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Factors Associated with Study Visit Compliance among Participants in a Simulated HIV Vaccine Efficacy Trial

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ABSTRACT

Factors Associated with Study Visit Compliance among Participants in a Simulated HIV Vaccine Efficacy Trial

By Shideh Delrahim Ebrahim-Zadeh

Background: Sub-Saharan Africa is home to over half of the total number of people living with HIV globally. Certain subpopulations such as female sex workers (FSW) and single mothers (SM) are disproportionately affected due to having multiple sex partners, poverty, higher chance of experiencing sexual violence, and lack of family/social support. This subpopulation can benefit from an HIV vaccine and should be included in efficacy trials. Vaccine trials are costly and time-intensive; therefore, having participants who adhere to the study protocol is crucial. We conducted a Simulated HIV Vaccine Efficacy Trial (SiVET) in Zambia in preparation for an HIV vaccine trial and evaluated factors associated with full visit compliance among participants.

Methods: SiVET enrolled 159 FSW/SM (recruited from an observational cohort) and randomized them to receive measles, mumps, rubella (MMR) and tetanus, diphtheria, pertussis, inactivated polio (Tdap-IPV) vaccines at month 0 or 3, and followed them for 12 months. Main-study group and the immunology sub-group had 11 and 15 visits, respectively. Participants received appointment reminders by phone or text (if available) and were visited at home if they missed a visit. Demographic, behavioral, and clinical data were used in logistic regression to model perfect clinic attendance within visit windows.

Results: Retention was 96.2%. 68 (42.8%) women attended all visits inside window, 58 (36.4%) attended all visits some outside window, and 33 (20.8%) missed at least 1 visit (median: 1). FSW/SM who had never been married (aOR = 2.17) and with more time in the cohort pre-SiVET (aOR = 1.73) were significantly more likely to have perfect attendance. Reasons for late/missed visits were unknown/unable to contact, traveling, and clinic closed for holidays. No significant differences were observed between the two risk groups, FSW and SM, or other factors including age, number of children, literacy/education, alcohol use, enrolled in sub-study, pregnancy, seroconversion, and adverse event.

Conclusions: Study retention was high. Having a preparatory cohort is conducive to enrolling the most compliant women. Providing participants with mobile phones may improve attendance. Screening should inquire about frequent travel. Visit calendars should be established in advance to ensure visit windows not fall over long holidays.

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INTRODUCTION

HIV in Zambia, sub-Saharan Africa

While great progress has been made in preventing and treating HIV since the human immunodeficiency virus type 1 (HIV-1) was first identified in 1983, HIV continues to be a major global public health issue (1) . UNAIDS estimates that since the start of the epidemic, 76.1 million people have become infected with HIV and 35.0 million have died from AIDS-related illnesses globally (2). Approximately, 36.7 million people were living with HIV worldwide at the end of 2016 (2). In that year, an estimated 1 million people died from AIDS-related illnesses, and 1 million people became newly infected (2). Sub-Saharan Africa disproportionately accounts for more than 70% of the global burden of this infection (3). Although, East and Southern Africa regions are home to 6.2% of the global population, they have over 50% of the total number of people living with HIV in the world (3). The Republic of Zambia, a landlocked country in Southern Africa with an estimated population of 16 million in 2017, has an overall adult (aged 15 to 49) HIV prevalence of 12.4% (2016 estimate), which is the seventh highest in the world (4, 5).

In Africa, women carry a higher burden of HIV infection compared to men due to many factors including physiological vulnerability to HIV infection; socioeconomic factors such as poverty and having limited access to schooling; high rate of sexual violence; and structural vulnerabilities, for instance, cultural practices and lack of knowledge and/or power to negotiate condom use (5, 6).

The prevalence for women (aged 15 to 49) is 14.5% compared to 10.3% for men in the same age group (5). Globally, female sex workers (FSW) are one of the key populations most affected by HIV infection due to multiple factors, including unsafe sexual practices and multiple sex partners (7). FSW of sub-Saharan Africa have the highest prevalence of HIV (39%) among all key populations worldwide (7). In addition, studies show that single women compared to married ones have a higher risk of HIV infection, and similar result holds for those with two or more sexual partners (in past year) in comparison to women who reported to have a single partner (8). A study conducted in South Africa by Hattingh and Walsh concluded that being the head of household and unmarried in an urban setting are possible risk factors for HIV infection among black women (9). Similarly, Ackerman et al. and Muula argue that compared to men, women in South Africa have a higher chance of HIV infection since they are more disadvantaged socially and economically (10, 11). Using all the available Demographic and Health Surveys for 35 countries in different regions of Africa, Milazzo and van de Walle concluded that about 26% of all households are headed by a female, and that approximately 43% of those females are single mothers (SM) (12). These general and specific findings about women in Africa place SM among key affected populations for HIV.

Current HIV Control Strategies

A holistic and effective approach to HIV prevention and control is a combination of behavioral, biomedical, and structural strategies (6, 13). Strategies to prevent HIV (encouraged by the CDC and international health

organizations) include abstinence; avoiding high-risk behaviors such as having multiple sex partners, having unprotected sex, or sharing needles; receiving pre-exposure prophylaxis daily to prevent HIV infection if at high risk of infection; and receiving post-exposure prophylaxis soon after potential exposure to HIV (14). The current standard HIV treatment method is antiretroviral therapy (ART), the use of a combination of three or more antiretroviral drugs, which slows the progression of HIV virus in the body and reduces the risk of HIV transmission to an HIV-negative sexual partner by 96% with perfect adherence (15) . ARTs reduce AIDS-related deaths and prevent HIV-related diseases and disabilities (15). One of the major challenges with current treatment options is that most underdeveloped and developing countries (which carry the highest burden of HIV infection) have limited access to ART (16).

