adolescents' own spouses or partners and families.[1-2] Most reproductive health (RH) and pregnancy services in public health settings are not adolescent friendly despite the adolescent population's high risk for adverse pregnancy outcomes and HIV/STI incidence.

Study Aims

AIM 1: To assess health care provider and adolescent mothers' Knowledge, Attitudes and Practices (KAP) regarding adolescent reproductive health and related health services and explore adolescents' risk perception and motivation to utilize reproductive health services and use of dual protection methods.

AIM 2: To compare the effectiveness of adolescent peer group support and education, one to one peer support and education and routine care to help pregnant adolescents aged 15 to 19 years to achieve effective family planning and reduce STI incidence through 6 to 9 months post-delivery. STIs to be evaluated will include HIV, Gonorrhea, Syphilis, Chlamydia, Bacterial Vaginosis and Trichomoniasis.

Design: This study is a 3 arm randomized controlled trial with a qualitative formative component at baseline, and qualitative and quantitative assessments at specific follow-up visits.

Study population: 519 adolescents who are pregnant attending antenatal care in Kampala and aged 15 to 19 years at enrollment with no diagnosed pregnancy complications or serious co-morbidity.

Duration: 12 months; the qualitative formative phase is planned to last 1 month and behavioral assessments to explore risk perception and motivation to utilize reproductive health services including uptake of dual protection will be conducted through the study duration. The randomized trial phase is planned to last about 12 months with 3 months of enrolment and 9 months of post-partum follow-up.

Interventions: Group Peer Support Education and Counseling (Arm 2) and Individual Peer Support and Education (Arm 3) as compared to routine care (Arm 1).

Study sites: Antenatal and postnatal clinics at Mulago Hospital and MU-JHU Research Clinic.
Noting Mulago Hospital is undergoing extensive renovation which may affect client volumes; one or more of KCCA Clinics including Kisenyi Health Center IV, Kawempe Health Centre IV, Komamboga Health Center III, Kawaala Health Center III and Kiswa Health Centre IV and/or **China-Uganda Friendship Hospital Naguru** *and Nsambya Hospital would be added as recruitment sites if inadequate recruitment rates are achieved at Mulago Hospital alone.*

Study outcomes

A. Quantitative data outcomes:

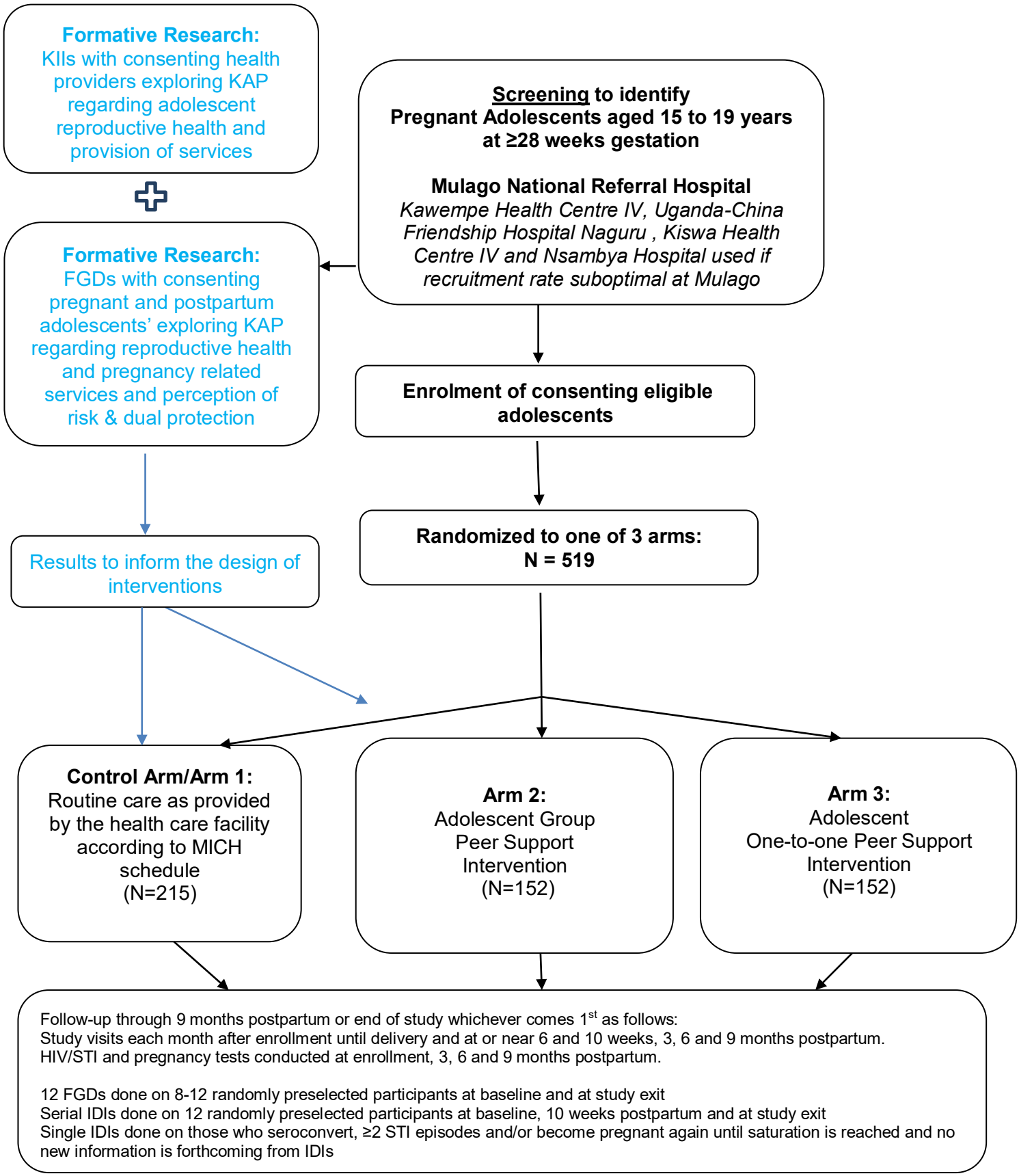
Primary:

i) Incidence of one or more STIs during study follow-up, with STIs confirmed by laboratory tests of HIV-1, Neisseria Gonorrhea, Treponema pallidum (Syphilis), Chlamydia trachomatis, Bacterial Vaginosis or Trichomonas vaginalis.
ii) Reported (and validated) consistent condom use and uptake of effective contraceptive method
Secondary:
iii) Acceptability and desirability of assigned clinic service model

B. Qualitative Data Outcomes:

i) Teen mothers' knowledge, attitudes and practice regarding teen reproductive health and related health services and risk perception and motivation to utilize reproductive health services and use of dual protection methods derived from FGD and single and serial IDIs
ii) Health providers' knowledge, attitudes and practice regarding provision of adolescent reproductive health services

STUDY SCHEMA



1 INTRODUCTION

1.1 Background and significance

Supporting pregnant adolescents and teen mothers to improve uptake of health services for themselves and their infants is a critical public health issue in Uganda. These health services include support during pregnancy and lactation to promote maternal and infant health and uptake of dual protection methods which both prevent HIV and other STIs and promote planning and spacing of subsequent pregnancies. Barriers to be overcome include negative and discriminatory attitudes among health care providers and the adolescents' own spouses or partners and families.[1-2] Most reproductive health (RH) and pregnancy services in public health settings are not at all adolescent friendly despite the adolescent population's high risk for adverse pregnancy outcomes, HIV/STI incidence and subsequent sustained health, education and socioeconomic harms.

Epidemiology of sexual and reproductive health among Ugandan teens

Drawing from the 2011 and prior Demographic and Health Surveys, the 2011 AIDS Indicator Survey and other surveys and studies, some sobering statistics emerge which paint a picture of the lived experiences of many young women in Uganda.

Uganda has one of the highest fertility rates in the world with a total fertility rate of 6.2 with a strong rural: urban (6.8:3.8) difference.[3-5] Teen motherhood is the norm with more than 1 in 5 (21%) of 17 year old adolescents and more than half (58%) of 19 year old women pregnant or already having had one or more children[6]. Although there has been a continuing decline in early teen pregnancies rates which parallel a decrease in early teen marriage over the last 20 years). Early marriage, household poverty, lack of education and rural residence are all associated with higher rates of teen pregnancy. Unmet family planning needs is highest in this age-group with 42% of mothers aged 19 or less reporting their babies were either wanted later or not at all.[5, 7]

Teen pregnancies are not without risk for both mother and baby. Sadly Uganda has one of the highest global rates of maternal mortality with a stagnant Maternal Mortality Ratio of 438 (CI 368-507). Around 1 in 6 female adolescent deaths (18%) among 15 to 19 year olds is a maternal death. 5% of mothers aged less than 20 reported receiving no antenatal care and two-thirds reported no postnatal check-up. Maternal age below 20 is also associated with a much higher rate of low birth weight and neonatal mortality (43/100 live births) than other maternal age groups under 40 years. Birth intervals less than the recommended 24 months is also highest (39%) among the 15-19 year old age group having their 2nd or subsequent pregnancy.

Female sexual debut is at a median age of 17.5 (for the younger age cohort), and is below age 15 for ~12% of women and below age 18 for ~58% of women while the median age of marriage among younger women is slightly less than 18 years. The age of sexual debut has remained stable between the 2006 and 2011 Demographic and Health Surveys although the proportion of girls less than 15 years old when married has declined over time to 3% among the 15-19 year old age cohort. Being married is strongly associated with a younger age of sexual debut and teen pregnancy.

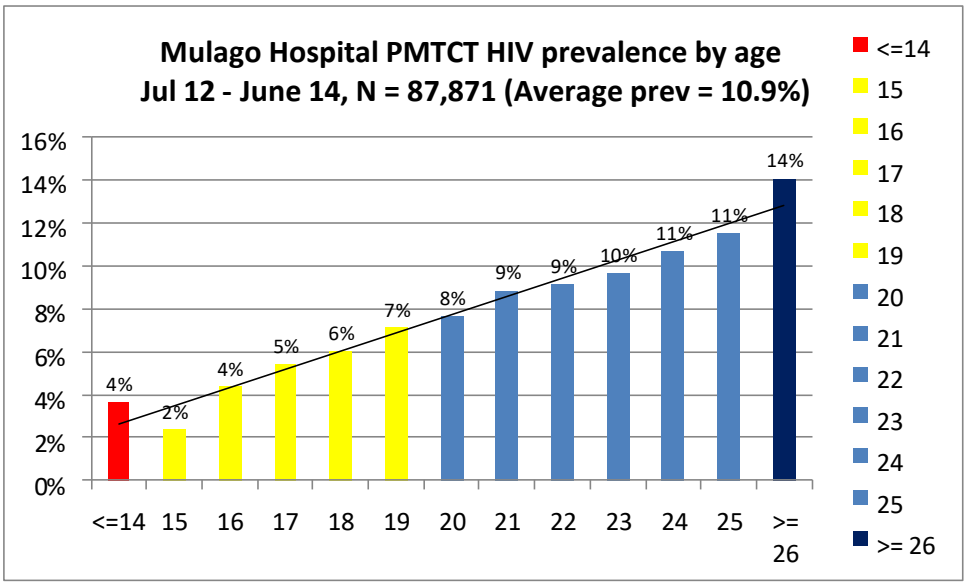
About 1 in 3 (33%) never married adolescents aged 18 to 19 years report having had sexual intercourse in the last 12 months with just over half (52%) using a condom at their last sexual encounter. Among 15-17 year old never married girls about 1 in 6 (14%) reported being

sexually active in the previous 12 months with a similar proportion (55%) who reported condom use. Among all 18-19 year old young women reporting being sexually active, almost 1 in 6 (16%) reported a partner at least 10 years older and almost 1 in 10 (9%) of 15 to 17 year olds reported a partner at least 10 years older. Being married had a very strong association with age-disparate relationships; with 19% of married women aged 15-19 reporting partners at least 10 years older versus 4% among unmarried women. In addition almost 1 in 6 (14%) of 15-19 year old married women reported co-wives as part of a polygynous marriage which was more prevalent in rural compared to urban areas.

