FANMI: Community Cohort Care for HIV-infected Adolescent Girls in Haiti

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National Institute of Child and Health Development (NICHD), National Institutes of Health (NIH)

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to epidemiological studies (45 CFR 46);
- International Conference on Harmonisation (ICH) E6; 62 Federal Register 25691 (1997);
- National Institutes of Health (NIH) Clinical Terms of Award, as applicable;
- Weill Cornell Institutional Review Boards (IRB);
- Groupe Haitien d'Etude du Sarcome et des Infections Opportunties (GHESKIO) IRB;
- International and local requirements.

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki and The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979).

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

The study and consent forms will be approved by an institutional review board at Weill Cornell and at GHESKIO.

Protocol Summary

Title: FANMI: Community Cohort Care for HIV-infected Adolescent Girls in Haiti

Study Summary: We will conduct a randomized controlled trial titled: FANMI: Community Cohort Care for HIV-infected Adolescent Girls in Haiti. A total of 160 girls ages 16-23 will be enrolled and randomized to FANMI (intervention arm) or standard individual care (control arm). FANMI includes receiving integrated clinical care, group counseling, and social activities in a single session by the same provider to simplify care and strengthen relationships between peers and providers. FANMI groups consist of 5-10 adolescents meeting once per month. The primary outcome is retention in HIV care at 12 months after randomization.

Population: We will recruit 160 HIV-infected adolescent girls. Inclusion criteria include: female; age 16-23 years; ART naïve, initiated ART in the past 3 months, or on ART for less than 1 year and defaulted from care for at least 3 consecutive months; lives in Port au Prince; willing to receive care at GHESKIO; willing to provide consent (age 18 – 23 years) or assent with parental/guardian consent (16 and 17 years).

Number of Sites: Single site: GHESKIO Center Port au Prince, Haiti

Study Duration: 3 years

Subject Duration: 12 months

Objectives: *Primary:* The primary hypothesis is that FANMI will improve retention at 12 months compared with standard Individual Care. The study has > 80% power to detect a difference in retention from 60% to 85%.

Secondary: A secondary hypothesis is that a greater proportion of the FANMI arm will achieve a plasma HIV-1 RNA level < 1000 copies/µl at 12 months when compared with the Individual Care arm, and this difference will be explained by better retention, earlier initiation of ART, and improved ART adherence measured by tenofovir diphosphate (TFV-DP) levels in dry blood spots. Other study outcomes include sexual behavior over the 12-month study, implementation measures including qualitative interviews with staff and patients, and a cost-effectiveness analysis of FANMI versus Individual Care.

Hypothesis: The primary hypothesis is that FANMI will improve retention in HIV care at 12 months compared with standard care. A secondary hypothesis is

that a greater proportion of the FANMI arm will achieve a suppressed viral load at 12 months when compared with the standard arm.

Primary study endpoint and analysis:

The primary endpoint is alive and in care at 12 months and is a binary outcome. We will compare the proportion of participants who remain alive and are retained in HIV care at 12 months between study arms using the Fisher exact test.[116-120] This is an individual randomized trial, and we anticipate the two arms will have similar baseline characteristics. Therefore, the primary analysis will be done without adjusting for baseline variables. Since we have one primary outcome, we will test the primary hypothesis without multiple testing adjustments. Statistical tests will be two-tailed, with a significance level of 0.05. If some variables at baseline are notably imbalanced, we will conduct adjusted analyses as secondary or sensitivity analysis using multivariable-adjusted logistic regression and Cochran–Mantel–Haenszel statistics. The results will be summarized in terms of proportions as well as odds ratio, along with confidence interval and statistical significance.

Secondary endpoints and analysis:

The secondary endpoint is viral load suppression at 12 months and is a binary outcome. We will compare the proportion of participants who have viral load suppression at 12 months between study arms using the Fisher exact test. Secondary outcomes will be analyzed and reported together with clear designation of “secondary” so that readers will be aware of the number of pre-specified analyses. Additional secondary end points and analyses are discussed in detail in the full protocol below.

