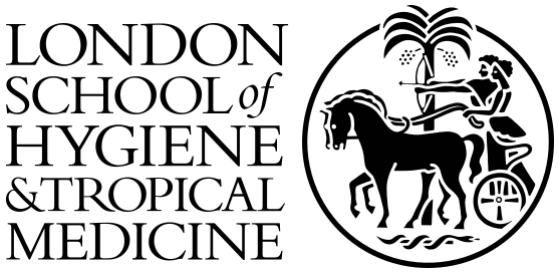

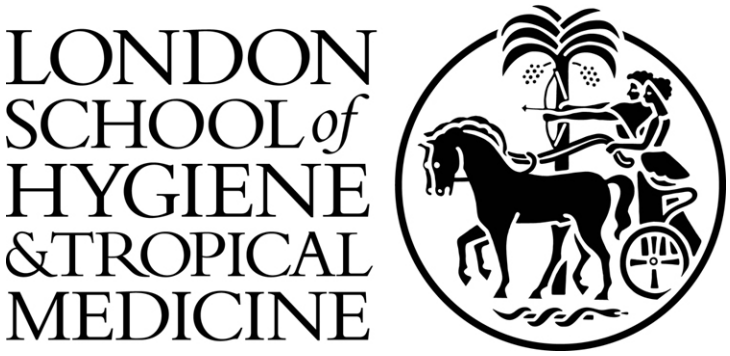

Using observational cohort data from Key populations to plan HIV intervention studies

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Declaration of own work

I Andrew Max Abaasa, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Andrew Max Abaasa

May 2020

Abstract

Background: Globally, new HIV-infections continue to occur mostly in Sub-Saharan Africa despite the known-to-work HIV-prevention interventions. Suboptimal adherence to the available HIV prevention interventions is cited. Vaccination could help minimise non-adherence to an HIV preventive intervention but does require the completion of the full vaccination schedule. An HIV vaccine would be a useful addition to HIV prevention packages, but vaccines need assessment in efficacy trials and investigators need suitable populations for trials. Key populations including Fisher-folks (FF) and Female Sex Workers (FSW) in Uganda could be useful. However, available data for planning trials in these populations come from observational cohorts and evidence suggests that trial environment and/or participants selection could differ from observational cohorts, which could alter trial targeted outcomes. This difference was investigated using Simulated HIV-vaccine efficacy trials (SiVETs); a trial that mimicked an HIV vaccine efficacy trial using a proxy vaccine.

Methods: Two SiVETs were nested within observational cohorts of FF (2012 – 2014) and FSW (2014-2017). The SiVETs screened and enrolled participants from observational cohorts, and administered a licensed Hepatitis B vaccine at 0, 1 and 6 months as a proxy for an HIV-vaccine. Over the 12 month follow-up, SiVETs conducted HIV testing, risk behaviour assessment, and promoted and provided reliable contraceptives to women.

Results: In total, there were 3989 [1575 FF & 2414 FSW] participants in the observational cohorts and 572 [282 FF & 290 FSW] of these were enrolled into SiVETs. There were significant differences between characteristics of participants in SiVETs and those in the observational cohorts. At 12-months, HIV incidence and risk behaviours were higher in the observational cohorts than SiVETs while retention was lower. Promotion and provision of reliable contraceptives in SiVETs increased the proportion of women using them from 55% at baseline to >90% at the end of vaccination.

Conclusion: Researchers designing HIV efficacy trials using observational data in these and similar populations need to consider potential for changes in the targeted trial outcomes following recruitment into trials and its effect on trial statistical power.

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I express my appreciation for the invaluable and timely guidance provided by my Supervisors Jim Todd, Stephen Nash, and Pontiano Kaleebu and advisors Matt Price and Patricia E Fast. Thank you very much.

I cannot forget the Late Basia Zaba who was the chief examiner at my upgrading; you did a great Job to help me improve my work. May almighty God receive you with both hands, rest in peace. I am grateful for the useful comments from Tansy Edwards, the other examiner at my upgrading. Not forgetting the tireless work done by my upgrading committee chair, Suneetha Kadiyala.

I recognize the timely support provided by LSHTM administrative staff including Jenny Fleming and Lauren Dalton, you were outstanding. I also extend my thanks to the LSHTM Registry, Fees and VISA teams; i enjoyed your quick and positive response to requests.

This work would not have been possible without the support of the MRC/UVRI and LSHTM Uganda Research Unit's statistics section staff, clinic and other teams that participated in the collection of the data used in this thesis. Heartfelt thanks go to study participants and their communities. These groups sacrifice a lot to support advancements in science.

Finally yet importantly, i would like to thank my wife Hope Grania Abaasa for continued support, encouragements and standing strong while I was away in London and other places for studies. May God keep you as solid as he has for these years.

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AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
BMC	Biomedical Central
CI	Confidence Interval
CROI	Conference on Retroviruses and Opportunistic Infections
DMPA	Depot Medroxyprogesterone Acetate
EDCTP	European & Developing Countries Clinical Trials Partnership
FF	Fisher-folk
FSW	Female Sex Worker
GD	Genital Discharge
GUD	Genital Ulcer Disease
HCT	HIV Counselling and Testing
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
IUCD	Intrauterine Contraceptive Device
KM	Kilo Metre
LSHTM	London School of Hygiene and Tropical Medicine
MMR	Measles, Mumps, and Rubella
MRC	Medical Research Council
MS	Microsoft
MSM	Men who have sex with men
OBC	Observational Cohort
PhD	Doctor of Philosophy
PrEP	Pre Exposure Prophylaxis
PSG	Population Studies Group
PYAR	Person Years At Risk
PYO	Person Years of Observation
R4P	Research for Prevention
RCT	Randomised Controlled Trials
SD	Standard Deviation
SiVET	Simulated Vaccine Efficacy Trial
SOM	Study Operations Manual
SOP	Standard Operating Procedure
SSA	Sub Sahara Africa
STI	Sexually Transmitted Infection
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
U=U	Undetectable=Untransmissable
UK	United Kingdom
UNAIDS	United Nations Programme on HIV/AIDS
USA	United States of America
UVRI	Uganda Virus Research Institute

Chapter one: Background

1.1 Global HIV burden

The burden of HIV continues to be a global challenge 38 years after diagnosis of the first case of HIV/AIDS (1). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2019 report, Sub Saharan Africa (SSA) is disproportionately affected (2). The report estimates that in 2018, 61% of global new HIV infections happened in SSA (2). In SSA, the new HIV infections vary by region with Eastern and Southern Africa accounting for most of these (2). The new infections are happening, despite the potential to curb them with effective biomedical HIV prevention interventions, including safe medical male circumcision (3, 4), antiretroviral therapy (ART) in form of Pre Exposure Prophylaxis (PrEP) (5-9) or treatment of the HIV infected partner to prevent transmission (10). Suboptimal adherence to available interventions has been identified as the key challenge in fighting against HIV infection in SSA (5).

1.2 Need for HIV vaccine

One of the long-term hopes for controlling the HIV/AIDS pandemic is a safe, effective and affordable preventive HIV vaccine (11-13). Historically, vaccines have been more effective than therapeutic medicines at curbing infectious diseases (14). Even in countries with limited resources, comprehensive national immunization programmes have led to eradication or reduction of smallpox, polio, measles, pertussis, meningococcal meningitis, diphtheria, hepatitis B, congenital rubella syndrome, and tetanus among other infectious diseases (15). Furthermore, vaccines have a unique public health importance through herd immunity (16-18) and are likely to reduce the burden of adherence compared to a daily pill (13).

1.2.1 Populations for HIV vaccine efficacy trials

The HIV vaccines in development have to go through rigorous assessment in efficacy trials. Therefore, populations with high HIV incidence, good retention in follow up and adequate access to and use of HIV related health services are needed to conduct successful HIV vaccine efficacy trials (19). Because of the high HIV incidence, SSA is likely to continue being a major destination for HIV prevention trials. However, in countries such as Uganda where the general population HIV prevalence is high > 7% (20, 21) but annual incidence low < 1% (20, 22, 23), HIV vaccine efficacy trials will have to be conducted among population subgroups. The subgroups could include HIV discordant couples, occupational women at high risk of HIV acquisition- Female Sex

Workers (FSW), members of the fishing communities-Fisher-folks (FF) on the shore of Lake Victoria and men who have sex with men (MSM). Observational cohorts conducted in these population subgroups have shown that, they are characterized by high HIV incidence, 3.4 to 11.4 new cases per 100 person years (24-30), high willingness to participate, > 89% (31, 32) and good retention in follow up, >75% (28, 33, 34).

Recent findings in HIV discordant couples confirmed that, ART significantly reduces the risk of HIV transmission from an infected to an uninfected partner (35). With evidence that Undetectable=Untransmissable (36), HIV vaccine efficacy trials conducted in discordant couples with a high use of ART may have lower HIV incidence, perhaps even low enough to undermine use of these populations for potential HIV vaccine efficacy trials. In Uganda, there is limited or no data on MSM and this population remains challenging to work with for a myriad of legal and related reasons (37). Therefore, occupational women in sex work (FSW) and members of fishing communities on the shoreline of Lake Victoria remain the only potential key populations eligible for HIV vaccine efficacy trials in Uganda.

1.2.2 Designing HIV efficacy trials in these Key populations

Designing HIV vaccine efficacy trials in the FSW and FF populations in Uganda requires accurate estimation of the expected HIV incidence in the control (placebo) arm, routine use of reliable contraceptives by female participants to prevent pregnancy, good retention in follow up and provision of other HIV risk reduction measures such as routine HIV counselling among others. The common practice includes obtaining estimates from previous efficacy trials in the same or similar population. To our knowledge, no HIV efficacy trials have completed follow up in the FF on the shoreline of Lake Victoria in Masaka or FSW in Kampala to provide this baseline data and key populations tend to be different from the general population.

In the absence of previous trials, data from historical observational cohorts, pilot cohorts and/or studies of willingness to participate may be used. One of the challenges in designing HIV prevention trials is that observational data in the target population is often very different from that found in a trial. While the efficacy trial environment is highly controlled with participants visiting study clinic more frequently for HIV risk reduction counselling, provision of condoms and treatment of other sexually transmitted infections, this might not be the case in observational

cohorts. The differences in procedures between efficacy trials and observational cohort could alter the efficacy trial control arm HIV incidence obtained from the underlying population observational cohort and used to plan efficacy trials, as seen previously (38, 39). If not carefully considered, this could lead to failure to calculate a proper trial sample size.

In light of lack of previous trials in the FF on the shore of Lake Victoria and FSW in Kampala Uganda, what may not be answered for these key populations is the effect of selection into trial on underlying population HIV incidence. Trial selection criteria include participants that accept to delay pregnancy through routine use of reliable contraceptives, keep in follow up for the trial duration and positively respond to HIV risk reduction measures provided in trials. These could alter HIV incidence and hence trial statistical power as previously highlighted in other trials, elaborated below.

1.3 Trial targeted outcome and other elements for planning trials

1.3.1 HIV incidence

The trial inclusion criteria select participants whose characteristics are different from those not selected from the source population (26, 40). Participants that consider themselves at high risk of HIV infection participate more in feasibility cohorts than clinical trials (40). This difference and/or trial controlled environment could in some way bias/diminish HIV incidence in the trial even in absence of an effective new HIV biomedical intervention. The lower HIV incidence in the control arm than that predicted at the trial design could affect the trial statistical power.

One systematic review (41) identified six HIV prevention studies that were unsuccessful or terminated because of reduced statistical power, due to observing lower HIV incidence during participant follow up than that predicted based on the source population observational data. Similar loss in statistical power was observed in 2007/8 in microbicides trials in Nigeria (38) and Ghana (39, 42). A similar reason led to premature termination of these trials. In the three trials, HIV incidence of 5 per 100 person years at risk (PYAR) had been predicted at the design stage but the investigators only observed HIV incidence of 1.5 per 100 PYAR (38), 1.1 per 100 PYAR (39) and 2.5 per 100 PYAR (42) in the control arms during participant follow up.

On the contrary, a more recent trial in South Africa in 2016 (43) had the sample size recalculated to a lower number after observing more than anticipated HIV incidence. In this trial, HIV incidence

of 3.9 per 100 PYAR had been predicted and used to determine the trial size at the design stage but the sample size was adjusted (on recommendation of independent data monitoring committee) basing on HIV incidence of 5 per 100 PYAR observed during follow up. At trial completion, the investigators observed HIV incidence of 4.5 per 100 PYAR in the control arm. Furthermore, in 2009, feasibility cohorts (40) conducted at trial sites before trial roll out showed annual HIV incidence of 6.2 per 100 PYAR. Investigators used HIV incidence of 4 per 100 PYAR to estimate the trial sample size citing the reason that women that correctly identified themselves at high risk of HIV infection may have been the first to come forward to participate in the feasibility cohorts. At the end of trial follow up, they observed HIV incidence of 4.3 per 100 PYAR in the control arm (44).

These clear differences in HIV incidence between trial control arm and source population observational data could mean that observational data should be used with caution while planning efficacy trials especially in populations without previous efficacy trial experience such as members of fishing communities on shores of Lake Victoria and Female sex workers in Kampala, Uganda. An astute clinical/statistical team should consider adjusting for these differences when estimating the required trial sample size.

1.3.2 Need for reliable contraceptives use in HIV vaccine efficacy trials

HIV vaccine efficacy trials recruit both men and women. These trials take months or years from recruitment to completion of follow up, therefore women could become pregnant. Women who become pregnant have to be withdrawn from vaccination to avoid exposing the foetus to a product whose effects are not known. Lately, there is a call to find vaccine candidates that allow inclusion of pregnant women in trials (45-47). Before this happens, more withdrawals of pregnant women from trials than that anticipated could significantly lower the trial sample size and negatively effect the trial statistical power. If women withdrawn from the trial follow up due to pregnancy are also those more likely to sero convert that would lower the estimated HIV incidence. Therefore, HIV vaccine efficacy trials need to be conducted in women who are not pregnant and willing to delay pregnancy. These trials need participants to be sexually active and potentially exposed to HIV, so it is important to prevent pregnancies through use of reliable, long-acting, reversible contraceptive methods. Cultural and logistical challenges in addition to the need to use and adhere to long-term contraceptive use among women may make it difficult to recruit them into such HIV vaccine

efficacy trials (48). The need to use reliable contraceptives excludes from trials women who do not want to use contraceptives and those wanting to get pregnant, creating a significant potential for selection bias.

1.3.2.1 Reliable contraceptives use, pregnancy incidence in previous HIV prevention trials

The baseline reliable contraceptives use reported in the previous efficacy trials of non HIV vaccine but other HIV preventive products in Africa has ranged 8.3% to 39% (38, 39, 49, 50) with minimal, 33% - 65% increase in their use reported during follow up (51). The incidence of pregnancy from these and other efficacy trials in Africa has ranged from 1 to 27 pregnancies per 100 women-years (52). These trials mainly recruited Women in HIV sero-discordant couple relationship (49-51) or in the general population (38, 39, 42).

1.3.2.2 Reliable contraceptives, pregnancy incidence in previous HIV vaccine efficacy trials

Of the concluded HIV vaccine efficacy trials (53, 54), only one reported data on reliable contraceptives use and incidence of pregnancy (55). In this trial, 36% of the women reported use of reliable contraceptives at baseline and no data on uptake during follow up is provided. The annual incidence of pregnancy was 9.6 per 100 women-years of follow up. These HIV vaccine efficacy trials recruited participant from the general population in South Africa (53) and Thailand (54).

1.3.2.3 Reliable contraceptives use and pregnancy incidence in FF and FSW

To date, no HIV vaccine or other efficacy trials have completed follow up in FSW in Kampala and FF on the shoreline of Lake Victoria in Masaka or elsewhere. Therefore, there is limited or no baseline data on uptake and use of reliable contraceptives to be used in planning HIV vaccine efficacy trials targeting women and their spouses in these key populations. Such data will have to come from observational or pilot studies. Observational studies conducted in these key populations in Uganda (56, 57) and elsewhere (58) have shown low contraceptives use 11%-60%. In Uganda, the only previous observational study (57) to report data on reliable contraceptives use in the FF showed that 35.2% of the women use reliable contraceptive methods. This is similar to 35% reported in the general population (59) in Uganda but lower than 59.6% shown in the FSW population in Kampala (56). The high reliable contraceptives use in the FSW population could be linked to the occupational demands of sex work. All the women, 100% in the FSW population depend on sex work for livelihood and unprotected sex has been associated with higher pay (36)

but higher risk of unwanted pregnancy. The need to stay free from pregnancy to satisfy male clients' demand for sex could be the motivator for the higher reliable contraceptives use.

One systematic review of observational cohorts of female sex workers in Low and Middle-income countries in Africa showed pregnancy incidence of 7 to 60 per 100 women years (60). This high incidence of pregnancy if replicated in future HIV vaccine efficacy trials anticipated in FSW or FF in Uganda, could have a far-reaching effect on the trial statistical power. It is important that women participating in HIV vaccine efficacy trials in these key populations use reliable contraceptives. Therefore, investigators will need baseline data on reliable contraceptives use in a trial specific context in these populations.

1.3.2.4 Contraceptives use data for planning efficacy trials (current practices)

Use of reliable contraceptives (non-barrier methods likely to reduce the risk of pregnancy) has become a key inclusion criterion in HIV prevention trials (61). In populations where no baseline data on reliable contraceptives use in a trial specific context is available, there is a practice of putting prospective trial participants on reliable contraceptive methods for at least three months before screening and enrolment (62). This increases the cost of conducting trials and delays rollout, but avoids costly dropout from trials due to non-compliance. Therefore, studies aimed at establishing reliable contraceptives use under HIV-vaccine efficacy trial conditions would provide baseline data for planning actual HIV vaccine efficacy trials in the FF and FSW populations where little or no information is available.

1.3.3 Study dropout rates in FSW and FF Key populations in Uganda

Another essential component of efficacy trial is good participant retention in follow up. One of the primary outcomes of any longitudinal study is the completion of the scheduled study follow up visits by the study participants (63). Studies have suggested that participants who do not complete study follow up may be more likely to experience the outcome of interest, resulting in an underestimate of the incidence of the primary study outcome (63, 64). Studies conducted in the FF and FSW in Uganda have estimated participant study dropout ranging 25-30% (28, 33, 34). In these feasibility studies, we see big dropout in the first six months, or at the first study visit, then stabilization over time (33, 34). Again, this information comes from observational cohorts and there is evidence suggesting that observational cohorts are usually different from efficacy trials.

Dropout rate in HIV vaccine efficacy trials planned in the FSW and FF in Uganda could pose a challenge if it is beyond that expected. However, it is expected that trials have better retention compared to observational cohorts. Therefore, estimation of actual dropout in the context of HIV vaccine efficacy trials in these key populations could provide robust data needed to guide the design of HIV vaccine efficacy trials in these populations.

1.3.4 HIV behavioural risk components in previous trials

Lastly but not least, lower than expected HIV incidence and hence loss of trial statistical power may be due to "better than usual" conditions (behavioural change messages and comprehensive HIV prevention package). The HIV risk reduction measures targeting behaviour change in trials could produce lower than anticipated HIV incidence and affect the trial statistical power. In the concluded HIV prevention trials (38, 39, 42), it has been shown that participants who join the trials tend to incline to lower HIV risk behaviour following vigorous trial risk-reduction measures. Ethics require that participants joining HIV vaccine efficacy trials be provided with the standard of care that encompass all biomedical and behavioral interventions known to prevent against HIV acquisition. Some of the concluded HIV prevention trials (38, 39) have shown that HIV risk reduction measures such as counselling on HIV risk behaviours increased the proportion of participants taking up HIV prevention measures that included condoms use with a new sexual partner, reduction in the number of sexual partners, number of sex acts and alcohol use. The response to HIV risk reduction measures in these trials, were thought to have led to the diminished HIV incidence beyond that predicted at trial design even in absence of an effective new biomedical product.

1.3.4.1 HIV behavioural risk components in FF and FSW in Uganda

Observational studies in the FF (27, 33, 34) in Masaka and FSW (65, 66) in Kampala Uganda have indicated very high levels of alcohol use, multiple sexual partners, non-condom use with these or a new sexual partner and high prevalence of other genital infections. Efficacy trials' controlled environment encompassing among others, frequent clinic visits for interventions such as HIV counselling and testing, HIV risk-reduction counselling, promotion and provision of condoms and treatment of other genital infections could lead to diminished HIV incidence in HIV vaccine efficacy trials planned in FF and FSW in Uganda even without an effective vaccine. Again, determining the decrease in HIV risk behaviours in these key populations in the context of HIV

vaccine efficacy trials could provide useful information for planning future trials in these populations.

1.3.5 Simulated HIV Vaccine Efficacy Trials (SiVET)

Simulation trials could help bridge the gap when extrapolating observational data to planning HIV vaccine efficacy trials in key population in Uganda. SiVET is a process of mimicking an actual vaccine efficacy trial using a commercially licensed vaccine as a proxy vaccine to provide insight and help guide the design of an actual efficacy trial, particularly where no previous trial specific information is available. This concept has been used elsewhere to see if women can participate in HIV vaccine trials (67). Participants in this simulation trial received attenuated commercially licensed MMR vaccine (measles, mumps, and rubella), Tdap-IPV vaccine (Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis) as a proxy for an experimental HIV vaccine.

1.3.5.1 SiVET in FF and FSW key populations in Uganda

In anticipation of HIV vaccine efficacy trials in the FF and FSW key populations in Uganda, the MRC/UVRI and LSHTM Uganda research unit in partnership with IAVI conducted two HIV simulated vaccine Efficacy Trials (SiVETs) between 2012 and 2017. The primary purpose of SiVETs was to determine if members of these key populations could accept and complete vaccination schedule in a trial specific context; additionally, they served to train trial staff. SiVETs were nested in long-term observational cohorts of FF and FSW. The aims of the observational cohorts were to determine HIV incidence and also create an enrolment pool of participants for future HIV prevention trials. Full details of the observational cohorts and SiVETs have been previously described (26, 29, 68-70). SiVET used a commercially licensed Hepatitis B vaccine in a study that followed the same procedures as a trial of an experimental HIV vaccine.

Because no HIV prevention trials have completed follow up in the FF or FSW to provide baseline data needed to plan HIV vaccine efficacy trials in these key populations, many elements for trial design such as; accurate HIV incidence, trial dropout and use of reliable contraceptives by women participants remain unknown. This PhD aimed at using the data collected in SiVETs as well as the source observational cohorts to provide this important information. Answering the PhD objectives has huge potential to inform investigators planning HIV vaccine and other efficacy trials in these and similar key populations.

Chapter 2: Thesis aim, objectives, structure, my contributions to studies included in the thesis and an outline of relevant publications

2.1 Introduction

This chapter presents the thesis aim, objectives, structure and my contribution to the conception and conduct of studies whose data was used in this thesis.

2.2 Thesis aim

To plan HIV vaccine efficacy trial, most data on targeted trial outcomes or other trial elements come from previous trials of the same or similar population. Where such data is not available, historical cohorts or other observational data may be used. However, observational data may not emulate the trial data because of the trial selection procedure and/or trial controlled environment. Therefore, the primary aim of this thesis was to investigate how the targeted outcome elements in HIV vaccine efficacy trials might differ from those in the source population observational cohorts within which they were nested.

2.3 Thesis objectives

1. To investigate how HIV incidence estimated from observational cohorts might differ from that in the HIV vaccine efficacy trials in the same population.

2. To determine uptake and use of reliable contraceptives by women participating in HIV vaccine efficacy trials.

3. To estimate and compare observational cohorts' participant dropout rate to that in HIV vaccine efficacy trial in the same population.

4. To compare HIV risk behaviours between trials and observational cohorts in the same population.

The four thesis objectives were answered through analysis of data collected in two longitudinal observational cohorts (OBC) and two simulated HIV vaccine efficacy trials nested within the OBCs in the Fisher-folk (FF) in Masaka district and Female sex workers (FSW) in Kampala city, Uganda. Prior to the SiVET, the total number of participants enrolled in these observational cohorts was 3,989, of whom 2,424 were FSW and 1,565 FF.

2.4 Thesis structure

The thesis consists of eight chapters and is written following the LSHTM 'research paper' style format, with four research papers. Each research paper was prepared as a standalone manuscript. Therefore, in some instances, there is minimal repetition of some information in the background, study setting, and inclusion-exclusion criteria among the different research papers.

- **Chapter One**: This thesis background chapter reviews the literature on HIV efficacy trials with emphasis on HIV vaccines, the likely pitfalls in extrapolation of observational data to planning efficacy trials, describes the current practices used to plan efficacy trials in populations without previous trial experiences, and gives summary justification.
- **Chapter Two**: Summarises the thesis primary aim, objectives, structure, and my role in the conception and acquisition of the data in the cohorts used in this thesis.
- **Chapter Three**: This is comprised of the thesis methods, definitions and classifications of the terms used throughout the thesis and description the methods used to answer thesis objectives 1, 2, 3 and 4
- **Chapter Four:** Presents thesis objective one "How HIV incidence estimated from observational cohorts might differ from that in the HIV vaccine efficacy trials in the same population"
- **Chapter Five**: Presents thesis objective two "Determine uptake and use of reliable contraceptives by women participating in HIV vaccine efficacy trials"
- **Chapter Six:** Presents thesis objective three "Comparing participant dropout rate in the observational cohorts and HIV vaccine efficacy trials in the same population"
- **Chapter Seven:** Presents thesis objective four "Comparing HIV risk behaviours between trials and observational cohorts within which they were nested"
- **Chapter Eight:** The discussions chapter summarises the PhD findings in relation to the existing literature, implications of the findings, strengths, limitations and conclusions.
- Appendix section captures other information relevant to this thesis. These include but not limited to ethical approval, training certificates and conference presentations.