Sexual and/or physical violence is reported by 58% of 15 to 19 year olds including 19% reporting sexual violence. The current or former husband or partner was identified as the perpetrator of sexual violence by 65% of women aged 15-49 who had experienced sexual violence. However non-spousal sexual abuse was also prevalent with 6% of women reporting non-spousal sexual abuse by age 15 and 9% by age 18. Alcohol intoxication and intergenerational patterns (with women's father having abused her own mother) were both associated with higher rates of violence of all forms whether emotion, physical and/or sexual.

Uganda has a mature HIV epidemic with overall HIV seroprevalence among adolescent girls aged 15-19 estimated at 3.0% [6]. There is a steady rise by age category from 1.6% among 15-17 year old adolescent girls to 5.1% among 18-19 year olds and 7.1% for young women 20 and 22 years old with a continued increase to an age-specific peak at 12.1% in women aged 30 to 34 [6]. In contrast age specific male prevalence remains much lower reaching 4.0% in the 25-29 year old category before a rapid increase to 9.1% in the 30-34 year old age cohort. The survey data suggests that peak HIV incidence for women is in the late teens and early twenties whereas for men peak HIV incidence is a decade or so older [6]. More than 500 young women aged 15 to 24 years are estimated to be infected with HIV each week in Uganda; extramarital relationships remain a driver for HIV transmission to young women as well as within marital relationships[8]

At the Mulago National Referral Hospital in Kampala Uganda there are over 43,000 pregnant women seen in the antenatal clinics (ANC) and almost 30,000 deliveries each year. Routine HIV testing with pre and post counseling is provided as part of PMTCT services and almost all women are tested. The figure below shows HIV testing by age for a 2 year period from July 2012 through June 2014 from MUJHU PMTCT program data. The average HIV prevalence was 10.9% and 15 to 19 year olds represented 14% of the total women seen and tested. Of note HIV prevalence in the younger age groups largely equates to incidence of new sexually transmitted HIV infections (with the exception of the small perinatally infected population reaching reproductive age). It is perhaps self-evident that pregnant teens are expected to (and do) have a higher age-specific HIV prevalence rate than that found in the general teenage girl population as pregnant teens are both sexually active and have had unprotected sexual intercourse.



Courtesy MU-JHU PMTCT program data Nov 2014

1 in 5 (19.7%) of teens aged 15 to 19 years self-report having had a sexually transmitted infection (STIs), genital sore, ulcer or discharge in the last 12 months. However sensitivity and specificity of these signs and symptoms among women is poor. Among men sensitivity and specificity is much higher and men aged 15 to 24 reported a prevalence of 14.3%. Among both women and men aged 15 to 49 slightly more than 1 in 4 (26 and 27% respectively) sought no treatment. A study carried out among adolescents in Kampala reported prevalence of 20.6% of at least one STI.[10] Access to diagnosis and treatment services for STIs as well as uptake and effective use of dual prevention methods to prevent STIs including HIV and effective contraception for prevention of unplanned pregnancies is an important public health issue among adolescents and youth. Adolescents who have already become pregnant are a particularly high risk group for repeat unplanned pregnancies and acquisition of STIs.[5]

With financial support from CDC/PEPFAR, MUJHU implements comprehensive PMTCT services at Mulago Hospital including routine HIV screening for all pregnant mothers, partner testing; support to initiate and adhere to lifelong antiretroviral treatment (known as 'Option B+') and follow-up of mother-infant pairs and linkage to ongoing HIV, reproductive health and infant care services for those found to be HIV infected. However, current very crowded antenatal, labor and delivery and maternal and infant health services at Mulago Hospital are far from adolescent friendly despite the adolescent population's increased risk for adverse pregnancy outcomes, repeat pregnancies and known relatively low health seeking behaviors.

Peer education and support interventions: Evidence and behavioral theories

Our intervention approach is primarily the provision and facilitation of education and support by peer educator/facilitators to their peers. Peer support is said to occur when people provide experience, emotional, social or practical help to each other. Peer support is distinct from other forms of social support in that the source of support is a Peer.[11] The effectiveness of peer support is derived from a number of psychological processes which were described by Mark Salzer in 2002.[12] These processes include; social support, experiential knowledge, social learning theory, social comparison theory and the helpertherapy principle.[13]

- Social support is the existence of positive psychosocial interactions with others with whom there is mutual trust and concern.[14] Positive relationships contribute to positive adjustment and buffer against stressors and adversities by offering (a) emotional

support[15] (esteem, attachment, and reassurance)[16] (b) instrumental support (material goods and services), (c) companionship [17] and (d) information support (advice, guidance, and feedback). [18]

- Experiential knowledge is specialized information and perspectives that people obtain from living through a particular experience such as substance abuse, a physical disability, chronic physical or mental illness, or a traumatic event such as combat, a natural disaster, domestic violence or a violent crime, sexual abuse, or imprisonment. Experiential knowledge tends to be unique and pragmatic and when shared contributes to solving problems and improving quality of life. [19-20]

- Social learning theory postulates that peers, because they have undergone and survived relevant experiences, are more credible role models for others. Interactions with peers who are successfully coping with their experiences or illness are more likely to result in positive behavior change [21]

- Social comparison means that individuals are more comfortable interacting with others who share common characteristics with themselves, such as a psychiatric illness, in order to establish a sense of normalcy. By interacting with others who are perceived to be better than them, peers are given a sense of optimism and something to strive toward.[22]

- The helper-therapy principle proposes that there are four significant benefits to those who provide peer support: [23-24] (a) increased sense of interpersonal competence as a result of making an impact on another person's life; (b) development of a sense of equality in giving and taking between himself or herself and others; (c) helper gains new personally-relevant knowledge while helping; and (d) the helper receives social approval from the person they help, and others.[25]

Peer education is a popular concept that implies an approach, a communication channel, a methodology, a philosophy, and a strategy. The English term ‘peer’ refers to “one that is of equal standing with another; one belonging to the same societal group especially based on age, grade or status”. The term ‘education’ (v. educate) refers to the “development”, “training”, or “persuasion” of a given person or thing, or the “knowledge” resulting from the educational process (Merriam Webster’s Dictionary, 1985). In practice, peer education has taken on a range of definitions and interpretations concerning who is a peer and what is education (e.g. advocacy, counseling, facilitating discussions, drama, lecturing, distributing materials, making referrals to services, providing support, etc.)[26]. Peer education typically involves the use of members of a given group to effect change among other members of the same group[27]. Peer education is often used to effect change at the individual level by attempting to modify a person’s knowledge, attitudes, beliefs, or behaviors. However, peer education may also effect change at the group or societal level by modifying norms and stimulating collective action that leads to changes in programmes and policies.[28]

There are a number of behavioral theories which provide a coherent framework in support of peer education approaches to behavior change which include **Social Learning Theory**, the **Theory of Reasoned Action**, **Diffusion of Innovation Theory** and the **Theory of Participatory Education.** Numerous studies including those specifically in the field of HIV and reproductive health and targeting young women suggest that peer lead education and support coupled with professional services are superior to professional services alone [26] . The importance of peer group support among adolescents has been emphasized in a recent survey of adolescents living with HIV (‘ALHIV’); the adolescents indicated the positive impact of peer group based psychosocial support.

We also draw heavily on the **Health Belief Model** (HBM) in our conceptualization of the behaviors of interest (health service attendance and uptake of dual protection methods) and how to influence them in this study. The HBM is a psychological model that attempts to explain and predict health behaviors. This is done by focusing on the attitudes and beliefs of individuals. The HBM was first developed in the 1950s by social psychologists Hochbaum, Rosenstock and Kegels working in the U.S. Public Health Services. The model was developed to help explain the failure of a free tuberculosis (TB) health screening program. Since then, the HBM has been adapted to explore a variety of long- and short-term health behaviors, including sexual risk behaviors and the transmission of HIV/AIDS.

Core Assumptions and Statements

The HBM is based on the understanding that a person will take a health-related action (i.e., use condoms) if that person:

1. Feels that a negative health condition (i.e., HIV) can be avoided,
2. Has a positive expectation that by taking a recommended action, s/he will avoid a negative health condition (i.e., using condoms will be effective at preventing HIV), and
3. Believes that s/he can successfully take a recommended health action (i.e., s/he can use condoms comfortably and with confidence

The HBM was spelled out in terms of four constructs representing the perceived threat and net benefits: perceived *susceptibility,* perceived *severity,* perceived *benefits,* and perceived *barriers.* These concepts were proposed as accounting for people's "readiness to act." An added concept, *cues to action,* would activate that readiness and stimulate overt behavior. A recent addition to the HBM is the concept of *self-efficacy,* or one's confidence in the ability to successfully perform an action. This concept was added by Rosenstock and others in 1988 to help the HBM better fit the challenges of changing habitual unhealthy behaviors, such as being sedentary, smoking, or overeating.

In the intervention arms, the peer educators will be explicitly trained to use the Health Belief Model and assist their peers to explore perceived susceptibility, perceived severity, perceived benefits, perceived barriers and self-efficacy with the aim of adopting healthier behaviors.

These peer mothers will offer individualized support and education to their assigned adolescents during study visits scheduled together with their routine clinic visits. The design of the individualized peer intervention arm builds on prior pilot work by MUJHU researchers in the Mulago PMTCT program. In 2012 the team completed an implementation science study providing individual peer support by “Family Planning (FP) Champions” to support uptake of family planning among newly delivered mothers. This pilot FP intervention showed increased uptake of FP services from 33% prior to the peer FP intervention to 61% among women during the intervention and 45% post intervention[29]. This preliminary work provides support for testing the one-to-one peer intervention in a randomized implementation study.

The peer educators selected will be young mothers who have successfully taken up contraception or dual methods (including consistent condom use) postpartum themselves who can thus serve as both peers and positive role models.

Study design, study population and setting

The MUJHU Clinical Research Site (CRS) under the Johns Hopkins University Clinical Trial Unit (JHU CTU) research scope includes primary prevention of HIV and reproductive health. This NIH sponsored **HI-4-TU** MUJHU Study is an adolescent focused implementation science study directed at improved social support and dual prevention of both HIV/STI's and subsequent unplanned pregnancies.

The intended study population is 519 currently pregnant adolescents (without diagnosed pregnancy related complications or serious co-morbidity) who are attending antenatal care in Kampala and are aged 15 to 19 years at enrollment with follow-up through 6 to 9 months after delivery.