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Sexually-active HIV-infected adolescent girls are an extremely vulnerable and underserved population, and account for 32% of all new HIV infections in Haiti and a similarly large percentage in other resource-poor countries. If treated promptly and retained in care, HIV-infected adolescents have a near normal life expectancy. Further, ART will decrease sexual and vertical HIV transmission in a population who have multiple seronegative sex partners and high rates of pregnancy. Long-acting parenteral antiretroviral drugs (e.g. cabotegravir) are currently being investigated in clinical trials as a once monthly intramuscular injection. This could be an ideal ART regimen for adolescent girls, if they can be retained in care.

However, data from Haiti and other resource-limited settings demonstrate that HIV-infected adolescents are not retained in standard clinical care with current procedures. While implementation of youth-friendly HIV services has increased HIV testing, linkage to care, and ART initiation, retention has not improved. One year after HIV diagnosis, only 54% of adolescents remain alive and in care at the GHESKIO Adolescent HIV Clinic. At other HIV clinics in Haiti, less than 50% of HIV-infected teens remain in care at 12 months. Reasons for poor retention are multifactorial and include adolescent behavior coupled with extreme poverty, social isolation, gender inequality, family rejection, and stigma.

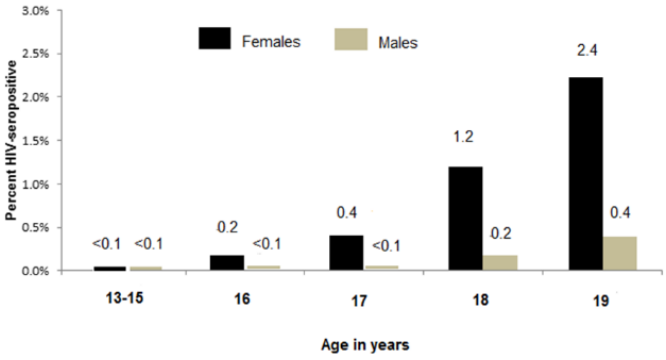
This study will validate an integrated, community-based, cohort model of care, FANMI, which addresses key environmental, social, and individual factors that influence the retention of HIV-infected adolescent girls in Haiti. FANMI addresses social isolation and family rejection by placing girls in cohorts of 5-10 peers who meet together each month for HIV care. The cohorts form extremely close peer relationships which are described by teens as surrogate families. FANMI decreases stigma and prioritizes social support by having care visits at a community center, rather than in a specialized HIV medical facility. FANMI integrates peer counseling, social support, and medical services into a single session with the same providers, rather than a series of sequential encounters with a number of providers as currently happens in the Adolescent HIV Clinic.

Preliminary data from our FANMI pilot study suggest dramatic improvement in outcomes with 91% of teens alive and in care at one year. We propose to conduct a randomized controlled trial comparing FANMI in the community versus standard of care in the GHESKIO Adolescent Clinic. GHESKIO is the premier HIV clinic in Haiti with outcomes superior to other HIV clinics in the country. If community-based FANMI outperforms the GHESKIO clinic, then this will provide gold-standard evidence for FANMI's efficacy and for the conduct of large scale implementation studies to demonstrate scalability and evaluate cost-effectiveness.

2.2 Scientific Rationale

HIV infection rates have declined in all segments of the population in Haiti, except in adolescents where HIV prevalence and mortality rates continue to rise. In Haiti, 40% of all new HIV infections are in adolescents and 80% of these are females. Adolescent girls account for 32% of all new HIV infections in the country. Sexual intercourse with older male partners is the major risk factor. The prevalence of HIV is <0.1% in 13-15 year olds but dramatically increases to 2.4% in girls age 19 years (Figure 2). In a 2009 study among adolescents presenting to GHESKIO for HIV testing, characteristics and risk factors for HIV infection were different in younger (13-15 years) and older (16-19 years) adolescents. Younger teens were 60% male and not sexually active. Risk factors were having a mother with documented HIV infection or being an orphan. Older adolescents age 16-19 years were 80% female and 90% were sexually active. HIV infection in this older group was associated with not living with parents (O.R 2.0, p <.0001); poor relationship with family (OR 1.5, p=.001); never attending school (OR 1.9, p=.003), and having a sexually-transmitted infection (STI) (OR 2.3, p < .0001).