The Need for an HIV Vaccine

Despite advances and innovations in the prevention and treatment of HIV, the continuous reduction in the number of deaths related to AIDS, and the decreasing rate of new infections globally, there is still no cure. The HIV pandemic remains one of the significant causes of morbidity and mortality, which in turn cause enormous economic loss across the world (17). The consensus among health organizations is that a potentially valuable and cost-effective intervention would be an HIV vaccine (18, 19) . "Successful antiretroviral therapy requires lifelong adherence, but adherence relies on behavior change, which can be difficult to maintain. In contrast, an HIV vaccine is a one-time intervention that is extremely cost-effective compared with the cost of lifelong treatment.

(20)" According to a recent Nature article, there are currently about twelve experimental "late-stage" HIV vaccine trials underway (21).

The clinical trials for vaccines are costly and time-intensive, which emphasizes the need for reliable participation from the population at risk to maintain the integrity of the trials. Adherence of participants in clinical trial protocols is important for successful completion of a study and for allowing a study to have the power to detect important associations. For example, in a study examining prophylaxis for HIV infected women in Africa, researchers struggled with participant adherence which impacted their ability to assess efficacy of the study treatment and side effects (22). This same concept can apply to vaccine trials and assessing efficacy of a vaccine and the potential side effects. A systematic review by Ambia and Agot (2013) describes that evaluation of product effectiveness in trials conducted in Africa depends mainly on participant adherence to study protocol and is related to factors such as missed visits (23). Magazi et al. emphasize the importance of reliable participation in study visits in influencing the quality of the trial and validity of the results (24). In Magazi et al.'s study, which assessed adherence in an HIV-prevention study in South Africa, they found that visit attendance was influenced by individual characteristics (e.g. age), social factors (e.g. kinship, economic and personal obligations), and study structure (e.g. timing and length of study visits) (24).

The aim of our study was to quantify and assess factors associated with study visit compliance among participants in a simulated HIV vaccine trial. In our study, participants were from two populations with high risk of HIV infection

in Zambia—FSW and single (not married or cohabiting) sexually-active mothers (SM) with children younger than 5 years of age.

METHODS

Study Design

The Rwanda Zambia HIV Research Group (RZHRG) was founded by Dr. Susan A. Allen in 1986 in Rwanda as an HIV-prevention research organization, promoting Couples' Voluntary Counselling and Testing (CVCT) for HIV (25). In 1994, RZHRG opened research centers in Zambia, and at present, it conducts observational studies and clinical trials in the two largest cities, Lusaka and Ndola. Together, these two sites comprise the Zambia Emory HIV Research Project (ZEHRP) (26).

In September 2012, ZEHRP Lusaka and Ndola initiated an observational prospective cohort study to determine the incidence and risk factors of HIV in high-risk single women of childbearing age. Women were recruited from two key populations, FSW and SM. In order to assess the feasibility of conducting a future HIV vaccine efficacy trial among HIV-negative women at high risk of HIV infection, a Simulated Vaccine Efficacy Trial (SiVET) was designed. This analysis uses the data collected through SiVET (26).

The SiVET study emulated an HIV vaccine efficacy trial using MMR (Measles, Mumps, and Rubella) and Tdap-IPV (Tetanus, Diphtheria, Pertussis, and Polio) vaccines as a proxy for an HIV vaccine to determine whether women with high risk of HIV infection could be enrolled and retained in future HIV vaccine efficacy trials. A preparatory cohort enrolled 637 women (FSW and SM) across two clinical trial sites in Lusaka (the largest city and the capital of Zambia) and Ndola (the third most populated city in Zambia) in 2015-2016. FSW were

recruited from community “hot spots”, and SM were recruited from under-5 infant vaccination clinics. The preparatory cohort was used as prescreening for SiVET enrollment (26). The sample size of up to 160 women enrolled in SiVET study was by convenience and dictated by the International AIDS Vaccine Initiative (IAVI) study budget.

Study participation spanned a total of 12 months, beginning in 2015, with frequent follow-up visits scheduled throughout. During this time, all participants were scheduled to attend a total of 9 clinic visits and participated in two house calls or at-home visits during which time behavioral, medical (physical exam, blood draw, and vaccination), sociodemographic (self-reported), and serological data were collected. Data were collected on paper forms, administered by trained study personnel. Participants were fingerprinted electronically and also by using paper and ink at every visit to ensure accurate identification. They were randomly (and double-blindly) assigned to two groups for vaccination. One group received MMR in Month 0 and Tdap-IPV in Month 3. The second group had a reversed vaccination schedule. The screening/enrolment visit took about 3-4 hours; the vaccination visits lasted about 2-3 hours; and all other visits were about 1-2 hours. After each vaccination, participants were observed for 30 minutes at the clinic, and they were asked to return to the site 7 days after each vaccination. They were given a vaccine diary card to record any health problems between the two visits. Participants were given 50 Kwacha (Zambian currency), which was equivalent to about 5-6 USD in 2016, as a compensation for their bus fares and their time, for every visit they attended (27). All enrollees were offered the option to participate in an immunology sub-study to measure immune response to

vaccines administered. If a participant declined the offer, the next participant enrolled was asked until a sample size of 30 participants (15 from each study site) was reached. This sub-study included 6 additional visits where additional clinical data were collected. Thus, women participating in the immunology studies had a total of 15 required visits, whereas the rest of the participants were required to attend only 9 clinic visits out of those 15 visits in addition to participating in 2 house calls or at-home visits. A more detailed outline of the study visits and activities is shown in Table 2.

Ethics

The SiVET was submitted to the Emory Institutional Review Board and the University of Zambia Biomedical Research Ethics Committee. Both regulatory boards reviewed and approved the study annually. All study participants passed an assessment of understanding and gave written informed consent to participate in the SiVET.