We will use a randomized study design to test the acceptability and effectiveness of two enhanced peer lead, reproductive health promotion interventions compared to routine health care. The study participants will be individually randomized to one of three arms.

- Routine Care (Arm 1): Group education and counseling from ANC clinic midwives, routine PMTCT services including routine HIV C&T and family planning and partner C&T services for those requesting it.
- Intervention Arm Two: Routine Care plus group peer education and support beginning every 4 weeks post enrollment to delivery and at 6 and 10 weeks, 3, 6 and 9 months post-delivery.
- Intervention Arm Three: Routine Care plus individual peer education and counseling beginning every 4 weeks post enrollment to delivery and at 6 and 10 weeks, 3,6 and 9 months post-delivery.

1.2 Study hypothesis and Rationale

1.2.1 Study Hypotheses

We hypothesize that there will be a significantly lower incidence of HIV/STIs and increased uptake of dual protection and effective family planning methods in the intervention groups compared to the group receiving routine care i.e. we hypothesize intervention arms will be superior to routine care for our primary outcomes.

We further hypothesize that the group peer support intervention will be superior to the individual peer support arm in achieving a secondary outcome of improved self-esteem and self-efficacy (possibly mediated through improved social connectedness and a reduced sense of isolation and internalized stigma) however our study is not powered to detect the small differences we would hypothesize in our primary outcomes of STI incidence and uptake of dual protection methods between intervention arms.

1.2.2 Rationale

Adolescent pregnancy often curtails a woman's opportunity for further education, employment and economic independence and is associated with a higher risk for pregnancy related complications including maternal and infant mortality, gender based violence, subsequent narrowly spaced pregnancies and HIV and other STI infection. The rates of pregnancy, maternal mortality, HIV incidence and gender based violence among adolescent girls in Uganda are among the world's highest and represent an unconscionable disease burden and violation of human rights[30]

In most resource-limited settings including Uganda, routine antenatal and postnatal services are not adolescent friendly and often present additional barriers for adolescents to access comprehensive health care including dual prevention methods, especially for unmarried

'minors'. Uganda National Guidelines for Research involving Humans as Research Participants (version July 2014)[31] defines "emancipated minors as individuals below the age of majority who are pregnant, married, have a child or cater for their own livelihood." Emancipated minors should be able to access health services primarily for their own health without the consent of parents or partners however practice and policy remain far apart.

These data highlight the need for innovative yet realistic and cost-effective interventions to promote adolescent reproductive health including among the especially vulnerable group of pregnant adolescents.

There is moderate strength data which suggests well run peer education and support services might provide just such practical and cost-effective intervention models however there are few randomized controlled trials to date with none among pregnant teens and none that compare individual to group peer education and support to our knowledge.[28] Given the need to allocate scarce resources to evidence-based interventions which achieve maximum cost-effectiveness we argue that the results of our study may have important policy implications for a highly vulnerable population suffering a disproportionate disease burden.

1.3 Innovative aspects of the proposed study

Innovative aspects of this study include:
Study design in that individually randomized controlled trials have not been conducted previously to evaluate peer interventions in this key neglected population nor to compare individual versus group peer interventions in an adolescent friendly clinic.
Peer lead model drawing on young mothers who are both peers and role models

- Use of currently available information & communication technology in Uganda to send study visit reminders and maintain contact with participants through sms or phone calls.
- Collection of cost data to inform planning of replication and scale-up if successful
- Capacity building among young peer leaders as a secondary study benefit

This project will test two, innovative, peer-lead, adolescent friendly, reproductive health interventions specifically tailored to pregnant and postnatal adolescent mothers which is a key neglected population suffering a high disease burden. In this study we seek to use peer lead interventions coupled with credible professional advice to educate, support and empower adolescent mothers to consider and achieve their reproductive goals (our study end points), which is conceptualized as critical to achieve their broader life goals (ultimate impact).

The peer education and support in both intervention arms will be provided by young peer mothers who have successfully dealt with a number of issues that the expectant adolescents and young mothers are dealing with in their lives including uptake of contraception (or dual prevention methods) after delivery. They are selected to be both a credible peer and a positive role model to the study participants. The peer mothers will receive training in the use of an adolescent tailored reproductive health curriculum that is interactive and that includes role playing to help sexually active adolescents identify and reduce sexual risks including negotiation of condom use. This will draw from the *Comprehensive Family Planning and Reproductive Health Training Curriculum* for adolescents.[32] In addition available Uganda MOH and other already developed IEC materials will be used and adapted.

The planned intervention study will also collect relevant human and other resource and cost data to inform subsequent replication and scale-up.

Capacity building is also anticipated as a secondary benefit with training and mentoring of young peer educators/leaders as well as training and mentoring of health service care providers in the provision of dual protection methods, adolescent friendly health service practices including screening and treatment of STIs and promotion of reproductive and sexual health tailored to adolescents.

1.4 Institutional Capacity

MUJHU celebrated its 25th anniversary in 2013 as a leading research institution focused on maternal and children's health in Uganda. MUJHU is a long standing collaboration between Makerere University and Johns Hopkins University and became a Ugandan not for profit registered company in 2006. MUJHU continues to participate in NIH sponsored clinical trial research networks focused on PMTCT, maternal and pediatric health and primary prevention (currently IMPAACT and MTN networks) and has conducted multiple perinatal HIV prevention clinical trials including the landmark HIVNET012, SWEN and HPTN046 studies. In addition MUJHU has successfully applied for clinical research, implementation science and programmatic implementation grants from a number of diverse sources (US, European, Canadian and other) both directly as a prime and in consortia with other partners (including University of California in San Francisco, Emory University, Harvard University and MJAP).

In the various clinical trials MUJHU has achieved very high retention rates due to the close monitoring of study participants using peers and health visitors, who counsel and advise, remind them about study visits, and visit them at home when necessary. MUJHU also works closely with the MUJHU Core Laboratory which is one of the few CLIA certified laboratories in SubSaharan Africa.

Through its founder Professor Mmiro (now deceased and former Chair of the Department of Obstetrics and Gynaecology), Dr Nakabiito (Study Co-Investigator) and Professor Mirembe (Study PI) and its many research studies and support to PMTCT program services MUJHU has a very deep and long standing relationship with Makerere University's Ob/Gyn Department and Mulago Hospital's reproductive health services. MUJHU has assisted Mulago to implement its PMTCT program since 2000 when the 1st efficacious simple ARV interventions for PMTCT were described. Since 2002, peer mothers have been a central element of this program providing testimony, education, support and hope to their peers in individual, couple, group and community settings.

Up to 2012 MUJHU also implemented a family model of comprehensive HIV care including care to all family members of HIV-positive female clients including adolescents many of whom were perinatally infected. MUJHU also hosts a vibrant mentored peer support program for children, adolescents and youth called 'Young Generation Alive' which from its beginning in 2005 with 5 members now boasts more than 300 members including charismatic inspiring peer leaders and success in reducing school dropouts, teen pregnancies and improved self-esteem. It is from among this group that some of the peer educators are expected to be recruited. MUJHU also successfully implemented a peer Senga study exploring partnership of HIV mothers(peers), community women and men (sengas/kojas) and village health teams to improve postpartum follow up in PMTCT[29]

2 RESEARCH AIMS AND OBJECTIVES

AIM 1: To assess health care provider and adolescent mothers' Knowledge, Attitudes and Practices (KAP) regarding adolescent reproductive health and related health services and explore adolescents' risk perception and motivation to utilize reproductive health services and use of dual protection methods.

Objective 1.1: To describe health workers knowledge, attitudes and practices about the provision of adolescent reproductive health services as well as their perceptions of barriers to adolescent uptake of services and health promoting behaviors.

Objective 1.2: To describe adolescent knowledge, attitudes and practices in relation to their own reproductive health and uptake of health services and explore adolescents' sexual risk perception and motivation and use of dual protection methods.

AIM 2: To compare the effectiveness of adolescent peer group support and education, one to one peer support and education and routine care to help pregnant adolescents aged 15 to 19 years to achieve effective family planning and reduce STI incidence through 6 to 9 months post-delivery. STIs to be evaluated will include HIV, Gonorrhea, Syphilis, Chlamydia, Bacterial Vaginosis and Trichomoniasis.

Note: Routine care currently includes PMTCT services with HIV C&T and Uganda Ministry of Health messages given by midwives about healthy pregnancies during antenatal visits, and reproductive health at the 6 week postnatal visit; with referral for family planning for interested women.

Objective 2.1: To describe and compare baseline demographic and clinical characteristics of the study participants at enrollment by arm.

Objective 2.2: To describe and compare incidence of one or more STIs (including HIV) during study follow-up by study arm.

Objective 2.3: To describe and compare uptake of dual prevention methods (contraceptive services and condom use) during study follow-up by study arm

3 DESIGN AND METHODS

3.1 Study Design

Formative Research

We will first conduct formative research with adolescents similar to the study participants to assess knowledge, attitudes and practices related to adolescent reproductive health and services. About two FGDs shall be conducted on consenting pregnant and postpartum adolescents aged 15 to 19 years, ensuring all ages are represented. Key informant interviews will be done prior to the study enrolment with targeted, experienced, reproductive health care providers to better understand their perceptions of reproductive health service needs and gaps among pregnant and postpartum adolescents. These data will together inform further refinement of the peer support and education interventions.

We shall also collect qualitative data soon after enrollment during pregnancy, at about 10 weeks postpartum and at study exit using serial in-depth interviews with about 12 randomly selected adolescent mothers as well as about two FGDs soon after enrollment and at study exit. In addition single IDIs will be conducted with participants who become HIV-infected, have ≥2 STIs or a repeat pregnancy during study follow-up until saturation is reached and no further new information appears forthcoming. These qualitative data will be triangulated to describe adolescents' knowledge, attitude, practices and risk perceptions related to their own sexual and reproductive health (RH) and related health services and to ascertain the extent to which they perceive the available RH services as teen friendly or not in terms of acceptability and accessibility.

Randomized Controlled Trial

We will conduct a 3-arm, randomized, controlled trial of 519 pregnant adolescents aged 15 through 19 years at enrollment to test the acceptability and effectiveness of two enhanced adolescent friendly reproductive health prevention interventions versus current routine care. In each intervention group, 152 adolescent mothers will be randomized to either the enhanced group peer support education and counseling intervention or to the enhanced one-to–one (individual) peer support education and counseling group with a young, model, peer educator trained to deliver RH education and counseling messages, beginning during pregnancy (≥ 28 weeks) and followed up to 9 months postpartum or study end at or after 6 months (whichever comes first). The control group will consist of 215 adolescent mothers randomized to routine care as provided at Mulago hospital (or the designated health facility) where midwives deliver group sessions during antenatal and postpartum care visits as well as standard PMTCT services including routine opt-out HIV C&T and availability of partner C&T. Syphilis testing should also be routinely provided and treatment provided for infected pregnant mothers and their partners as per local standard of care.

The 3 groups will be enrolled with study visits at 3, 6 and 9 months post-partum however the intervention groups (Arms 2 and 3) will have additional visits at 36 weeks Antepartum, delivery, 6 and 10 weeks postpartum, Quantitative baseline data will be collected on routine demographic characteristics, reproductive history, pregnancy intentions and sexual risk/perceptions and HIV/STI status.