Figure 2
Prevalence of HIV Infection in Adolescent Females and Males Aged 13 -19 in Port au Prince



Treatment Outcomes in HIV-Infected Adolescents: Studies from multiple resource-poor settings demonstrate that adolescents have inferior HIV treatment outcomes compared to adults. Only 40-60% of HIV-infected adolescents remain alive and in care 12 months after HIV diagnosis compared with 65-85% in adults. Viral load suppression is also extremely poor among adolescents. These poor outcomes have contributed to a 50% increase in mortality among HIV-1 infected adolescents over the past decade, as compared to a 30% decrease in mortality in HIV-infected adults over the same time period. The WHO has declared adolescent girls who live in settings with a generalized HIV epidemic to be a particularly vulnerable group in need of specialized interventions to improve their health outcomes.

GHESKIO Interventions to Improve Adolescent Outcomes: Since 2003 GHESKIO has conducted research and implemented programs to improve HIV services for HIV infected girls age 16-23 years. Innovations in community-based testing and implementation of a youth-friendly Adolescent Clinic improved HIV testing, linkage to care, and rates of ART initiation but did not significantly improve long-term retention in care.

2.3 Potential Risks and Benefits

Potential Risks

A. Loss of Confidentiality: All samples and subject data will be coded at the GHESKIO Center. Each subject will be assigned a study identification number consisting of a unique code unrelated to any patient identifying information, as per Good Clinical Practice guidelines. Any identifiers linked to the participant will be secured and only available to staff at the GHESKIO Center, to ensure subject confidentiality. All source documents will be kept in locked file cabinet. GHESKIO computers and servers are protected by firewall protection and are only accessible with a password.

   All participants will be counseled on the importance of maintaining confidentiality of the HIV status of other patients whom they may see in waiting rooms or during group counseling sessions.

B. Social Harms: Study staff have been working with the Adolescent Community Advisory Board (Ado CAB) and are sensitized to the challenges experienced by HIV-infected adolescent girls as a vulnerable population. Additionally, they have been working with this population in the Adolescent Clinic for over three years. As such, they are trained on how to respond to any social harm reported by a participant.

C. Discomfort: As part of the informed consent process, all potential participants will be instructed that they do not have to disclose personal information that they are uncomfortable sharing and that they can withdraw from the study at any time.

D. Phlebotomy: Participants will be informed of the possible risks of slight bruising or tenderness at the site of the blood draw. They will be encouraged to call or visit the study site if symptoms persists or worsen.

Known Potential Benefits

The results of this study may provide evidence for a new model of HIV care and treatment for adolescent HIV-infected girls. Outcomes will be used to better understand barriers to retention in HIV care and medication adherence to support future models of HIV for adolescent HIV populations. If clinically and cost-effective, Cohort Care can be adapted to similar resource-limited settings.

If we find that Cohort Care is superior to Standard Care then all participants enrolled in this trial will have the option to enroll in Cohort Care. Further, we will transition the GHESKIO Adolescent Clinic to a Cohort Care model of care. Finally, Dr. Pape, the Haiti Site PI of this proposal, is a senior advisor to the Haitian Ministry of Health, and he will work with the Ministry to adopt Cohort Care as a national model of care. Thus we will assure that the potential benefits of this study are available to participants and the population where the study is conducted.

3 STUDY PROTOCOL

Study Objective

The primary outcome is remaining alive and retained in HIV care at 12 months after randomization. The primary hypothesis is that FANMI will increase the proportion alive and in care at 12 months compared with standard care. The study has >80% power to detect a difference in the primary study outcome from **60%** to **85%**. A secondary hypothesis is that a greater proportion of the FANMI arm will achieve a suppressed viral load at 12 months when compared with the standard arm, and this difference will be explained by better attendance at monthly visits and improved ART adherence measured by tenofovir diphosphate (TFV-DP) levels in dried blood spots. Other study outcomes include sexual risk behaviors, acceptability of FANMI, and health care utilization and costs.