Eligibility Criteria

Inclusion and exclusion criteria are listed below in Table 1. This study population consists of healthy single women aged 18 to 40 years, at high risk of, but not having, HIV infection residing in two cities in Zambia, Lusaka and Ndola. This cohort comprises a convenience sample of 159 healthy FSW and SM, chosen as described in Study Design section. The inclusion criteria also contained the following: the participants were planning to stay in Lusaka or Ndola for at least 12 months and return for follow-up visits; they were willing and able to provide

locator information for tracking purposes and willing to be contacted by the study staff at home or by phone, if available; they were willing and able to undergo HIV and pregnancy testing; and they were not planning to get pregnant and were willing to use contraceptives in forms of injectable, implant, or IUD until four months after the last vaccination during the study.

Data Collection

Demographic, behavioral, and clinical data/variables collected using data forms designed for each risk group and administered during the original preparatory observational prospective cohort study prior to SiVET study enrollment. Data collected included: city of residence (Lusaka or Ndola), years of residence, age, number of living children, marital status (SM population only), formal education, English literacy, Nyanja/Bemba literacy, recreational drug use (FSW population only), alcohol use and frequency, age of sexual debut, and years of sexual history. The data used in our study, except for the number of visits attended and body mass index (BMI), were self-reported and collected during one-on-one interviews at baseline. This information is summarized in Table 3.

Analysis

The present analysis investigates if participants' baseline characteristics, demographic or behavioral, were associated with whether they would come to all study visits during the visit window. The outcome of interest for the analysis is dichotomous and compares those who attended all visits within the visit window versus others (including those who missed one or more visits and those who had

at least one visit outside the visit window). The definition of attending all visits within the visit window took into account the difference in the two study groups (those who were enrolled in the immunology subgroup and those who were not). The group with standard follow-up was required to attend a total of 9 visits. Those in the immunology group were required to attend the same 9 visits as the standard group, plus 6 additional visits, visits 2, 4, 5, 8, 10, and 11 (previously noted in Table 2 above).

All variables available (listed in Table 3) were considered for bivariate analysis. Some were modified or combined. We merged some levels of variables that could be combined logically because the numbers were low. For maximum severity of any adverse event during the SiVET study, reactions were combined into mild or moderate and severe or life-threatening. Formal education was categorized into none/primary and secondary/college. If a participant could understand either Bemba or Nyanja easily, she was considered as understanding a local language. The same logic was applied for reading a local language. For first intercourse, we combined pressured and forced into one category, versus willingly. For frequency of alcohol use, we collapsed the levels into zero to three times per month and weekly/daily.

Statistical Analysis Software (SAS) version 9.4 was used to perform this analysis. Frequencies were calculated for all variables captured at baseline for the study sample. Kolmogorov-Smirnov test was used to decide whether a continuous variable was normally distributed. For continuous variables that were normally distributed, mean and standard deviation were calculated, whereas for non-normally distributed variables, median and interquartile range (IQR) were

used. For categorical variables, counts and percentages were reported. Statistical tests were used to determine the significance of variation by the outcome of interest. For continuous variables that were normally distributed, p-values from t-tests were used, and for non-normally distributed variables, p-values from Wilcoxon Two-Sample tests were reported. For categorical variables, Chi-square (or Fisher's Exact) tests were used, as appropriate. Descriptive statistics were reported for the entire study sample and by participant group categories (FSW, SM).

A logistic regression model was fitted initially using all variables that had univariate p-values of < 0.10 as potential factors of interest. Collinearity was assessed using a collinearity macro developed in the Emory University, Department of Epidemiology. Final models for the entire study population combined as well as for each participant group (FSW or SM) were examined to identify factors associated with full-adherence to all study visits and to determine if factors differed between the two participant populations (FSW and SM).

RESULTS

Of the 637 women from the preparatory cohort, 356 women were prescreened and attended Vaccine Education Sessions. From this pool of vaccine-educated women, a group of 175 were screened, and 15 were excluded. Reasons for excluding these 15 individuals were lacking locator information (3), failing an assessment of understanding about the vaccine trial (2), not meeting the age requirement (18-40 years of age) (2), not willing to comply with the follow-up schedule (2), being HIV-infected (2), being pregnant or planning to get pregnant (2), being unwilling or unable to consent to the study (1), and being excluded due to investigator decision (1). Lastly, one individual became HIV positive on the day of enrollment after randomization; although she remained in the study, she was not eligible for analysis. Finally 159 were enrolled--79 from Lusaka and 80 from Ndola. The SiVET study had the overall retention rate of 96% (FSW: 98.3% and SM: 95.0%)--5 participants were lost to follow-up, and 1 withdrew voluntarily.

Distribution of Visit Attendance

Of the 159 women who participated in the SiVET study, 68 (42.8%) attended all study visits within the visit window (Table 4); this proportion was similar for both risk groups FSW (40.7%) and SM (44.0%), p = 0.6825. Over one-third (36.4%) of all participants attended all visits but at least one visit was early or late. One-fifth (n = 33, 20.8%) missed at least one visit. Reasons for late/missed visits were unknown/unable to contact, traveling, and clinic closed

for holidays. No significant differences in visit attendance were observed between the two risk groups, FSW and SM.

Bivariate Analysis

Bivariate analysis assessing attendance at all visits within the visit window (vs. other) by participant demographic characteristics are described in Tables 5a, 5b, and 5c for FSW and SM combined, FSW only, and SM only, respectively.

FSW and SM combined (Table 5a)

On average, women who participated in the SiVET were 23 years of age (median age of FSM: 27, SM: 22) and had lived in Lusaka or Ndola for an average of 20 years prior to joining the study. Women participated in the preparatory cohort for a median of 1 year (IQR: 1) prior to SiVET study enrollment (p = 0.0384). Marital status differed by visit attendance when FSW and SM women combined (p =0.0661). A higher proportion of women who attended all visits within the visit window were never married (77.9%) versus women who did not attend all visits on time (64.4%) (p = 0.0661). Among those who attended all visits within the visit window, 79.4% described their first intercourse as being done willingly (vs. being pressured/forced) compared to 67.0% for the women who did not attend all visits within the visit window (p = 0.0843). Among those who attended all visits in the visit window, 10.3% participated in the immunology sub-study compared to 25.3% for the group that did not attend all visits within the visit window (p = 0.0169). City of residence, number of years living in the Lusaka/Ndola area, age, number of living children, planning to have more

children, and severity of any adverse events, level of formal education, literacy and frequency of alcohol use were not significantly different by visit attendance.