Research papers one to four, where applicable, have been written following guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (71).

2.5 Candidate's contribution

I joined MRC/UVRI and LSHTM Uganda Research Unit in 2007, since that time I have had many career growth opportunities, growing through ranks from a Statistical Research Associate to Acting Head of Statistics Department. In the period between 2007 and 2020, I carried out data management for 17 studies (11-Observational and 6-Randomised Controlled Trials (RCTs)). In the same period, I conducted statistical analyses for 15 studies (8 –Observational and 7-RCTs). I have been a co-investigator on four studies (3-Observational and one-RCT). Additionally, I participated in fieldwork data collection in two observational studies. During the same period, I led a team in the Statistics Department at MRC/UVRI and LSHTM Uganda research unit, directly supervising eight Statisticians, nine data managers, two database programmers, 25 data management assistants and 4 performing other roles.

2.6 My role in the cohorts whose data were used to answer the PhD objectives

Cohort	***Primary role (s)***	***Specific assignments***
Fisher-folks (cohort1) 2009-2011	*Led the data management team*	*Developed the data Standard Operating Procedures (SOPs), trained the data management team to ensure that the data collected conforms to the protocol guidelines and Good Clinical Practice.*
	Cohort Statistician	*Developed the data collection tools, data management and data analysis plans, analysed the data and co-authored the primary manuscript. Led the authorship of the cohort's retention paper.*
Fisher-folks (cohort 2) 2012-2018	*Co-investigator*	*Participated in the protocol development through discussions of the scope, analysed data from previous cohorts to inform the design and conduct of this cohort and estimated the sample size.*
	Led the cohort's data management team	*Developed the data Standard Operating Procedures, data collection tools, guided the database development, periodically checked the data for errors (inconsistencies, missing forms and fields) as part of periodic data monitoring.*
	Cohort Statistician	*Developed the data analysis plan and analysed the data for periodic cohort reports and the final primary analysis. Co-authored the primary paper (second co-author).*
Female Sex Workers (cohort) 2008-2018	*Led the Statistics and Data Management Teams*	*Key roles were limited to supervising the Statistics and Data Management team directly involved in the day to day data acquisition, cleaning and analysis.*

SiVETs	*Co-Investigator*	*Conception of the simulated HIV vaccine trial (SiVET) concept. Participated in the protocol development through decisions of the scope, design, conduct and sample size estimation. Participated in the development of the Study Operations Manual (SOM), and Standard Operating Procedures.*
	SiVETs Statistician and Head of Data Management team	*Developed the data collection tools, data management and analysis plans, analysed the data and co-authored the primary manuscripts from the SiVETs (Second co-author on $SiVET_1$ (FF) and $SiVET_2$ (FSW) papers).*

2.7 My contribution to publications from the cohorts prior to or during PhD enrolment

1. *Yunia Mayanja, **Andrew Abaasa**, Gertrude Namale, Gershim Asiki, Matthew A. Price and Anatoli Kamali. Factors associated with vaccination completion and retention among HIV negative female sex workers enrolled in a simulated vaccine efficacy trial in Kampala, Uganda. BMC Infectious Diseases (2019) 19:725 https://doi.org/10.1186/s12879-019-4328-1. (Reference number 72)*
2. *Gershim Asiki, **Andrew Abaasa**, Eugene Ruzagira, Freddie Kibengo, Matt Price, Linda-Gail Bekker, Willi McFarland, Pat Fast, Anatoli Kamali. Study retention and HIV incidence in a simulated vaccine trial (SiVET) among adults in fishing communities, Uganda. Submitted to PlosOne 2019. (Reference number 70)*
3. *Gertrude Namale, Onesmus Kamacooko, Daniel Bagiire, Yunia Mayanja, **Andrew Abaasa**, William Kilembe, Matt A Price, Deogratius Ssemwanga, Sandra Lunkuse, Maria Nanyonjo, William Ssenyonga, Robert Newton, Pontiano Kaleebu, Janet Seeley. Sustained Virological Response and Drug Resistance among Female Sex Workers Living with HIV on Antiretroviral Therapy in Kampala, Uganda; a cross sectional study. Sexually Transmitted Infections, 2019.*
4. *Bahemuka UM, **Abaasa A,** Ruzagira E, Lindan C, Price MA, Kamali A, Fast P. Retention of adults from fishing communities in an HIV vaccine preparedness study in Masaka, Uganda. PLoS ONE (2019) 14(1): e0198460. https://doi.org/10.1371/journal.pone.0198460. (Reference number 34)*
5. ***Andrew Abaasa**, Gershim Asiki, Matthew A. Price, Eugene Ruzagira, Freddie Kibengo, Ubaldo Bahemuka, Patricia E. Fast, Anatoli Kamali. Comparison of HIV incidence estimated in clinical trial and observational cohort settings in a high risk fishing population in Uganda: Implications for sample size estimates. Vaccine, 2016. 34 (15): p. 1778-1785. (Reference number 26)*
6. ***Andrew Abaasa**, Gershim Asiki, Juliet Mpendo, Jonathan Levin, Janet Seeley, Leslie Nielsen, Ali Ssetaala, Annet Nanvubya, Jan De Bont, Pontiano Kaleebu and Anatoli Kamali. Factors associated with dropout in a long-term observational cohort of fishing communities around Lake Victoria, Uganda. BMC research notes, 2015. 8(1): p. 815. (Reference number 33)*

7. *Gershim Asiki, **Andrew Abaasa**, Eugene Ruzagira, Freddie Kibengo, Ubaldo Bahemuka, Jerry Mulondo, Janet Seeley, Linda-Gail Bekker, Sinead Delany, Pontiano Kaleebu, Anatoli Kamali. Willingness to participate in HIV vaccine efficacy trials among high-risk men and women from fishing communities along Lake Victoria in Uganda. Vaccine, 2013. 31(44): p. 5055-5061. (Reference number 32)*
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9. *Gershim Asiki, Juliet Mpendo, **Andrew Abaasa**, Collins Agaba, Annet Nanvubya, Leslie Nielsen, Janet Seeley, Pontiano Kaleebu, Heiner Grosskurth, Anatoli Kamali. HIV and syphilis prevalence and associated risk factors among fishing communities of Lake Victoria, Uganda. Sexually transmitted infections, 2011: p. sti. 2010.046805. (Reference number 78)*

2.8 My contribution to conference presentations of the cohorts data prior to PhD enrolment

1. *Ubaldo Bahemuka, **Andrew Abaasa**, Freddie Mukasa Kibengo, Eugene Ruzagira, Matt Price, Patricia Fast, Anatoli Kamali. HIV Vaccine Preparedness Study in a Mobile Fishing Population in Uganda: Assessing; Feasibility, Retention and Estimating HIV Incidence. HIV Research for prevention (R4P) conference 2016 Chicago United States of America.*
2. ***Andrew Abaasa**, Martin Mbonye, Gershim Asiki, Eugene Ruzagira, Matt Price, Patricia E Fast, Frances Priddy, Pontiano Kaleebu, Anatoli Kamali. Use of Fingerprinting Technology in HIV Prevention Studies. Experience from Fishing Communities in Southwestern Uganda .HIV Research for prevention (R4P) conference 2016 Chicago United States of America.*
3. *Ubaldo Mushabe Bahemuka, **Andrew Abaasa**, Eugene Ruzagira, Freddie Mukasa Kibengo, Juliet Ndibazza, Gershim Asiki, Jerry Mulondo, Matthew Andrew Price, Patricia Fast, Anatoli Kamali. Trends of Reported HIV Sexual Risk Behaviour and HIV Incidence among Fisherfolk in Uganda Receiving Clinic-based Routine HIV Counseling and Testing. HIV Research for prevention (R4P) conference 2014 Cape Town South Africa.*
4. *Gershim Asiki, **Andrew Abaasa**, Ubaldo Bahemuka, Jerry Mulondo, Freddie Kibengo, Eugene Ruzagira, Anatoli Kamali, Pat Fast. Participation of Individuals from Fishing Communities in a Simulated Vaccine Efficacy Trial in Preparation for Future HIV Prevention Work. HIV Research for prevention (R4P) conference 2014 Cape Town South Africa.*
5. ***Andrew Abaasa**, Gershim Asiki, Jonathan Levin, Ubaldo Bahemuka, Eugene Ruzagira, Freddie M. Kibengo, Jerry Mulondo, Juliet Ndibazza, Matthew A. Price, Pat Fast, Anatoli Kamali. Participation in Clinical Research Could Modify Background Risk for Trial Outcome Measures. HIV Research for prevention (R4P) conference 2014 Cape Town South Africa.*

6. *Elizabeth Mbabazi, **Andrew Abaasa**, Gershim Asiki, Ubaldo Bahemuka, Eugene Ruzagira, Margaret Nambooze, Cissy Lilian Nalubega, Mathew A. Price, Anatoli Kamali. Determinants of Informed Consent Comprehension among Fisher Folk Cohort in HIV Vaccine Preparatory Studies in SW Uganda. HIV Research for prevention (R4P) conference 2014 Cape Town South Africa.*

7. *Richard Rwanyonga, **Andrew Abaasa**, Gershim Asiki, Benjamin Twefeho, Ubaldo Bahemuka, Emanuel Aling, Eugene Ruzagira, Matthew A. Price, Anatoli Kamali. The "Worried Well" Among Clients Attending HIV/AIDS Counselling and Testing Services at a Clinical Research Centre in SW Uganda. HIV Research for prevention (R4P) conference 2014 Cape Town South Africa*

8. ***Andrew Abaasa**, Gershim Asiki, Jessica Nakiyingi-Miiro, Emanuel Aling, Jonathan Levin, Juliet Mpendo, Janet Seeley, Pontiano Kaleebu, Anatoli Kamali: Correlates of dropout in a fisher folk HIV vaccine preparedness observational cohort, in rural and semi urban Uganda. The sixth European and Developing Countries Clinical Trials Partnership (EDCTP) forum at the United Nations Conference Centre in Addis Ababa, Ethiopia October 2011.*

2.9 Publications developed from the cohorts' data during my PhD studies

1. ***Research paper 1:** Simulated vaccine efficacy trials to estimate HIV incidence for actual vaccine clinical trials in key populations in Uganda. Vaccine 37 (2019) 2065–2072.*
2. ***Research paper 2:** Use of reliable contraceptives and its correlates among women participating in Simulated HIV vaccine efficacy trials in key populations in Uganda. Nature Scientific Reports 2019.*
3. ***Research paper 3:** Comparison of dropout rate in the longitudinal observational cohorts and nested Simulation Efficacy Trials in the Key populations in Uganda. BMC Medical Research Methodology (2020) 20:32.*
4. ***Research paper 4:** Comparison of HIV risk behaviors between clinical Trials and observational cohorts in Uganda. AIDS & Behavior. 2020;10.1007.*

2.10 Conferences and workshop presentations of cohort data during my PhD studies

No	*Date*	*Presentation title*	*Mode*	*Type & location*
1	*Oct 21-25,2018*	*Uptake and use of reliable contraceptives and correlates of use among women participating in HIV efficacy trials preparatory studies in key populations in Uganda.*	*Poster (P07.11)*	*HIVR4P, 2018 Madrid Spain.*
2	*Mar 04-07,2019*	*Simulated Vaccine Efficacy Trials to estimate HIV incidence in key populations in Uganda.*	*Poster (1088)*	*CROI, 2019 Seattle Washington United States of America.*
3	*Jun 03,2019*	*Use of reliable contraceptives by women participating in HIV Simulated Vaccine Efficacy Trials in key populations in Uganda*	*Oral seminar*	*The Population Studies Group (PSG), LSHTM, United Kingdom.*
4	*Oct 22,2019*	*Using observational cohort data from Key populations to plan HIV intervention studies*	*Oral seminar*	*MRC/UVRI & LSHTM Uganda Research Unit, Statistics department biweekly seminar series.*
5	*Nov 29,2019*	*Using observational cohort data from Key populations to plan HIV intervention studies*	*Oral seminar*	*MRC/UVRI & LSHTM Uganda Research Unit, senior scientific monthly seminar series.*

2.11 Other relevant transferrable skills and other training in the course of my PhD studies

No	*Date*	*Training , location*	*Training organizer*
1	*Apr 26-May 19,2017*	*Advanced statistical methods in Epidemiology (ASME), LSHTM*	*London School of Hygiene and Tropical Medicine*
2	*Nov 13-17,2017*	*Scientific Manuscript Writing Workshop, Johannesburg*	*South Africa National Blood Services Johannesburg*
3	*Nov 22-23,2017*	*Study designs, MRC/UVRI and LSHTM Uganda Research Unit*	*MRC/UVRI and LSHTM Uganda Research Unit*
4	*Jul 09-27,2018*	*Scientific manuscript writing mentorship, University of California San Francisco*	*University of California San Francisco Centre for Global Health*
5	*Aug 20-31,2018*	*Uganda Advanced Statistical Methods course (UASME), MRC/UVRI and LSHTM*	*MRC/UVRI and LSHTM Uganda Research Unit*
6	*Feb 25-Mar 01,2019*	*Scientific Manuscript writing workshop, University of Nairobi Kenya*	*International AIDS Vaccine Initiative (IAVI)*
7	*Apr 03,2019*	*Assessing data quality and disclosure risk in numeric data workshop, LSHTM*	*London School of Hygiene and Tropical Medicine*
8	*Apr 25-May 17,2019*	*Advanced Statistical Modelling (ASM), LSHTM*	*London School of Hygiene and Tropical Medicine*
9	*May 22,2019*	*Preparing to submit your thesis, LSHTM*	*London School of Hygiene and Tropical Medicine*
10	*Jul 08-26,2019*	*Scientific manuscript writing mentorship University of California San Francisco*	*University of California San Francisco Centre for Global Health*

Chapter 3: Methodology

3.1 Introduction

This chapter describes in detail the longitudinal observational cohorts (OBCs) and the HIV Simulated Vaccine Efficacy Trials (SiVETs) cohorts used to answer the PhD objectives. It also provides the study settings, detailed cohort descriptions, data layout, estimation of the minimum sample size for each objective, statistical methods for each thesis objective, ethical considerations, defines and classifies the terms used in the thesis.

3.2 Definitions and classifications

Fisher-folk (FF): This term refers to not only fishermen but to all people living on the lakeshore who directly or indirectly derive their livelihoods from the fishing industry. These include fish traders, fish processors, boat builders, members of families of fishermen, restaurant and bar workers, sex workers and others engaged in small-scale businesses (33).

Fishing community: A group of persons living in a village or trading Centre that is adjacent to lake landing site where the main economic activities and livelihood are derived directly or indirectly from fishing activities (72).

Sex work: The provision of sexual services for money or other goods (73).

Female sex worker (FSW): A woman receiving money, goods or other favours in exchange for sexual services with a non-legal spouse and who consciously defines that activity as income generating even if she does not consider sex work as her occupation (73).

Clients: Men who usually pay with cash or other resources for sexual services either explicitly or within an agreed package that includes other services such as entertainment or domestic service (73).

Source population: This refers to Fisher-folk or female sex worker populations.

Observational cohort (OBC): Longitudinal prospective follow up of participants in a study of FF or FSW to determine HIV incidence among other evaluations.

Simulated HIV Vaccine Efficacy Trial (SiVET): A process of mimicking an actual HIV vaccine efficacy trial using a commercially licensed vaccine (Hepatitis B vaccine in this case) as a proxy vaccine (29).

Pre SiVET cohorts: Longitudinal observational cohorts conducted in the period prior to the initiation of the SiVET cohort in a given source population. More specifically , Sept 2009- June 2012 in the FF population and Apr 2008- Apr 2014 in FSW population.

Non-SiVET cohorts: This refers to participants that screened failed or were not screened into SiVET because of SiVET recruitment accrual but fulfilled the inclusion exclusion criteria for continued follow up in the given source population observational cohort.

SiVET concurrent period: Refers to the period of conduct of non-SiVET and SiVET cohorts. Non-SiVET cohort in the SiVET concurrent period began on the date the SiVET cohort began enrollment, and ended on the date of the last SiVET participant clinic visit in a given source population.

Post-SiVET cohorts: All prospective observational cohort data for 12 months after the final SiVET participant study visit in a given source population.

Reliable contraceptives: Non-barrier contraceptives methods likely to reduce the risk of pregnancy (51). These included injectable Depot medroxyprogesterone acetate (DMPA), pills, Norplant-implant and intrauterine contraceptive device (IUD).

3.3 Study setting

The data used to answer the PhD objectives one to four were obtained from longitudinal observational cohorts and SiVETs nested within these observational cohorts in two key-populations in Uganda, (i) the Fishing communities on the shore of Lake Victoria in Entebbe and Masaka Uganda (Feb 2009- Apr 2015) and ii) female sex workers in Kampala Uganda (Apr 2008- Apr 2018).

3.3.1 Fishing communities

3.3.1.1 Location

These are located on the shoreline of Lake Victoria in Entebbe and Masaka district, respectively, about 40km and 100 km from Kampala city, the capital of Uganda (Figure 1). The fishing communities are on average 10km from the Trans-African high way (high way stretching from North Africa through East Africa to Southern Africa).

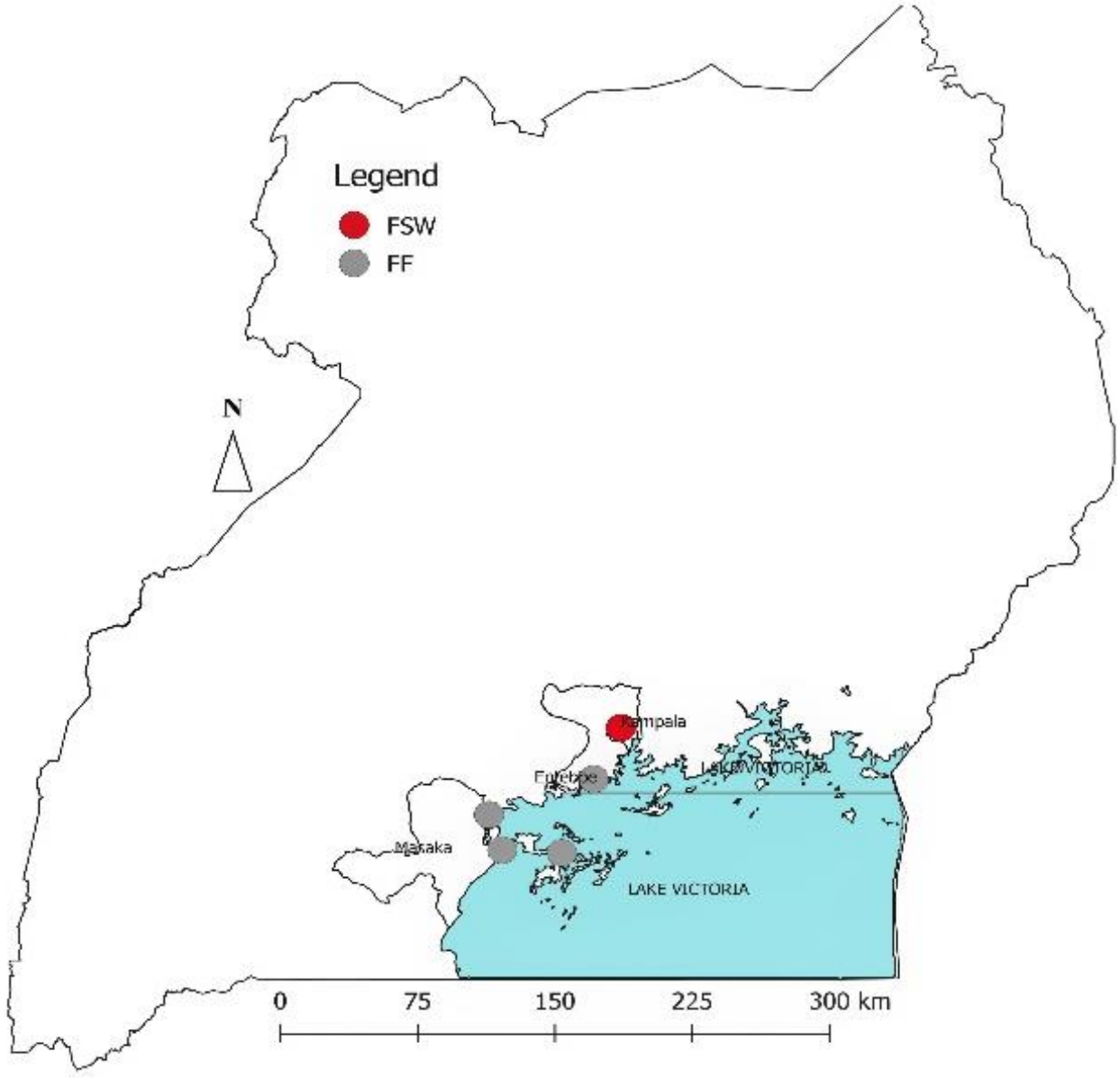


Figure 1: Location of the fishing communities on the shoreline of Lake Victoria in Uganda

3.3.1.2 Structure

A typical fishing community consists of wattle-and-mud or corrugated metal iron sheet wall-and-iron sheet roof houses with one or two rooms (figure 2 and 4). The communities are concentrated on the edge of a swamp (figure 3) about half a kilometre from the landing site.

Figure 2: Typical fishing community settlement in Masaka district, Uganda 2012

Figure 3: Typical fish landing site on the shore of Lake Victoria, Uganda 2012

3.3.1.3 Economic activities in the fishing communities

Although the main economic activity is fishing, other activities support the fishing occupation. These include but are not limited to small-scale fish processing (figure 4), work in restaurants/bars/hair salons to serve a wide range of individuals, small-scale businesses, carpentry shops making wooden boats, and film shows among others.

Figure 4: Silver fish processing (drying on the sand) on the shoreline of Lake Victoria, Uganda 2012

Because of the wide range of economic activities, studies in these communities recruit participants from all the occupations but the term fisher-folk (section 3.2) is used to refer to all participants in the studies and in this thesis.

3.3.1.4 Local leadership and health care in fishing communities

These fishing communities have administrative structures including the local government councils and the beach management units that take care of all administrative needs on behalf of the central government (74). Individuals in these communities live in clusters of isolated locations and this makes it difficult for them to access basic healthcare services. They lack access to safe water, latrines etc., making them vulnerable to illness. They have to move further afield to seek for health care needs in established government of Uganda health centres, located between 10km to 40km from the fish landing sites or to more specialized regional referral hospitals in Masaka and Entebbe (figure 5).

Figure 5: Masaka and Entebbe, Uganda government regional referral hospitals 2012 and 2018

3.3.1.5 Estimated population of and HIV epidemiology in fishing communities in Uganda

3.3.1.5.1 Population size

The fishing communities on the Lake Victoria basin in Uganda are estimated to have over 400 fish landing sites (72), each fishing community having about 250 households with average household size of four individuals. This translates to about 400,000 individuals in these communities. A more recent study using satellite images identified 509 fishing communities in Uganda and estimated the total population size of about 320,000 individuals (75).

3.3.1.5.2 HIV and risk behaviour epidemiology

The adult HIV prevalence is estimated to be about 25% (31, 76) and annual HIV incidence of 5 per 100 person years at risk (27). These vary with population subgroups (27). The FF population is characterised by very high HIV risk behaviours such as multiple sexual partnership, with 87% reporting having more than one sexual partner, and only a quarter reporting condom use with these partners (76). The prevalence of other sexually transmitted diseases and infections is equally high; syphilis (3.6%), general STIs (19.0%), reported genital discharge (19.5%) and sores (29.0%) (76). More than half of the adult population regularly consume alcohol (76) and only 35% of the women use modern contraceptives (57).

3.3.2 Female sex workers

3.3.2.1 Location

Female sex workers defined in section 3.2 operate within Kampala city's hangout places including bars, restaurants and selected city streets. These places are within a radius of 5KM from the MRC/UVRI and LSHTM Uganda Research clinic at Mengo hill, which is about 2 KM from the city centre (figure 1).

3.3.2.2 Structure

Women in the sex work occupation meet their clients on the streets and/or nightclubs (figure 6) and retreat to lodges within the city for sexual activity. The lodges are hired for as low as $3 to $ 10 depending on the duration of stay and location.

Figure 6: Setup of nightclubs and streets in Kampala city where sex workers meet clients

3.3.2.3 Health care access

Female sex work in Uganda is illegal therefore; women operate undercover for fear of being identified and rested by the police. This makes provision of health care to this particular group difficult. However, of late these women and their well-wishers are demanding for rights to operate freely in the sex work occupation (figure 7).

Source: https://www.upi.com/Top_News/World-News/2012/12/13

Figure 7: Female sex workers and well-wishers demanding for rights to operate freely in Uganda

Studies in this population recruit women operating from HIV hot spots in Kampala city including; bars, night clubs, local beer breweries, eating places, lodges and guesthouses known to provide rooms for sex work, or selected street spots often frequented by sex workers in search of clients (65).

3.3.2.4 Estimated population of and HIV epidemiology in FSW in Uganda

3.3.2.4.1 Population size

The FSW population in Uganda is estimated at about 192,000 and about 40% operating from Kampala city, the capital of Uganda (77). Sex work in Uganda is illegal and this creates challenges of identifying individuals engaged in this activity, making provision of health care services difficult.