Key Personnel

Daniel Fitzgerald, MD (PI) is a Professor of Medicine, Clinical Epidemiology and Health Services Research at Weill Cornell Medical College and will provide overall study leadership.
Jean Pape, MD is the founding Director of GHESKIO and a pioneer in HIV/AIDS care and prevention. Dr. Pape is an adviser to the Haitian Minister of Health and will translate the results of the trial into a national adolescent HIV treatment program.
Margaret McNairy, MD, MSc is an Assistant Professor of Medicine at Cornell and currently leads the adolescent community testing and FANMI pilot in Haiti. She will train the study team and implement study procedures and data collection.
Bruce Schackman, PhD is an expert in health economics and has conducted costing analyses of PEPFAR and WHO programs in Haiti. He will lead this study's health care utilization and cost analyses.

Study Site

The trial will be conducted in Port au Prince Haiti. The standard arm will receive care in the GHESKIO Adolescent Clinic located in central Port au Prince.

Study Population

The study population will be 160 HIV-infected adolescent girls. They will be recruited from the ~370 adolescents who are newly diagnosed with HIV infection at GHESKIO each year.

Inclusion and Exclusion Criteria

Inclusion criteria are: female, age 16-23 years; ART naïve, initiated ART in the past 3 months, or on ART for less than 1 year and defaulted from care for at least 3 consecutive months; participant

knowledge of HIV-infection; lives in Port au Prince; willing to receive care at the clinic or in the community; willing to provide consent (age 18-23 years) or assent with parental/guardian consent (16-17 years).

Exclusion criteria include: pregnancy at the time of enrollment, a severe HIV/AIDS illness requiring hospitalization or intensive medical follow-up, or based on the primary clinician's judgement that the adolescent is at a developmental stage not suited for study participation. Based upon our experience with the FANMI pilot study, we estimate that 240 (65%) of the newly diagnosed HIV-infected adolescents each year will satisfy the above entry criteria and be willing to enroll in the study. Therefore, over the **18-month enrollment period**, we are confident that we can enroll 160 participants.

Recruitment and Informed Consent

We will recruit HIV-1 infected adolescent girls within 2 weeks of HIV diagnosis while they are undergoing initial medical assessment and counseling at the GHESKIO Adolescent Clinic. Adolescents who test HIV-positive at GHESKIO are linked to the Adolescent Clinic on the same day to initiate medical assessment and counseling by a nurse practitioner. We will also recruit HIV-1 infected adolescent girls who were on ART for less than 1 year and defaulted from care for at least 3 consecutive months. At the initial visit, a clinic nurse performs a history, a physical exam, orders routine laboratory tests including a CD4 T cell count, and screens for opportunistic infections (OIs) including tuberculosis. All patients are eligible for ART per WHO guidelines with the goal of initiating ART within 2 weeks of diagnosis. The first-line ART regimen in Haiti is tenofovir (TFV), lamivudine (3TC), and efavirenz (EFV). Renal dysfunction is rare in adolescents in Haiti and > 99% of adolescents start TFV regimens.

At the first clinic visit, the Adolescent Clinic nurse will ask adolescent girls 16-23 years if they are interested in participating in the study. The clinic nurse will accompany interested adolescents to the GHESKIO Research Unit to meet a study nurse. The study nurse is a research staff member independent from the clinical team and will not participant in patient care. The research nurse will complete a study eligibility checklist and initiate informed consent procedures. The informed consent process at GHESKIO consists of two educational sessions and will be completed in the first week after HIV diagnosis. Eligible adolescents age $\geq$18 years will provide written informed consent as an adult participant. Adolescents 16-17 years will be asked to return to the clinic with a parent/guardian. Those who do not provide parental/guardian consent will still be provided with free HIV services at GHESKIO. Adolescents age 16-17 years will provide written informed assent and their parent/guardian will provide written informed consent. We will document the number screened and reasons for study exclusion.