FSW only and SM only (Tables 5b, 5c)

Similar to the FSW and SM combined, the distribution of years in cohort prior to SiVET enrollment differed by visit attendance for FSW only (p = 0.0355) but not for SM only (p = 0.1475). Number of living children differed by visit attendance for SM (p = 0.0679) but not for FSW (p = 0.8254). Having a plan to have more children differed by visit attendance for FSW (p = 0.0529) but not for SM (p = 0.3107). Marital status (never married vs. divorced/separated/widowed) differed by visit attendance for SM (p = 0.0433) but not for FSW (p = 0.7112). Similar to the combined group, first intercourse (willingly vs. pressured/forced) differed by outcome for FSW only (p = 0.0559) but not for SM only (p = 0.5084). Again, similar to FSW and SM combined, participation in the immunology sub-study differed by visit attendance for FSW only (p = 0.0691); the p-value for SM only was 0.1090.

Logistic Regression

Model 1: FSW and SM combined (Table 6)

For our logistic regression analysis for the combined group (FSW and SM), we used only those variables that were significant at the alpha = 0.10 level in our bivariate analysis for the combined group. The odds of participating in all visits within the visit window was more than two times higher for those who were never

married compared to those who were either separate, divorced or widowed (aOR = 2.17, 95% CI: 1.01-4.6 p = 0.0459). For years in the preparatory cohort prior to SiVET study enrollment was significant with those in the preparatory cohort for a longer period of time being more likely to attend all visits in the visit window (aOR = 1.73, 95% CI: 1.03-2.91, p = 0.0403). The remaining variables included in the model were not significant at the alpha level of 0.05; these variables included the risk group (FSW or SM), first intercourse (willingly vs. forced/pressured), participation in immunology sub-study. However, there was a trend for not being forced/pressured into first intercourse and attending all study visits (p = 0.0926). FSW, in general, were less likely to attend all visits within the visit window compared to SM, although this was not significant at the alpha level of 0.05 (aOR = 0.57, 95% CI: 0.26-1.26, p = 0.1657)

Models 2 and 3: FSW only and SM only (Table 6)

The same method was used to select factors for the FSW only and SM only models. When we applied the logistic regression model to FSW only or SM only, none of the variables were significant. For FSW we assessed first intercourse (willingly vs. forced/pressured), participation immunology sub-study, years in preparatory cohort prior to SiVET study enrollment and having planned to have more children. For the model that included SM only, none of the two variables we assessed were significant: marital status and number of living children. SMs with more children were less likely to attend all visits, though not statistically significantly (aOR = 0.77, 95% CI: 0.47-1.27, p = 0.3053).

DISCUSSION

Statement of Principal Findings

In this study, we assessed the feasibility of retaining participants in a simulated HIV vaccine trial and factors associated with study participation. Participants were FSW and SM from two cities in Zambia, Lusaka and Ndola. In our analysis, we found that overall participation was high. Having the full contact information, such as home addresses and/or telephone numbers, enabled the study staff to encourage participation. However, a large proportion of women did not attend all visits in window. We found that the longer duration of participation in the cohort prior to the SiVET study and not ever being married (versus separated/divorced/widowed) were associated with the attending all visits within the visit window when assessing both FSW and SM combined. When FSW and SM were assessed separately, none of the factors assessed were significant.

Explanation of Findings and Relation to Other Studies

We found that women who stayed longer in the cohort prior to the SiVET study were more likely to attend all visits within the visit window. Being in the preparatory cohort prior to the SiVET study may have been conducive to establishing a trusting relationship between the participants and study staff. Another reason may be that they have more experience balancing their daily activities with study participation. Prior to the SiVET study, the participants were educated about vaccines which may impact their adherence to the visit schedule in the SiVET study.

We also found that women who were never married were more likely to attend all visits on time. Some pre-ART studies found that never having been married was not associated with study completion (28); however, other studies have found that never having been married to be related to higher loss-to-follow-up (28). Our findings may be related to the possibility that women who were never married have more time or fewer obligations, and therefore, are more likely to have a flexible schedule enabling them to attend all visits.

There was a trend for not being forced/pressured into first intercourse and attending all study visits ($p = 0.0926$). This factor might be representative of having experienced violence in the past that indicates some instability in one's current life that could affect study attendance. Along these lines, Magazi states that "powerlessness to negotiate 'safer sex'" and other "social characteristics contribute towards instability and poor prospects for being retained in trials" (24). In contrast, an HIV prevention effectiveness trial in South Africa and Zimbabwe found no association between study completion and having experienced domestic violence (29).

We did not find education or age to be related to visit attendance. In contrast, an analysis conducted by Feldblum et al., which combined data from four vaginal microbicide trials in sub-Saharan countries, found that the older and more educated the participants were, the more likely they were to complete the study (30). Similarly, in a clinical trial of candidate HIV vaccines, de Bruyn et al. found that older participants were less likely to be loss-to-follow-up (31). It is possible that because our participants attended vaccine education sessions prior

to SiVET study enrollment, this extra education may have mitigated the association between visit attendance and both age and education of the women.

Our study did not assess monetary or non-monetary incentives which may be important in encouraging participation, as suggested in Geldsetzer et al.'s systematic review of interventions to improve retention for prevention of mother to child transmission (PMTCT) care in sub-Saharan Africa (32) and Gappoo et al.'s study on community based HIV prevention effectiveness trial (29). We did not collect data assessing the effectiveness of texting, whereas, in a PMTCT retention study done by DiCarlo, et al., they found that visit reminder via text messages might be useful for encouraging attendance (33). In our study, not everyone had a telephone, potentially making it harder to contact participants to remind them about study visits.