3.3.2.4.2 HIV and risk behaviour epidemiology

The HIV prevalence in this population is estimated at between 33% and 37% (65) and annual HIV incidence of about 3 per 100 PYAR (25, 29). The prevalence of other sexually transmitted diseases and infections is equally high; N. gonorrhoea 13%, C. trachomatis 9%, T. vaginalis 17% and syphilis 21%, bacterial vaginosis 56% and candida infection 11% (65).

Similarly, this population is characterised by high multiple sexual partnerships, with over 80% reporting having sex with more than one partner in the last month. The reported condom use with these partners is very low at 40% and the use of contraceptives other than condoms is equally low (40%). There is high alcohol use, with over two-thirds reporting alcohol use on a regular basis (65).

3.4 Description of FF, FSW observational, and SiVET cohorts used in this PhD thesis

3.4.1 FF observational cohort pre SiVET

Two successive OBCs (Feb 2009 - Dec 2011, and Jan 2012 - Apr 2015) were established in this population. The first OBC recruited 1000 participants from five fishing communities, three in Entebbe sub district and two in Masaka district, Uganda. The five fishing communities were selected using pre-defined criteria; located within 50km from MRC/UVRI and LSHTM research clinic in Entebbe (50Km, South of Kampala) or Masaka town (100km, West of Kampala), ≥1000 adults (≥18 years) and gazetted by Uganda Ministry of Fisheries. The primary aim of this cohort was to investigate the possibility of enrolling and retaining FF in follow up in an OBC but also determine HIV incidence.

To establish this cohort, trained field workers mapped households in the five communities, carried out a census, and assigned identification numbers to all residents and regular visitors. They sought written consent and offered screening for HIV to those aged 18-49 years at the study clinics established in each of the five fishing communities. They referred those found to be HIV positive to a local HIV services provider for HIV treatment and care. The rest were enrolled into an observational cohort with six monthly follow up clinic visits (for HIV testing and behavioural risk assessment) for 18 months, if they were HIV negative and at high risk for HIV infection. High risk was defined as self-report of any of the following in the previous 3 months: unprotected sex with ≥one or new sexual partners, history of sexually transmitted infections (STIs), use of illicit drugs and/or alcohol, and being away from home for ≥2 nights per week. Data were collected on demographic and behavioural risk variables using a structured questionnaire and a blood sample taken to determine HIV status at baseline and at each of the follow up visits. The census and cohort details are previously described (27, 33, 76).

In this first FF cohort, participant recruitment and follow up happened at clinics established in each of the participating fishing communities but future HIV vaccine efficacy trials may not take place at the clinics established in the fishing communities because of lack of adequate infrastructure such as laboratory, vaccine pharmacy and office space to conduct large phase trials. Therefore, the first FF cohort data was used to inform the design of the second FF cohort (similar aims as the first one but also to create a pool of participants to enroll in future HIV prevention trials) and was planned

to maintain at least 400 volunteers in follow up at any one time. Unlike the first FF cohort, participants in the second FF cohort had to travel (for all their study visits) to the MRC/UVRI and LSHTM research clinic (with all HIV vaccine efficacy trial infrastructure) located in Masaka town, about 50km from the fishing communities. Similar procedures as the first FF cohort were followed to establish the second FF cohort but follow up for HIV counselling and testing happened every three months. At each clinic visit completed, participants received approximately $1.4 as reimbursement for the cost of transport and compensation for time. Similarly, the cohort details have been previously described (26, 29, 34).

3.4.2 FSW observational cohort

The FSW cohort Apr 2008 - Apr 2018 was established at MRC/UVRI and LSHTM Uganda research Unit's Mengo field station in Kampala city. The primary objective of establishing this cohort was similar to that of the two FF cohorts, section 3.4.1 above. To establish the FSW cohort, trained fieldworkers identified and mapped hotspots initially in the two (Makindye and Rubaga) of the five divisions of Kampala city until 2010 when it was expanded to include all the five divisions (Makindye, Rubaga, Kawempe, Nakawa and Kampala central). The hotspots were defined as clusters of bars, nightclubs, local beer breweries, eating places, lodges and guesthouses known to provide rooms for sex work, or selected street spots often frequented by sex workers in search for sexual clients. The fieldworkers' mobilised women engaged directly in female sex work or employed around the entertainment facilities and invited them to the cohort clinic at MRC/UVRI and LSHTM office. At the clinic, information about the cohort objective was provided to the women by the study staff that included physicians, nurses and counsellors. Those willing (providing written informed consent) to join the cohort were screened for eligibility. Those eligible (aged≥18years, HIV negative, engaged in female sex work) were given an appointment to return within one week for their enrolment visit. Those found to be HIV positive were referred to a local ART treatment and care provider. At enrolment visit, data were collected on socio demographic and HIV behavioural risk using interviewer administered questionnaires. Participants were scheduled to return every 3 months for follow up visits. At each of the follow up visits, repeat HIV testing was done and behavioural risk assessment at annual visits. At each clinic visit completed, participants received approximately $1.2 as reimbursement for the cost of transport and compensation for time. Similarly, the cohort details have been previously described (25, 29, 65).

3.5 HIV risk reduction measures in the observational cohorts

Participants in observational cohorts received HIV counselling and testing every three months, counselling on having concurrent multiple sexual partners or causal sexual partners and were provided with condom on request. Participants in these cohorts only received presumptive treatment for sexually transmitted infections if a study physician suspected an infection.

3.6 HIV Simulated Vaccine Efficacy Trials (SiVETs)

$SiVET_1$ and $SiVET_2$ cohorts were nested within the observational cohorts in FF and FSW respectively. SiVETs were carried out to determine the feasibility of conducting HIV vaccine efficacy trials among the two HIV high risk key populations in Uganda, but using a commercially licensed hepatitis B vaccine (ENGERIX-BTM GlaxoSmithKline Biologicals Rixensart, Belgium) as a proxy vaccine.

3.6.1 SiVET population

Participants were recruited into SiVETs in FF and FSW if they fulfilled the inclusion exclusion criteria in table 1 below.

Table 1: SiVET and non-SiVET cohorts' inclusion exclusion criteria in the SiVET concurrent period

Time	**SiVET cohorts**	**non-SiVET cohorts**
SiVET Concurrent period	**Inclusion** • At least 3 and no more than 18 months of follow up in the parent source population observational cohort • HIV-1 negative and willing to undergo HIV testing • Aged ≥18 years and ≤49 years • Able and willing to provide written informed consent • Able and willing to provide adequate locator information • Able and willing to return for follow-up clinic visits • Intending to reside in study area for at least one year • Willing to undergo pregnancy testing • Not breastfeeding and no intent for pregnancy in the next one year	**Inclusion** • At least 3 months and no more than 18 months of follow up in the parent observational cohort • Aged ≥18 years and ≤49 years • HIV negative • Still in active follow up in the observational cohort

	• Willing to use effective contraception during the study and at least 3 months after the last vaccination	
	Exclusion • History of severe allergic reaction to any substance • An acute or chronic illness • Contraindication for Hepatitis B vaccine • Participation in another clinical trial • Hepatitis B positive (only SiVET$_2$)	**Exclusion** • HIV positive

3.6.2 Administration of Hepatitis B vaccine

In addition to the procedures (HIV testing and risk assessment) in the parent observational cohorts, SiVET participants were administered 1ml of a commercially licensed Hepatitis B vaccine (ENGERIX-B™ GlaxoSmithKline Biologicals Rixensart, Belgium) following the standard schedule of 0, 1 and 6 months, akin to what might happen in an actual HIV vaccine efficacy trial. In line with HIV vaccine efficacy trial, participants had a reactogenicity assessment at least 30 minutes after each vaccination and attended a post vaccination visit three days later. Other trial visits were scheduled at months 3,5, 8, 9 and 12 and trial visits had scheduled clinic visit windows as follows: vaccination visits (±3 days), 3-day post vaccination visits (±1 day) and all other visits (±7 days).

3.6.3 HIV risk reduction measures

3.6.3.1 Counselling interventions

Participants received HIV counselling and testing every 3 months and counselling on HIV risk behaviours including; alcohol consumption, alcohol use before sex, multiple or causal sexual partnerships among others, every six months.

3.6.3.2 Other interventions

A trial counsellor promoted and provided condoms to participants estimated (depending on frequency of sex defined by participants) to last them the period before returning to the clinic for the next follow up visit. Participants were also encouraged to return to the clinic for more condoms in case they ran out before the next scheduled visit. A trial physician carried out physical examinations diagnosed sexually transmitted infections and other genital infections at the visits happening every six months. Those found infected with STIs were treated before leaving the trial

clinic or asked to return for their results and receipt of treatment. All participants were encouraged to return to the clinic any time for checkup whenever they did not feel well.

3.6.4 Reliable contraceptives

To prevent pregnancy, a trial nurse promoted and provided reliable contraceptives (injectable Depot Medroxyprogesterone Acetate (DMPA), implant, pills, and intrauterine device (IUD)) according to women's choice to women who were not using a reliable method at enrolment. Those already using a reliable method were encouraged to continue with their method. Contraceptive use data were recorded at baseline and at each of the follow-up clinic visits.

3.6.5 Participant clinic follow up schedule and procedures

Indicated in table 2 below, are the details of assessments conducted at each participant clinic visit.

Table 2: Procedures conducted at each trial scheduled clinic visit

Procedures	Month of clinic visit								
	M0*	**M0+ 3days**	**M 1***	**M1+ 3days**	**M 3**	**M6***	**M6+ 3days**	**M 9**	**M 12**
Hepatitis B vaccination	X		X			X			
HIV risk assessment questionnaire	X					X			X
Medical history, including STI	X								
Physical exam, vital signs, height, weight, genital exam	X								
Directed medical history, including STI		X	X	X	X	X	X	X	X
Directed physical exam, genital exam		X	X	X	X	X	X	X	X
HIV counselling and testing	X		X		X	X		X	X
Promotion and provision of condoms	X		X		X	X		X	X
Contraception promotion and provision	X		X		X	X			
Concomitant medication assessment	X	X	X	X	X	X	X	X	X
Local and systemic reactogenicity	X	X	X	X		X	X		
Adverse events	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X
Urine pregnancy test (women)	X		X		X	X		X	X
Syphilis serology	X								X

****Vaccination visits, M-month***

3.6.6 SIVET sample size determination

SiVETs were powered on assessment of retention within one year among participants enrolled from observational cohorts in the fishing communities in Masaka and female sex work in Kampala. The assumption was a retention of 80% or more at one-year would be sufficient to inform future HIV vaccine efficacy trials in these populations. SiVET concept would improve retention from 72% (average retention from previous observational cohorts in these populations) to at least 80% at 5% level of significance and 80% power. Under these assumptions, a sample size of 233 participants in each SiVET was required to allow for assessment of retention. This sample was

increased by 20% (assumed average loss to follow up in these populations) giving a minimum of total sample size of 280 i.e. 560 for both SiVETs (one in each of FF and FSW populations).

3.7 Stratification of cohorts data used in this thesis

To create clarity in the comparisons in this thesis and throughout the publications included, the designs and meaning of each of Pre SiVET, SiVET, non-SiVET, SiVET concurrent and post-SiVET cohorts are provided in this section. Figure 9 below, shows more details of the same.

3.7.1 Pre SiVET cohort data

Though in some cases this has been stratified by the source population (FF or FSW), generally, pre SiVET cohorts data throughout this thesis will refer to observational cohorts data before conduct of SiVET in that source population. Specifically, data from participants enrolled in the observational cohorts between Feb 2009 and Jun 2012 in the FF and Apr 2008-Jul 2014 in the FSW, figure 9.

3.7.2 SiVET cohorts data

Similarly this may be stratified by the source population but generally SiVET cohort data throughout this thesis will refer to data from participants enrolled into SiVETs nested within the FF observational cohort (Jul 2012-Apr 2014) and within the FSW observational cohort (Apr 2014-Apr 2017).

3.7.3 non-SiVET cohorts data

Throughout this thesis, non-SiVET cohorts' data will refer to data from participants in the observational cohorts in FF or FSW that screened failed or were not screened/recruited into SiVET because of SiVET sample size accrual but fulfilled the inclusion exclusion criteria in table 1.

3.7.4 SiVET concurrent period

Throughout this thesis, this will refer to data from both SiVET and non-SiVET cohorts (mutually exclusive) beginning on the date the SiVET began enrolling, and ending on the date of the last SiVET participant clinic visit.

3.7.5 Post SiVET cohorts data

Throughout this thesis, this will refer to all observational cohort data recorded in the twelve months after the final SiVET participant study visit, including new recruitments in that source population.

3.8 Layout of the participant data used to answer PhD objectives

Figure 8 lays out the flow of participants from observational cohorts into SiVET, non-SiVET cohorts in the SiVET concurrent period and post-SiVET. In addition provides reasons why participants were not eligible to continue at each stage.

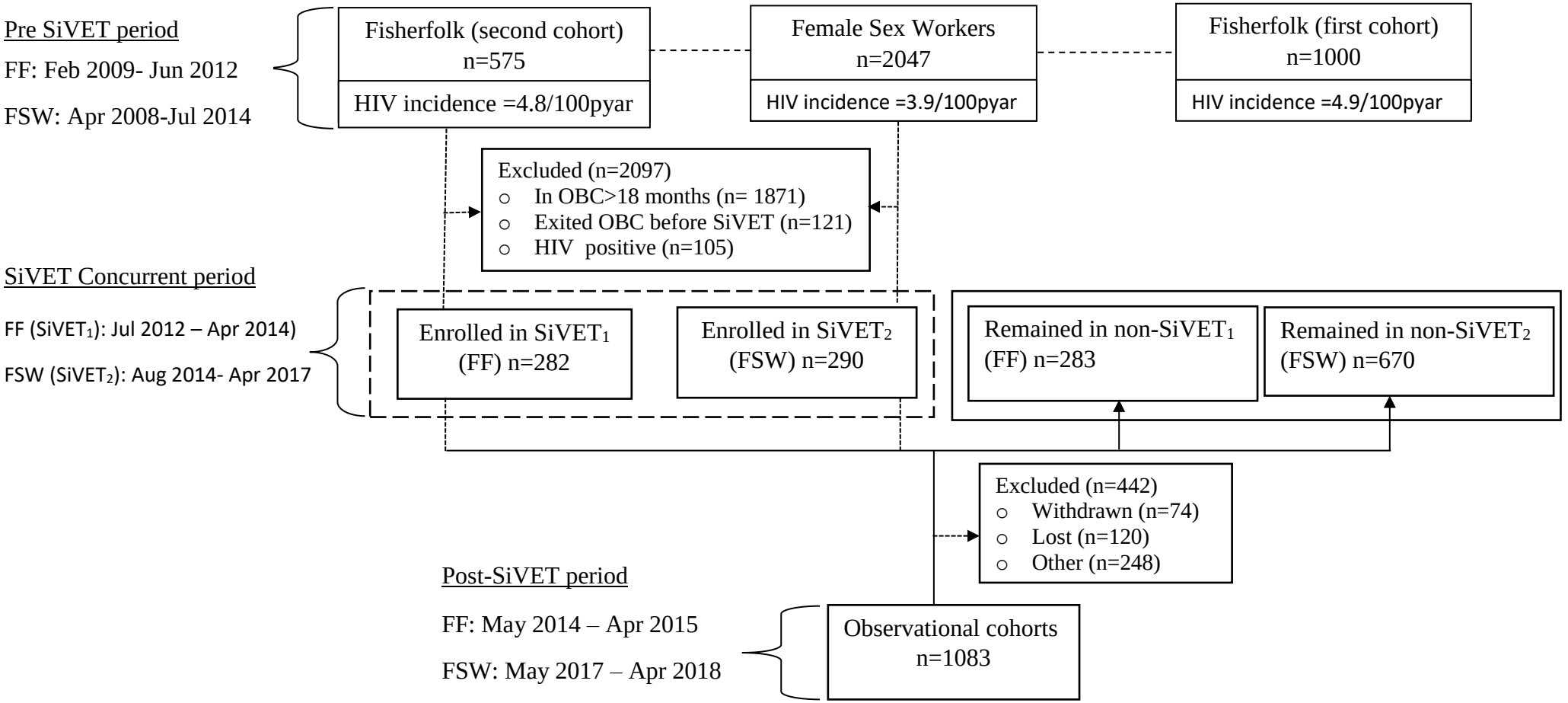


Figure 8: Flow of participants from the observational cohorts pre-SiVET to SiVET concurrent and post-SiVET periods

Table 3: Data available for answering PhD objectives, pre SiVET, SiVET concurrent and post-SiVET periods by population

P	Collected data	FF									FSW					
Pre-SiVET*		FF (first cohort)				FF (second cohort)										
	Month of clinic visit	0	6	12	18	0	3	6	9	12	0	3	6	9	12	18
	HIV results	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		FF (Second cohort)									**FSW**					
SiVET Concurrent*		$SiVET_1$					non-$SiVET_1$					$SiVET_2$					non-$SiVET_2$				
	Month of clinic visit	0	3	6	9	12	0	3	6	9	12	0	3	6	9	12	0	3	6	9	12
	Retention	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	HIV results	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	HIV behavioural risk	x		x		x	x		x		x	x		x		x	x				x
	Contraceptives use	x	x	x								x	x	x							
	Pregnancy	x	x	x								x	x	x							
	Demographics	x					x					x					x				
Post SiVET*		SiVET & non-SiVET combine into one observational cohort										SiVET & non-SiVET combine into one observational cohort									
	Month of clinic visit	12		15	18	21	24					12	15	18	21	24					
	HIV results	x		x	x	x	x					x	x	x	x	x					

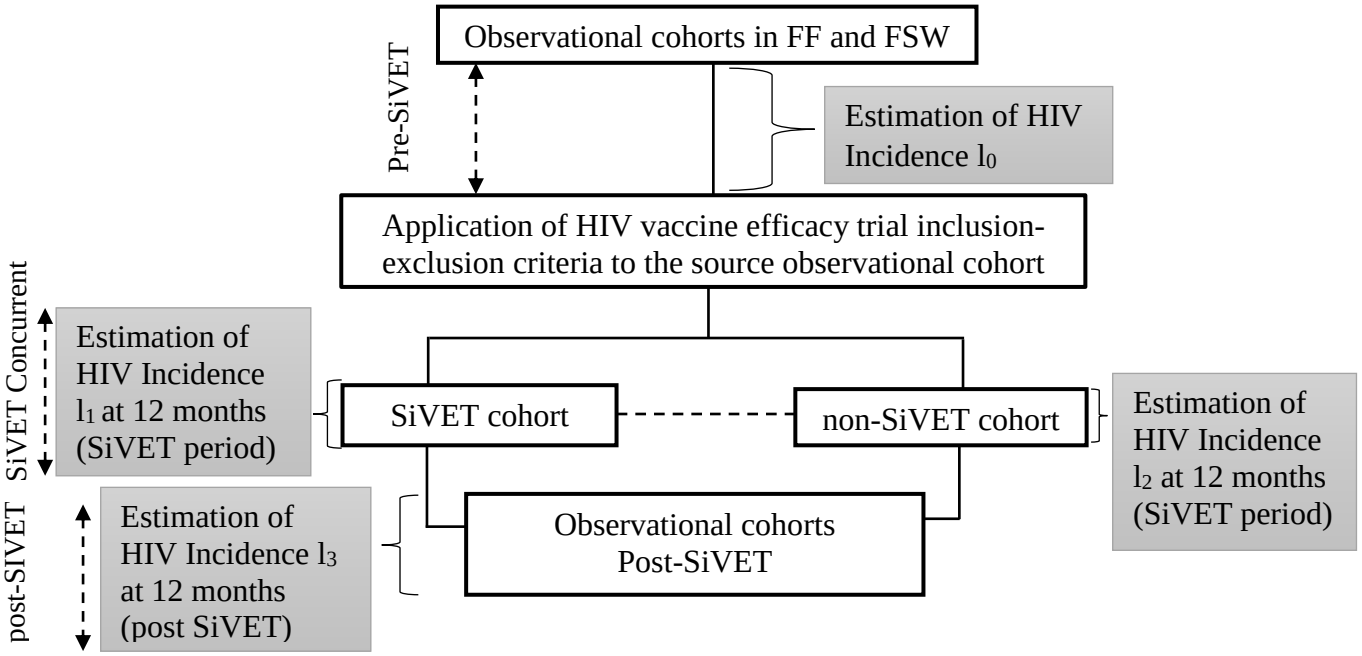
Period details are indicated in figure 9, P-Period, X-indicates procedures carried out

3.9 Answering PhD objective one

Objective: How HIV incidence estimated from observational cohorts might differ from that in the HIV vaccine efficacy trials in the same population.

Answering this was achieved by estimating and comparing HIV incidence in the SiVET cohorts to that in the observational cohorts pre-SiVET, in the non-SiVET cohorts in the SiVET concurrent period and post-SiVET cohorts (structured in figure 9 and detailed in chapter four).

Figure 9: Diagrammatic illustration of the design used to answer PhD objective one



In practice, the following comparisons were made to answer PhD objective one;

- l_1 compared to l_0
- l_1 compared to l_2
- l_1 compared to l_3

3.9.1 Estimation of the minimum sample size needed to answer PhD objective one

Because the primary sample size in the SiVET cohort was determined based on retention within 12 months of follow up, a sample size needed to compare HIV incidence in SiVET cohort to observational cohort pre-SiVET was retrospectively estimated. To estimate this sample, the following assumptions were made; HIV incidence in the source population observational cohort of 5 per 100 person years at risk (PYAR) i.e. the average HIV incidence observed in the FF and FSW population in Uganda (9). Selection and HIV risk reduction measures in the SiVET would reduce this incidence by 40% i.e. to HIV incidence of 3 per 100 PYAR, the minimum average HIV incidence that would be required for a given population to qualify as a recruitment source for an actual HIV vaccine efficacy trial (78). Therefore, with 80% power, 5% level of significance and 20% loss to follow up (assumed from observational cohorts in these key populations), a sample size of 315 participants in each of SiVETs ($SiVET_1$ + $SiVET_2$) and non-SiVETs cohorts would be sufficient to demonstrate a 40% reduction in HIV incidence.

3.9.2 PhD objective one statistical analysis

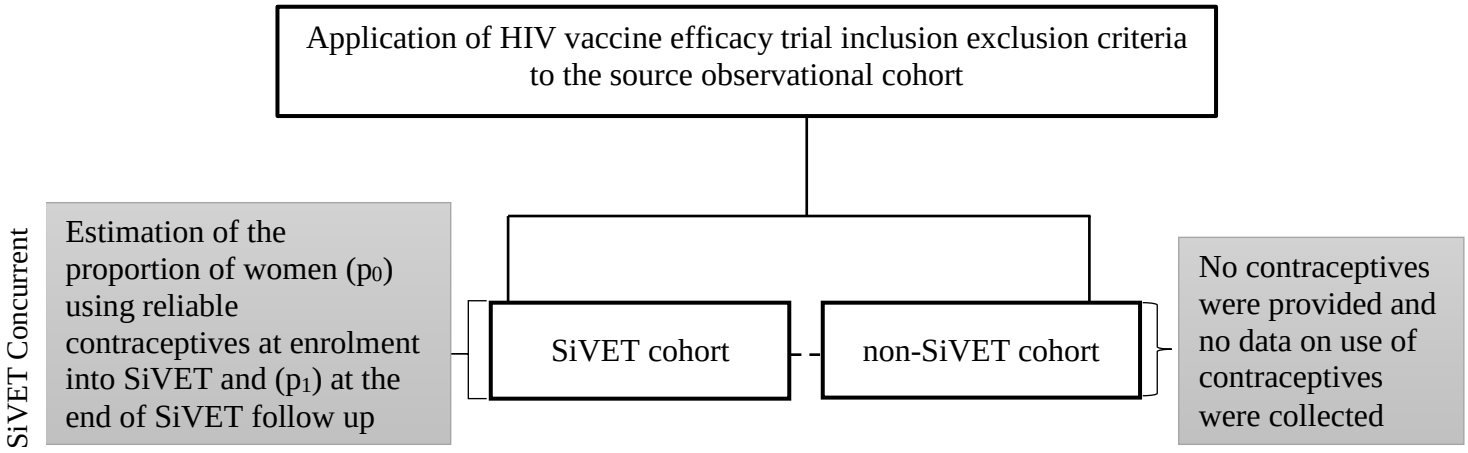
To estimate HIV incidence l_0 (pre-SiVET), l_1 (SiVET cohort), l_2 (non-SiVET cohort), and l_3 (post-SiVET), figure 9, HIV test results data for all participants who completed at least one follow-up visit in a given cohort were considered. HIV incidence was estimated as the number of HIV positive cases in a given period divided by the total person years at risk (PYAR) in the same period expressed as per 100 PYAR. PYAR were calculated as the sum of the time from the period specific analysis entry date to the date of the last HIV seronegative result, or to the estimated date of HIV infection. The date of HIV infection was defined as a random (multiple imputation) date between last HIV-negative and the first HIV-positive result dates. Further details are provided in the publication in chapter four.

3.10 Answering PhD Objective two

Objective: Determining uptake and use of reliable contraceptives by women participating in HIV vaccine efficacy trials.

Answering this was achieved by estimating the proportion of participants that were using a reliable method of contraception at enrolment into SiVET and that at the end of SiVET follow up (structured in figure 10 and detailed in chapter five).

Figure 10: Diagrammatic illustration of the design used to answer PhD objective two



In practice, the following comparisons were made to answer PhD objective two;

- Compare p_0 to p_1
- Determine correlates of reliable contraceptives use at baseline and end of follow up (vaccination) among women participants in the SiVET cohort.