Study Enrollment and Randomization

Participants who complete the informed consent process will be enrolled in the trial. We will enroll consecutively until we reach a sample size of 160 subjects. The research nurse will assign a unique study identification number to each participant, collect demographic and clinical data from the EMR, administer a baseline questionnaire, and draw blood and collect urine. Participants will be randomized to either FANMI or Standard Care in a 1:1 ratio using a computer generated

random assignment. Subsequent monthly HIV visits for participants randomized to FANMI will be in the community center, and participants in the standard arm will be seen in the GHESKIO Adolescent Clinic.

HIV Services and Study Interventions

HIV services provided to all participants in both study arms: Provision of HIV services including ART will adhere to national guidelines in both study arms. Monthly visits will include monitoring for new symptoms and assessment for medication toxicity. One month medication refills will be provided. Plasma HIV-1 viral load testing will be performed at enrollment, 6 and 12 months for all participants. Patients with a plasma HIV-1 RNA level > 1,000 copies/µl at 6 or 12 months will meet with their treatment nurse for an adherence assessment and development of an individualized adherence plan per Haitian guidelines. Family planning counseling and contraceptive methods will be provided. Girls who become pregnant will continue HIV care at the Adolescent Clinic or in FANMI and will also receive three antenatal care visits at the GHESKIO obstetric clinic. Prior to transition to adult care, adolescents will receive three counseling sessions to facilitate the transition. Participants in the study will benefit from retention support services provided to all HIV-infected patients at GHESKIO. All patients are asked to provide a cell phone number, another contact phone number, and a nurse routinely calls all patients who miss a visit. In addition a home address is recorded and consent is obtained to send a field worker to the patient's home if they miss a visit and cannot be contacted by phone.

All clinical, laboratory and pharmacy information is routinely entered by clinic staff into the GHESKIO electronic medical record (EMR). The GHESKIO Data Management Center operates the EMR with data on over 200,000 patients. All clinical data including patient demographics, contact information, HIV diagnoses, WHO stage, tuberculosis history, and physical exam findings are entered by the nurse in real time at each clinic visit. All laboratory results including HIV-1 viral load tests, CD4 T cell counts, and tests for TB and STI are entered directly into the EMR by laboratory technicians. Pharmacy records including number and date of all antiretroviral drugs dispensed are entered. In the FANMI pilot, clinical data are entered by the nurse onto an encryption protected laptop at the community center and then downloaded when the nurse returns to GHESKIO. The EMR is programmed in VB.NET, and data are stored in SQL Server with multiple backups daily.

Standard of Care: Adolescents randomized to the standard arm will receive monthly HIV care in the GHESKIO Adolescent Clinic. Clinical care is provided in an individual exam room by a nurse. If ART has not been initiated, the nurse will provide individual counseling and ART initiation during the monthly visits. The patient is sequentially referred to the laboratory, social worker, and pharmacy for medication refills. A peer counselor provides counseling on topics chosen by the patients and counselor. A physician is available for consultation. A typical visit, including wait time, lasts 3 hours.

FANMI: Adolescents randomized to FANMI will receive all monthly HIV care in the community room of the Prince Albert School in Village of God. Adolescents will be grouped in cohorts of 5-10 peers. Cohorts will be formed with at least 2 group members and additional group members

will be added sequentially. We estimate that it will take 4-8 weeks to constitute a full cohort of 5-10 teens; monthly meetings will occur while each cohort fills. A visit will start with 30 minutes of peer socialization, followed by 45 minutes of group counseling using a structured curriculum. This will be followed by a 30 minute social activity. Patients will be seen individually by a nurse for ~10 minutes during peer socialization or the social activity. CD4 T cell counts will be measured on site with the point of care FACSPresto (Becton Dickinson). For HIV viral load and other labs, the nurse will collect the samples and transport them to GHESKIO. The nurse will distribute the adolescents' monthly medication refills at the community center. If ART has not been initiated, the nurse will provide individual counseling and ART initiation during the monthly visits. Adolescents with an acute illness may be referred to a physician at the GHESKIO HIV clinic. The nurse will enter clinical information into the EMR using a laptop. The entire visit will take **~ 2 hours**.
Cohort members will be encouraged to text or call to remind each other about monthly visits.