Weaknesses of Our Study

Due to thorough screening of the participants for health issues, all women in this study were relatively healthy which may make our results less generalizable to less healthy women. Overall, our results are most generalizable to high-HIV risk, young urban FSWs and SMs. An important shortcoming of this study is that our analysis was a secondary analysis using data initially collected for other purposes, so data on other covariates possibly related to study retention (e.g., food insecurity, mental health) were not collected. Additionally, all self-reported data is subject to information bias, which may or may not be differential by the outcome interest.

Strengths of Our Study

This is one of the only studies to look at the feasibility of retaining participants in a simulated HIV vaccine trial and factors associated with study participation among extremely high HIV-risk women. Having participants in a cohort (for several months) prior to this study made it possible to collect detailed data on various socioeconomics, clinical, and demographic factors. The study length (duration of follow-up being 12 months, up to 15 visits) and procedures (assessments at each visit) were done very similarly to an actual HIV vaccine trial, including being staffed by trained health workers. Standardized forms and procedures were followed in both local languages and in English.

Public Health Implications and Future Research

Public health implications

There is critical need for an HIV vaccine in order to prevent the continued spread of HIV, particularly among high-risk populations (18). Development of a vaccine will require clinical trials to identify an effective and safe vaccine while also considering the economic and time costs of conducting the trials. The validity and quality of these trials will require full adherence to study protocols, including attendance at study visits (23). Previous HIV prevention trials have had challenges retaining participants, impacting their results (22-24). The results of our study are valuable for future researchers by helping them identify factors that may be associated with attending all study visits in the visit window.

High rate of retention in our study indicates that among other factors, investing time and educating participants, familiarizing participants with procedures, implications of getting HIV, and advantages of vaccine prior to the start of study is beneficial and important in improving participation and adherence to the study visit schedule. Our results suggest many similarities but important differences in FSW and SM populations. For example, duration of time in prior preparatory cohort seems to be beneficial for retaining FSW but perhaps less important for SM. Choosing SM who were never married may help in retaining participants in the study.

Future research

Much more research can be done in this field. We do not know how improving communication with participants through text messages would enhance participation. In future studies in which all participants would get a cellular phone, we can assess the role of text and phone communication between participants and the study personnel. In a real HIV vaccine trial, the participants might experience adverse side effects from the vaccine which may influence participation. Other future studies can look into other variations of the outcome, such as attended all visits but not all on time or the number and timing of missed visits. Studying other key populations (men or individuals with health problems for example) and other factors such as psychological condition of the participants; level of hunger and food insecurity of the participants, their children and cohabitants; health conditions of their children and cohabitants; and whether they have family support would be beneficial.

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TABLES

Table 1. Inclusion and exclusion criteria for SiVET study enrollment, Zambia, 2017

Inclusion Criteria

- Women aged 18-40 years old
- At high risk of HIV, defined by occupation (female sex workers) or recent delivery (single mothers)
- Planning to stay in Lusaka or Ndola for at least 12 months
- Willing to undergo HIV testing, counseling and receive HIV test results
- Able and willing to provide adequate locator information for tracking purposes, and willing to be contacted by the study staff
- Willing and able to provide adequate locator information and willing to be contacted by phone if available or home visit by study staff.
- Willing to answer questions on HIV risk factors, and if infected, questions related to the route and timing of exposure
- Willing and able to return for follow-up visits
- Willing and able to provide informed consent
- Willing to undergo pregnancy testing and use an injectable, implant or IUD from screening until four months after the last vaccination during the study

Exclusion Criteria

- HIV-1/2 infection
- Pregnant or intending to become pregnant during the study
- History of severe allergic reaction to any substance including eggs, gelatin, and neomycin
- Any clinically significant acute illness or chronic medical condition that is considered progressive, or in the opinion of the investigator, makes the volunteer unsuitable for participation in the study
- Immunosuppressive therapy
- Women who opt out of HIV counseling and testing services provided by the clinic
- Women who have any condition that in the opinion of the Investigator or designee, would preclude provision of informed consent, or otherwise interfere with achieving the study objectives
- Participation in another clinical trial unless approved by the
- Principal Investigator and IAVI
- Recent receipt of an investigational blood product or vaccine
- Failure of assessment of understanding

List pulled directly from IAVI Protocol SiVET RZHRG version: 4.0, September 2015;
SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;

Table 2. SiVET study participation timeline and activities, by study group, Zambia, 2017

Visit Number	Month	Day	Visit Type & Procedures	
			Main Study	Additional Sub-Study Procedures
V0			Screening	
V1	M0	0	Informed Consent, Medical History, Physical Exam, Randomization, Vaccine 1, Reactogenicity	
V2		3	Telephone Post-vaccination contact	In-Clinic Post-vaccination contact + Blood Draw
V3		7	Reactogenicity	
V4		14	N/A	Immunology: additional blood draw
V5		21	N/A	Immunology: additional blood draw
V6	M1	28	Follow-up	
V7	M3	84	Physical Exam, Vaccine 2, Reactogenicity	
V8		87	Telephone Post-vaccination contact	In-Clinic Post-vaccination contact + Blood Draw
V9		91	Reactogenicity	
V10		98	N/A	Immunology: additional blood draw
V11		105	N/A	Immunology: additional blood draw
V12	M4	112	Follow-up	
V13	M6	168	Follow-up	
V14	M9	252	Follow-up	
V15	M12	336	Follow-up, Study Exit	

N/A = “not applicable” for participants in standard group;
SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;

Table 3. Data collected by risk group prior to SiVET study enrollment, Zambia, 2017