3.10.1 Estimation of the minimum sample size needed to answer PhD objective two

It was estimated that a sample size of 366 women in the SiVETs ($SiVET_1$ + $SiVET_2$) would be sufficient to demonstrate an increase in reliable contraceptive to 70% with 99% power, 5% level of significance and base reliable contraceptives use of 35% (observed in a cross sectional study of modern contraceptives use in the fishing communities, North of Lake Victoria in Uganda) (10).

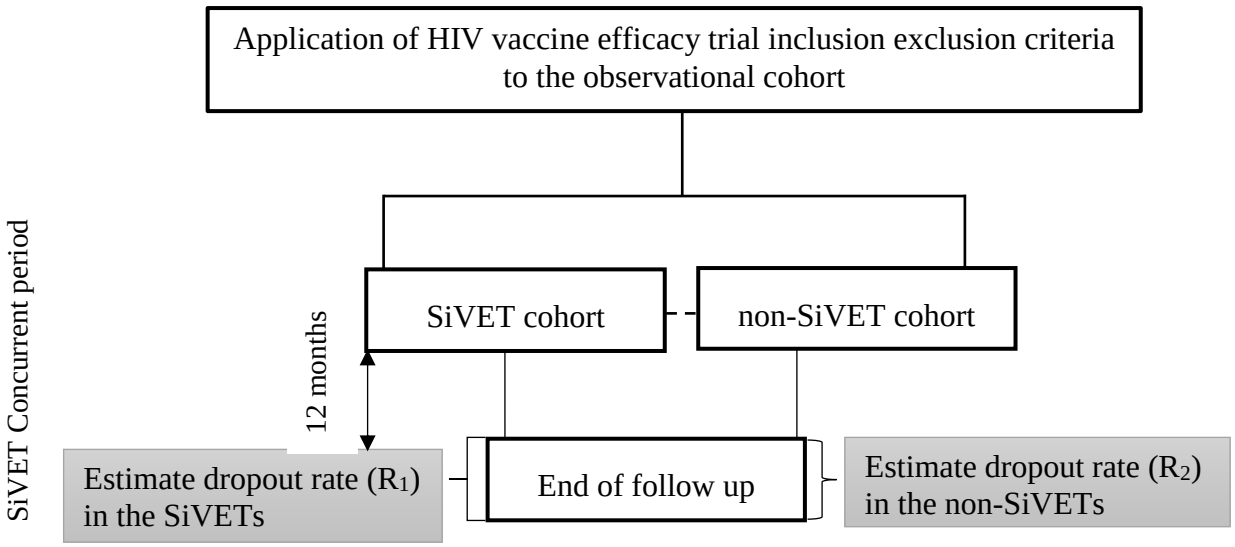
3.10.2 PhD objective two statistical analysis

To estimate the proportion of women using reliable contraceptives at baseline p_0 and that at the end of SiVET follow up p_1, the number using reliable contraceptives at a given time point was divided by the total number of women enrolled and expressed as a percentage. Simple logistic regression models were fitted to determine baseline correlates of reliable contraceptives use at enrolment and at the last vaccination visit (six months of follow up). Further details are provided in the publication in chapter five.

3.11 Answering PhD Objective three

Objective: Comparing observational cohorts' participant dropout rate to that in HIV vaccine efficacy trial in the same population. Answering this was achieved by estimating the rate of participant dropout in the non-SiVET cohort and that in the SiVET cohort in the SiVET concurrent period (structured in figure 11 and detailed in chapter Six).

Figure 11: Diagrammatic illustration of the design used to answer PhD objective three



In practice, the following comparisons were made to answer PhD objective three;

- Compare R_1 to R_2
- Determine factors associated with dropout in the SiVETs and non-SiVETs cohorts

3.11.1 Estimation of the minimum sample size needed to answer PhD objective three

It was estimated that a sample size of 324 participants in each of SiVETs ($SiVET_1$ + $SiVET_2$) and non-SiVETs cohorts would be sufficient to demonstrate a 40% decrease in dropout rate (i.e. dropout rate of 15 /100 PYO in SiVETs cohort) with 80 % power, 5% level of significance. Taking base non-SiVETs cohorts dropout rate of 25/100, PYO (observed in the fishing community observational cohort in Masaka, Uganda) (34).

3.11.2 PhD objective three statistical analysis

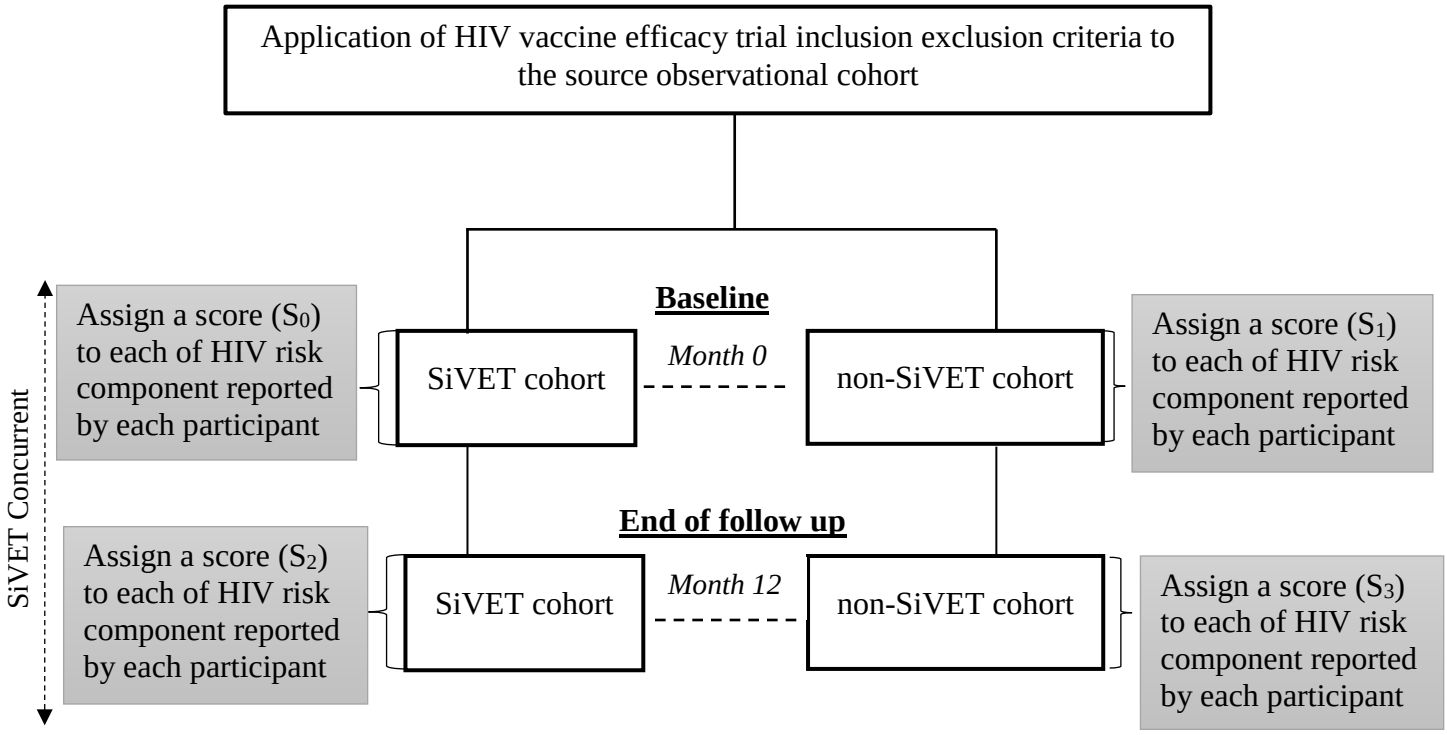
To estimate the dropout rate in the SiVETs (R_1) and non-SiVETs (R_2) cohorts, the number of cases (dropouts) in a given cohort were divided by total person years of observation (PYO) in the same cohort expressed as per 100 PYO. To determine factors associated with dropout, Poisson regression models were fitted for both bivariable and multivariable analyses. Similarly, further details are provided in the publication in chapter six.

3.12 Answering PhD objective four

Objective: Comparing participants HIV risk behaviours between trials and observational cohorts in these key populations.

Answering this was achieved by assigning a score to each HIV risk component reported by the participants at baseline and at the end of follow up (structured in figure 12 and detailed in chapter Seven). For each participant, their composite risk score was defined as the sum of: alcohol consumption; use of alcohol prior to sex; number of sexual partners; starting a new sexual relationship recently; condom use; and presence of genital discharge and/or disease. A higher score indicates higher risk behaviour. The difference in this composite score between baseline and end of follow up (12 months) was defined as a measure of change in risk components.

Figure 12: Diagrammatic illustration of the design used to answer PhD objective four



In practice, the following comparisons were made to answer PhD objective four;

- Determine the proportion of participants with decreased risk score at the end of follow up ((S_0-S_2) in the SiVETs and (S_1-S_3) in the non-SiVETs).
- Compare the decrease in risk score between the SiVETs and non-SiVETs cohorts
- Determine baseline factors associated with decrease in risk score in both SiVETs and non-SiVETs cohorts.

3.12.1 Estimation of the minimum sample size needed to answer PhD objective four

Non-condom use with a new sexual or other casual partners was considered as a measure of high HIV risk behaviours and the following assumptions made; non-condom use in the source population observational cohort of 60% (27). Enrolment into SiVET would reduce this by a half i.e. to non-condom use of 30%. Therefore, with 80% power, 5% level of significance and 20% loss to follow up (assumed from observational cohorts in these key populations) (27), a sample size of 77 participants in each of SiVETs ($SiVET_1$ + $SiVET_2$) and non-SiVETs cohorts would be sufficient to demonstrate a 50% reduction in non-condom use with a new sexual partner.

3.12.2 PhD objective four statistical analysis

Bar graphs were used to display (i) the proportion of participants reporting each risk component at baseline and at 12 month of follow up and (ii) the proportion of participants whose discrete (each variable) risk score at 12 month of follow up decreased from that reported at baseline. For each study participant, the composite score at baseline was subtracted from that at the end of follow-up to create a score difference, where a positive value indicates an increase in risky component and a negative value indicates a decrease. Categorized the score difference into a binary variable, 1 for decreased risk component (difference <0) and 0 otherwise (difference ≥0). The proportion of participants with decreased risk component was estimated as the number with difference <0 divided by the total number of participants in the analysis expressed as a percentage. Linear regression models were fitted stratified by the study population to determine the relationship of risk score at 12 months with study (non-SiVET vs SiVET) or other baseline participants variables adjusted for baseline risk score. After bivariable analyses, a multivariable model was fitted. Further details are provided in the publication in chapter seven.

3.13 Ethical considerations

Both the Uganda Virus Research Institute (UVRI) Research and Ethics Committee, references GC127, GC/127/14/04/454, GC/127/12/04/22 and GC127/12/06/01, and the Uganda National Council for Science and Technology, references MV834, HS364 and HS1584 approved the conduct of SiVETs and observational cohorts. The London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee, reference LSHTM14588 (appendix one) approved the concepts leading to all analyses presented in this PhD thesis. All participants that participated in these studies provided written informed consent before enrolment. We immediately referred to the local HIV treatment and care providers of their choice in the community for further management all participants diagnosed with HIV at screening or during follow up. The data used in this PhD thesis was kept with strict confidentiality. The individual participant unique identifiers used to link the data in the different tables during data cleaning and merging were removed from the final dataset analysed.

Chapter Four: How HIV incidence estimated from observational cohorts might differ from that in the HIV vaccine efficacy trials in the same population

4.1 Research in context

Globally, new HIV infections continue to occur most especially in Sub-Saharan Africa (SSA) amidst available HIV prevention interventions. In SSA, either lack of access or adherence problems or both have blunted the available HIV interventions. Vaccination could help minimise non-adherence to an HIV preventive intervention but does require the completion of the full vaccination schedule. The vaccines in development will have to go through assessment in efficacy trials. Because of the high HIV incidence, SSA will likely remain a key destination for efficacy trials. In Uganda, the general population HIV incidence is low; therefore, such trials will have to be conducted in subpopulations such as the key populations in the Fisher-folks (FF) on the shoreline of Lake Victoria and female sex workers (FSW) in Kampala. These two subpopulations are characterized by very high HIV incidence and good retention in follow up as shown in the HIV vaccine preparedness observational cohorts conducted by the International AIDS vaccine Initiative (IAVI) and its partners in Africa.

4.2 HIV incidence in Efficacy Trials

Designing the intended HIV vaccine efficacy trials in the FF and FSW populations will require an accurate estimate of the HIV incidence in the control (placebo) arm. To achieve this, the common practice is that investigators use HIV incidence from the control (placebo) arms of previous efficacy trials in the same or similar populations. Unfortunately, to date no HIV vaccine efficacy trials have been conducted in the FF or FSW populations in Uganda. Where such data is not available, HIV incidence from historical or pilot cohorts can fill the void. Therefore, the HIV incidence estimated in the IAVI and its partners' HIV vaccine preparedness cohorts in the FF and FSW can be used.

4.3 Pitfalls in estimating HIV incidence in trials

The available evidence shows that participants who join efficacy trials may have a different HIV incidence from that estimated in the observational cohorts because the trial environment is highly controlled. A systematic review, Padian NS et al 2010, published in AIDS journal identified six HIV prevention trials that were unsuccessful and/or terminated before end of participants follow

up due to observing lower HIV incidence during participant follow up than that obtained from underlying observational cohort data. Furthermore, three microbicides trials (two by Peterson et al 2007 published in PloS one and Plos clinical trials, and one by Feldblum PJ et al, 2008 in PloS one) in West Africa were planned assuming placebo arm HIV incidence of 5 per 100 person years at risk (pyar) derived from observational data. The three trials were prematurely terminated after all of them had observed less than half the assumed HIV incidence. On the contrary, a recent dapivirine ring trial, Baeten et al, 2016 in South Africa published in the New England Journal of Medicine assumed HIV incidence of 3.9 per100 pyar in the control arm. HIV incidence of 5 per 100 pyar was observed during participant follow up and the sample size was recalculated assuming the new observed incidence. At the end of the trial follow up, HIV incidence of 4.5 per 100pyar was observed in the control (placebo) arm. The discrepancies between the assumed and observed HIV incidence show that while planning HIV vaccine efficacy trials, observational data need to be used with caution.

4.4 Trials simulating HIV vaccine efficacy trials to estimate incidence

IAVI and its African partners have conducted two Simulated HIV Vaccine Efficacy Trials (SiVETs), mimicking an HIV vaccine efficacy trial conducted with a Hepatitis B vaccine (a commercially licensed vaccine with potential benefit for participants) to simulate the procedures and schedule of an HIV vaccine efficacy trial, with full knowledge of participants. SiVETs were nested in longitudinal observational cohorts in the FF and FSW populations in Uganda. The proxy vaccine used here was not expected to have any effect on the risk of HIV infection but to provide a trial environment similar to the placebo arm of an actual HIV vaccine trial in these populations.

4.5 Data to answer PhD Objective one

Data from SiVETs and observational cohorts were used to answer the PhD objective one i.e. Comparing HIV incidence in SiVETs to that in the observational cohorts, in the pre-SiVET, the concurrent non-SiVET cohort, and post SiVETs periods. This aimed at investigating how HIV incidence in SiVETs differs from that in the observational cohorts within which SiVETs were nested.

4.6 Key findings

Overall, the HIV incidence in the SiVETs of 3.5 per 100 person years at risk (PYAR), 95% Cl: 2.2 - 5.6 was lower than 4.5 per 100 PYAR, 95% Cl: 3.8 - 5.5 in the source observational cohorts pre-SiVET and 5.9 per 100 PYAR, 95% Cl: 4.3 - 8.1 in the concurrent non-SiVET cohort. The HIV incidence in the post-SiVETs observational cohorts of 3.7 per 100 PYAR, 95% Cl: 2.5 - 5.8 was similar to that in the SiVETs. The same pattern (differences in HIV incidence between SiVET and observational cohort) was observed in the FF and FSW populations, with a greater difference in the population of Fisher-folk. Additionally, participants who joined SiVETs differed in important ways from those who did not. Furthermore, HIV incidence varied by the different participant characterisitcs, suplimentary table 4 below. Further details are provided in the Publication below.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	lsh133215	**Title**	Mr
First Name(s)	Andrew Max		
Surname/Family Name	Abaasa		
Thesis Title	Using observational cohort data from Key populations to plan HIV intervention studies		
Primary Supervisor	Jim Todd		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Vaccine		
When was the work published?	08 March 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not Applicable (NA)		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	NA
Please list the paper's authors in the intended authorship order:	NA
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I participated in the conceptualization of the Simulated HIV Vaccine Efficacy Trial (SiVET) concept, drafting of the studies documents (protocol, standard operating manuals and procedures, case report and consent forms), conduct of the studies (data management and cleaning). I headed the data management team for both observational cohorts (performing data management tasks and statistical analysis). I aggregated the datasets from the different observational cohorts and SiVETs, carried out statistical analysis, drafted the initial manuscript and interpreted the study findings.

SECTION E

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Date	29 Nov. 19

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Date	3rd Feb 2020

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Simulated vaccine efficacy trials to estimate HIV incidence for actual vaccine clinical trials in key populations in Uganda

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ABSTRACT

Background: Fisherfolks (FF) and female sex workers (FSW) in Uganda could be suitable key populations for HIV vaccine efficacy trials because of the high HIV incidence and good retention in observational cohorts. However, the observed HIV incidence may differ in participants who enroll into a trial. We used simulated vaccine efficacy trials (SiVET) nested within observational cohorts in these populations to evaluate this difference.

Methods: SiVETs were nested in two observational cohorts (Jul 2012–Apr 2014 in FF and Aug 2014–Apr 2017 in FSW). From Jan 2012 all observational cohort participants (aged 18–49 years) presenting for quarterly visits were screened for enrolment into SiVETs, until 572 were enrolled. Those not enrolled (screened-out or not screened) in SiVET continued participation in the observational cohorts. In addition to procedures in the observational cohorts (HIV testing & risk assessment), SiVET participants were given a licensed Hepatitis B vaccine mimicking a schedule of a possible HIV vaccine, and followed-up for 12 months.

Findings: In total, 3989 participants were enrolled into observational cohorts (1575 FF prior to Jul 2012 and 2414 FSW prior to Aug 2014). Of these 3622 (90.8%) returned at least once, 672 (44.1%) were screened and 572 enrolled in the SiVETs. HIV incidence pre SIVETs was 4.5/100 person years-at-risk (pyar), 95%CI (3.8–5.5). HIV incidence in SiVET was 3.5/100 pyar, (2.2–5.6) and higher in those not enrolled in the SiVET, 5.9/100 pyar, (4.3–8.1). This difference was greatest among FF. In the 12 months post-SIVET period (FF, May 2014–Apr 2015 and FSW, May 2017–Apr 2018), the HIV incidence was 3.7/100 pyar, (2.5–5.8).

Interpretation: HIV incidence was lower in SiVET participants compared to non-SiVET. This difference was different for the two populations. Researchers designing HIV efficacy trials using observational cohort data need to consider the potential for lower than expected HIV incidence following screening and enrolment.

1. Introduction

The burden of HIV continues to be a global challenge but there are several opportunities for HIV prevention, including antiretroviral therapy (ART) for those living with HIV, and Pre Exposure Prophylaxis (PrEP) for HIV uninfected partners. The high HIV burden has been attributed to less than optimal adherence to the available HIV prevention interventions [1,2], and an HIV vaccine would be a very useful addition. Rigorous assessment of such a vaccine through randomized controlled efficacy trials would be needed, but there are methodological issues facing such trials [3]. Populations with high HIV incidence, good retention in follow up and adequate access and use of HIV services are needed to conduct successful HIV vaccine efficacy trials [4]. In countries, where the general population HIV incidence is relatively low [5,6], these trials will have to be conducted among sub-populations who are at high risk of HIV acquisition. Such sub-populations could include men and women with multiple partners or who live in high HIV prevalence areas, such as the fishing communities on Lake Victoria (Fisherfolks, FF) shoreline and female sex workers (FSW) in Kampala.

In Uganda, HIV incidence data are available from observational cohort in FSW [7,8] and FF [9–13]. Observational cohort data may not always predict efficacy trial outcomes because the efficacy trial

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environment is highly controlled with respect to adherence to trial product, clinic visits and HIV risk reduction measures. In addition, there is evidence that participants who join clinical trials differ from those in the source population [14]. Participants who join the clinical trial may have a different HIV incidence from that estimated from the wider observational cohort. Such differences may affect the sample size and power estimates that are used to plan efficacy trials.

One systematic review [15] identified six HIV prevention studies that were unsuccessful and/or terminated because of reduced statistical power, due to observing lower HIV incidence during participant follow up than that predicted based on observational data. The lower than anticipated HIV incidence happened in 64% of the trials evaluated [15]. In three microbicides trials in Nigeria [16] and Ghana [17,18] in 2007/8, an HIV incidence of 5 per 100 person years at risk (PYAR) was predicted in the placebo arms of the trial communities. During the trial, the observed HIV incidence in the respective trial placebo arms were 1.5 per 100 PYAR [16], 1.1 per 100 PYAR [17] and 2.5 per 100 PYAR [18], resulting in the trials being stopped prematurely. On the contrary, a trial in South Africa in 2016 [19] observed an HIV incidence of 3.9 per 100 PYAR prior to the trial, but during participant follow up in the placebo arm of the trial, the HIV incidence was more than 5 per 100 PYAR. This resulted in the investigator re-calculation of the sample size to a lower figure than that planned and they observed an HIV incidence of 4.5 per 100 PYAR in the placebo arm at the end of trial follow up. These discrepancies show that observational data need to be used with caution while planning HIV vaccine efficacy trials, especially in populations without baseline data from previous efficacy trials such as the FF in Uganda.

The simulated vaccine efficacy trial (SiVET) concept has been suggested to assess feasibility, acceptability and retention for a clinical trial of a new product, through a "simulated" trial using a commercially available vaccine [20,21]. This concept can also inform designs and sample size estimation for the future trials [22–24]. We use data from two SiVETs nested within observational cohorts of FSW and FF sub-populations in Uganda, to estimate HIV incidence, in order to help plan a future HIV vaccine efficacy trial.

Table 1
Observational cohorts and SiVETs eligibility criteria in the three periods.

Time	OBSCs pre SiVETs
Period (i)	**Inclusion** • HIV negative and willing to undergo HIV testing • Age 18–49 years • Able and willing to provide written informed consent • Willing to provide adequate locator information • Available for follow-up • Sexually active and at high risk for HIV infection as defined by self-report of any of the following in the previous 3 months: (a) Unprotected sex with ≥one or new sexual partner (b) History of sexually transmitted infections (c) Use of illicit drugs and/or alcohol (d) Being away from home for ≥2 nights per week • Engaged in sex work (only $OBSC_2$) **Exclusion** • HIV infection
Period (ii)	**SiVETs** **Inclusion** • At least 3 and no more than 18 months of follow up in the observational cohort • HIV-1 negative and willing to undergo HIV testing • Aged ≥18 years and ≤49 years • Able and willing to provide written informed consent • Able and willing to provide adequate locator information • Willing and able to return for follow-up clinic visits • Intending to reside in study area for at least one year • Willing to undergo pregnancy testing • Not breastfeeding and no intent for pregnancy in the next year • Willing to use effective contraception during the study and at least 3 months after the last vaccination **Exclusion** • History of severe allergic reaction to any substance • An acute or chronic illness • Contraindication for Hepatitis B vaccine • Participation in another clinical trial • Hepatitis B positive (only $SiVET_2$) **Non-SiVETs concurrent period** **Inclusion** • At least 3 months and no more than 18 months of follow up in the observational cohorts • Still in active follow up in the observational cohort • HIV negative **Exclusion** • HIV positive
Period (iii)	**Post- SiVETs** **Inclusion** • HIV Negative**Exclusion** • HIV positive

2. Methods

2.1. Study design

We use data from two longitudinal observational cohorts in Uganda (observational cohort one ($OBSC_1$) in FF, Feb 2009–Apr 2015 and observational cohort two ($OBSC_2$) in FSW, Apr 2008–Apr 2018). The primary objective of establishing the observational cohorts was to determine HIV incidence and retention in follow up of these key populations in addition to creating enrolment pool for future HIV efficacy trials. From those observational cohorts, two SiVETs ($SIVET_1$ (Jul 2012–Apr 2014) and $SiVET_2$ (Aug 2014–Apr 2017)) were nested within $OBSC_1$ and $OBSC_2$ respectively. The eligibility criteria for the observation cohorts and the SiVETs are shown in Table 1.

2.2. Description of observational cohorts and SiVETs

2.2.1. $Obsc_1$

Eligible participants (Table 1) were enrolled into $OBSC_1$ at MRC/UVRI and LSHTM clinics supported by International AIDS Vaccine Initiative located in Masaka town (about 50 km) from the fishing communities (about 100 km west of Kampala) with quarterly follow up clinic visits for HIV testing and six-monthly visits for HIV behavioral risk assessment. At enrolment, data were also recorded on participants' socio demographic and clinical characteristics using interviewer administered questionnaires. The $OBSC_1$ details are previously described [9,12,13]. From Jul 2012 to Apr 2014, FF attending the $OBSC_1$ clinic were assessed for eligibility (Table 1) for enrolment into $SiVET_1$.