Summarized table 1 of the study schedule and evaluation

		SCR/ ENR	36 weeks APT	Birth†	6 weeks PPT	10 weeks PPT	3 months PPT	6 months PPT	9 months PPT†
Arm 1– Routine Care		**X**					**X**		**X**
Intervention: Enhanced Counseling Education Sessions/Routine care as provided		**X**			**X**	**X**	**X**	**X**	**X**
Behavioral Assessments using IAQ and ACASI		**X**				**X**		**X**	**X**
Psychosocial Assessment		**X**					**X**		**X**
Obtain/review and update RH and Medical History		**X**	**X**	*	*	*	*	*	**X**
Clinical Examination – Blood Pressure, Weight, Obstetric exam		**X**	**X**						
Prescribe contraceptives					**X**	*	*	*	*
Provide available test results		**X**	**X**		*	*	**X**	*	**X**
Provide treatment/referral as appropriate		*	*	*	*	*	*	*	*
LABORATORY									
Blood	HIV-1 Serology (rapid tests)	**X**					**X**		**X**
	Syphilis serology RPR (TPAB if positive)	**X**					**€**		**X**
Urine	Protein and Glucose	**X**	**X**						
	Rapid test for Gonorrhea infection	**X**	*		*	*	*	*	**X**
	Rapid test for Chlamydia infection	**X**	*		*	*	*	*	**X**
	HCG test				*	*	*	*	**X**
Pelvic	Rapid test for Trichomoniasis	**X**	*		*	*	*	*	**X**
	Collect Vaginal swab for Bacterial Vaginosis testing	**x**	*		*	*	*	*	**X**
	Collect vaginal swab for testing presence of Y chromosome ‡								**X**
QUALITATIVE COMPONENT									
Serial In-depth Interview (SIDI)		**X**				**X**			**X**
Focus Group Discussion (FGD)		**X**							**X**
Single In-depth Interview (IDI)					*	*	*	*	*

X mandatory, *If indicated, †contact at birth only for the intervention groups, **€** repeat at 6months if positive at enrolment, ‡ done only at study exit for participants with self-reported consistent condom use,

† month 9 will be the study exit visit for most participants however month 6 may the exit visit for the last participants to enroll hence additional exit evaluations would be done then

3.2 Study Setting and population

3.2.1 Study Setting

The study will enroll participants from Mulago National Referral hospital antenatal clinics in Kampala. If recruitment at Mulago hospital is insufficient (due to the current ongoing hospital rehabilitation works), we will recruit patients from the Uganda China Friendship hospital, Naguru in Kampala, KCCA Clinics including Kisenyi Health Center IV, Komamboga health center III, Kawaala Health center III and Kiswa Health Centre III and/or Nsambya hospital. All these hospitals have established PMTCT programs and see a substantial number of pregnant adolescents in their antenatal care clinics and they provide PTCT services and group education sessions in the ANC and PNC Clinics on maternal and child health as part of routine care.

In order to prevent cross-contamination between the control and intervention arm populations, the group education and counseling sessions will take place at the MU-JHU Research premises. All other routine and individual peer support and education services will take place on site at the health care facility providing ANC and PNC services.

3.2.2 Study Populations

3.2.2.1 Study populations for formative phase:

Randomly selected pregnant and postpartum adolescent girls similar to the study population will have 2 FGDs conducted; each FGD will involve 8-10 participants.
KIIs will be conducted with 8 experienced health providers providing RH services at Mulago Hospital and the other targeted health facilities.

3.2.2.2 Study population for the randomized controlled trial component:

519 pregnant adolescents' ages 15-19 years recruited from the Mulago Hospital* ANC Clinic who are interested in participating in this study; agree to follow up and provide written informed consent with no diagnosed comorbidities including significant pregnancy related complications.
Selection of participants will be by systematic sampling to ensure that the study population is evenly sampled.
** KCCA Clinics including Kisenyi Health Center IV, Kawempe Health Centre IV, Komamboga Health center III, Kawaala Health centerIII* and *Kiswa Health center IV,* Uganda-China Friendship hospital Naguru *and Nsambya hospitals will be used if accrual of recruitment from Mulago hospital is not sufficient*

3.2.2.3 Study population for the qualitative component:

Randomly selected pregnant adolescents will have 12 FGDs (8 – 12) participants in each group) at baseline and at study exit visit.

We will also have serial IDIs (SIDI) with other randomly selected pregnant adolescents at baseline, 10 weeks and at study exit. A total of 12 participants will be interviewed, 4 in each study arm.
Selection of participants will be by maximum variation sampling to ensure that all age groups are well represented.

Single IDIs will be conducted with participants who seroconvert, become pregnant (second pregnancy), or those who acquire 2 or more episodes of STIs during the study duration until saturation is reached with no new information forthcoming.

3.3 Qualitative Component

3.3.1 Focus Group Discussion (FGD)

FGDs will be conducted for each of the study arms at baseline and at study exit (6 to 9 months postpartum). The participants will be categorized according to age groups for each of the arms; 15-17 years and 18-19 years with each of the groups having FGDs at baseline and study exit. The total number of FGDs will be 12, and the target number per group will be 8-12 participants (n=8-12). A focus group interview guide will be used to obtain information from the FGDs and the sessions will be audio recorded and transcribed. Themes for FGD guide will be developed and will have the same themes for both pregnant adolescents and adolescent mothers but probes will be modified to suit targeted periods.

3.3.2 Key Informant Interviews (KII)

KIIs will be conducted with 8 experienced RH providers at the Mulago hospital and other targeted health facilities. An interview guide will be used that will elicit information on key informants knowledge, attitudes and practices towards provision of RH services to adolescents and perceptions of the barriers to uptake of RH services and healthier sexual and RH related behaviors among adolescent girls.

3.3.3 In-depth Interviews (IDI)

Serial IDIs (SIDI) with 12 randomly preselected pregnant adolescents (4 each arm) will be conducted at baseline, 10 weeks and at study exit. Participant's attitudes, beliefs and practices towards pregnancy and RH services will be collected using behavioral CRFs at baseline, 10 weeks and study exit to assess any changes over time. In addition, participants HIV/STI risk perception and motivation to utilize RH services including condom use will also be assessed.

Single In-depth Interviews will also be conducted for participants who seroconvert, become pregnant, or those who acquire 2 or more episodes of STIs during the study duration. Serial In-depth Interviews will be conducted for randomly pre-selected participants at baseline, 10 weeks and about 2 weeks post study exit. In the event that a participant selected for a serial IDI either seroconverts, becomes pregnant, or acquires 2 or more episodes of STIs, then the last IDI will be conducted at the point when the end point occurs.

3.4 The Randomized Controlled Trial Component

3.4.1 Recruitment

Recruitment of the adolescent mothers aged 15 to 19 years will be done from the Antenatal clinic (ANC) at Mulago Hospital. If the recruitment rate is below predetermined levels then recruitment will be expanded to one or more of KCCA Clinics including Kawempe Health Centre IV, Komamboga Health Center III, Kawaala Health center III and Kiswa Health Centre IV, Uganda-China Friendship Hospital Naguru, and Nsambya Hospital. The expectant adolescent mothers will be ≥28 weeks of gestation as ascertained by their medical records. Potential participants will be informed about the study and those interested will be supported through the informed consent process.

3.4.2 Selection of the Study Population

The inclusion and exclusion criteria in Sections 3.4.3.1 and 3.4.3.2 are used to ensure the appropriate selection of study participants.

3.4.3 Study eligibility criteria

3.4.3.1 Inclusion criteria

At the time of screening participants must meet all of the following criteria to be eligible for inclusion in the study:

I. Aged 15 through 19 years (inclusive)
II. Pregnant at ≥28 weeks of gestation as documented in her medical records
III. Able and willing to provide written informed consent to be screened for and take part in the study
IV. Able and willing to provide adequate locator information with residence within 30 km radius from the MUJHU study clinic and to receive a home visitor visit
V. Able and willing to come for follow up visits and to receive study follow up phone calls

3.4.3.2 Exclusion criteria

Participants who meet the following criterion will be excluded from the study:

I. Serious illness or social conditions that would prevent adherence to study requirements
II. High risk pregnancy or fetal death in utero (with the exception of risk defined only by maternal age)

Of note, HIV infection is NOT an exclusion criterion.

3.4.4 Informed consent processes

Written informed consent will be obtained from all potential participants for the formative research including adolescents participating in the FGDs and health professionals participating in the KIIs. The Informed Consent Forms (ICF), in English and Luganda will provide information about the FGD and any possible risks and benefits associated with participation. As the KII is with health providers, the KII ICF will be in English.

Written informed consent will be obtained from all potential study participants prior to enrolling in the randomized clinical trial. The Informed Consent Form (ICF), in English and Luganda will provide detailed information on what the study is about, the study procedures, and any possible risks and benefits associated with study participation in accordance with Good Clinical Practice Guidelines.

3.4.5 Randomization procedures

Prior to the study commencing, a randomization list will be prepared by the Data Manager at MU-JHU. This list will be computer-generated using random-sized block groups and will include consecutive intervention numbers with corresponding random intervention assignments. The randomization list will be encrypted in a password-protected file and backed up on the MU-JHU server. Encrypted copies of the original randomization list and documentation of the procedure used to generate the lists will be stored in the project administrative computers in MU-JHU and backed up on the MUJHU server. At enrolment, the MU-JHU Data Center will issue randomization numbers to the study coordinator based on the participants' group allocation. These random numbers will be placed in envelopes and placed at a centralized location where study counselors may access them. After signing the informed consent and the participant is deemed eligible (based on the study eligibility criteria listed above), the participant will then open the sealed envelope and reveal the study group they are randomly assigned to. Assignment of randomization is considered the effective act of participant enrolment.

3.4.6 Intervention (Enhanced Peer Support Education and Counseling):

Routine care is the care currently provided at the hospitals/ health centers during pregnancy, delivery and postpartum.

Per the Uganda clinical guidelines 2012 [33], the main objectives of antenatal care are: prevention and treatment of any complications, emergency preparedness, birth planning, satisfying any unmet nutritional, social, emotional, and physical needs of the pregnant woman, provision of patient education, including successful care and nutrition of the newborn, Identification of high-risk pregnancy and encouragement of (male) partner involvement in antenatal care.

For normal uncomplicated pregnancies, pregnant mothers are usually scheduled to have 4 routine visits during pregnancy; at 10–20 weeks, 20–28 weeks, 28–36 weeks and >36 weeks. At all these visits, risk assessment, fetal growth monitoring, health education and plans for delivery are made by nurses/midwives with referral to clinicians/obstetricians (where clinically indicated and available). Risk assessment is done by history taking, examination including blood pressure and weight measurement and investigations (recommended routine laboratory investigations include RCT, RPR for syphilis, Hb, urine for albumin and glucose). Other tests are recommended as appropriate for the individual patient to assess maternal well-being, e.g. ultrasound, amniotic fluid, fetal heart/movements)

Health promotion/education is usually delivered in group sessions by the nurses/midwives and issues discussed include; involvement of husbands in ANC, delivery plans, discuss future FP, discuss symptoms of miscarriage, pregnancy-induced hypertension (PIH), education and counseling on PMTCT of HIV and malaria prevention and use of insecticidetreated bed-net (ITN), education on danger signs in pregnancy, proper nutrition, adequate hygiene, breastfeeding and breast care, sexual activity during pregnancy, dual protection for FP/HIV, avoidance of smoking and alcohol and any problems are addressed.