Data collected	FSW	SM
Years in cohort prior to SiVET enrollment	x	x
City of residence, Lusaka/Ndola	x	x
Number of years living in Lusaka/Ndola	x	x
Age (years)	x	x
Number of living children	x	x
Has plan to have more children	x	x
Marital Status, Never married vs. Widowed/Divorced/Separated	x	x
Formal education	x	x
Can understand the local language, Nyanja or Bemba	x	x
Can read the local language, Nyanja or Bemba	x	x
Can understand English	x	x
Can read English	x	x
Age (years) at first sexual intercourse of any kind	x	x
BMI (Kg/m^2)	x	x
The first intercourse was done willingly or forced/pressured	x	x
Total number of male sex partners in entire life	x	x
Participation in immunology sub-study	x	x
Frequency of alcohol use	x	x
Age when started sex work	x	-
Has been a victim of violence by clients	x	-
Knows of programs to help or support FSW	x	-
Recreational drugs used in the previous month	x	-
Lives with Family/Alone	-	x
Number of male sex partners in the previous year	-	x

FSW: female sex worker; SM: single woman with a child under 5 years of age;
SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;
BMI: body mass index;

Table 4. Distribution of visit attendance, SiVET study, Zambia, 2017

	FSW and SM		FSW		SM		p-value
	Total		Total		Total		
	N	%	N	%	N	%	
Visit attendance	159	100.0	59	100.0	100	100.0	0.6825
Attended all visits in window	68	42.8	24	40.7	44	44.0	
Other	91	57.2	35	59.3	56	56.0	
Attended all visits, but some either	58	36.4	24	40.7	34	34.0	0.3981
Missed at least one visit	33	20.8	11	18.6	22	22.0	0.6142
Number of missed visits among those who missed at least one visit, *median (IQR)*	1	(1 to 2)	1	(1 to 4)	1	(1 to 2)	0.6314

Chi-square (or Fisher's Exact) tests were used for categorical variables, as appropriate, and Wilcoxon's Two-Sample tests were used for non-normally distributed continuous variables.
P-values are two tailed.
FSW: female sex worker; SM: single woman with a child under 5 years of age; IQR: interquartile range;
SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;

Table 5a. SiVET Study participant demographic characteristics stratified by risk group, Zambia, 2017

	FSW and SM						
	Total		Attended all visits in window		Did not attend all visits in window		
	N	**%**	**N**	**%**	**N**	**%**	**p-value⁺**
Participant status at the end of study							0.0716
Finished the study	153	96.2	68	100.0	85	93.4	
Lost to follow-up	5	3.1	0	0.0	5	5.5	
Voluntarily withdrawal	1	0.6	0	0.0	1	1.1	
Years in cohort prior to SiVET enrollment, *median (IQR)*	1	0	1	1	1	1	0.0384
City of residence							0.5669
Lusaka	79	49.7	32	47.1	47	51.6	
Ndola	80	50.3	36	52.9	44	48.4	
Number of years living in Lusaka/Ndola, *median (IQR)*	20	(15 to 24)	20	(15 to 22)	20	(15 to 24)	0.8100
Age (years), *median (IQR)*	23	(21 to 28)	23	(21 to 28)	24	(21 to 30)	0.5237
Number of living children, *median (IQR)*	1	(1 to 2)	1	(1 to 2)	2	(1 to3)	0.1446
Has plan to have more children							0.8648
Yes	52	32.7	23	33.8	29	31.9	
No	107	67.3	45	66.2	62	68.1	
Became pregnant during SiVET study							0.5180
Yes	10	6.3	3	4.4	7	7.7	

No	149	93.7	65	95.6	84	92.3	
Total number of adverse events during SiVET study, *median (IQR)*	0	(0 to 1)	0	(0 to 1)	0	(0 to 1)	0.9921
Maximum severity of any adverse event during SiVET study							0.4212
Life Threatening or Severe	3	1.9	0	0.0	3	3.3	
Moderate or Mild	65	40.9	29	42.6	36	39.6	
None	91	57.2	39	57.4	52	57.1	
HIV seroconversion during the SiVET study							0.6361
Yes	4	2.5	1	1.5	3	3.3	
No	155	97.5	67	98.5	88	96.7	
Marital Status							0.0661
Never Married	111	70.3	53	77.9	58	64.4	
Divorced / Separated / Widowed	47	29.7	15	22.1	32	35.6	
Formal education							0.5051
Secondary or College	75	47.2	30	44.1	45	49.5	
Primary or None	84	52.8	38	55.9	46	50.5	
Can understand the local language, Nyanja or Bemba							1.0000
Easily	157	98.7	67	98.5	90	98.9	
With difficulty OR Not at all	2	1.3	1	1.5	1	1.1	
Total	159	100	68	100	91	100	
Can read the local language, Nyanja or Bemba							0.5242
Easily	96	60.4	43	63.2	53	58.2	
With difficulty OR Not at all	63	39.6	25	36.8	38	41.8	
Can understand English							0.8996
Easily	57	35.8	24	35.3	33	36.3	
With difficulty OR Not at all	102	64.2	44	64.7	58	63.7	
Can read English							0.2427
Easily	50	31.4	18	26.5	32	35.2	

With difficulty OR Not at all	109	68.6	50	73.5	59	64.8	
Age (years) at first sexual intercourse of any kind, *median (IQR)*	16	(15 to 18)	16	(15 to 18)	16	(15 to 18)	0.5139
BMI (Kg/m²), *median (IQR)*	22	(19 to 25)	22	(19 to 25)	22	(20 to 25)	0.7010
The first intercourse was done							0.0843
Willingly	115	72.3	54	79.4	61	67.0	
Pressured or Forced	44	27.7	14	20.6	30	33.0	
Total number of male sex partners in entire life, *median (IQR)*	4	(2 to 30)	4	(2 to 30)	4	(2 to 30)	0.7514
Participated in immunology sub-study							0.0169
Yes	30	18.9	7	10.3	23	25.3	
No	129	81.1	61	89.7	68	74.7	
Frequency of alcohol use							0.3003
Daily / Weekly	41	26.5	20	30.8	21	23.3	
0 - 3 times per month	114	73.5	45	69.2	69	76.7	