Study Measures and Schedule

A questionnaire will be administered at enrollment and months 6 and 12. Data on factors from the SAT model will be collected including demographics, HIV knowledge, HIV-related stigma, HIV disclosure, social and family support, depression, and alcohol use, problem solving skills, and food insecurity.

Clinical characteristics including height, weight, WHO stage, new diagnoses, pregnancies, chemistry, hematology tests, and CD4 T cell counts will be extracted from the GHESKIO EMR at each study visit.

Alive and in care at 12 months (primary outcome) is defined as being alive at 12 months and having a care visit between 11 and 13 months after enrollment. Deaths, cause of deaths, and missed care visits are documented in the GHESKIO EMR and will be recorded by the research team.

Number of monthly HIV care visits attended is defined as number of monthly care visits attended out of 12 possible visits during the study period. We will continue to document the number of visits attended after 12 months as a measure of long term retention including visits during transitions to adult care.

Plasma HIV-1 RNA levels will be measured in all participants at enrollment and at month 6 and 12 by the Abbott Real Time PCR Assay with a lower limit of detection of 50 copies/µl. Testing will be performed in the GHESKIO Laboratory and results available to clinicians within one week.

Study Measures and Schedule

	Month of Study Visit				
Characteristics	**0**		**6**	**12**	**>12**
Demographic information	X				
HIV knowledge and beliefs	X		X	X	
HIV-related stigma	X		X	X	
HIV disclosure	X		X	X	
Social and family support	X		X	X	
Depression	X		X	X	
Alcohol and drug use	X		X	X	
Food insecurity	X		X	X	
Height, Weight	X		X	X	
WHO Stage	X		X	X	
New HIV related diagnoses	X		X	X	
CD4 T cell count	X		X	X	
Outcomes					
Alive and in care at 12 months (primary outcome)				X	
Number of care visits attended			X	X	X
Plasma HIV-1 RNA level	X		X	X	
Time to ART initiation			X	X	
ART adherence			X	X	
Tenofovir-DP level			X	X	
Sexual risk behavior	X		X	X	
Sexually transmitted infections	X		X	X	
Pregnancy	X		X	X	
Health care utilization			X	X	

Participants in both study arms will complete three study visits with a research nurse at the GHESKIO Research Unit at enrollment, 6, and 12 months. Each study visit will include a questionnaire, extraction of clinic attendance and medical information from the GHESKIO EMR, and laboratory assessments. An HIV-1 RNA level will be measured at enrollment for research purposes and at 6 and 12 months per routine medical care. ART adherence measured by pill recalland Tenofovir-DP level in dried blood spots will be measured at 6 and 12 months after ART initiation. In addition to the four study visits, a subset of 30 participants in the FANMI arm will be recruited for qualitative interviews at 6 months and 12 months with Dr. Jessy Devieux to assess acceptability of FANMI. (See section D.2.i for details of these interviews). This will entail two additional study visits for this subset of 30 people. The research team will also contact all participants who are not retained in care at 12 months (estimated 12 in FANMI and 32 in the standard arm) and invite them to return for a single study visit and qualitative interview to explore reasons for non-retention.

Laboratory

The GHESKIO Clinical Laboratory is the premiere lab in Haiti and is certified by the NIH and CDC to perform CD4 T cell counts, HIV-1 viral loads, routine chemistry, hematology, microbiology, and assays for the detection of *M. tuberculosis* and sexually transmitted infections.

Data Collection and Management

Research nurses will abstract clinical and laboratory information from the EMR at each study visit and enter the data onto Case Report Forms (CRFs). Research nurses will also administer and complete research questionnaires at each visit. GHESKIO laboratory staff will complete a CRF with results of plasma HIV-1 RNA levels. Individuals will be identified by a study ID number and no participant identifying information (name, address) will be recorded on questionnaires or CRFs. Completed research questionnaires and CRFs will be entered by Adias Marcelin (data manager) into the NIH approved REDcap data management system. The REDcap system is encrypted and password protected and has been used in prior Cornell-GHESKIO NIH supported trials. Questionnaires and CRFs are entered via an internet interface with data stored at the Weill Cornell Clinical and Translational Science Center in New York.