Postpartum, the mother is counseled on contraception and appropriate method provided if required, mother is advised to abstain from sexual activity for at least 6 weeks after birth, mother is asked if both her and baby are sleeping under ITN (encouraged if not), new born hygiene and baby care, she is also advised on when to seek care as follows: scheduled infant immunizations 6 and 10 weeks, 3, 6, 9 and 12 months postpartum and at other times should the baby fall sick.

Routine care in ANC/PNC clinics varies within hospitals/health centers depending on available resources and also among healthcare providers; hence the standard of care described above is not what is provided. The basic minimum that is usually provided is obstetric care, delivery plans and health education which is not standardized and there may be stock-outs of essential laboratory commodities and pharmacy hours are restricted. In practice even at the national referral hospital it is not uncommon for pregnant women not to receive Hemoglobin, syphilis or urine screening tests (as confirmed by triangulated data from women's self-reports in AIS 2011. [6]

The routine care group (control Arm 1) will have their visits conducted in the ANC/PNC clinic following the usual care as provided in these clinics, as summarized above.
The intervention groups will also have the routine care as provided within Mulago hospital or the designated health facility and in addition will have the enhanced interventions which will focus on providing support and education including reproductive health information to the pregnant and postnatal adolescents on their risk of HIV/STI acquisition, and condom use utilizing adolescent friendly IEC materials and interactive exchanges either in a group or one-

to-one. They will also receive counseling on the importance of family planning and those interested will be referred to the family planning clinic for provision of their choice of the effective available family planning methods. In addition, the interventions will also provide education on the importance of delivery in a hospital, post-natal care, infant feeding and importance of immunization for the baby. Both enhanced intervention groups will receive pre appointment reminders of follow up appointments through sms or phone calls if they agree. The adolescent group education counseling sessions will be done by trained, experienced peer educators during around 6 sessions conducted in the MU-JHU clinic. The one-to-one peer support and education counseling sessions will occur in the ANC for pregnant adolescents (in different clinic space from the routine care group) and postpartum the sessions will be held in the adolescent clinic (ward 15) in Mulago Hospital. The enhanced intervention sessions will occur in different places from each other and from the control group so as to minimize cross-contamination between the groups.
For all the intervention groups, the peer educators will be young mothers who will receive formal training on adolescent education and support with a focus on HIV/STIs and adolescent RH. The intervention messages for the one on one education and support will be similar as that provided to the group but they will be tailored to the adolescent's particular situation.

3.4.6.1 Counseling guide:

We will adapt the *Comprehensive Family Planning and Reproductive Health Training Curriculum* for adolescents.[32] Per the copyright instructions, any part of the curriculum may be reproduced or adapted to meet local needs without prior permission from Pathfinder International provided Pathfinder International is acknowledged, and the material is made available free of charge or at a cost. We plan to avail any materials that we develop from this study free of charge to the MOH and other stakeholders while acknowledging use of materials from Pathfinder International.

Two facilitators will pretest this curriculum with pregnant adolescent girls and they will take detailed notes of issues encountered during the pre-test and refine the guide accordingly and conduct further pretesting if needed. The guide will be adopted primarily for use to train peer educators with the support of trained counselors/facilitators.

3.4.6.2 Training of study staff

MCH staff from Mulago (and, if needed, other targeted health facilities) and community support groups will be sensitized to the study objectives, and technical staff including peer educators, counselors, research assistants and study coordinators will be trained in good clinical practices (GCP) and human subject protection (HSP) and use of the study protocol, standard operating procedures (SOPs) and case record forms (CRFs). In addition to the training above, experienced peer educators will also be trained in depth in the use of the *Comprehensive Family Planning and Reproductive Health Training Curriculum* guide. All trained staff will be mentored on a regular basis by on-site investigators, counseling supervisors and the Study Coordinator.

3.5 Study Procedures

Information is provided below and in Appendix I on when each study procedure is to be performed.

Pre-screening:

Study staff may pre-screen potential study participants from the ANC clinic. During these interactions they may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed during screening. These include age of the potentially

eligible participant and her estimated gestational age and lack of diagnosed pregnancy complications. Potentially eligible participants will then be referred to the counselors who will conduct the screening and enrolment procedures, on the same day as the prescreening or a different day depending on how many participants are available on a particular day.

Screening/Enrollment Visit

During the screening and enrolment visit, the participant will provide written consent prior to conducting any screening procedures. Screening for the study involves administering the study eligibility criteria and for participants who do not meet eligibility criteria, screening will be discontinued once ineligibility is determined. Consenting eligible participants will be enrolled and randomized into one of the three arms. The procedures done at the screening and enrolment visit are outlined in the table below.

Table2: Screening/Enrolment Visit

Component		**Procedure/Analysis**
Administrative: Screening		• Eligibility Determination • Obtain written Informed Consent for Screening and Enrolment.
Administrative: Enrollment		• Assign Participant ID • Randomization • Update Locator Information • Collect Demographics • Schedule Next Visit • Reimbursement
Behavioral		• Baseline Behavioral Questionnaire and ACASI • HIV pre and posttest counseling • Demonstration and Provision of Condoms
Clinical		• Collect baseline RH and Medical History • Record any Clinical Events • Perform Clinical Examination (abdominal palpation) • Provide available test results • Provide treatment/referral as appropriate
Laboratory	Blood	Collect Blood 2mls for HIV-1 Serology (rapid tests) 2mls for Syphilis serology RPR (TPAB if positive)
	Urine	Collect Urine (20mls) Rapid test for Gonorrhea infection Rapid test for Chlamydia infection
	Pelvic	• Collect vaginal swab for rapid Trichomonas vaginalis testing • Collect swab for Bacterial vaginosis testing (PH, Whiff and Clue cells

Enhanced Peer Support Education and Counseling (Intervention)	Depending on the group the participant is randomized to, the intervention will be done around 4 weeks after enrolment as this is logistically appropriate for the study. Participants in Arm 2 will be put in homogenous groups (similar gestation, age group and language preference) of 8 – 12 adolescents, while the Arm 3 participants will schedule their individual follow-up visits on the same day as their clinic visits. Participants in the Control Arm will receive routine antenatal, delivery and follow-up services with next study visit at 3 months postpartum
Qualitative component	Participants preselected for the serial IDIs and FGDs will have the baseline interviews and FGDs within 3 weeks of enrolment **prior to receiving the intervention**

The participant will be provided with an appointment card (usual cards used in the ANC/PNC clinics) however a round colored sticker (different colors for each study arm) will be placed on the card to differentiate the 3 study groups.

STI treatment will be provided for any curable STI diagnosed at screening and in follow-up for the participant and her partner/s in accordance with national treatment algorithms.[33-34] Participants found to be HIV positive (by two separate rapid tests) will not be excluded from this proposed study but will be counseled, encouraged to disclose to their partner/s and will receive PMTCT services including Option B+ with ARV treatment for life as per national guidelines. As part of PMTCT services they will be encouraged to invite their partner/s for HIV C&T and their HIV-exposed infants will be followed up with linkages to ongoing services. Participants with positive syphilis tests will be treated and have repeat testing done per local national guidelines and also at the final visit.

3.5.1 Follow-up and Study Exit Visits

3.5.1.1 Every month after enrolment during pregnancy through delivery and at 6, 10 and 14 weeks and 6 and 9 months postpartum

During follow-up the study procedures and STI screening tests will be done as summarized in the table below.

Table 3: Week **36 Antepartum, Delivery, Week 6 and 10, Month 3, 6 and 9 Postpartum**

Component	Procedure/Analysis
Administrative and Regulatory (all visits including delivery contact for intervention groups)	• Review/update locator information • Provide reimbursement for study visit* • Schedule next visit
Behavioral (at 3, 6 and 9 months)	• Conduct behavioral assessment • HIV pre- and post-test counseling†
Clinical (at 36 weeks Antepartum, and as indicated)	• Review and update RH and Medical History • Perform Clinical Examination¥ • Prescribe/provide preferred contraceptive method • Provide available test results • Provide treatment/referral as appropriate

Laboratory	Blood	□ Collect Blood □ 2mls for HIV-1 Serology (rapid tests)† □ 2mls for Syphilis serology RPR (TPAB if positive)
	Urine	□ Collect Urine (20mls) □ Rapid test for Gonorrhea infection □ Rapid test for Chlamydia infection □ Urine for Protein and glucose¥
	Pelvic	• Collect vaginal swab for rapid Trichomonas vaginalis testing • Collect swab for Bacterial vaginosis testing (PH, Whiff and Clue cells0 • Collect vaginal swab for testing presence of Y chromosome ‡
Enhanced Peer Support Education and Counseling (Intervention) (at 6, 10 and 14 weeks ,6 and 9 months		Depending on the group the participant is randomized to, the intervention will be done ±2 weeks at all scheduled study visits. This is to allow flexibility in scheduling the sessions for the intervention groups Participants in the Control Arm will have the routine care provided to postpartum in the postnatal clinic
Qualitative component		Participants preselected for the serial IDIs and FGDs will have the final interviews and FGDs within 2 weeks of the scheduled final education and support session at study exit. In addition, single IDIs will be conducted for participants who
		seroconvert, have ≥2 STIs or have recurrent pregnancy at any time during follow-up.

.*Only at 3 months and study exit (month 9 or 6 for the last participants to enroll), † Pre/posttest counseling and HIV testing done only at 3 months and study exit, α STI lab tests done at study exit and when clinically indicated, ¥done at 36 weeks of gestation for all study groups, ‡ done only at study exit for participants with self-reported consistent condom use

3.5.2 Behavioral Evaluations

Behavioral evaluations assessed by ACASI and interviewer administered questionnaires include;

- Frequency of unprotected sex (self-report of penetrative sexual intercourse since previous visit)/report of condom use
- Risk behaviors – including any new sexual partners/ encounters, concurrent sexual partners (stable or casual), alcohol/drug use, domestic violence e.t.c.
- HIV/STI risk perception and motivation to utilize RH and pregnancy related services
- Reproductive intentions and family planning
- Male partner/s involvement – presence, cohabitation, economic, psychosocial support, health care support, gender based violence etc

3.5.3 Psychological Assessments

The following psychological assessments will be conducted at enrolment (baseline), 3 months & at study exit;

- Psychosocial risk assessment using the HEADDS assessment instrument
- Self-esteem assessment using the Rosenburg self-esteem scale[35]
- Psychological wellbeing using Ryff's scale[36] of psychological wellbeing

3.5.4 Clinical Evaluations and procedures

This involves history taking, physical and/or pelvic exams and other evaluations as indicated.