2.2.2. $Obsc_2$

Similarly, eligible participants (Table 1) were enrolled into $OBSC_2$ at MRC/UVRI and LSHTM clinic in Kampala with similar assessments and follow up schedules as $OBSC_1$ above. The $OBSC_2$ details have been previously described [7]. Similarly, from Aug 2014 to May 2016, FSW attending the quarterly clinic visits in $OBSC_2$ were assessed for eligibility for enrolment into $SiVET_2$ (Table 1).

2.2.3. $SiVET_1$

Eligible participants (Table 1) were enrolled into $SIVET_1$ (nested in $OBSC_1$ in the FF population) and had their follow up visits in $SiVET_1$ synchronized with their source $OBSC_1$ participants clinic visits for HIV and behavioral risk assessment. In addition to their $OBSC_1$ procedures, they were further administered a commercially licensed Hepatitis B vaccine (ENGERIX-B™ GlaxoSmithKline Biologicals Rixensart, Belgium) following the standard schedule of 0, 1

and 6 months, and under conditions that mimicked a possible HIV vaccine efficacy trial with extra follow ups at 9 and 12 months under the $SiVET_1$ protocol. Upon completion of $SiVET_1$ follow up, participants were followed-up under $OBSC_1$ procedures only, for another12 months (post-$SiVET_1$).

2.2.4. $SiVET_2$

Similar procedures as in $SiVET_1$ above were followed to establish $SiVET_2$, though this was nested in $OBSC_2$ in the FSW population.

Observational cohort participants that were eligible for screening for enrollment into SiVETs but not screened because of completion of SiVETs accrual, and those screened but not enrolled into SiVETs (i.e., screened out by SiVET enrollment criteria), remained in follow-up in their respective observational cohorts during the SiVET concurrent period (Fig. 1).

When SiVET participants completed 12 months of follow up in the SiVET protocol, they automatically reverted to the post-SiVET cohorts, joining the non-SiVET participants for further follow-up and HIV incidence assessment.

We stratified our data into three periods for each source population (FF or FSW), as shown in Fig. 1:

(1) Pre-SiVETs period (i), including only observational cohort data prior to the initiation of the SiVET in that source population.
(2) SiVET period (ii), including both non-SiVET data and data from the SiVET participants (mutually exclusive) beginning on the date the SiVET began enrolling, and ending on the date of the last SiVET participant clinic visit.
(3) Post-SiVET period (iii), including all observational cohort data recorded after the final SiVET participant study visit (including new recruits) in that source population.

As indicated in Fig. 1, the 3622 participants analyzed in observational cohorts were the basis for period (i) incidence estimates. The 1525 participants eligible for screening for enrollment into SiVETs were the basis for period (ii) incidence estimates for both the SiVET and non-SiVET cohorts, and the 886 participants analyzed for HIV incidence post-SiVET were the basis for period (iii) incidence estimates.

2.3. Key evaluations in this analysis

- Participant baseline characteristics, compared between SiVETs data and non-SiVET data in the concurrent period (ii).
- HIV incidence in SiVET compared to that in the observational pre-SiVET cohort, the concurrent non-SiVET cohort, and post-SiVET cohort.

2.4. Laboratory HIV testing

All HIV testing was carried out at the MRC/UVRI and LSHTM clinical diagnostic laboratories. A single HIV antibody rapid test was performed using Alere Determine™ HIV-1/2 (Alere Medical Co Ltd, Matsuhidai, Matsudo-shi, Chiba, Japan). All rapid HIV positive results were confirmed by two parallel enzyme linked immunosorbent assay (ELISA) tests (Murex Biotech Limited, Dartford, United Kingdom, and Vironostika, BioMérieux boxtel, The Netherlands). Either Statpak (Chembio Diagnostic Systems Inc., USA) or Western Blot (Cambridge Biotech, USA) confirmed any discordant results.

2.5. Data management and statistical analysis

All observational cohort data were entered and managed in MS Access 2003 (Microsoft Corporation, Redmond, WA), and SiVET data in OpenClinica 3.5 (Waltham, MA). Data were analyzed in Stata 14.0 (Stata Corp, College Station, TX, USA). Baseline characteristics of the participants in the non-SiVET cohort (period ii, concurrent non-SiVET data) and those that joined SiVETs (period ii, SiVET) were summarized using percentages, stratified by the study population (FF or FSW) and compared using chi square tests. We estimated HIV incidence as the number of HIV positive cases in a given period divided by the total person years at risk (PYAR) in the same period expressed as per 100 PYAR. PYAR were calculated as the sum of the time from the period specific analysis entry date to the date of the last HIV seronegative result, or to the estimated date of HIV infection. The date of HIV infection was defined as a random (multiple imputation) date between last HIV-negative and the first HIV-positive result dates. The analysis entry dates were defined in the three respective periods as follows: period (i), date of enrolment into a given observational cohort; period (ii) concurrent non-SiVET cohort, three months visit date in the observational cohort (from the start of a given SiVET); period (ii) SiVETs data; date of enrolment into a given SiVET and period (iii) post-SiVET period; date of completion of a given SiVET or date of enrolment for those enrolled post-SiVET.

To put the results in the context of an actual HIV vaccine efficacy trial, we estimated required sample sizes using HIV incidence in period i, and ii (SiVETs data). First, overall and stratified by the study population. We compared the sample size estimated using HIV incidence in period (i) to that in period ii (SiVETs data) to estimate the magnitude of decrease (loss in statistical power) if observational data HIV incidence in period (i) were used to estimate trial sample size as opposed to SiVETs i.e. period (ii) (SiVETs data). While estimating the required sample sizes, we based on the following design; an HIV vaccine efficacy trial uses a superiority study design, an investigational product likely to reduce background HIV incidence by 70%, statistical power of 80%, two-sided alpha of 5% and same loss to follow up in the observational cohorts as in the SiVETs.

2.6. Ethical considerations

The Uganda Virus Research Institute (UVRI) Research and Ethics Committee (GC127, GC/127/14/04/454, GC/127/12/04/22 and GC127/12/06/01) and the Uganda National Council for Science and Technology (MV834, HS364 and HS1584) approved the conduct of observational cohorts and SiVET protocols. The London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee (LSHTM14588) approved the concept leading to this analysis. Written informed consent/assent was obtained for each participant before enrolment. All participants diagnosed to be HIV positive were immediately referred to the local HIV related service providers in the community for treatment and care.

3. Results

3.1. Screening, enrolment and follow up in observational cohorts pre SiVETs, period (i)

In total, 5902 participants were screened and 3989 (67.6%) enrolled into observational cohorts pre SiVETs, period (i). The median age was 26 years (interquartile range, IQR: 22–32). The primary reasons for not enrolling were HIV positive (n = 739), low risk for HIV infection (n = 681) and, for $OBSC_2$, not in sex work (n = 430) Fig. 1. Of those enrolled, 3622 (90.8%) completed at least one follow up visit in the observational cohorts and were analysed to determine HIV incidence pre SiVETs, period (i). The primary

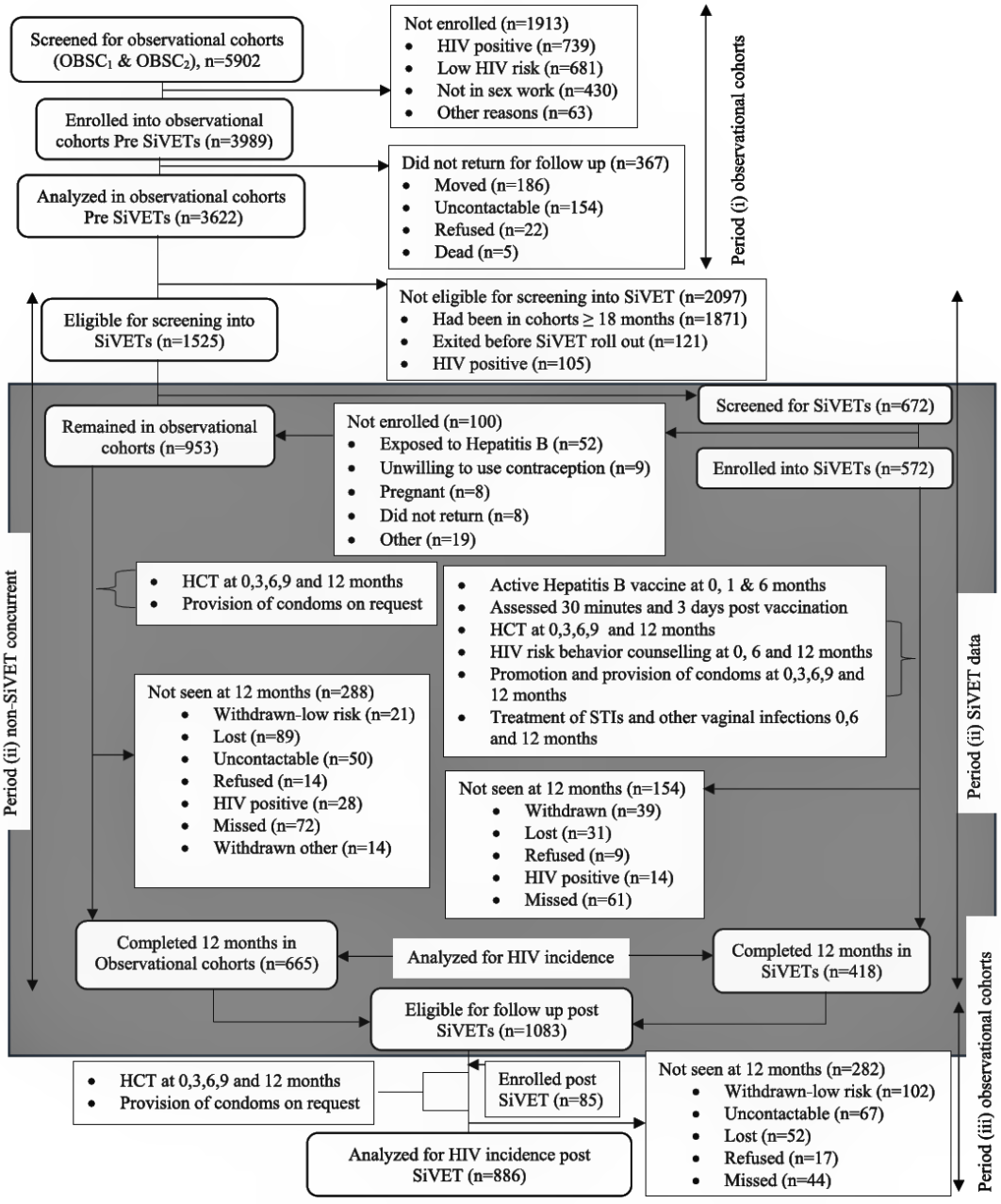

Fig. 1. Study profile for participants screened and enrolled Pre, during and post SiVET in two key populations in Uganda.

reasons for not returning for any follow up were participant moved out of study area (n = 186) and being uncontactable (n = 154).

3.2. Screening, enrolment & follow-up in the concurrent non-SiVET cohort & SiVET, period (ii)

Of the 3622 participants that returned for at least one follow up visit in the observational cohorts pre SiVETs, 1525 (42.1%) were eligible for screening into SiVETs when the SiVET protocols were introduced and 2097 (57.9%) were not eligible. The primary reasons for ineligibility were having been in the observational cohorts for ≥18 months (n = 1871), exiting observational cohort before SiVETs roll out (n = 121) and being HIV positive (n = 105) Fig. 1. Of the 1525 (median age 26 years IQR: 22–31) eligible for screening, 672 (44.1%) were screened (under 50% were screened because of sample size accrual) and 572 (85.1%) enrolled into SiVETs. The primary reasons for not enrolling into SiVETs were previous hepatitis B exposure (n = 52), not willing to use contraception (n = 9), pregnancy (n = 8) and not returning for enrolment (n = 8). In total, 953 (62.5%) of 1525 eligible for screening into SIVETs remained in follow up in the non-SiVET cohorts in the SiVETs concurrent period (period (ii) non-SIVET data) Fig. 1. Retention at 12 months was

83.8% in SiVETs vs. 76.4% in non-SiVET cohorts in the concurrent period (ii), p < 0.01.

In the $OBSC_1$, compared to those that were not eligible for screening into $SiVET_1$, eligible participants were younger (mean age 26.5 vs 28.5: p = 0.038), mostly males 60.5% vs 54.8%, p = 0.029 and were less likely to have lived for more than one year at the current location 59.8% vs 75.2%, p < 0.001 but were otherwise similar in terms of other characteristics. Similarly, in the $OBSC_2$, compared to those that were not eligible for screening into $SiVET_2$, eligible participants were more likely to have lived at the current location for more than one year 91.5% vs 68.5%, p < 0.001 but were otherwise similar in terms of other characteristics.

3.3. Post SiVETs, period (iii)

In total 1168, participants (1083 from period ii and 85 new recruits into observational cohorts post-SiVETs) were followed up quarterly for 12 months in the observational cohorts post-SiVETs, period (iii). Retention at 12 months was 84.6%.

3.4. Baseline characteristics, SiVETs vs non-SiVET cohorts in the concurrent period (ii)

Table 2, presents the baseline characteristics of the participants who were recruited into $SiVET_1$ (FF) and $SiVET_2$ (FSW) compared to those in the source population who were not recruited into the SiVETs (non-$SiVET_1$ and non-$SiVET_2$) in the same period (ii). In the FF population, compared to $SIVET_1$, non-$SiVET_1$ cohort had greater numbers of females 51.6% vs 27.3%, those aged 18–24 years 44.9% vs 31.2%, those without formal education 12.4% vs 6.7%, those working in Hotel/Bar/Hair salon 23.0% vs 8.2%, and those that had lived at the current location for one year or less 33.9% vs 17.0%. Similarly, in the FSW population, compared to $SiVET_2$, non-$SiVET_2$ cohort had greater numbers of participants aged 18–24 years 45.4% vs 29.3%, those without formal education 40.6% vs 5.5%, those engaged in sex work 67.5% vs 56.9% [noting that there are FSW who don't consider sex work as their main occupation] and those that had lived at the current location for one year or less 33.1% vs 17.6%.

3.5. HIV incidence in periods i, ii and iii

The HIV incidence in the SiVETs (period ii) was lower than that in the observational cohorts pre-SiVETs (period i), and the concurrent incidence in the non-SiVET cohorts during period ii (Table 3). The HIV incidence in the post-SiVET observational cohorts (period iii) was lower than that in the pre-SiVET observational cohorts i.e. period (i) and similar to the HIV incidence in the SiVET cohort in period (ii), (Table 3). In all periods, HIV incidence was higher in the FF population than FSW population. HIV incidence was greater

Table 2
Baseline characteristics of the participants in the non-SiVET and SiVET cohorts, period (ii) in Masaka and Kampala.

	Period (ii), FF (N = 565)				Period (ii), FSW (N = 960			
Variables	Overall n (%)	Non-$SiVET_1$ n (%)	$SiVET_1$ n (%)	p-value	Overall n (%)	Non-$SiVET_2$ n (%)	$SiVET_2$ n (%)	p-value
Overall	565 (100)	283 (100)	282 (100)	–	960 (100)	670 (100)	290 (100)	–
Sex					–			
Male	342 (60.5)	137 (48.4)	205 (72.7)	<0.001				
Female	223 (39.5)	146 (51.6)	77 (27.3)		960 (100)	670 (100)	290 (100)	
Age group (years)								
18–24	215 (38.1)	127 (44.9)	88 (31.2)	0.001	389 (40.5)	304 (45.4)	85 (29.3)	<0.001
25–34	242 (42.8)	115 (40.6)	127 (45.0)		432 (45.0)	289 (43.1)	143 (49.3)	
35+	108 (19.1)	41 (14.5)	67 (23.8)		139 (14.5)	77 (11.5)	62 (21.4)	
Tribe								
Baganda	242 (42.8)	114 (40.2)	128 (45.4)	0.018	448 (46.7)	295 (44.0)	153 (52.8)	0.035
Banyankole	81 (14.3)	50 (17.7)	31 (11.0)		141 (14.7)	109 (16.3)	32 (11.0)	
Banyarwanda	123 (21.8)	69 (24.4)	54 (19.2)		60 (6.2)	40 (6.0)	20 (6.9)	
Other	119 (21.1)	50 (17.7)	69 (24.4)		311 (32.4)	226 (33.7)	85 (29.3)	
Education								
None	54 (9.5)	35 (12.4)	19 (6.7)	0.046	288 (30.0)	272 (40.6)	16 (5.5)	<0.001
Primary	401 (71.0)	190 (67.1)	211 (74.8)		431 (44.9)	282 (42.1)	149 (51.4)	
Secondary+	110 (19.5)	58 (20.5)	52 (18.5)		241 (25.1)	116 (17.3)	125 (43.1)	
Marital status								
Single never married	170 (30.1)	86 (30.4)	84 (29.8)	0.173	308 (32.1)	240 (35.8)	68 (23.5)	0.001
Married	268 (47.4)	125 (44.2)	143 (50.7)		60 (6.2)	42 (6.3)	18 (6.2)	
Single ever married	127 (22.5)	72 (25.4)	55 (19.5)		592 (61.7)	388 (57.9)	204 (70.3)	
Religion								
Christian	433 (76.6)	216 (76.3)	217 (77.0)	0.861	726 (75.6)	507 (75.7)	219 (75.5)	0.959
Muslim	132 (23.4)	67 (23.7)	65 (23.0)		234 (24.4)	163 (24.3)	71 (24.5)	
Occupation								
Fishing/fish related	293 (51.8)	124 (43.8)	169 (59.9)	<0.001	–	–	–	0.019
Small scale business	132 (23.4)	59 (20.8)	73 (25.9)		28 (2.9)	17 (2.5)	11 (3.8)	
Hotel/Bar/Hair saloon	88 (15.6)	65 (23.0)	23 (8.2)		307 (32.0)	196 (29.3)	111 (38.3)	
Sex work	–	–	–		617 (64.3)	452 (67.5)	165 (56.9)	
Other	52 (9.2)	35 (12.4)	17 (6.0)		8 (0.8)	5 (0.7)	3 (1.0)	
Duration lived at the current location (years)								
0–1	144 (25.5)	96 (33.9)	48 (17.0)	<0.001	273 (28.4)	222 (33.1)	51 (17.6)	<0.001
>1	421 (74.5)	187 (66.1)	234 (83.0)		687 (71.6)	448 (66.9)	239 (82.4)	
Illicit drug use					187 (19.5)	132 (19.7)	55 (19.0)	0.791
No	499 (88.3)	254 (89.7)	245 (86.9)	0.288	773 (80.5)	538 (80.3)	235 (81.0)	
Yes	66 (11.7)	29 (10.2)	37 (13.1)					

SiVET-Simulated Vaccine Efficacy Trial.

Table 3
Overall HIV incidence pre, during and post-SiVET and stratified by the study population.

Target population	Period (i)		Period (ii)				Period (iii)	
	HIV+/PYAR	Incidence (95%CI)	Non-SiVET data		SiVET data			
			HIV+/PYAR	Incidence (95%CI)	HIV+/PYAR	Incidence (95%CI)	HIV+/PYAR	Incidence (95%CI)
Fisherfolk	69/1404.9	4.9 (3.9–6.2)	24/289.5	8.3 (5.6–12.4)	10/263.5	3.8 (2.0–7.1)	12/291.2	4.1 (2.3–7.3)
FSW	36/904.8	4.0 (2.9–5.5)	15/368.6	4.1 (2.5–6.7)	7/221.4	3.2 (1.5–6.6)	9/266.1	3.4 (1.8–6.5)
Overall	105/2309.7	4.5 (3.8–5.5)	39/658.1	5.9 (4.3–8.1)	17/484.9	3.5 (2.2–5.6)	21/557.3	3.7 (2.5–5.8)

PYAR: person years at risk, SiVET: Simulated Vaccine Efficacy Trial, CI: confidence interval, FSW: Female sex work, HIV+: HIV positive cases.

in the non-SiVET than in the corresponding SiVET in the concurrent period i.e. period (ii), and the difference was highest in the FF population 8.3 per 100 PYAR vs 3.8 per 100 PYAR, p = 0.017 compared to FSW population 4.1 per 100 PYAR vs 3.2 per 100 PYAR, p = 0.300. However, the difference in the FSW was not statistically significant.

Supplementary Table 4 shows HIV incidence by the different characteristics of the participants in the three periods. In all the periods, HIV incidence tended to be higher among participants that had spent one year or less in the current location and lower among Baganda (indigenous occupants of the geographical location of the two study areas), but it varied in the other participant characteristics in the different periods.

3.6. Contextualizing HIV incidence observed to actual HIV vaccine efficacy trial

Putting these results in the context of a future HIV vaccine efficacy trial, a sample size can be calculated using the overall HIV incidence in the SiVETs of 3.5/100 PYAR. With that HIV incidence in the control (placebo) arm of the trial, the actual sample size would be 1626 participants (813 in each arm) to show an incidence risk ratio (RR) of 0.30 with a significance of 5% and power of 80%. However, in absence of the SiVETs, the HIV incidence in the control arm would be estimated from the HIV incidence of 4.5/100 PYO in the pre-SiVETs (period i). In that case the estimated sample size would be 1266 participants (633 in each arm) to show the RR of 0.30, with a significance of 5% and a power of 80%. This would under estimate the true trial sample size by 360 participants, an under estimate of 22% of the expected number of study participants and only achieve 67.8% power. The direction of underestimate in the sample size was similar in each of the subpopulations (FF and FSW), and calculations of sample size based on the pre-SiVET HIV incidence would give reduced power for the HIV incidence observed under the SiVET selection with the highest reduction in the FF population.

4. Discussion

In this analysis, we investigated how HIV incidence in two HIV Simulated Vaccine Efficacy Trials (SiVETs) differs from the observational cohorts within which they were nested. We compared HIV incidence in SiVETs to that in the observational cohorts, in the pre-SiVET period, the concurrent non-SiVET cohort, and post-SiVETs periods. The combined HIV incidence in the SiVETs (3.5 per 100 PYAR) was lower than in the observational pre-SiVET combined cohort (4.5 per 100 PYAR) and the concurrent non-SiVET cohort (5.9 per 100 PYAR). The HIV incidence in the post-SiVETs observational cohorts was similar to that in the SiVETs. Stratifying the results by the study population, we found the same pattern in each, with a greater difference in the population of Fisherfolk.

Our findings suggest the likely effect of selection into trials and/or trials environment on background HIV risk. We conjecture two possible causes of these differences: (a) people who volunteer to take part in trials have lower risk of HIV infection, and (b) the trial environment changes people's behavior, which results in lower risk of HIV infection. These two causes are not mutually exclusive. Although the observational cohorts were the recruitment source for the SiVETs, participants who joined SiVETs differed in important ways from those who did not. The proportions of each of male sex, those aged over 25 years, with formal education, and having lived in the community for over one year were higher in the SiVET cohort than in the non-SiVET cohort. These participant characteristics have been previously associated with lower risk of HIV acquisition in these populations [8,11,13,25] and other HIV at-risk populations [26–29]. The selection difference between trials and source population have been previously highlighted [14,17].

Secondly, the reduction in HIV incidence could be attributable to the difference between the trial and observational cohort environment. This has been previously noted in microbicides trials in West Africa [16–18]. In these trials, investigators observed a reduction in HIV incidence in the placebo arms during participants follow up of between 50% and 78% from that predicted at baseline. These trials were prematurely terminated. The investigators hypothesized that diminished HIV incidence within a trial may follow from vigorous responses to trial HIV risk-reduction measures and a possible inclination to safer HIV risk behavior. Furthermore, HIV incidence in earlier trials in a similar population was used to plan the current trials instead of specifically measuring incidence in each population before starting a trial. In the case of SiVETs in both FF and FSW, we provided HIV risk reduction measures (counselling on multiple concurrent sexual partnership, condom use and being faithful to one partner), provided free condoms as well as active diagnosis and treatment for STIs and other genital infections. These were as well provided to the non-SiVET cohorts except condoms were provided on request and no active diagnosis and treatment for STIs and other genital infections was done. These HIV risk reduction interventions in an efficacy trial could lower the risk of HIV infection during participant follow up even in the absence of a preventive HIV vaccine or other investigational product.

Our findings build on the results of an earlier pilot analysis [30] of the data from the FF population. The pilot analysis was smaller, in one study population, with shorter follow up in the observational cohort and showed a bigger difference between the HIV incidence in the SiVET cohort (3.8 per 100 PYAR) and the non-SiVET cohort (11.4 per 100 PYAR).

In our estimation of the required sample size, the results overall show that using HIV incidence from observational data to plan a possible HIV vaccine efficacy trial would underestimate the trial sample size by about one-quarter. This sample size underestimation, achieves a statistical power of 68%. The underestimation of the study size was highest in the Fisherfolk population.

Our study strengths included an adequate follow up period in the pre, concurrent and post SiVETs periods, sufficient sample size, two key populations in different geographical location, same study teams conducting study procedures in the respective populations and comparing SiVETs participants to non-SiVET participants in

the same population and period. The results provide strong evidence to researchers planning HIV vaccine efficacy trials in these populations that, in communities with a high HIV burden, HIV incidence observed in existing observational cohorts might differ from that they will see in trials even in the absence of a preventive vaccine or other interventions.

Our study limitations included; the procedures in SiVETs and observational cohorts were not blinded (to either participants and/or researchers) and were performed by the same study teams. However, at the time of SiVET roll out, the primary objective was not to compare attributes in the two studies and therefore the lack of blinding may or may not have affected measurement of outcomes considered in this analysis. Although recruitment into SiVETs had a run-in period of at least three months, an actual vaccine efficacy trial may not wait this long. Selection bias could have played a role in recruitment of participants into SiVETs. This could be inform of self-selection or the study teams recruited into SiVETs participants that came on time for their observational cohort visits (SiVETs screening visits). Such participants could have been easier to follow up and likely to come from the low-risk strata (older, men (FF population) and residents for a longer time).