Data Analysis

Aim 1: Alive and in care at 12 months is a binary outcome. We will compare the proportion of participants who remain alive and are retained in HIV care at 12 months between study arms using the Fisher exact test.[116-120] This is an individual randomized trial, and we anticipate the two arms will have similar baseline characteristics. Therefore, the primary analysis will be done without adjusting for baseline variables. Since we have one primary outcome, we will test the primary hypothesis without multiple testing adjustments. Statistical tests will be two-tailed, with a significance level of 0.05. If some variables at baseline are notably imbalanced, we will conduct adjusted analyses as secondary or sensitivity analysis using multivariable-adjusted logistic regression and Cochran–Mantel–Haenszel statistics. The results will be summarized in terms of proportions as well as odds ratio, along with confidence interval and statistical significance. Categories of non-retention (i.e., death, lost to follow-up) will be described, and as a secondary analysis, we will examine differences between the two arms for these categories. We will analyze cohort effect in the intervention arm in secondary analyses using generalized estimating equations. For example, some cohorts of 5-10 girls may perform better than others.

Aim 2a: Viral load suppression at 12 months is a binary outcome. We will compare the proportion of participants who have viral load suppression at 12 months between study arms using the Fisher exact test. Secondary outcomes will be analyzed and reported together with clear designation of "secondary" so that readers will be aware of the number of pre-specified analyses.

Aim 2b: Sexual risk behavior: These include self-reported sexual activity, condom use, incidence of sexually-transmitted infections, and pregnancy. For 'time to event' outcomes (e.g. time to first pregnancy), we will use the Kaplan-Meier estimate and Cox model, along with log-rank test and

estimation and inference about the hazard ratio. For repeated measures (condom use at each visit), we will use statistical methods suited for longitudinal data analysis – (generalized) linear mixed effect models that account for correlations within subject. Within these models, intervention, time and intervention*time interaction will be included as covariates. For count data aiming at estimating rate (number of STIs), we will consider Poisson test and regression. When data are severely nonlinear, variable transformation (e.g., log) or nonparametric tests may be adopted, with justifications documented.

Aim 2c: Acceptability: All qualitative interviews will be transcribed verbatim, translated in English, and then entered into qualitative software (e.g. Atlas-ti) for coding and analysis. A thematic coding scheme will be created following the main points of the interview guide.

Aim 2d: Healthcare utilization and costs: Utilization will be summarized for each arm as descriptive counts such as number of HIV care visits, laboratory tests, medications, and hospitalizations. Unit costs will be determined for each type of healthcare utilization by applying labor rates and materials costs available from GHESKIO and other expense costs available from previous studies. Differences in costs between arms will be compared using non-parametric methods if required (e.g. Wilcoxon tests for medians, non-parametric bootstrap for means) due to the skewness often found in cost data.

Sample Size and Power

We performed sample size (N)/power calculation using the Fisher exact test for the primary outcome in the two independent prospective study arms. With alpha of 5% and with N=80 per arm, we will have 93% power to detect a difference between 60% vs. 85% per our primary hypothesis. If there is within cohort effect in the FANMI arm, then we will still have **83%** power to detect a difference in our primary outcome. If we assume potential average within-cohort correlation of 5% and cohort sizes of 5-10, the resulting variance inflation factor is 1.3 so that with N=80 per arm (or total N of 160), we will have 83% power to detect a difference of 60% vs. 85%.[126] Our sample size will also provide reasonable power for important secondary analyses. We will have >80% power to detect a difference between 30% and 60% suppressed viral load at 12 months between the two study arms.

Timeline

In months 1-3, we will finalize study operating procedures, data collection tools, and staff training. We will enroll participants in months 4-22 and complete all follow up visits by month 36. In months 36-42 we will conduct individual interviews, and complete laboratory assays. In months 43-48, we will finalize the data set and conduct analysis. Of note, all follow up visits will be completed by 36 months, and we will be able to report preliminary findings and begin planning for large scale implementation studies within three years of initiating this project.