History Taking

- Demographic information is obtained
- Risk assessment during pregnancy to rule out any maternal problems (medical and obstetric history and update this history as appropriate)
- Postpartum, obtain history on any maternal problems (medical, gynecological (including symptoms of STIs) and contraceptive use history and update as appropriate

Physical Exam:

- General physical exam – signs of anemia, BP, weight, breast
- Obstetric exam during pregnancy
- Additional clinical assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam

Other procedures which shall be done as indicated: prescribe contraceptives, provide available test results and provide treatment/referral as appropriate

3.5.5 Laboratory Evaluations

- Urine (25mls)
  - Urine dipstick for protein and glucose
  - HCG for pregnancy (5mls)
  - Rapid test for Gonorrhea infection (10mls)
  - Rapid test for Chlamydia infection (10mls) Blood (4mls)
  - 2mls for HIV serology (using national algorithm) [37]
  - Hemoglobin Concentration (Hb) by Hemocue ®
  - 2mls for RPR for syphilis (TPAB if positive)

Throughout the study duration, the total amount of blood collected from each participant will be about 10mls. Pelvic

- Rapid test for Trichomonas

- Bacterial Vaginosis Testing – PH, Clue Cells, whiff test and homogenous abnormal vaginal discharge.
  Bacterial vaginosis will be diagnosed using the following Amsel criteria. The presence of three of the following four criteria provides sufficient evidence for a clinical diagnosis of BV.
  a) Vaginal pH >4.5 ((normal range 3.8 to 4.5)
  b) The presence of clue cells (bacterial clumping upon the borders of epithelial cells) on wet mount examination. Clue cells should constitute at least 20% of all epithelial cells (an occasional clue cell does not fulfill this criteria).
  c) Positive amine, "whiff" or "fishy odor" test (liberation of biologic amines with or without the addition of 10% Potassium Hydroxide (KOH)).
  d) Homogeneous, nonviscous, milky-white discharge adherent to the vaginal walls

- Vaginal fluid for testing presence of Y chromosomes sequences. This is to validate women sexual behavior reporting whether there was unprotected sex in last 14 days.

3.5.6 Retention

Once a participant is enrolled and randomized into the study, the study staff must make every effort to retain her in follow-up to minimize possible bias associated with loss-to-followup. Standard operating procedures (SOPs) for participant retention to target loss-to-follow-up rates less than 10% shall be developed. As such, the average retention rate of 95% will be targeted for this study. All study staff are responsible for implementing local SOPs to achieve this. Components of such procedures may include the following:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit. Also as part of the informed consent process, encouragement of participants to discuss potential study participation with their husbands/partners and other influential family members or persons.
- Thorough explanation of the importance of all study groups to the overall success of the study.
- Collection of detailed locator information at the study screening and enrolment visits, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Ensuring ongoing contact with the study participant including soon after delivery and reminders about scheduled study visits

3.6 Study Endpoints

3.6.1 Quantitative data outcomes

Primary outcomes

1. Incidence of one or more STIs during study follow-up, with STIs confirmed by laboratory tests of HIV-1, Neisseria Gonorrhea, Treponema pallidum (Syphilis), Chlamydia trachomatis, Bacterial Vaginosis or Trichomonas vaginalis (Composite outcome)
   - New HIV-1 diagnosis by 2 separate HIV tests with negative HIV-1 test at enrollment AND/OR
   - New Neisseria Gonorrhea, Treponema pallidum (Syphilis), Chlamydia trachomatis, Bacterial Vaginosis or Trichomonas vaginalis test having been negative at enrollment OR with completed treatment if positive at baseline
2. Reported (and validated) consistent condom use and uptake of effective contraceptive method (Composite outcome)
   - Absence of repeat pregnancy (diagnosed by rapid urine pregnancy testing for HCG)
   - Uptake of effective contraceptive method with insertion/prescription by clinic staff from 3 months postpartum to 9 months or study completion (which ever comes 1st)
   - Self-reported consistent use of condoms during penetrative anal or vaginal sex including a) since enrollment b) since last visit c) at last penetrative sex act
   - Absence of Y-chromosome in analysis of vaginal swabs

Secondary outcomes

3. Acceptability/desirability of assigned clinic service model

Acceptability of clinic service model (composite)

- Frequency of visits
- Relevance of information to own life
- Sense of psychosocial support

3.6.2 Qualitative data outcomes

Data collected from focus group discussions and key informant interviews will be triangulated with quantitative data to address:

(1) Adolescents' knowledge, Attitudes and Practices towards RH and pregnancy related services
(2) Health care providers' attitude towards adolescent RH services, perception of adolescents' attitudes towards pregnancy, RH services and challenges for adolescents follow up in the current ANC and post-delivery care
(3) Effect of adolescents' HIV/STI risk perception and motivation to utilize services including condom use

3.7 Statistical considerations and analysis plan

3.7.1 Sample size determination

Sample size determination

Sample size for this study was based on the outcomes, uptake of effective contraceptive, or prevalence of STIs, at last follow-up comparing each of the two interventions to the control in this three-arm trial. We assumed the uptake of effective contraceptives and consistent condom use as a composite outcome to be 10% [38] (in control/standard), 30% and 35% at the last follow-up in the two intervention arms. At 80% power, and 5% type 1 error rate, and a 10% loss to follow-up, the sample size in the intervention arms was 100 (each 50), while the control/standard was adjusted to 71; this follows a recommendation by Fleiss et al for multiple-arm trials that control arms have a bigger sample size than the intervention.

For the prevalence of STIs, we assumed 20%[10] in control/standard arm, 10% in the intervention-1, and 8% in intervention-2 at the last follow-up, suggesting an average of 55% reduction in prevalence of STI. With similar power of 80%, 5% type-1 error rate and 10% loss to follow-up, a total of 215 respondents in control/standard arm, and 152 per each of the intervention arms resulting in a total of 519. Since 519 respondents are sufficient to address the objectives of the uptake of effective contraceptives + consistent condom use, we determined that the final sample size for this study will be 519 (215 control/standard arm; 152 per each of the two intervention arms).

3.7.2 Statistical analysis

Exploratory data analysis will be conducted on all variables including the binary outcomes. Descriptive statistics will be generated providing proportions (percentages) for categorical data, and mean (SD)-for normally distributed data, and median (IQR) nonnormal continuous variables. A consort diagram will also be generated to show the time of enrollment, and follow-up. Bar charts showing the distribution of categorical data will also be generated. Data will be assessed for missingness especially as a result of non-follow-up in this prospective study design. In order to address this concern, a comparison of non-follow-up and those followed up will be done, and propensity scores will be constructed to use as weights in the regression models. For categorical/dichotomous outcomes, we will use Fishers Exact Test or chi-square as appropriate, and will report the respective 95% confidence intervals around point estimates, which offer important interpretation for the trial findings.

Primary outcome-1: Composite measure of consistent condom-use and use of an effective FP method. A comparison of this binary outcome will be conducted at the last follow-up. A log-

binomial regression model will be used to obtain the prevalence rate ratios (PRR) as the measure of effect or association, because the outcomes are greater than 10%. The primary exposure variable is study arm. The two intervention arms will be compared to the control arm in the same model. Potential confounders will be adjusted for, after assessing for interaction of some variables with the study-arm in the association with the primary composite outcome. Respondents from the same facility may be correlated, and so adjustment for potential clustering of observations within the selected facilities will be done.

Primary outcome-2: Incidence of any STI. Kaplan-Meier survival analysis will be conducted to determine differences in the probability of STI infection between study arms. Differences in the KM will be determined by log-rank test. Further analysis will be conducted using Poisson regression models to obtain incidence rate ratios (IRR) comparing the two intervention arms to the control arm in the same model. Potential confounders will be adjusted for, after assessing for interaction of some variables with the study-arms in the association with the incidence of STI. Adjustment for potential clustering of observations within the selected facilities will be done.

Potential confounders to be adjusted for in these analyses will include participant characteristics such as age, education level. The primary analyses are the intention to treat; for descriptive analysis, baseline data will be summarized separately by study arm. All the analysis will use STATA version 12

3.7.3 Qualitative data analysis

Data Sources

The qualitative data from this study will include the following data sources:

a) Handwritten notes and summaries of IDIs and KIIs
b) IDI and KII debriefing reports
c) Transcripts from audio-recorded KIIs, IDIs and FGDs.
d) Summaries from the psychological assessments

Analysis Overview

The primary source of qualitative data used in the analysis will consist of raw textual data. Qualitative data will be audio-recorded, transcribed, translated into English and coded for qualitative analyses, using NVivo or a similar qualitative software. Data coding will be used as a primary analytical approach, for data reduction, that is, to summarize, extract meaning, and condense the data. The transcripts will be coded first through descriptive coding for key themes and topics, using a preliminary codebook. Additional codes will be identified through an iterative process of reading the textual data to identify emergent themes, and the codebook will be modified accordingly. In addition to descriptive codes, pattern codes, which achieve a greater level of abstraction, will be used to start linking themes and topics together. The analysis will be done by the investigative team, working interactively through regular face-to-face meetings, emails, and regular phone calls. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data.

The primary final output of the qualitative analysis will include a synthesized report with representational quotes that will describe the health care provider and adolescent mothers' Knowledge Attitude and Practice (KAP) regarding adolescent reproductive health and pregnancy related services with pregnant and postnatal adolescent mothers and postdelivery care.

3.8 Data quality and management

SOPs will be developed for all data management process and procedures to ensure consistency and quality of data.

Quantitative data will be collected and entered by research staff on CRFs and Android electronic tablets (hand-held computers) using a computer-assisted personal interviewing (CAPI) software for the ACASI.
Qualitative data will be collected manually and on a voice recorder and will be transcribed into laptop computers by research assistants for subsequent coding in NVivo software and analysis. All discussions will be conducted in the local languages, will last no more than 90 minutes, and will be digitally recorded and transcribed into English. Interviewers/research assistants will have experience in qualitative methods including in-depth interviewing and probing where appropriate and relevant. Digital recordings will be transferred to secure computers and deleted from source computers.

All data clerks and managers will have received training on the requirements of strict confidentiality regarding patient identifying information, and laptop security. To protect detailed health and personal information data, study record keeping and access to participant identifying information will follow strict written SOPs and data will be subjected to a variety of quality control procedures. All records will be kept on password protected computers at MU-JHU. Participants will be identified primarily by their study number. All CRFs and identifiers will be kept in individual files in secured, access-limited room at the site. No individual participant identifier will be used in any reports or publications resulting from the study. Study investigators and coordinators will continuously mentor and monitor staff to ensure these procedures are followed according to SOPs in order to ensure data quality and confidentiality.

4 ANTICIPATED CHALLENGES AND MITIGATION PLANS

4.1 Maintaining Long –Term cohesion among peers

This will depend on the individual stability of the members, the group leader capability, and the quality of their relationships. This will require close monitoring and support by the group leaders and peer educators. We will ensure that there is continuous training, counseling and ongoing support sessions to address issues as they arise and support long-term cohesion including an understanding and commitment of protecting each other's privacy and not sharing confidential disclosures outside the group.

4.2 Stigma and discrimination:

HIV-related stigma and discrimination continue to be important issues in Uganda. MUJHU may be perceived as being associated with HIV research; so participants attending MUJHU may be suspected by others of being HIV-infected (despite many HIV-uninfected persons attending MUJHU). MUJHU will consult with youth and attempt to mitigate against this risk by rebranding and marking the lower building ground floor which has a separate entrance and exit as a

Youth-Friendly Service. Clinic services for teens will be on the ground floor and separated from other clinic and study populations.