[+] Chi-square (or Fisher's Exact) tests were used for categorical variables, as appropriate, and Wilcoxon's Two-Sample tests were used for non-normally distributed continuous variables.
P-values are two tailed.
Counts may not sum to totals due to missingness
FSW: female sex worker; IQR: interquartile range; SM: single woman with a child under 5 years of age;
BMI: body mass index; SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;

Table 5b. SiVET Study participant demographic characteristics stratified by risk group (FSW only), Zambia, 2017

	FSW						
	Total		Attended all visits in window		Did not attend all visits in window		
	N	%	N	%	N	%	p-value+
Participant status at the end of study							1.0000
Finished the study	58	98.3	24	100.0	34	97.1	
Lost to follow-up	1	1.7	0	0.0	1	2.9	
Voluntarily withdrawal	0	0.0	0	0.0	0	0.0	
Years in cohort prior to SiVET enrollment, *median (IQR)*	1	1	2	1	1	1	0.0355
City of residence							0.3739
Lusaka	43	72.9	16	66.7	27	77.1	
Ndola	16	27.1	8	33.3	8	22.9	
Number of years living in Lusaka/Ndola, *median (IQR)*	20	(8 to 26)	19	(9 to 24)	21	(8 to 27)	0.6780
Age (years), *median (IQR)*	27	(22 to 31)	26	(23 to 30)	27	(22 to 31)	0.5486
Number of living children, *median (IQR)*	2	(1 to 3)	2	(1 to 3)	2	(1 to 3)	0.8254
Has plan to have more children							0.0529
Yes	12	20.3	8	33.3	4	11.4	
No	47	79.7	16	66.7	31	88.6	

Became pregnant during SiVET study							0.6392
Yes	4	6.8	1	4.2	3	8.6	
No	55	93.2	23	95.8	32	91.4	
Total number of adverse events during SiVET study, *median (IQR)*	1	(0 to 1)	1	(0 to 1)	1	(0 to 1)	0.6486
Maximum severity of any adverse event during SiVET study							0.5741
Life Threatening or Severe	1	1.7	0	0.0	1	2.9	
Moderate or Mild	32	54.2	15	62.5	17	48.6	
None	26	44.1	9	37.5	17	48.6	
HIV seroconversion during the SiVET study							0.5091
Yes	2	3.4	0	0.0	2	5.7	
No	57	96.6	24	100.0	33	94.3	
Marital Status							0.7112
Never Married	42	72.4	18	75.0	24	70.6	
Divorced / Separated / Widowed	16	27.6	6	25.0	10	29.4	
Formal education							0.1660
Secondary or College	31	52.5	10	41.7	21	60.0	
Primary or None	28	47.5	14	58.3	14	40.0	
Can understand the local language, Nyanja or Bemba							1.0000
Easily	58	98.3	24	100.0	34	97.1	
With difficulty OR Not at all	1	1.7	0	0.0	1	2.9	

Can read the local language, Nyanja or Bemba							0.3409
Easily	29	49.2	10	41.7	19	54.3	
With difficulty OR Not at all	30	50.8	14	58.3	16	45.7	
Can understand English							0.4607
Easily	28	47.5	10	41.7	18	51.4	
With difficulty OR Not at all	31	52.5	14	58.3	17	48.6	
Can read English							0.1125
Easily	27	45.8	8	33.3	19	54.3	
With difficulty OR Not at all	32	54.2	16	66.7	16	45.7	
Age (years) at first sexual intercourse of any kind, *median (IQR)*	16	(15 to 18)	16	(15 to 18)	16	(15 to 19)	0.4414
BMI (Kg/m²), *median (IQR)*	23	(20 to 26)	22	(20 to 26)	24	(21 to 26)	0.5703
The first intercourse was done							0.0559
Willingly	41	69.5	20	83.3	21	60.0	
Pressured or Forced	18	30.5	4	16.7	14	40.0	
Total number of male sex partners in entire life, *median (IQR)*	40	(20 to 100)	50	(20 to 282)	40	(15 to 80)	0.5039
Participated in immunology sub-study							0.0691
Yes	9	15.3	1	4.2	8	22.9	
No	50	84.7	23	95.8	27	77.1	
Frequency of alcohol use							0.4095
Daily / Weekly	36	63.2	16	69.6	20	58.8	
0 - 3 times per month	21	36.8	7	30.4	14	41.2	

Age when started sex work, *median (IQR)*	19	(16 to 23)	19	(16 to 26)	19	(17 to 22)	0.8170
Has been a victim of violence by clients							0.9774
Yes	26	45.6	11	45.8	15	45.5	
No	31	54.4	13	54.2	18	54.5	
Knows of programs to help or support FSW							0.5091
Yes	2	3.4	0	0.0	2	5.7	
No	57	96.6	24	100.0	33	94.3	
Recreational drugs used in the previous month							0.3478
Marijuana	1	2.2	1	6.3	0	0.0	
None	45	97.8	15	93.8	30	100.0	

[+] Chi-square (or Fisher's Exact) tests were used for categorical variables, as appropriate, and Wilcoxon's Two-Sample tests were used for non-normally distributed continuous variables.
P-values are two tailed.
Counts may not sum to totals due to missingness.
FSW: female sex worker; SM: single woman with a child under 5 years of age; IQR: interquartile range;
BMI: body mass index; SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;

Table 5c. SiVET Study participant demographic characteristics stratified by risk group, Zambia, 2017