In conclusion, in two key populations, FF and FSW, we have seen that people who volunteer for a vaccine trial are different from the source population in crucial ways. These differences, together with a trial environment, could result in lower HIV incidence in both arms of a trial, even in the absence of an effective HIV vaccine or other biomedical intervention. SiVET HIV incidence could be a useful aid for sample size calculations for future HIV vaccine trials. In populations where such data is not available, we recommend use of the observed incidence in observational cohorts but adjusting the sample size by approximately one quarter to accommodate for the likely lower incidence in the trial. This strategy could provide a better estimate. Interestingly, even with these differences, the HIV incidence in these key populations remains high, in an era of wide spread use of antiretroviral treatment, and while reduced in SiVETs, it is still suitable for actual HIV vaccine efficacy and other intervention trials.

Authors' contribution

AA: Lead Author, drafted initial manuscript draft, carried out data management for $OBSC_1$ and both SiVETs, data analysis and interpreted the data. SN: contributed to data analysis and interpreted the data. YM: contributed to the design of the $SiVET_2$ protocol, study coordination ($OBSC_2$ and $SiVET_2$). MP: contributed to the design of both SiVETs and $OBSC_1$ and interpreted the data. PEF: contributed to the design of both SiVETs and $OBSC_1$, and interpreted the data. AK contributed to the design of both SiVETs and OBSCs and directed their implementation, PK: directed the implementation of both OBSCs and SiVETs. JT: contributed to data analysis and interpreted the data. All authors critically commented and provided revisions to the manuscript. The authors have approved this final version for submission.

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Conflict of interest

The authors declare that they have no competing interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.072.

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Supplementary, Table 4: HIV incidence by cohorts' participant characteristics in the three periods not stratified by population

Variables	Period (i)		Period (ii)				Period (iii)	
			Non-SiVET data		SiVET data			
	HIV+/ PYAR	Incidence (95%CI)	HIV+ /PYAR	Incidence (95%CI)	HIV+ /PYAR	Incidence (95%CI)	HIV+ /PYAR	Incidence (95%CI)
Sex								
Male	38/773.0	4.9 (3.6-6.8)	8/138.9	5.8 (2.9-11.5)	7/193.1	3.6 (1.7-7.6)	6/206.2	2.9 (1.3-6.5)
Female	67/1536.7	4.4 (3.4-5.5)	31/519.2	6.0 (4.2-8.5)	10/291.8	3.4 (1.8-6.4)	15/351.1	4.3 (2.6-7.1)
Age group (years)								
18-24	44/823.8	5.3 (4.0-7.2)	13/291.1	4.5 (2.6-7.7)	6/141.6	4.2 (1.9-9.4)	5/209.4	2.4 (1.0-5.7)
25-34	48/1040.7	4.6 (3.5-6.1)	18/276.2	6.5 (4.1-10.3)	8/226.5	3.5 (1.8-7.1)	8/247.0	3.2 (1.6-6.5)
35+	13/445.2	2.9 (1.7-5.0)	8/90.8	8.8 (4.4-17.6)	3/116.8	2.6 (0.8-8.0)	8/101.0	7.9 (4.0-15.8)
Tribe								
Baganda	48/1101.0	4.4 (3.3-5.8)	15/274.6	5.5 (3.3-9.0)	6/235.6	2.5 (1.1-5.7)	6/271.3	2.2 (1.0-4.9)
Banyankole	14/274.4	5.1 (3.0-8.6)	7/118.5	5.9 (2.8-12.4)	5/53.0	9.4 (3.9-22.6)	3/73.2	4.1 (1.3-12.7)
Banyarwanda	18/278.8	6.5 (4.1-10.2)	7/94.7	7.4 (3.5-15.5)	3/68.5	4.4 (1.4-13.6)	3/81.3	3.7 (1.2-11.4)
Other	22/653.6	3.4 (2.2-5.1)	10/170.2	5.9 (3.2-10.9)	3/127.7	2.4 (0.8-7.3)	9/130.6	6.9 (3.6-13.2)
Education								
None	19/512.7	3.7 (2.4-5.8)	10/176.0	5.7 (3.1-10.6)	2/29.7	6.7 (1.7-26.9)	6/117.4	5.1 (2.3-11.4)
Primary	63/1252.0	5.0 (3.9-6.4)	19/347.1	5.5 (3.5-8.6)	10/312.8	3.2 (1.7-5.9)	10/330.3	3.0 (1.6-5.6)
Secondary+	23/545.0	4.2 (2.8-6.4)	10/135.0	7.4 (4.0-13.8)	5/142.4	3.5 (1.5-8.4)	5/109.7	4.6 (1.9-11.0)
Marital status								
Single never married	29/549.3	5.3 (3.7-7.6)	8/210.1	3.8 (1.9-7.6)	7/132.5	5.3 (2.5-11.1)	4/167.7	2.4 (0.9-6.4)
Married	44/968.1	4.5 (3.4-6.1)	12/156.7	7.7 (4.4-13.5)	4/146.0	2.7 (1.0-7.3)	4/169.4	2.4 (0.9-6.3)
Single ever married	32/792.3	4.0 (2.9-5.7)	19/291.3	6.5 (4.2-10.2)	6/206.5	2.9 (1.3-6.5)	13/220.2	5.9 (3.4-10.2)
Religion								
Christian	83/1789.4	4.6 (3.7-5.8)	29/478.2	6.1 (4.2-8.7)	10/370.6	2.7 (1.5-5.0)	16/418.0	3.8 (2.3-6.2)
Muslim	22/520.3	4.2 (2.8-6.4)	10/180.0	5.5 (3.0-10.3)	7/114.3	6.1 (2.9-12.9)	5/139.4	3.6 (1.5-8.6)
Occupation								
Fishing/fish related	26/486.7	5.3 (3.6-7.8)	7/129.6	5.4 (2.6-11.3)	6/158.5	3.8 (1.7-8.4)	7/181.7	3.9 (1.8-8.1)
Small scale business	21/531.6	3.9 (2.6-6.1)	8/80.4	9.9 (5.0-19.9)	3/77.5	3.9 (1.2-12.0)	1/69.2	1.5 (0.2-10.3)
Hotel/Bar/Hair saloon	29/559.0	5.2 (3.6-7.5)	8/159.9	5.0 (2.5-10.0)	6/107.0	5.6 (2.5-12.5)	2/98.4	2.0 (0.5-8.1)
Sex work	17/352.4	4.8 (3.0-7.8)	13/238.1	5.5 (3.2-9.4)	2/123.6	1.6 (0.4-6.5)	8/171.8	4.7 (2.3-9.3)
Other	12/380.0	3.2 (1.8-5.6)	3/50.0	6.0 (1.9-18.6)	0/18.3	-	3/36.3	8.3 (2.7-25.7)
Duration lived at the current location (years)								
0-1	33/541.8	6.1 (4.3-8.6)	14/200.3	7.0 (4.1-11.8)	6/76.9	7.8 (3.5-17.4)	6/134.7	4.5 (2.0-9.9)
>1	72/1767.8	4.1 (3.2-5.1)	25/457.8	5.5 (3.7-8.1)	11/408.0	2.7 (1.5-4.9)	15/422.7	3.5 (2.1-5.9)
Illicit drug use								
No	86/1846.0	4.7 (3.8-5.8)	25/321.3	7.8 (5.3-11.5)	9/271.5	3.3 (1.7-6.4)	1/45.1	2.2 (0.3-16.5)
Yes	19/463.7	4.1 (2.6-6.4)	14/336.9	4.2 (2.5-7.0)	8/213.4	3.7 (1.9-7.5)	20/512.3	4.1 (2.7-6.3)

PYAR: person years at risk, SiVET: Simulated Vaccine Efficacy Trial, CI: confidence interval, HIV+: HIV positive cases

Chapter five: Determining uptake and use of reliable contraceptives by women participating in HIV vaccine efficacy trials

5.1 Research in context

Sub-Saharan Africa (SSA) suffers the highest burden of HIV. Some sub-populations, such as members of fishing communities, fisher-folks (FF) and female sex workers (FSW), are disproportionately affected. Because of the high HIV incidence, these communities are attractive for the conduct of HIV vaccine efficacy trials. However, such trials could take months or years from recruitment to completion. In this long period, women could become pregnant and might have to be withdrawn from follow up due to unknown effects of the new investigational product on the foetus. More withdrawals than that anticipated could have negative effects on the trial statistical power. To avoid pregnancy in trials, women are required to take up and adhere to use of reliable, long-acting, reversible contraceptive methods. The common practice is to exclude women not agreeing to reliable contraceptive use during follow up. Such exclusion could introduce selection bias. Many women in SSA do not use contraceptive methods because of lack of access or misconceptions about contraceptives. Supporting women's use of reliable contraceptives, helps to avoid selection bias at enrolment and a loss of statistical power by limiting the risk of unintended pregnancies leading to withdrawals during participant follow up in efficacy trials.

5.2 Contraceptives data for planning efficacy trials (common practices)

To prevent pregnancy in HIV vaccine efficacy trials anticipated, use of reliable contraceptives has become a key inclusion criterion. Data on reliable contraceptives use for planning such efficacy trials come from previous trials in the same or similar populations. Completed HIV vaccine efficacy trials have shown that one third of the enrolled women were already using a reliable method of contraceptives at baseline but did not indicate any data on uptake during follow up. The annual incidence of pregnancy was high, 9.6 per 100 women years of follow up. This data come from trials conducted in the general population but key populations tend to be special populations.

In populations where no trial specific context data exist such as Fisher-folks on the shoreline of Lake Victoria and Female Sex Workers in Kampala Uganda, the common practice is prospective trial participants may be required to use reliable contraceptive methods for ≥3 months before

screening and enrolment. This increases the cost of conducting trials and delays rollout, but avoids costly drop out from trials due to non-compliance.

As indicated in chapter four (section 4.4), SiVET concept was used to investigate reliable contraceptive use among women Fisher-folks and Female sex workers during two Simulated HIV Vaccine Efficacy trials in Uganda.

5.3 Key findings

Overall, the promotion and provision of reliable contraceptive methods in the SiVET improved their use from one in every two women at baseline to nine in every 10 women at the end of the vaccination schedule follow up. Secondly, the use of reliable contraceptives methods at baseline was particularly higher among young women and illicit drug users. Similarly, young women, those with secondary or more education and the FSW population used reliable contraceptives more than their counterparts did by end of vaccination. Promotion and provision of reliable contraceptives to women not using them at baseline improved the proportion using them mainly within the first month of follow up. A low proportion of participants, 3% got pregnant during follow up. Further details are provided in the publication below.

5.4 Implications for future HIV vaccine efficacy trials in these key populations

Promotion and provision of reliable contraceptives in these key populations leads to high uptake and use, and lowers the incidence of pregnancy. Investigators planning HIV vaccine efficacy trials in these and similar populations may not need to put women volunteers on reliable contraceptives for atleast three months before screening and enrollment. Provision of reliable contraceptives as well as screening and enrolment could happen concurrently.

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Student ID Number	lsh133215	**Title**	Mr
First Name(s)	Andrew Max		
Surname/Family Name	Abaasa		
Thesis Title	Using observational cohort data from Key populations to plan HIV intervention studies		
Primary Supervisor	Jim Todd		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Nature Scientific Reports		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I participated in the conceptualization of the Simulated HIV Vaccine Efficacy Trial (SiVET) concept, drafting of the studies documents (protocol, standard operating manuals and procedures, case report and consent forms), conduct of the studies (data management and cleaning). I headed the data management team for both observational cohorts (performing data management tasks and statistical analysis). I aggregated the datasets from the different observational cohorts and SiVETs, carried out statistical analysis, drafted the initial manuscript and interpreted the study findings.

SECTION E

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Use of reliable contraceptives and its correlates among women participating in Simulated HIV vaccine efficacy trials in key-populations in Uganda

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To prevent pregnancy in trials, reliable contraceptive use is key. We investigated reliable contraceptive use at baseline and six months in key-populations in Uganda, during two Simulated HIV Vaccine Efficacy trials (SiVETs). SiVETs were nested within observational cohorts of Fisherfolk (2012–2014) and Female sex workers (2014–2017). Women in the observational cohorts were screened and enrolled into the SiVET. The trial administered a licensed Hepatitis B vaccine at 0, 1 and 6 months. Contraceptive use data were recorded at baseline and follow-up clinic visits. Reliable contraceptives (injectable Depot Medroxyprogesterone Acetate (DMPA), implant, pills, and intrauterine device (IUD)) were promoted and provided to women not using a reliable method at enrolment. Overall, 367 women were enrolled. At baseline 203 (55%) reported use of reliable contraceptive. Of the 164 women not using a reliable method at enrolment, 131 (80%) started using them during follow-up bringing the overall number to 334 (91%) at the end of follow-up. Young age (≤35 years) was an independent predictor of reliable contraceptive use at both time points while other factors varied. Promotion and provision of reliable contraceptives increased the proportion using them and could help reduce the risk of pregnancy in future HIV prevention trials.

Sub-Saharan Africa (SSA) suffers the highest burden of HIV with 70% of the people living with HIV in 2017 being residents in SSA[1]. Similarly, global estimates show that 65% of new HIV infections in 2017 happened in this region[1]. Some sub-populations, such as members of fishing communities (fisherfolks-FF) and female sex workers (FSW), are disproportionately affected. The HIV prevalence in fishing communities is as high as 37%[2–6] and annual HIV incidence of more than 3 per 100 person years have been reported[7,8]. The HIV burden is worse among women[2,4]. Because of the high HIV incidence, these communities are attractive for the conduct of HIV vaccine efficacy trials. However, trials could take months or years from recruitment to completion. In this long period, women could become pregnant and might have to be withdrawn from follow up due to unknown effects of the new investigational product on the fetus. More withdrawals than that anticipated could have negative effects on the trial statistical power[9–11]. In such efficacy trials, it is important to prevent pregnancies in women participants through the use of reliable, long-acting, reversible contraceptive methods.

Reliable contraceptives defined as non-barrier methods likely to reduce the risk of pregnancy include injectable Depot medroxyprogesterone acetate (DMPA), pills, Norplant-implant and intrauterine contraceptive device (IUCD)[12]. The use of reliable contraceptives in women of reproductive age is low, at 64% globally, 28% in SSA and 40% in East Africa[13]. Lack of access to and concerns regarding side effects or health risks associated with contraceptives use have been the main reasons advanced for the low use in SSA[14]. In Uganda, 35% of women in the general population use reliable contraceptives, although this may be higher in specific sub-groups of the population[15].

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Eligible	Ineligible
• At least 3 and no more than 18 months of follow up in the observational cohort	• HIV-1 infection
• HIV-1 negative and willing to undergo HIV testing	• Pregnant or intending to get pregnant
• Aged ≥18 years and ≤49 years	• Previous exposure to Hepatitis B or current infection (only Kampala clinic)
• Able and willing to provide informed consent	• History of severe allergic reaction to any substance
• Able and willing to provide adequate locator information	• An acute or chronic illness
• Willing and able to return for follow-up clinic visits	• Contraindication for Hepatitis B vaccine
• Intending to reside in the study area for at least one year	• Participation in another clinical trial
• Willing to undergo pregnancy testing	
• Not breastfeeding and no intent for pregnancy in the next year	
• Willing to use a reliable method of contraceptives during the study	

Table 1. Eligibility Criteria for screening/enrolment into SiVET at Kampala & Masaka clinics, Uganda.

Previous HIV prevention trials in non-fishing communities in Africa (East, West and Southern Africa) have shown that reliable contraceptive use is low, ranging between 5% to 28%[12,16–19]. In a 2013 review of microbicide trials in Africa the incidence of pregnancy ranged from 4.0 to 64 per 100 women-years[20]. There is little data on uptake of reliable contraception and the impact of contraception on pregnancy during these trials.

High levels of willingness (>95%) to participate in HIV vaccine efficacy trials have been shown in Africa[21,22]. However, among women this decreased to 23% when the need to prevent or delay pregnancy through use of reliable contraceptives was mentioned[21]. To date, no HIV vaccine efficacy trials have been conducted in women at high-risk of HIV infection in Uganda, and there is no baseline information on the use of reliable contraceptive methods to delay pregnancy during HIV prevention trials. It is unknown how the use of reliable contraceptives and risk of pregnancy would change among study participants and how this would affect HIV vaccine efficacy trials in these populations.

In populations where no baseline data on reliable contraceptives use is available, prospective trial participants may be required to use reliable contraceptive methods for at least three months before screening and enrolment[23]. This increases the cost of conducting trials and delays rollout, but avoids costly drop out from trials due to non-compliance. Studies aimed at establishing factors associated with reliable contraceptives use under efficacy trial conditions, can provide baseline data to be used in planning such trials in the FF and FSW populations where little or no information is available.

Recently, we conducted two "Simulated HIV Vaccine Efficacy Trials (SiVETs)" in which procedures and criteria for the trial mimicked an HIV vaccine efficacy trial, but the vaccine used was a licensed Hepatitis B vaccine. Participants were informed that this trial was a simulation and the vaccine would protect them against Hepatitis B, not HIV. The SiVET concept is suggested to be useful in assessing the feasibility for conduct of clinical trials of a new product, through a "simulated" trial using a commercially available vaccine[24,25]. This concept can inform the design and sample size estimation for the future trials[26–28].

In this paper, we use data from the two SiVETs, in which reliable contraceptives were promoted and provided at no cost to female participants, to: determine the proportion of women using a reliable method (i) at baseline and (ii) at the end of vaccination schedule (6 months of follow up), and to determine the correlates of reliable contraceptives use (iii) at baseline and (iv) at 6 months of follow up.

Methods

The data for this paper come from two Simulated HIV Vaccine Efficacy Trials (SiVETs) in Uganda. To assess and improve readiness for efficacy trials of HIV preventive vaccines or other investigational agents among key populations in Uganda, we conducted two trials in which licensed Hepatitis B vaccine was used in a protocol that otherwise resembled an efficacy trial for HIV vaccine. These were nested in, respectively, an observational cohort of FF (Jul 2012–Apr 2014) in Masaka and a cohort of FSW (Aug 2014–Apr 2017) in Kampala. Both studies were conducted by MRC/UVRI & LSHTM Uganda Research Unit clinics supported by the International AIDS Vaccine Initiative (IAVI). The observational cohorts details have been previously described[6,8,29,30]. Sexually active (self-reported having sex in the preceding three months) HIV negative women who had been part of the observational cohorts' quarterly follow up (aimed at determining HIV incidence) for between three and 18 months were screened for eligibility (Table 1) for enrollment into the SiVET. Those eligible were asked if they were using any method of contraceptive. The contraceptive methods were classified as either reliable (injectable DMPA, implant, oral pills, and IUD), or unreliable (condoms, lactational amenorrhea, withdrawal etc.). The study nurse promoted reliable contraceptives to women who were not using any method, or were using an unreliable method, at baseline. Eligible women who were either already using a reliable method or were willing to initiate one were enrolled into the SiVET. They were provided with a reliable contraceptive method of their choice. While DMPA and oral pills were provided at both study site clinics (Kampala and Masaka), implant and IUD were provided by the study staff only at the Kampala clinic. At the Masaka clinic, women were referred to a Marie Stopes clinic located about one kilometre from the study research site clinic where they could obtain implant or IUD.

All enrolled women were provided with a contraceptive card, which captured the method they were using and any future changes or renewals. They were requested to carry their card every time they visited the study research clinic. Contraceptive use data was collected at enrolment, and at months one, three, and six. At enrolment, women were administered a licensed Hepatitis B vaccine (ENGERIX-BTMGlaxoSmithKline Biologicals

Rixensart, Belgium) following the standard schedule of 0, 1 and 6 months, akin to what might happen in an HIV vaccine efficacy trial. After each vaccination, women were retained in the clinic for at least 30 minutes for reactogenicity events assessment. Furthermore, they were requested to return after three days for further review. Details of the trial procedures and follow up have been previously described[31,32].

Pregnancy testing: Women were asked to provide a urine sample at each clinic visit for pregnancy testing. A QuickVue One-Step human chorionic gonadotropin (HCG) test (manufacturer: Quidel Q20109IN) was used to determine pregnancy.

Statistical analysis. SiVET data were captured using OpenClinica 3.5 (Waltham, MA). The data were transferred to Stata 14 (StataCorp, College Station, TX USA) for cleaning and analysis. Variables examined included; social demographics- age, tribe, education, religion, marital status, occupation and duration of residency. Behavioral - frequency of alcohol consumption, having sex under the influence of alcohol, illicit drug use, number of sexual partners, having a new sexual partner other than the regular partner, frequency of condom use with a new sexual partner and being away from home for at least 3 days per week. Clinical – having had a genital discharge and/or genital sores/ulcer disease in the three months preceding the interview. Participant baseline socio-demographic, study site, HIV risk behavior, and clinical characteristics were summarized using counts and percentages and further stratified by study population and whether or not a participant reported use of a reliable contraceptive method at enrolment. Similarly, participant characteristics were compared between those who took up a reliable contraceptive method and those who did not. The numbers of women who took up a reliable contraceptive method overall, and at each clinic visit, were presented using a bar graph. We defined uptake of reliable contraceptives as a woman using an unreliable or no method at enrolment into SiVET but taking up one of the reliable methods at any one point during follow up. Simple logistic regression models were fitted to determine correlates of reliable contraceptives use at baseline and at the last vaccination visit (six months of follow up). After bivariable analyses, a multivariable model was fitted. In the multivariable model, factors were removed from the model using a backward elimination algorithm retaining any factors, which caused a change in the log odds of 20% or more.

Results

Screening. In total, 464 [FF = 83 and FSW = 381] sexually active women were screened for entry into the SiVETs, of whom 367 (79%; FF = 77 (93%) and FSW = 290 (76%)) non-pregnant women were enrolled, overall screening-enrolment ratio of 5:4. Of the 97 women ineligible for enrolment, the primary reason was prior exposure to Hepatitis B (54%, n = 52). Eight women (8%) were excluded because of pregnancy; other reasons for exclusion are shown in Fig. 1.

Baseline characteristics. In the FF population, the average age of enrolled women was 30 years (SD = 7.5, range 18–49), with 38 (49%) being of the indigenous Baganda tribe, 57 (74%) of Christian faith, 49 (64%) had primary education and 54 (70%) had lived at the current location for more than one year. All participants reported having a new sexual partner (not a regular sexual partner) in the three months preceding the interview and 47 (61%) reported never using a condom while having sex with the new sexual partner (Table 2). In the FSW population, the average age was 28 years (SD = 7.5, range 18–49), with 153 (53%) being of the indigenous Baganda tribe, 219 (76%) of Christian faith, 149 (51%) had primary education, 204 (70%) single but previously married. Two hundred and thirty nine (82%) had lived at the current location for more than one year. A total of 235 (81%) reported illicit drug use, 287 (99%) reported two or more sexual partners, 266 (92%) reported having a new sexual partner in the 3 months preceding the interview and 207 (78%) reported that they always use a condom while having sex with a new sexual partner (Table 2).

Baseline contraceptives use (Table 2). Of the 367 women enrolled, 213 (58%; FF = 30 (39%) and FSW = 183 (63%)) reported use of some form of contraceptive at baseline. Reliable methods were used by 203 women (55%; FF = 24 (31%) and FSW = 179 (62%)) which included 136 (67%) women using injectable DMPA, 30 (14.8%) using an implant, 29 (14%) using oral pills, 6 (3%) using an IUD and 2 (1%) women sterilized. A further 9 (3%) women used condoms and one woman (0.3%) used lactational amenorrhea. No reasons were documented for the 154 women not using contraceptives. In total, 164 women (10 using unreliable and 154 not using any method) were not using any reliable contraceptives at baseline. Adjusting for factors indicated in Table 2, age and self-reported illicit drug use were independently associated with reliable contraceptives use at baseline. Women aged 18–34 years were twice as likely to use a reliable method, adjusted odds ratio (aOR) = 2.07, 95%CI: 1.21–3.54 compared to those aged 35 years or more. Similarly, self-reported illicit drug users were twice more likely to use reliable contraceptives aOR = 2.45, 95%CI: 1.38–4.35 compared to non-illicit drug users (Table 2).

Retention. In total, 294 (84% of 350 expected and 80% of 367 enrolled; FF = 64/71 (90%) and FSW = 230/279 (82%)) completed all four study visits, up to six months. Overall, 23 (6%) were withdrawn from the study over the six months follow up, 11 (3%) due to pregnancy, and 12 (3%) for other reasons (see Fig. 1). Of the 11 women who became pregnant, seven (four on injectable and three on oral pills) reported using reliable contraceptive before the pregnancy while four were not using any method. The four on injectable had delayed injection by 25, 27, 35 and 40 days. Of the 367, 357 and 350 women expected at month one, three and six respectively, 94%, 87% and 84% were seen. The reasons for missing a given visit are indicated in Fig. 1. Compared to those who completed all the study follow up visits, those that missed any one visit were younger (mean age, 26.3 vs. 29.7 years), with one or no sexual partner 44% vs two or more 29%, new sexual partner 42% vs none 31%, spent up to one year at the current location 41% vs more than one year 29%.