4.3 Vulnerability of pregnant and postpartum women to relocate:

The time immediately after delivery may be associated with geographic displacement as many new mothers move for several weeks or months to their village of origin after delivery both because of the care needed by the new infant (and mother) and Uganda cultural norms among several tribes. We will attempt to minimize this through exploring this theme in our FGDs as well as our screening and enrollment procedures inquiring about intentions to remain within 30Kms of the clinic and encouraging women to advise of any temporary or permanent change in residence and maintain contact with the study team. We will also maintain regular contact with participants through their scheduled visits and by phone calls/sms using agreed general language with no mention of HIV or MUJHU).

4.4 Male partner and family involvement:

Male partner involvement continues to be a challenge in many parts of the country due to cultural, historical and structural factors. Among pregnant and postpartum adolescents there is a higher proportion without the ongoing support of male partners and a higher proportion dependent on their parents compared to adult women. In this intervention we will continuously encourage the participant to bring their partner/s to the education sessions on case by case basis and we will also encourage partner C&T.

4.5 Depression and psychological distress:

Pregnant adolescents and young mothers may be at a greater risk for anxiety and depression (including postpartum depression) and have a relatively low rate of health seeking behavior for their own health and that of their infants. While it is unlikely that the study itself would be causal (and would be more likely to assist young persons) the study evaluations are likely to identify any significant psychological distress or psychiatric disorder which would allow for early and appropriate referrals to an appropriate health provider (such as the Mulago Specialist Adolescent Clinic).

5 HUMAN SUBJECTS PROTECTIONS

5.1 Institutional Review Boards/Ethics Committees

This protocol and the associated consent documents and study-related documents (such as participation education and recruitment materials) will be reviewed by the primary IRB in Uganda and other regulatory bodies responsible for oversight of NIH sponsored research conducted in Uganda as well as regulatory bodies required by the sponsor. Any amendments to the protocol will be approved by the IRBs prior to implementation. Subsequent to the initial review and approval, the responsible IRBs will review the study at least annually in accordance with national requirements. Investigators will make safety and progress reports to the IRBs at least annually and within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

5.2 Risk Benefit Statement

5.2.1 Risks

This study involves the vulnerable population of pregnant adolescents. Pregnant adolescents under the age of 18 are by definition considered emancipated minors.

The provision of routine clinical antenatal, delivery and postnatal services are not part of this study. Additional study related procedures do include provision of specific clinical services such as HIV and STI tests (requiring blood draws, vaginal swabs and urine specimens) as well as clinical examination and counseling and provision of contraception.
The main risks would be potential loss of privacy. The investigators will make all possible efforts to minimize risks to these adolescent study participants and to ensure confidentiality of the study participants and their study data. All staff will be trained on Human Subjects Protection and Good Clinical Practice. Before beginning the study, the investigators will have obtained approval from all relevant IRBs and from the Uganda National Council for Science and Technology (UNCST). The investigators will permit monitoring by relevant regulatory authorities, the NIH, applicable US/local government bodies, IRBs and UNCST, or their appointed agents. Subsequent to the initial review and approval, the responsible IRBs will review the study at least annually. Investigators will make safety and progress reports to the IRBs at least annually and within three months after study termination or completion. Adverse events will be reported according to local regulatory and NIH guidelines.

Since participation in the proposed clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of certain questions asked as part of the study, every effort will be made to protect participant privacy and confidentiality. All participant information will be stored in locked file cabinets in secure areas with access limited to authorized study staff. Individual participants' study information will not be released without their written permission, except as necessary for regulatory monitoring, and/or auditing.

5.2.2 Benefits

Participants may benefit directly from the individual or group educational and supportive counseling provided, treatment for HIV and other STIs for themselves and/or their husband/partner/s and from counseling and provision and uptake of dual protection methods with effective contraception and barrier protection. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help improve interventions which provide psychosocial support and education and prevent STIs/HIV and unwanted pregnancies among adolescent girls.

5.3 Informed Consent Process

Written informed consent will be obtained from all potential study participants including those emancipated minors aged 15 to 17 years following the National Guidelines for Research involving Humans as Research Participants issued by UNCST [31]. Parents or guardians need not be involved in the informed consent process since these adolescents are emancipated minors. However should the adolescents less than 18 years of age wish to include one or both parents (or their spouse/partner) in the informed consent process they will be free to do so.

Study staff will administer a comprehension checklist to potential participants prior to obtaining written informed consent to ensure that participants fully comprehend the nature of the study. In obtaining and documenting informed consent, the investigators and their designees will comply with applicable local and domestic regulatory requirements and will adhere to Good

Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. Participants are always offered a copy of their informed consent form. The consent forms will clearly indicate the purpose of the study, the procedures to be followed, and the potential risks and benefits of participation, in accordance with all applicable regulations.
.

5.4 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality of client information. The study staff will implement confidentiality protections and the input of study staff and community representatives to identify potential privacy and confidentiality issues and strategies to address them. All studyrelated information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing IRB, regulatory bodies or sponsor.

5.5 Special Populations

This section outlines considerations made for the inclusion or exclusion of special populations in this study.

As pregnant adolescents have a high burden of disease and social exclusion/stigma and this study is purposely designed to assess acceptability and effectiveness of strategies to address these issues it is critical that pregnant adolescents is included as the study population. The risks associated with participating in the study are minimized and mitigated by the study design. As such they meet the ethical criteria of being both at risk and standing to benefit from the proposed interventions.

We have determined however that pregnant adolescents with significant comorbidity or fetal loss should be excluded from the study as they would be likely not to be able to comply with the study requirements (of visit attendance) and/or would require additional specialized counseling and other support over that available within the study.

5.5.1 Pregnant Women

Pregnant women will be offered enrollment in this study in accordance with guidelines set forth in the Ugandan ethics guidelines [31] and current US guidelines.[39] Given that the primary purpose of the research is to meet the health needs of the mother informed consent will not be sought from the father of the baby. However should the pregnant women wish to include her spouse in the informed consent process they will be free to do so.

5.5.2 Children

This study plans to include emancipated minors as study participants; that is pregnant children who are aged 15 to 17 years at the time of enrollment.[31] Informed consent procedures follow Uganda ethical requirements for emancipated minors.

5.6 Compensation

Compensation for participants' time and travel will be provided to participants at a rate of 10, 000 Uganda shillings per scheduled study visit.

Of note if FGD and IDIs are scheduled on a separate day to other study visits these would be considered as a scheduled study visit. If scheduled on the same day as a scheduled study visit an additional 5,000 Uganda shillings would be paid to compensate participants for the additional time involved.

If a study participant moved more than 30kms away (despite indicating they would stay within 30kms in the enrollment interview) or experienced transport costs greater than 10,000 Ugandan shillings, the study team would reserve the right to consider this on a case by case basis with the possibility of reimbursing actual transport costs.

5.7 Access to HIV-related Care (HIV Counseling and Testing and HIV care)

HIV testing for participants will be offered together with pre-test and post-test counseling by trained study counselors. Referral for additional counseling will occur if identified as a need by the counselor or the participant. Participants diagnosed as HIV-positive will receive appropriate referrals to nearby adolescent HIV care and treatment services at the Baylor Adolescent Clinic (Centre of Excellence) for ongoing management. Sexual partner/s of teen participants with positive HIV or other STI tests will be invited to attend the clinic and receive counseling, testing, treatment (if applicable) for other STIs and referred for appropriate services. HIV exposed infants will also be followed up appropriately in the PMTCT program the mother is referred to.

5.8 Study Discontinuation

This study may be discontinued at any time by NIAID, the OHRP, other governmental or regulatory authorities, or site IRBs/ECs

6 PUBLICATIONS AND DISSEMINATION OF STUDY FINDINGS

6.1 Dissemination of findings:

Research findings will be shared with all the stakeholders including study participants, CAB members, participating health facilities' staff, Ministry of Health, the Ugandan Society for Adolescent Health, PEPFAR and donor representatives and other policymakers. The implementation science findings will also be submitted for presentation at regional and international meetings and for publication/s in the peer-reviewed scientific literature.

6.2 Sustainability:

Both the Ministry of Health Reproductive Health staff and the Makerere University Department of Obstetrics/Gynecology are highly supportive of this project as noted in their letters of support. If either or both of the enhanced adolescent group or individualized peer support interventions show acceptability, feasibility coupled with significantly improved uptake of effective contraceptives and barrier protection and reduced incidence of HIV/STIs when compared to the routine care control group, the investigators will work with MOH, PEPFAR and other donors to mobilize resources and implement these adolescent reproductive services in other parts of Kampala and other health districts across Uganda.

7 TIMELINE

This administrative supplement proposal will be conducted over a 12 month period from the point of IRB approval. The proposed activities and timeframes are summarized in the GANNT chart below.

Schedule for implementation of study activities

	Year 1											
Activities	1	2	3	4	5	6	7	8	9	10	11	12
Hiring staff												
FGDs of formative research												
Training of staff												
Pretesting of Intervention curriculum												
Site Activation												
Enroll participants												
Follow up of participants												
Study Annual Renewal IRBs												
Data Analysis and Manuscript writing												
Dissemination of findings												

REFERENCES

1. Atuyambe, L., et al., *Experiences of pregnant adolescents-voices from Wakiso district, Uganda.* African health sciences, 2007. **5**(4): p. 304-309.
2. Atuyambe, L., et al., *Seeking safety and empathy: adolescent health seeking behavior during pregnancy and early motherhood in central Uganda.* Journal of adolescence, 2009. **32**(4): p. 781-796.
3 http://www.unicef.org/uganda/UNICEF_UGANDA_FAST_FACTS_July_2012.pdf.
4. Nalwadda, G., et al., *Persistent high fertility in Uganda: young people recount obstacles and enabling factors to use of contraceptives.* BMC Public Health, 2010. **10**(1): p. 530.
5. Uganda Bureau of Statistics (UBOS) and ICF International Inc. 2012. Uganda Demographic and Health Survey 2011 K, U.U.a.C., Maryland: ICF International Inc.
6. *Uganda AIDS Indicator Survey*. *Report*. 2011 [cited 2014 08 December]; Available from: http://health.go.ug/docs/UAIS_2011_Report.pdf.
7. Neema, S., et al., *Adolescent sexual and reproductive health in Uganda: results from the 2004 National Survey of Adolescents.* Occasional Report, 2006. **25**.