	SM						
	Total		Attended all visits in window		Did not attend all visits in window		
	N	%	N	%	N	%	p-value+
Participant status at the end of study							0.1283
Finished the study	95	95.0	44	100.0	51	91.1	
Lost to follow-up	4	4.0	0	0.0	4	7.1	
Voluntarily withdrawal	1	1.0	0	0.0	1	1.8	
Years in cohort prior to SiVET enrollment, *median (IQR)*	1	1	1	0	1	1	0.1475
City of residence							0.9465
Lusaka	36	36.0	16	36.4	20	35.7	
Ndola	64	64.0	28	63.6	36	64.3	
Number of years living in Lusaka/Ndola, *median (IQR)*	20	(18 to 22)	20	(18 to 22)	19	(17 to 22)	0.7096
Age (years), *median (IQR)*	22	(20 to 25)	23	(21 to 25)	22	(20 to 27)	0.9362
Number of living children, *median (IQR)*	1	(1 to 2)	1	(1 to 2)	1	(1 to 2)	0.0679
Has plan to have more children							0.3107
Yes	40	40.0	15	34.1	25	44.6	
No	60	60.0	29	65.9	31	55.4	

Became pregnant during SiVET study							0.692
Yes	6	6.0	2	4.5	4	7.1	
No	94	94.0	42	95.5	52	92.9	
Total number of adverse events during SiVET study, *median (IQR)*	0	(0 to 1)	0	(0 to 1)	0	(0 to 1)	0.6636
Maximum severity of any adverse event during SiVET study							0.6433
Life Threatening or Severe	2	2.0	0	0.0	2	3.6	
Moderate or Mild	33	33.0	14	31.8	19	33.9	
None	65	65.0	30	68.2	35	62.5	
HIV seroconversion during the SiVET study							1.0000
Yes	2	2.0	1	2.3	1	1.8	
No	98	98.0	43	97.7	55	98.2	
Marital Status							0.0433
Never Married	69	69.0	35	79.5	34	60.7	
Divorced / Separated / Widowed	31	31.0	9	20.5	22	39.3	
Formal education							0.7951
Secondary or College	44	44.0	20	45.5	24	42.9	
Primary or None	56	56.0	24	54.5	32	57.1	
Can understand the local language, Nyanja or Bemba							0.4400
Easily	99	99.0	43	97.7	56	100.0	
With difficulty OR Not at all	1	1.0	1	2.3	0	0.0	
Can read the local language, Nyanja or Bemba							0.1315
Easily	67	67.0	33	75.0	34	60.7	

With difficulty OR Not at all	33	33.0	11	25.0	22	39.3	
Can understand English							0.5820
Easily	29	29.0	14	31.8	15	26.8	
With difficulty OR Not at all	71	71.0	30	68.2	41	73.2	
Can read English							0.9542
Easily	23	23.0	10	22.7	13	23.2	
With difficulty OR Not at all	77	77.0	34	77.3	43	76.8	
Age (years) at first sexual intercourse of any kind, *median (IQR)*	17	(15 to 18)	17	(16 to 18)	16	(15 to 18)	0.1980
BMI (Kg/m²), *median (IQR)*	21	(19 to 24)	21	(19 to 24)	21	(19 to 24)	0.9173
The first intercourse was done							0.5084
Willingly	74	74.0	34	77.3	40	71.4	
Pressured or Forced	26	26.0	10	22.7	16	28.6	
Total number of male sex partners in entire life, *median (IQR)*	2	(1 to 3)	3	(2 to 4)	2	(1 to 3)	0.4448
Participated in immunology sub-study							0.1090
Yes	21	21.0	6	13.6	15	26.8	
No	79	79.0	38	86.4	41	73.2	
Frequency of alcohol use							0.1611
Daily / Weekly	5	5.1	4	9.5	1	1.8	
0 - 3 times per month	93	94.9	38	90.5	55	98.2	
Lives with							0.4610
Family	93	93.0	42	95.5	51	91.1	
Alone	7	7.0	2	4.5	5	8.9	

Number of male sex partners in the previous year, *median (IQR)*	1	(1 to 2)	1	(1 to 2)	1	(1 to 1.5)	0.2160

[+] Chi-square (or Fisher's Exact) tests were used for categorical variables, as appropriate, and Wilcoxon's Two-Sample tests were used for non-normally distributed continuous variables.
P-values are two tailed.
Counts may not sum to totals due to missingness
FSW: female sex worker; SM: single woman with a child under 5 years of age; IQR: interquartile range; BMI: body mass index; SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;

Table 6. Logistic regression results describing the association between attending all visits in window (versus not) and participant demographic characteristics, stratified by risk group, SiVET study, Zambia, 2017

	FSW and SM				FSW				SM			
	aOR	95%CI		p-value	aOR	95%CI		p-value	aOR	95%CI		p-value
Risk group (FSW vs. SM)	0.57	0.26	1.26	0.1657								
The first intercourse (willingly vs. forced/pressured)	1.94	0.90	4.22	0.0926	3.04	0.78	11.86	0.1090				
Participated in immunology sub-study (did not vs. did participate)	2.23	0.85	5.90	0.1046	5.69	0.55	58.63	0.1443				
Years in cohort prior to SiVET enrollment	1.73	1.02	2.91	0.0403	1.52	0.69	3.36	0.2988				
Marital Status (never married vs. separated/divorced/widowed)	2.17	1.01	4.65	0.0459					1.75	0.57	5.37	0.3306
Has plan to have more children (yes vs. no)					3.64	0.76	17.57	0.1074				
Number of living children									0.77	0.47	1.27	0.3053

Variables selected based on p-value = 0.10 cutoff determined from bivariate analysis (see Tables 5a-5c).
Chi-square (or Fisher's Exact) tests were used for categorical variables, as appropriate, and Wilcoxon's Two-Sample tests were used for non-normally distributed continuous variables.
P-values are two tailed.
FSW: female sex worker; SM: single woman with a child under 5 years of age; aOR: Adjusted odds ratio;
CI: confidence interval; SiVET: Simulated Vaccine Efficacy Trial, Zambia SiVET MMR Tdap-IPV;