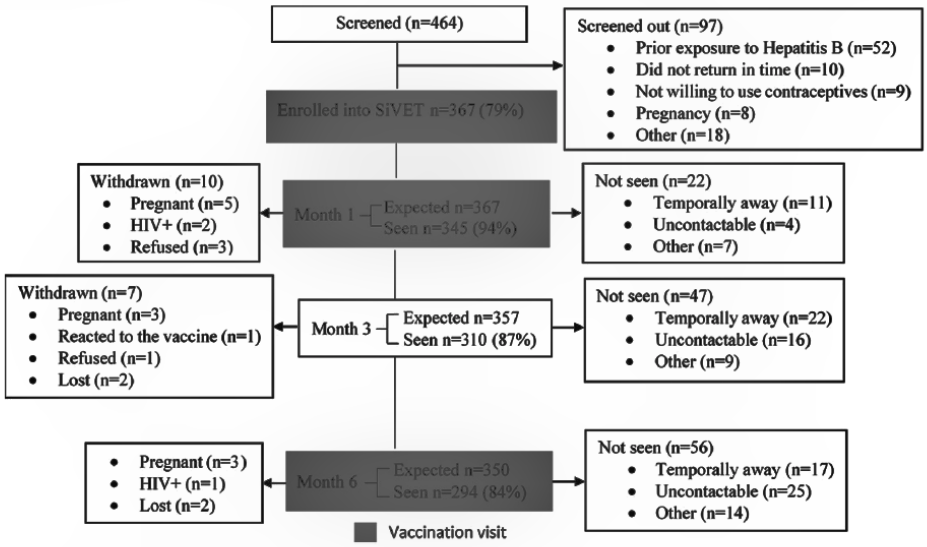

Figure 1. Study profile of screening, enrolment and follow up of 367 participants in SiVET at Kampala and Masaka clinics, Uganda (2012–2017).

Uptake of reliable contraceptives. The trial promoted reliable contraceptive methods to the 164 women (FF = 53 and FSW = 111) not using a reliable method at baseline; of these women 131 (80%; FF = 39 (74%) and FSW = 92 (83%)) reported using a reliable contraceptive method during at least one follow up visit. Figure 2 shows the number of women that used reliable contraceptives at each of the follow up visits, throughout the trial. The graph illustrates that 125 (76%) women started using reliable contraceptive in the first month of follow-up and 80% used reliable contraceptives at month 6. Overall, 73 (45%) of 164 women used DMPA, and 36 (22%) oral pills.

In the 164 women that were eligible for promotion of reliable contraceptives at baseline, age group and reporting having sex under the influence of alcohol in the month preceding the interview were independently associated with uptake of reliable contraceptives by six months of follow up (in a model adjusted for factors in Table 3). Women aged 18–34 years were twice more likely to take up a reliable method, adjusted odds ratio (aOR) = 2.47, 95%CI: 1.01–6.07 compared to those aged 35 years or more. Those reporting sometimes having sex under influence of alcohol were less likely to take up a reliable method compared to never (aOR = 0.37, 95%CI: 0.14–0.96, Table 3). Though not statistically significant, in this sample, women who had attained some formal education were three times (aOR = 3.21, 95%CI: 0.73–14.16) for primary education and four times (aOR = 4.41, 95%CI: 0.89–21.87) for secondary education more likely to take up a reliable method compared to those without any formal education.

Furthermore, 334 (91%; FF = 63/77 (82%) and FSW = 271/290 (93%)) of 367 women enrolled (including the 203 that were already using a reliable method of contraception at baseline) used a reliable method by the end of trial follow up. Of the 334 women that used a reliable method, 197 (59%) used DMPA. Other methods were oral pills (n = 60; 18%), implant (n = 31; 9%), IUD (n = 7; 2%), and sterilized (n = 2; 0.6%). Thirty-seven women (11%) switched between reliable methods. Of these women, most 19 (51%) switched from DMPA to oral pills. All women (131 new reliable contraceptives users and 203 already using at baseline) reported sustained use of a reliable method throughout the follow up period. Less than one tenth of women (n = 33; 9%; FF = 14 and FSW = 19) did not use any reliable method throughout the study. Of these, seven (FF = 6 and FSW = 1) used condoms and 26 (FF = 8 and FSW = 18) did not use any form of contraception.

In the 367 women enrolled in the trial, overall factors independently associated with use of reliable contraceptives by six month of follow up included; age group, with women aged 18–34 years being thrice more likely to use a reliable method of contraceptives (aOR = 2.86, 95%CI: 1.31–6.24) compared to those aged 35 or more years. Other factors included study site [Kampala, aOR = 3.09, 95%CI: 1.36–6.98) compared to Masaka] and education (borderline) [secondary or more, aOR = 3.06, 95%CI: 0.78–12.02) compared to no education].

Discussion

We investigated in women of reproductive age in the FF and FSW use of reliable contraceptive methods and associated factors at baseline and at the end of a six-month vaccination schedule in two SiVETs. We found that the proportion of sexually active women using a reliable method at baseline was low, about one in every two women. Promotion and provision of reliable methods by the trial staff increased the proportion of women using a reliable method to over 90% at the end of six months of follow up. The baseline use of reliable methods in these populations was higher than the 35% reported in the general population in Uganda[15]. It was also higher than 5%-28% reported in other HIV prevention trials in West Africa[16,17] and East Africa and Southern Africa[18]. Contrary to

Participant characteristic	FF n (%)	FSW n (%)	Contraceptive use		uOR (95%CI)	LRT-pvalue	aOR (95%CI)
			FF	FSW			
Overall	77 (100)	290 (100)	24 (31.2)	179 (61.7)			
Site						<0.001	
Masaka	77 (100)	na	24 (31.2)	na	1.00		1.00
Kampala	na	290 (100)	na	179 (61.7)	3.56 (2.08–6.09)		1.56 (0.66–3.69)
Age group (years)						0.001	
35+	21 (27.3)	62 (21.4)	5 (23.8)	28 (45.2)	1.00		1.00
18–34	56 (72.7)	228 (78.6)	19 (33.9)	151 (66.2)	2.26 (1.37–3.72)		2.07 (1.21–3.54)
Tribe						0.107	
Muganda	38 (49.3)	153 (52.8)	12 (31.6)	98 (64.1)	1.00		
Munyankole	7 (9.1)	32 (11.0)	2 (28.6)	19 (59.4)	0.86 (0.43–1.72)		
Munyarwanda	18 (23.4)	20 (6.9)	4 (22.2)	10 (50.0)	0.43 (0.21–0.88)		
Other	14 (18.2)	85 (29.3)	6 (42.9)	52 (61.2)	1.04 (0.64–1.70)		
Education						0.183	
None	7 (9.1)	16 (5.5)	3 (42.9)	10 (62.5)	1.0		1.00
Primary	49 (63.6)	149 (51.4)	14 (28.6)	87 (58.4)	0.80 (0.34–1.91)		0.81 (0.32–2.05)
Secondary+	21 (27.3)	125 (43.1)	7 (33.3)	82 (65.6)	1.20 (0.49–2.92)		1.00 (0.38–2.61)
Religion						0.685	
Christian	57 (74.0)	219 (75.5)	20 (35.1)	131 (59.8)	1.00		
Muslim	20 (26.0)	71 (24.5)	4 (20.0)	48 (67.6)	1.10 (0.68–1.78)		
Marital status						0.319	
Single, never married	15 (19.5)	68 (23.5)	7 (46.7)	38 (55.9)	1.00		
Married	30 (39.0)	18 (6.2)	11 (36.6)	11 (61.1)	0.71 (0.35–1.46)		
Single, previously married	32 (41.5)	204 (70.3)	6 (18.7)	130 (63.7)	1.15 (0.77–1.82)		
Occupation						0.002	
Fishing/related	21 (27.3)	0 (0.0)	5 (23.8)	0 (0.0)	1.00		
Small scale business	27 (35.1)	11 (3.8)	6 (22.2)	9 (81.8)	2.09 (0.63–6.90)		
Hotel/Bar/Saloon	19 (24.6)	111 (38.3)	10 (52.6)	67 (60.4)	4.65 (1.61–13.46)		
Sex work	0 (0.0)	165 (56.9)	0 (0.0)	101 (61.2)	5.05 (1.76–14.46)		
Other	10 (13.0)	3 (1.0)	3 (30.0)	2 (66.7)	2.00 (0.45–8.98)		
Duration lived at current location						0.614	
0–1, year	23 (29.9)	51 (15.6)	8 (34.8)	31 (60.8)	1.00		
>one year	54 (70.1)	239 (82.4)	16 (29.6)	148 (61.9)	1.14 (0.68–1.90)		
Alcohol consumption (previous one month)						0.099	
None	33 (42.9)	57 (19.7)	11 (33.3)	30 (52.6)	1.00		
Inconsistent	38 (49.3)	147 (50.6)	11 (29.0)	98 (66.7)	1.71 (1.03–2.85)		
Daily	6 (7.8)	86 (29.7)	2 (33.3)	51 (59.3)	1.62 (0.90–2.92)		
Sex under alcohol influence (previous one month)						0.222	
Never	45 (58.4)	103 (35.5)	12 (26.7)	63 (61.2)	1.00		
Sometimes	24 (31.2)	169 (58.3)	10 (41.7)	105 (62.1)	1.44 (0.93–2.21)		
Frequently	8 (10.4)	18 (6.2)	2 (25.0)	11 (61.1)	0.97 (0.42–2.24)		
Drug use (previous one month)						<0.001	
No	71 (92.2)	55 (19.0)	21 (29.6)	24 (43.6)	1.00		1.00
Yes	6 (7.8)	235 (81.0)	3 (50.0)	155 (66.0)	3.43 (2.18–5.38)		2.45 (1.38–4.35)
Genital discharge (previous 3 months)						0.055	
Yes	51 (55.2)	88 (30.3)	14 (27.4)	54 (61.4)	1.00		
No	26 (33.8)	202 (69.7)	10 (38.5)	125 (61.9)	1.52 (0.99–2.31)		
Genital sores/ulcer disease (previous 3 months)						0.009	
Yes	40 (52.0)	48 (16.6)	11 (27.5)	27 (56.3)	1.00		
No	37 (48.0)	242 (83.4)	13 (35.1)	152 (62.8)	1.90 (1.17–3.09)		
Number of sexual partners (previous 3 months)						<0.001	
0/1	47 (61.0)	3 (1.0)	13 (27.7)	2 (66.7)	1.00		1.00
2+	30 (39.0)	287 (99.0)	11 (36.7)	177 (61.7)	3.40 (1.78–6.48)		1.30 (0.52–3.29)
New sexual partner (previous 3 months)						0.758	
No	0 (0.0)	24 (8.3)	0 (0.0)	14 (58.3)	1.00		
Yes	77 (100)	266 (91.7)	24 (31.2)	165 (62.0)	0.88 (0.38–2.03)		

Continued

Participant characteristic	FF n (%)	FSW n (%)	Contraceptive use		uOR (95%CI)	LRT-pvalue	aOR (95%CI)
			FF	FSW			
Condom use with the new sexual partner						0.001	
Never	47 (61.0)	9 (3.4)	15 (31.9)	6 (66.7)	1.00		
Sometimes	19 (24.7)	50 (18.8)	6 (31.6)	26 (52.0)	1.44 (0.70–2.96)		
Always	11 (14.3)	207 (77.8)	3 (27.3)	133 (64.3)	2.76 (1.51–5.07)		
Away from home ≥3 days/week						0.741	
Yes	24 (31.2)	98 (33.8)	6 (25.0)	60 (61.2)	1.00		
No	53 (68.8)	192 (66.2)	18 (34.0)	119 (62.0)	1.08 (0.70–1.67)		

Table 2. Participant baseline characteristics, proportion and factors associated with using reliable contraceptives among 367 participants enrolled in SiVET in Uganda (2012–2017). uOR-Unadjusted odds ratio, aOR-Adjusted odds ratio, CI-Confidence interval, %-percent, na-Not applicable, LRT = likelihood ratio test. FF-Fisherfolk, FSW-Female sex workers.

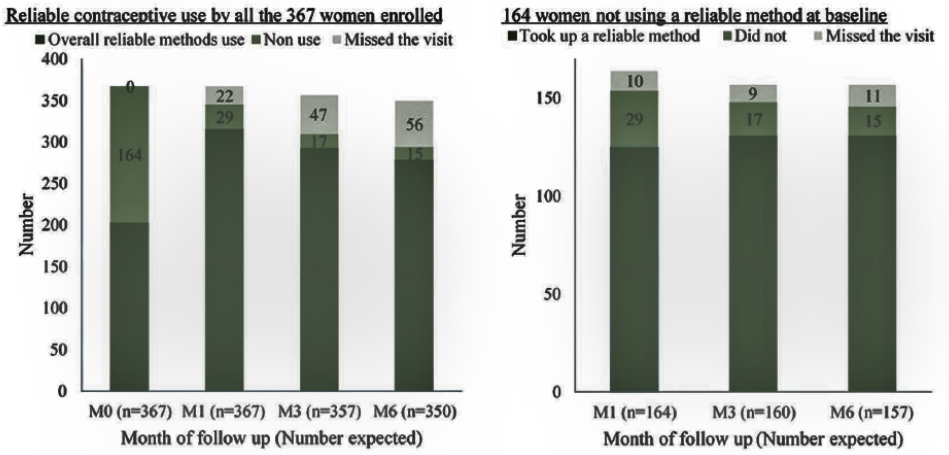

Figure 2. Reliable contraceptives use overall and uptake by the 164 women that were not using a reliable method at enrolment into SiVET, Uganda (2012–2017).

these HIV prevention trials, women enrolled into SiVET were selected based on willingness to delay pregnancy through use of a reliable method of contraceptive during the vaccination period. In SiVET, the majority of women reporting reliable contraceptive use at baseline and at the end of vaccination used injectable DMPA, which is consistent with both national data[15] and data from concluded HIV prevention trials[12,23] in Uganda.

At baseline, reliable contraceptive use differed significantly by age group and self-reported illicit drug use. Nationally age[15] has been associated with contraceptive use. This is also consistent with previous studies in East and Southern Africa[18] that reported association of effective contraceptives use with age. Contrary to previous studies[33,34] that showed high contraceptives use among non-drug users, we found a twofold higher use of reliable contraceptives among illicit drug users. Women involved in sex work dominated the SiVET protocol and these have been linked to high illicit drug[35] and contraceptives use[36]. It is likely that the perceived risk of pregnancy in this category of women is higher than that of the general population and could influence practices.

About half of the women were not using reliable contraceptive methods at baseline but majority started using them mainly within the first month of follow up. By six months, nine in every ten women were using a reliable method of contraceptives. Uptake of reliable contraceptives in women that were not using such methods at baseline was independently associated with age group, education (borderline) and self-reported having had sex under alcohol influence. Similarly, older age and lower educational status are associated with lower contraceptive use nationally[15]. Women that reported sometimes or frequently having sex under influence of alcohol were less likely to use reliable contraceptives. Alcohol use has been linked to impaired decision making in complex situations[37].

Though women switched between contraceptive methods, it was encouraging that the switches were within reliable methods and women sustained use of these methods throughout follow up. Uptake and sustained use coupled with higher baseline use of reliable methods than that in the general population could have played a role in the relatively lower proportion of pregnancy than that observed in other HIV prevention trials[20]. Seven women got pregnant while using reliable contraceptives in the trial. The four women on injectable DMPA had all delayed an injection by about one month perhaps indicating they were unaware of the need to renew on time. Three women were using oral pills and adherence issues with use of oral pills have been well-documented[11]. In an actual HIV vaccine efficacy trial, these women would have to be withdrawn from the trial. Encouraging women

Participant characteristic	FF n (%)	Uptake		FSW n(%)	uOR (95%CI)	LRT p-value	aOR (95%CI)
		FF	FSW				
Overall	53 (100)	111 (100)	39 (73.6)	92 (82.9)	na	na	na
Site							
Masaka	53 (100)	na	39 (73.6)	na	1.00	0.172	1.00
Kampala	na	111 (100)	na	92 (82.9)	1.74 (0.79–3.81)		1.37 (0.50–3.73)
Age group (years)							
35+	16 (30.2)	34 (30.6)	8 (50.0)	27 (79.4)	1.00	0.041	1.00
18–34	37 (69.8)	77 (69.4)	31 (83.8)	65 (84.4)	2.29 (1.04–5.02)		2.47 (1.01–6.07)
Tribe							
Muganda	26 (49.1)	55 (49.6)	22 (84.6)	44 (80.0)	1.00	0.120	
Munyankole	5 (9.4)	13 (11.7)	3 (60.0)	11 (84.6)	0.80 (0.23–2.76)		
Munyarwanda	14 (26.4)	10 (9.0)	7 (50.0)	8 (80.0)	0.38 (0.14–1.03)		
Other	8 (15.1)	33 (29.7)	7 (87.5)	29 (87.9)	1.64 (0.55–4.87)		
Education							
None	4 (7.6)	6 (5.4)	2 (50.0)	4 (66.7)	1.00	0.086	1.00
Primary	35 (66.0)	62 (55.9)	25 (71.4)	50 (80.7)	2.27 (0.59–8.78)		3.21 (0.73–14.16)
Secondary+	14 (26.4)	43 (38.7)	12 (85.7)	38 (88.4)	4.76 (1.07–21.17)		4.41 (0.89–21.87)
Religion							
Christian	37 (69.8)	88 (79.3)	27 (73.0)	73 (83.0)	1.00	0.945	
Muslim	16 (30.2)	23 (20.7)	12 (75.0)	19 (82.6)	0.97 (0.40–2.36)		
Marital status							
Single never married	8 (15.1)	30 (27.0)	7 (87.5)	25 (83.3)	1.00	0.156	1.00
Married	19 (35.8)	7 (6.3)	12 (63.2)	5 (71.4)	0.35 (0.11–1.16)		0.39 (0.10–1.62)
Single ever married	26 (49.1)	74 (66.7)	20 (76.9)	62 (83.8)	0.85 (0.31–2.35)		1.08 (0.35–3.39)
Occupation							
Fishing/related	16 (30.2)	0 (0.0)	11 (68.8)	0 (0.0)	1.00	0.223	
Small scale business	21 (39.6)	2 (1.8)	17 (81.0)	2 (100)	2.16 (0.48–9.77)		
Hotel/Bar/Saloon	9 (17.0)	44 (39.6)	7 (77.8)	33 (75.0)	1.40 (0.41–4.78)		
Sex work	0 (0.0)	64 (57.7)	0 (0.0)	56 (87.5)	3.18 (0.88–11.57)		
Other	7 (13.2)	1 (0.9)	4 (57.1)	1 (100)	0.76 (0.13–4.49)		
Duration lived at current location							
0–1, year	15 (28.3)	20 (18.0)	13 (86.7)	15 (75)	1.00	0.984	
>one year	38 (71.7)	91 (82.0)	26 (68.4)	77 (84.6)	0.99 (0.39–2.52)		
Alcohol consumption (previous one month)							
Non	22 (41.5)	27 (24.3)	17 (77.3)	23 (85.2)	1.00	0.173	
Inconsistent	27 (50.9)	49 (44.1)	21 (77.8)	43 (87.8)	1.20 (0.46–3.10)		
Daily	4 (7.6)	35 (31.6)	1 (25.0)	26 (74.3)	0.51 (0.19–1.37)		
Sex under alcohol influence (previous one month)							
Never	33 (62.3)	40 (36.0)	26 (78.8)	36 (90.0)	1.00	0.343	1.00
Sometimes	14 (26.4)	64 (57.7)	10 (71.4)	49 (76.6)	0.55 (0.24–1.26)		0.37 (0.14–0.96)
Frequently	6 (11.3)	7 (6.3)	3 (50.0)	7 (100)	0.59 (0.14–2.50)		0.70 (0.15–3.34)
Drug use (previous one month)							
No	50 (94.3)	31 (27.9)	36 (72.0)	26 (83.9)	1.00	0.292	
Yes	3 (5.7)	80 (72.1)	3 (100)	66 (82.5)	1.51 (0.70–3.26)		
Genital discharge (previous 3 months)							
Yes	37 (69.8)	34 (30.6)	27 (73.0)	26 (76.5)	1.00	0.146	
No	16 (30.2)	77 (69.4)	12 (75.0)	66 (85.7)	1.77 (0.82–3.81)		
Genital sores/ulcer disease (previous 3 months)							
Yes	29 (54.7)	21 (18.9)	21 (72.4)	15 (71.4)	1.00	0.103	1.00
No	24 (45.3)	90 (81.1)	18 (75.0)	77 (85.6)	1.94 (0.88–4.28)		1.92 (0.78–4.73)
Number of sexual partners (previous 3 months)							
0/1	34 (64.2)	1 (0.9)	26 (76.5)	1 (100)	1.00	0.653	
2+	19 (35.8)	110 (99.1)	13 (68.4)	91 (82.7)	1.23 (0.50–3.04)		
New sexual partner (previous 3 months)							
No	0 (0.0)	10 (9.0)	0 (0.0)	9 (90.0)	1.00	0.374	

Continued

Participant characteristic	FF n (%)	Uptake		FSW n(%)	uOR (95%CI)	LRT p-value	aOR (95%CI)
		FF	FSW				
Yes	53 (100)	101 (91.0)	39 (73.6)	83 (82.2)	0.42 (0.05–3.47)		
Condom use with the new sexual partner							
Never	32 (60.4)	3 (3.0)	24 (75.0)	3 (100)	1.00	0.721	
Inconsistently	13 (24.5)	24 (23.7)	9 (69.2)	22 (91.7)	1.53 (0.47–5.00)		
Always	8 (15.1)	74 (73.3)	6 (75.0)	58 (78.4)	1.00 (0.39–2.56)		
Away from home ≥3 days/week							
Yes	18 (34.0)	38 (34.2)	16 (88.9)	29 (76.3)	1.00	0.912	
No	35 (66.0)	73 (65.8)	23 (65.7)	63 (86.3)	0.96 (0.43–2.15)		

Table 3. Proportion and factors associated with uptake of reliable contraceptives among 164 women that were not using reliable methods at enrolled into SiVET in Uganda (2012–2017). uOR-Unadjusted odds ratio, aOR-Adjusted odds ratio, CI-Confidence interval, %-percent, na-Not applicable, FF-Fisherfolk, FSW-Female sex workers.

to receive their contraception injection or take their pills on time through phone calls and/or home visits would improve adherence.

The retention in SiVET was higher than the average (75%) reported in observational cohorts[7,29,30] in these populations. High retention in the trial setting is likely a result of the rigorous participant tracking system employed compared to observational cohorts. Though it took about three months for 5% of the new reliable contraceptive users to get on reliable contraceptives, most had done so within a month of enrolment. In these key populations, it may not be necessary to put women on reliable contraceptives for atleast three months before screening for trial enrolment instead these could happen concurrently. The high retention coupled with high screening-enrolment ratio and high use of reliable contraceptives make women in these key populations attractive to enroll in the future HIV vaccine efficacy and other HIV prevention trials.

A limitation of our trial is that we did not collect data on the reasons for not using reliable or any contraceptives. Furthermore, we did not collect data on reasons for switching between reliable methods. Such reasons would have been instrumental in informing modification of messages on contraceptives use in HIV prevention trials in these key populations. Even though the trials (in FF and FSW) were similar, two different study teams with a somewhat different protocol conducted them. Differences in correlates of reliable contraceptive use may exist by site, but the small sample size prevented site stratification. However, other than occupation and illicit drug use, most of the women characteristics in the two populations were comparable.

The major strength of our trial is that we promoted and provided reliable contraceptives in the context of HIV vaccine efficacy trial, counselled women on the importance of reliable contraceptives use and provided them with a method of their choice.

Conclusion

In this SiVET, the proportion of women using reliable contraceptives improved from one in every two women at baseline to nine in every 10 women at the end of follow up. The use of reliable methods at baseline was particularly higher among young women and illicit drug users. Promotion and provision of reliable contraceptives to women not using them at baseline improved the proportion using them within the first month of follow up. Uptake of reliable contraceptives increased with increasing education and decreased with increasing age and the frequency of having sex under alcohol influence. All women using reliable methods continued to use them (or another reliable method) throughout follow-up. The sustained use highlights the importance of promoting and providing reliable contraceptives to trial participants in populations where pregnancy could lead to discontinuation of the use of investigational product. We observed a lower proportion of women becoming pregnant during the trial follow up than that reported in the concluded HIV prevention trials in the region. This trial could have filled the unmet need for reliable contraceptives in these populations in term of promotion and provision as well as enhancing accurate contraceptive messaging. It is particularly encouraging that concurrent vaccination and provision of contraceptives was possible in these populations making them good candidates for future HIV vaccine efficacy and other prevention trials.

Declarations

Ethics approval and consent to participate. The Uganda Virus Research Institute (UVRI) Research and Ethics Committee (GC/127/12/04/22 and GC127/12/06/01) and the Uganda National Council for Science and Technology (HS364 and HS1584) approved the conduct of the SiVET protocols. The London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee (LSHTM14588) approved the concept leading to this analysis. Written informed consent/assent was obtained for each participant before enrolment.

Study methods confirmation. We confirm that all methods in this manuscript were performed in accordance with the relevant guidelines and regulations.

Data availability

The MRC/UVRI and LSHTM Uganda Research Unit has a data sharing policy accessible at https://www.mrcuganda.org/publications/data-sharing-policy. The policy summarizes the conditions under which data collected by the Unit can be made available to other bona fide researchers, the way in which such researchers can apply to have access to the data and how data will be made available if an application for data sharing is approved. Should any of the other researchers need to have access to the data from which this manuscript was generated, the processes to access the data are well laid out in the policy. The corresponding and other co-author emails have been provided and could be contacted anytime for further clarifications and/or support to access the data.