8. Muhumuza, R. *Associated Press World AIDS Day: As HIV rises, activist targets youths*. 2014; Available from: http://www.freep.com/story/news/world/2014/12/01/world-aids-day-hiv-rises-activistreaches-youths/19730505/.
10. Råssjö, E.-B., et al., *Prevalence of sexually transmitted infections among adolescents in Kampala, Uganda, and theoretical models for improving syndromic management.* Journal of adolescent health, 2006. **38**(3): p. 213-221.
11. ; Available from: http://en.wikipedia.org/wiki/Peer support?oldid=632669948.
12. Mead, S., D. Hilton, and L. Curtis, *Peer support: a theoretical perspective.* Psychiatric rehabilitation journal, 2001. **25**(2): p. 134.
13. Salzer, M.S., *Consumer-Delivered Services as a Best Practice in Mental Health Care Delivery and The Development of Practice Guidelines: Mental Health Association of Southeastern Pennsylvania Best Practices Team Philadelphia.* Psychiatric Rehabilitation Skills, 2002. **6**(3): p. 355-382.
14. Mead, S. and C. MacNeil, *Peer support: What makes it unique.* International Journal of Psychosocial Rehabilitation, 2006. **10**(2): p. 29-37.
15. Sarason, I.G., et al., *Assessing social support: the social support questionnaire.* Journal of personality and social psychology, 1983. **44**(1): p. 127.
16. Flannery Jr, R.B., *Social support and psychological trauma: A methodological review.* Journal of traumatic stress, 1990. **3**(4): p. 593-611.
17. Young, K.W., *Social support and life satisfaction.* International Journal of Psychosocial Rehabilitation, 2006. **10**(2): p. 155-164.
18. Thoits, P.A., *Social support as coping assistance.* Journal of consulting and clinical psychology, 1986. **54**(4): p. 416.
19. Solomon, P., *Peer support/peer provided services underlying processes, benefits, and critical ingredients.* Psychiatric rehabilitation journal, 2004. **27**(4): p. 392.
20. Schubert, M.A. and T. Borkman, *13. Identifying the Experiential Knowledge Developed Within a Self-Help Group.* Understanding the self-help organization: Frameworks and findings, 1994: p. 227.
21. Coyne, J.C. and A. DeLongis, *Going beyond social support: the role of social relationships in adaptation.* Journal of consulting and clinical psychology, 1986. **54**(4): p. 454.
22. Salzer, M.S. and S.L. Shear, *Identifying consumer-provider benefits in evaluations of consumer-delivered services.* Psychiatric rehabilitation journal, 2002. **25**(3): p. 281.
23. Festinger, L., *A theory of social comparison processes.* Human relations, 1954. **7**(2): p. 117-140.
24. Riessman, F., *The" helper" therapy principle.* Social Work, 1965.
25. Skovholt, T.M., *The client as helper: A means to promote psychological growth.* The counseling psychologist, 1974.
26. UNAIDS, *Peer education and HIV/AIDS concepts, uses and challenges*. 1999, UNAIDS: Geneva.
27. Shoemaker, K., *Educating with peers - others do- should you?* 1998, George town University.
28. UNAIDS, *PEER EDUCATION AND HIV/AIDS: Concepts, uses and challenges. Geneva, Switzerland.* 1999.
29. Musingye, E., et al., *Integration of peers in the PMTCT and postnatal clinics (PNC), increased subsequent family planning refill visits by HIV-infected women in an urban hospital in Kampala.*, in *Conference on HIV Pathogenesis and treatment*. 2012.
30. Lynn Atuyambe, P., et al., *Coping Responses During Pregnancy and Early Motherhood Among Adolescents in Central Uganda.* 2008. **13**: p. 18.

31. Uganda National Council for Science and Technology (UNCST). 2014. National Guidelines for Research involving Humans as Research Participants. Kampala, U.
32. PATHFINDER. *Module-16-Reproductive-Health-Services-For-Adolescents-Training Guide*. 2004; Available from: http://www.pathfinder.org/publicationstools/pdfs/Module-16-Reproductive-Health-Services-for-Adolescents-TrainingGuide_pdf.pdf.
33. UMDPC. *Uganda-Clinical-Guidelines*. 2012; Available from: umdpc.com/wpcontent/.../2014/02/Uganda-Clinical-Guidelines-2012.pdf.
34. WHO, *Guidelines for the Management of Sexually Transmitted Infections.* 2003.
35. Rosenberg, M., *Society and adolescent self image.* Princeton ,NJ. Princeton University Press, 1965.
36. Ryff, C. and C. Keyes, *The structure of psychological wellbeing revisited.* Journal of personality and Social psychology, 1995. **69**: p. 718-727.
37. MOH. *Uganda National Policy Guidelines for HIV Counselling and Testing*. 2005; Available from: http://www.who.int/hiv/pub/guidelines/uganda_art.pdf.
38. Wanyenze, Rhoda K., Nazarius M. Tumwesigye, Rosemary Kindyomunda, Jolly Beyeza-Kashesya, Lynn Atuyambe, Apolo Kansiime, Stella Neema, Francis Ssali, Zainab Akol, and Florence Mirembe. "Uptake of family planning methods and unplanned pregnancies among HIV-infected individuals: a cross-sectional survey among clients at HIV clinics in Uganda." *Journal of the International AIDS Society* 14, no. 1 (2011): 35.
39. NIH. *Regulations, Policies & Guidance; Ethical Guidelines & Regulations*. Available from: http://grants.nih.gov/grants/policy/hs/ethical_guidelines.htm.
40. Conner, M. and P. Norman, *The role of social cognition in health behaviours.* 1996.

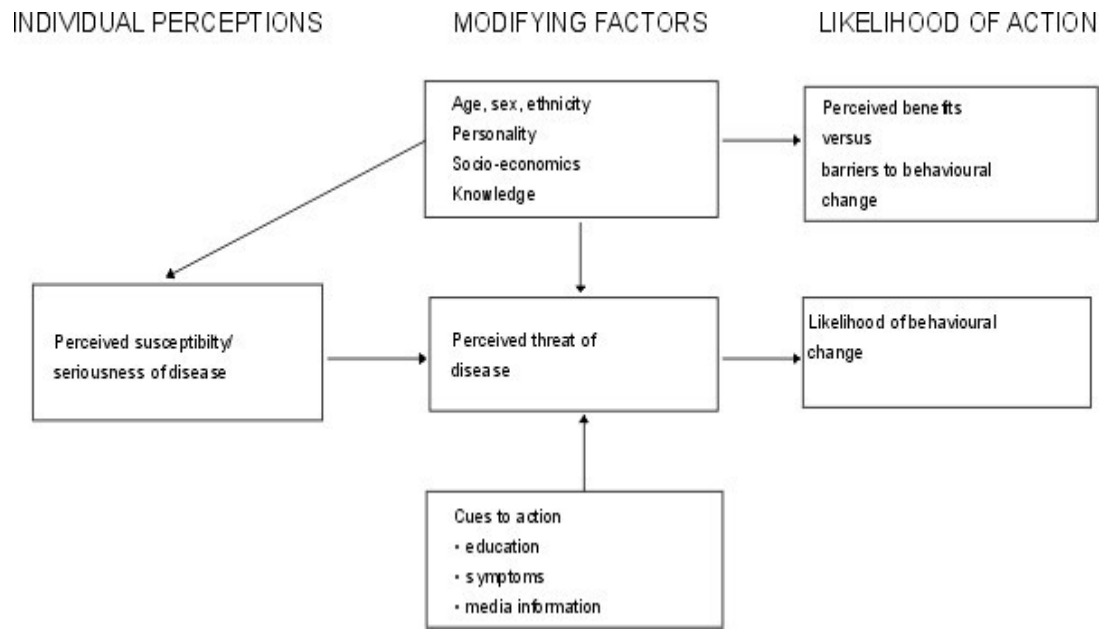
APPENDIX A: ADDITIONAL BACKGROUND ON THE CONCEPT AND USE OF THE HEALTH BELIEF MODEL

Table from “Theory at a Glance: A Guide for Health Promotion Practice" (1997)

Concept	Definition	Application
Perceived Susceptibility	One's opinion of chances of getting a condition	Define population(s) at risk, risk levels; personalize risk based on a person's features or behavior; heighten perceived susceptibility if too low.

Perceived Severity	One's opinion of how serious a condition and its consequences are	Specify consequences of the risk and the condition
Perceived Benefits	One's belief in the efficacy of the advised action to reduce risk or seriousness of impact	Define action to take; how, where, when; clarify the positive effects to be expected.
Perceived Barriers	One's opinion of the tangible and psychological costs of the advised action	Identify and reduce barriers through reassurance, incentives, assistance.
Cues to Action	Strategies to activate "readiness"	Provide how-to information, promote awareness, reminders.
Self-Efficacy	Confidence in one's ability to take action	Provide training, guidance in performing action.

Conceptual Model



Source: Glanz et al, 2002, p. 52

Scope and Application

The Health Belief Model has been applied to a broad range of health behaviors and subject populations. Three broad areas can be identified (Conner & Norman, 1996):[40]
1) Preventive health behaviors, which include health-promoting (e.g. diet, exercise) and health-risk (e.g. smoking) behaviors as well as vaccination and contraceptive practices. 2)

Sick role behaviors, which refer to compliance with recommended medical regimens, usually following professional diagnosis of illness.
3) Clinic use, which includes physician visits for a variety of reasons.

APPENDIX B: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR/ ENR	36 weeks APT	Birth †	6 weeks PPT	10 weeks PPT	3 months PPT	6 months PPT	9 months PPT
ADMINSTRATIVE AND REGULATORY								

Obtain Informed Consent		**X**							
Assign a unique Participant Identification (PTID) number		**X**							
Asses and/or confirm eligibility		**X**							
Collect/review /update locator information		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Randomization		**X**							
Provide reimbursement		**X**			**X**	**X**	**X**	**X**	**X**
Schedule next visit		**X**	**X**		**X**	**X**	**X**	**X**	**X**
INTERVENTION									
Enhanced Counseling Education Sessions/Routine care as provided		**X**			**X**	**X**	**X**	**X**	**X**
BEHAVIORAL									
Behavioral Assessments using IAQ and ACASI		**X**				**X**		**X**	**X**
Psychosocial Assessment		**X**							**X**
HIV pre and post test counseling		**X**					**X**		**X**
Provision of Condoms		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Conduct Social harms assessment						**X**		**X**	**X**
CLINICAL									
Obtain/review and update RH and Medical History		**X**	**X**	*	*	*	*	*	**X**
Clinical Examination – Blood Pressure, Weight, Obstetric exam		**X**	**X**						
Prescribe contraceptives					**X**	*	*	*	*
Provide available test results		**X**	**X**		*	*	**X**	*	**X**
Provide treatment/referral as appropriate		*	*		*	*	*	*	*
LABORATORY									
Blood	HIV-1 Serology (rapid tests)	**X**					**X**		**X**
	Syphilis serology	**X**						**€**	**X**
	RPR (TPAB if positive)								
Urine	Protein and Glucose	**X**	**X**						
	Rapid test for Gonorrhea infection	**X**	*		*	*	*	*	**X**
	Rapid test for Chlamydia infection	**X**	*		*	*	*	*	**X**
	HCG test				*	*	*	*	**X**
Pelvic	Rapid test for Trichomoniasis (self collected vaginal swab)	**X**	*		*	*	*	*	**X**
	Collect Vaginal swab for Bacterial Vaginosis testing	**x**	*		*	*	*	*	**X**

	Collect vaginal swab for testing presence of Y chromosome ‡								**X**
QUALITATIVE COMPONENT									
Serial In-depth Interview (SIDI)		**X**				**X**			**X**
Focus Group Discussion (FGD)		**X**							**X**
Single In-depth Interview (IDI)					*	*	*	*	*

X mandatory, *If indicated †only for intervention groups, **€** repeat at 6months if positive at enrolment, ‡done only at study exit for participants with self reported condom use.