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Author contributions
A.A. Lead Author, drafted initial manuscript draft, carried out data management for SiVET, data analysis and interpreted the data. J.T. contributed to data analysis and interpreted the data. Y.M. contributed to the design of the SiVET protocol and study coordination, M.P. contributed to the design of the SiVET protocol and interpreted the data, P.E.F. contributed to the design of the SiVET protocol and interpreted the data, P.K. directed the implementation of the SiVET protocol and S.N. contributed to data analysis and interpreted the data. All authors critically commented and provided revisions to the manuscript. The authors approved this final version for submission.

Competing interests
The authors declare no competing interests.

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Chapter Six: Comparison of retention in observational cohorts and nested Simulated HIV Vaccine Efficacy Trials in the Key populations in Uganda

6.1 Research in context

Global estimates show that 65% of new HIV-infections occur in Sub-Saharan Africa (SSA) in presence of available HIV prevention interventions, but poor adherence to the interventions limit their effectiveness (5). Vaccination is an intervention that does not rely on individual adherence but does require the completion of the full vaccination schedule. Because of the high HIV incidence in SSA, an affordable HIV vaccine is urgently needed, and SSA would be a key destination for HIV vaccine efficacy trials. In Uganda, these trials can be conducted in the population subgroups such as fisher-folks and Female sex workers, but these groups are very mobile. There are still methodological issues on the best way to measure retention in efficacy trial especially in subpopulations where no such trials have been previously conducted. Available data on retention come from observational cohorts, but participants that join trials might have different retention to the observational cohorts they are drawn from. Therefore, extrapolating the retention of an observational cohort to the planning of HIV vaccine efficacy trial may be complicated. An under or over estimation of the number expected to complete follow up could affect the trial statistical power or expose more participants than necessary to an investigational product with unknown effects.

6.2 Trials simulating HIV vaccine efficacy trials to estimate retention

Data from two Simulated HIV Vaccine Efficacy Trials (SiVETs) that mimicked an HIV vaccine efficacy trial conducted with Hepatitis B vaccine (a commercially licensed vaccine with potential benefit for participants) with full knowledge of the participants was used to answer this objective. The SiVETs were nested within observational cohorts of Female Sex Workers (FSW) and Fisher-folks (FF) subpopulations in Uganda, enabling estimates of participant dropout, in order to provide accurate data needed to plan future HIV vaccine efficacy trial in these key populations. To answer PhD objective 3, dropout rate in observational cohorts was compared to that in the nested Simulated HIV Vaccine Efficacy Trials in the same population of FF or FSW in Uganda. Further details are provided in the publication below.

6.3 Results of alternative approach using time to event analysis

Figure 13: Time to study dropout analysis

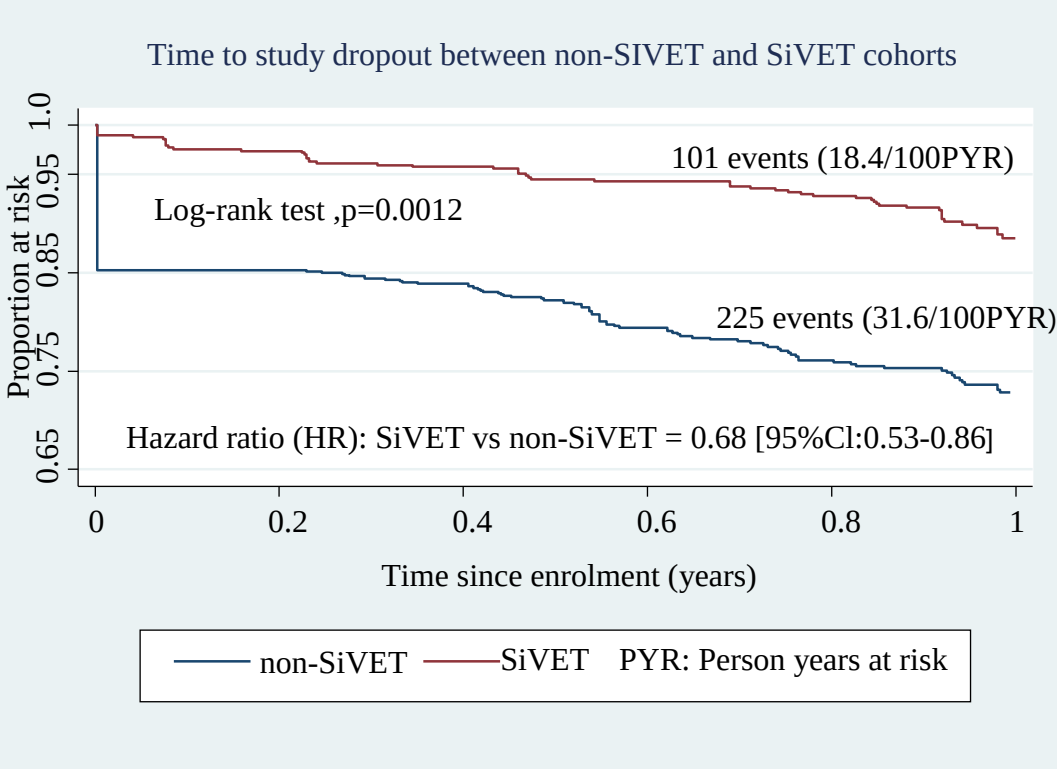

Figure 13 shows a Kaplan-Meier plot of the time to dropout analysis stratified by non-SiVET and SiVET cohorts. The results of a survival analysis are shown in the same figure including the results of fitting a Cox regression model comparing between the two cohorts. The stratified log-rank test provided strong evidence that the risk of dropping out of studies was higher in the non-SiVET cohort than in the SiVET cohort , log-rank test; $\chi 2 = 10.49$; ($P = 0.0012$). This was confirmed by the results of the Cox regression model: hazard ratio (HR); 0.68 (95% Cl: 0.53-0.86), p=0.002. From the same figure, it can be deduced that a higher number of participants dropped out of the cohorts at enrolment and towards the end of follow up with greater dropouts in the non-SiVET cohort.

6.4 Keys findings

Overall, results suggest that the annual dropout rate in the SiVETs of 18.4 per 100 person years of observation (PYO), 95%Cl: 15.1 - 22.4 was lower than 31.6 per 100 PYO, 95%Cl: 27.8 - 36.1 in the source observational cohorts. Though the difference in dropout between SiVET and the source

observational cohort was generally similar, the actual dropout rates were higher in the FSW population.

6.5 Implications for anticipated HIV vaccine efficacy trials in these key populations

Conduct of SiVETs in these key populations could mean that designing HIV Vaccine Efficacy Trials will benefit from relative lower dropout rate shown in SiVET than source observational cohort. In absence of the SiVETs conducted in these key populations, the trial sample size would be adjusted by a higher dropout rate observed in the source observational cohort. This could lead to exposing more participants to a new investigational product than necessary. In similar populations where no previous HIV prevention trials or SiVETs have been conducted, to provide information on dropout, observational cohorts' data on dropout rate might be useful but this will need to take into consideration the nearly 50% drop in the participant dropout rate observed in SiVET.

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First Name(s)	Andrew Max		
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Thesis Title	Using observational cohort data from Key populations to plan HIV intervention studies		
Primary Supervisor	Jim Todd		

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SECTION B – Paper already published

Where was the work published?	BMC Medical Research Methodology		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I participated in the conceptualization of the Simulated HIV Vaccine Efficacy Trial (SiVET) concept, drafting of the studies documents (protocol, standard operating manuals and procedures, case report and consent forms), conduct of the studies (data management and cleaning). I headed the data management team for both observational cohorts (performing data management tasks and statistical analysis). I aggregated the datasets from the different observational cohorts and SiVETs, carried out statistical analysis, drafted the initial manuscript and interpreted the study findings.

SECTION E

Student Signature	Abaasa
Date	20 May. 20

Supervisor Signature	Todd
Date	21st May 2020

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RESEARCH ARTICLE Open Access

Comparison of retention in observational cohorts and nested simulated HIV vaccine efficacy trials in the key populations in Uganda

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Abstract

Background: Outcomes in observational studies may not best estimate those expected in the HIV vaccine efficacy trials. We compared retention in Simulated HIV Vaccine Efficacy Trials (SiVETs) and observational cohorts drawn from two key populations in Uganda.

Methods: Two SiVETs were nested within two observational cohorts, one in Fisherfolk (FF) and another one in Female Sex Workers (FSW). Adult participants in each observational cohort were screened for enrolment into SiVETs. Those screened-out or not screened continued participation in the observational (non-SiVET) cohorts. SiVET participants were administered a licensed hepatitis B vaccine in a schedule that mimicked an actual HIV vaccine efficacy trial. Both cohorts were followed for 12 months and retention was assessed through dropout, defined as lost to follow up, being uncontactable, refusal to continue or missing the last study clinic visit. Dropout rates were compared using Poisson models giving rate ratios and 95% confidence intervals (95%CI).

Results: Out of 1525 participants (565 FF and 960 FSW), 572 (38%) were enrolled into SiVETs (282-FF and 290-FSW), and 953 (62%) remained in the non-SiVET cohorts. Overall, 326 (101 SiVET, 225 non-SiVET) dropped out in 1260 Person Years of Observation (PYO), a dropout rate of 25.9 /100 PYO (95%CI: 23.2–28.8); fewer dropped out in the SiVET cohorts (18.4, 95% CI: 15.1–22.4) than in the non-SiVET cohorts (31.6, 95% CI: 27.8–36.1), rate ratio (RR) =0.58, 95% CI: 0.46–0.73. In all cohorts, the dropout was more marked in FSW than in FF population. Duration lived in community was associated with dropout in both SiVETs and religion in both non-SiVET cohorts.

Conclusion: The rate of dropout was lower in SiVET compared to non-SiVET cohort. Though the difference in dropout between SiVET and non-SiVET was generally similar, the actual dropout rates were higher in the FSW population. Conduct of SiVETs in these key populations could mean that designing HIV Vaccine Efficacy Trials will benefit from lower dropout rate shown in SiVET than non-SiVET observational cohort.

Keywords: Retention dropout observational cohorts vaccine trials key-populations

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Background

Populations with high HIV incidence and good retention in follow up are needed to ensure successful conduct of efficacy trials of the HIV vaccines being developed [1]. In countries, where the general population HIV incidence is low [2, 3] to be used for this purpose, sub populations such as key populations could be a better alternative. However, key populations are perceived to be highly unstable and difficult to keep in follow up [4–7]. Observational cohorts in key populations in Africa have shown high HIV incidence [8–13] but slightly lower study completion (70–76%) [9, 13–15] than in the general population (85%) [3]. Attrition from studies could bias the estimate of outcome measures and diminish statistical power. Estimation of expected trial attrition is an important component of trial planning to avoid the risk of type II error or higher expense and unethical concern of following up more than the necessary number of trial participants.

Contrary to perception that Fisherfolks (FF) on the shoreline of Lake Victoria and Female sex workers (FSW) in Kampala, Uganda are highly mobile populations and hard to maintain in follow up [6, 16], these populations could be suitable for HIV vaccine efficacy trials. Studies in these key populations have demonstrated very high HIV incidence of 3 to 11 per 100 person years [8, 9, 11, 12, 14, 15], willingness to participate > 90% [17, 18] and relatively good retention in follow up > 75% [6, 9, 19, 20].

To date, no HIV efficacy trials have completed follow up in these populations and the available information comes from observational cohorts. Studies have shown how differences in the selection of participants into a trial affects HIV incidence compared to observational cohorts in the same populations [8, 21–23] but we do not know how the dropout rate would compare under similar settings. During the conduct of efficacy trials, participants are seen more regularly and techniques such as phone call reminders and home visits are employed to keep participants in follow up. This level of attention is likely to be higher than that in observational cohorts and could improve adherence to clinic attendance as well as completion of trial procedures beyond what is seen in observational cohorts. Therefore, planning HIV vaccine efficacy trials in key populations assuming the same dropout rate seen in observational data could be misleading. Inaccurate information on dropout rates predicted at trial planning stage could result in an over or under estimate of the study sample size, resulting in either unnecessary cost or diminished statistical power for the outcome. Accurate information on attrition in the FF and FSW populations is needed to inform the design of HIV vaccine efficacy trials in these and similar populations. In this paper we use data from two Simulated Vaccine Efficacy Trials (SiVETs) nested within observational cohorts in the FF and FSW populations in Uganda to (i) compare the dropout rates in the SiVET (interventional) cohorts to that in the non-SiVET (observational) cohorts, (ii) report reasons for dropout and (iii) determine factors associated with dropout.

Methods

Design and setting

The data used in this paper were obtained from two observational cohorts. Observational cohort one (OBC_1) was in the FF population, from January 2012 to April 2015 at MRC/UVRI and LSHTM Uganda Research Unit clinic located in Masaka town about 100 km West of Kampala, the capital of Uganda. OBC_1 recruited from fishing communities located on the shoreline of Lake Victoria in Masaka district. Houses in the fishing communities are mainly made of wattle-and-mud or iron sheeting, and concentrated on the edge of swamps. While the main economic activity is fishing, there are small-scale businesses and services supporting the fishing occupation and the cohort was recruited from all occupations.

The second observational cohort (OBC_2) was in the FSW population in Kampala, April 2008 to April 2017.The cohort of FSW was established at a clinic located on Mengo hill, about 2 km from Kampala city center. This cohort (OBC_2) recruited women from the city's sex work hot spots, including clusters of bars, nightclubs, lodges and guesthouses. Both cohorts details have been previously described [8, 11, 14, 20, 24].

SiVET cohort

Two Simulated Vaccine Efficacy Trials were nested within the observational cohorts. $SiVET_1$ (FF), in the FF communities, ran from June 2012 until April 2014. $SiVET_2$ (FSW), in the FSW cohort, ran from August 2014 until April 2017. The SiVETs used a hepatitis B vaccine as a proxy for an HIV vaccine, with the aim of assessing acceptability of vaccination and retention in a future HIV vaccine trial environment. Cohort participants who had been enrolled for 3 to 18 months were consecutively screened for eligibility (Table 1) and enrolled until the required sample size was accrued. Those enrolled were administered a licensed Hepatitis B vaccine (ENGERIX-BTM GlaxoSmithKline Biologicals Rixensart, Belgium) following the standard schedule of 0, 1 and 6 months, under conditions that mimicked a possible HIV vaccine efficacy trial. In addition to the vaccination visits, participants in the SiVET cohort were followed up every 3 months for 12 months in line with the source observational cohort objective of determining HIV status every quarter.

Non-SiVET cohort

Participants in OBC_1 and OBC_2 that screen failed SiVETs eligibility (Table 1), and those that were not screened because SIVET enrolment was complete, but

Table 1 SiVETs and non-SiVETs cohorts' participant eligibility criteria

SiVET cohorts	non-SiVET cohorts
Inclusion • At least 3 and no more than 18 months of follow up in the OBC_1 or OBC_2 • HIV-1 negative and willing to undergo HIV testing • Aged ≥18 years and ≤ 49 years • Able and willing to provide written informed consent • Able and willing to provide adequate locator information including physical address • Willing and able to return for follow-up clinic visits • Intending to reside in study area for at least one year **Females only** • Willing to undergo pregnancy testing • Not breastfeeding and no intent for pregnancy in the next one year • Willing to use effective contraception during the study and at least 3 months after the last vaccination	**Inclusion** • At least 3 months and no more than 18 months of follow up in OBC_1 or OBC_2 • Still in follow up in the OBCs • HIV-1 negative and willing to undergo HIV testing
Exclusion • HIV positive • History of severe allergic reaction to any substance • An acute or chronic illness • Contraindication for Hepatitis B vaccine • Participation in another clinical trial • Hepatitis B exposure, as assessed by surface antigen (HBsAg) and core antibody (HBcAb) titers (only $SiVET_2$) • Not willing to provide written consent	**Exclusion** HIV positive

SiVET- Simulated Vaccine Efficacy Trial, *OBC*- Observational cohort

fulfilled the criteria (Table 1) for continuing follow up in OBC_1 (FF) and OBC_2 (FSW), remained in follow up in the respective OBCs in the SiVET concurrent period, forming non-$SiVET_1$ (FF) cohort in OBC_1 and non-$SiVET_2$ (FSW) cohort in OBC_2. Participants in the non-SiVET cohort were followed up every 3 months for 12 months in the SiVET concurrent period (Fig. 1).

Retention strategies

SIVET cohorts At the onset of the SiVET cohorts, each participant provided a cell phone number, and additionally a physical contact address and phone contact of a neighbor or someone who could easily reach them any time. This information was checked at each follow up clinic visit. Study field staff reminded participants of their next scheduled clinic visits using their cell phone at least 2 days before a scheduled clinic visit and visited their physical location the day after the scheduled visit if they did not attend. Participants who needed help to access the clinic were offered transport.

Non-SiVET cohorts At the onset of the non-SIVET cohorts, each participant provided a cell phone contact number. This information was checked at each follow up clinic visit. When a participant missed a scheduled clinic visit the study field staff contacted him/her by cell phone and encouraged clinic attendance.

Definitions

Study completion For the purpose of this paper, we defined study completion as a participant completing 12 months of follow up in the non-SiVET or SiVET cohorts concurrent period, or until HIV infection, or being withdrawn from a given cohort for any of the following reasons; reaction to hepatitis B vaccine, pregnancy (SiVETs only), being at low risk of HIV infection (non-$SiVET_1$ only) and investigator discretion.

Lost to follow-up This was defined as missing at least two sequential follow up clinic visits.

Dropout This was defined as either lost to follow up, participant being uncontactable, refusal to continue or missing the 12-month study clinic visit.

Primary outcomes in this paper This analysis compares the rate of dropout between SiVET and non-SiVET cohorts in the 12 months of SiVET concurrent period, reports the main reasons for dropping out, and investigates factors associated with dropout in each cohort.

Statistical methods

The data collected in the non-SiVET cohorts were managed in MS Access, 2003 (Microsoft Corporation, Redmond, WA), while data from the SiVET cohorts were managed in OpenClinica 3.5 (Waltham, MA). We summarized participant characteristics using counts and percentage and compared them between non-SIVET and SiVET

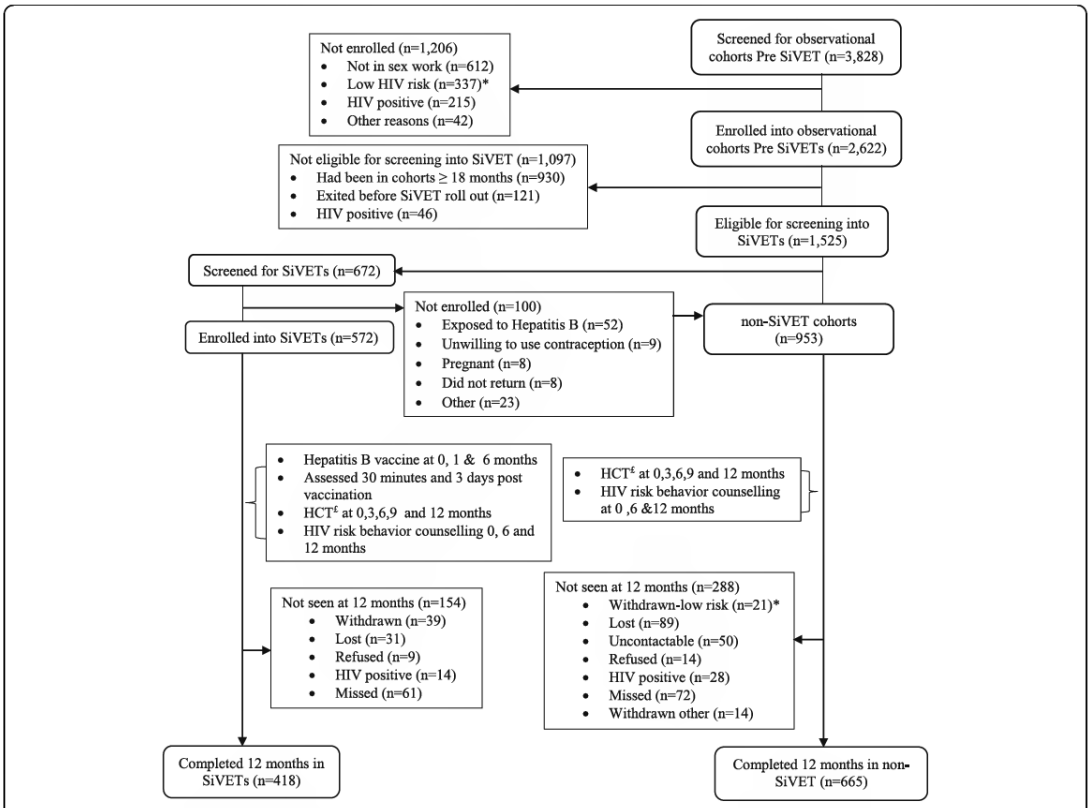

Fig. 1 Study profile for participants screened and enrolled in observational cohorts before SiVET, in the non-SiVET and SiVET cohorts in the key populations, Uganda 2012–2017. *Low HIV risk defined as having protected sex with ≥one or new sexual partner, no history of STIs, non-use of illicit drugs and /or alcohol and not being away from home for ≥2 nights per/week, [ε]HIV counselling and Testing

cohorts in the respective key population using chi-square tests. Participants who enrolled into either study and did not return for any follow up visit were given an arbitrary follow-up time of 1 week to allow inclusion in regression models. The dropout rate was estimated as the number of people who dropped out divided by the total person years of observation (PYO), expressed as a rate per 100 PYO. PYO were estimated as sum of the time from enrolment into SiVET to the date of SiVET completion or censoring. In the non-SiVET cohort, PYO were estimated as sum of time from the date SiVET began enrolment, ending on the date of the last SiVET participant clinic visit or date of censoring. Unadjusted rate ratios (uRR) and adjusted rate ratios (aRR) and their 95% confidence intervals (CI) were used to find factors associated with dropout by fitting Poisson regression models. Bivariable analysis was performed initially. Multivariable analysis was performed, including all variables which caused a change in the rate of more than 20%, except for sex and age which were included a priori.

Results

Screening and enrolment

In total 3828 participants were screened for possible enrolment into observational cohorts before SiVET rollout and 2622 (69%) were enrolled, Fig. 1. The main reasons for screen failure were non-involvement in sex work ($n = 612$), being at low risk for HIV infection ($n = 337$) and HIV infection ($n = 215$). At the time of introduction of the SiVET protocol, 1525 (58%) of the participants enrolled into observational cohorts before SiVETs were eligible for screening into SiVETs. The main reasons for ineligibility were having spent more than 18 months in observational cohorts ($n = 930$) and exiting observational cohorts before SiVET protocol roll out ($n = 121$), Fig. 1. Of the 1525 eligible for screening, 672 (44%) were consecutively screened and 572 (85%) of these enrolled into SiVETs (282 from FF and 290 from FSW). The main reason for screening but not enrolling into SiVETs was exposure to Hepatitis B ($n = 52$) (assessed as shown in Table 1). In total, 953 (283 from FF and 670 from FSW)

participants were eligible for follow up in the non-SiVET cohorts in the SiVET concurrent period, Fig. 1.

Baseline participant characteristics

FF

Compared to non-$SiVET_1$ cohort, $SiVET_1$ cohort had more men 73% vs 48% and more participants aged ≥35 years, 24% vs 14%, Table 2. Furthermore, non-$SiVET_1$ cohort had more participants without any education 12% vs 6%, working in restaurant/bar/hair salon occupation 23% vs 8% and lived at the current location for 1 year or less 34% vs 17%, Table 2.

FSW

Compared to the non-$SiVET_2$ cohort, $SiVET_2$ cohort had fewer participants aged ≥35 years, 12% vs 22%, Baganda tribe 44% vs 53% and those working in restaurant/bar/hair salon occupation 29% vs 38% Table 2. Additionally, the non-$SiVET_2$ cohort had more participants without any education 41% vs 6%, single never married 36% vs 24% and those that lived at the current location for zero to one year 33% vs 18%, Table 2.

Primary outcome (study dropout)

Among the 1525 participants, 326 (21%) dropped out of the cohorts. Of these 225/953 (24%) dropped out of the non-SiVET cohorts compared to 101/572 (18%), $p = 0.01$ in the SiVET cohorts.

Dropout rates

Overall, 326 participants dropped out of cohorts in 1260 Person Years of Observation (PYO), a dropout rate of 25.9 /100 PYO, 95%CI:23.2–28.8. The dropout rate was higher in the non-SiVET cohorts 31.6, 95%CI: 27.8–36.1 compared to SiVET cohorts 18.4, 95%CI: 15.1–22.4, rate ratio (RR) =0.6, 95%CI: 0.5–0.7, Table 3. Stratifying the dropout rate by the study populations, it was still higher in the non-SiVET cohort compared to SiVET cohort in a given population but generally, the dropout rate was highest in the FSW population, Table 3.

Similarly, comparing dropout rates by similar participant characteristics, the rates were generally higher in non-SiVET cohorts, except for participants that had lived at the current location for zero to 1 year in the $SiVET_2$ cohort, Table 4.

Reasons for dropping out of cohorts

Of the 225 participants that dropped out of non-SiVET cohorts, 89 (40%) were lost to follow up other reasons are shown in Fig. 1. Similarly, of 101 participants that dropped out of the SiVET cohorts, 31 (31%) were lost to follow up, Fig. 1.

Factors associated with dropout

FF

Factors independently associated with dropout in the non-$SiVET_1$ cohort included sex [female: adjusted rate ratio (aRR) = 0.5, 95%CI: 0.3–0.9)], religion [Muslim: 0.4 (0.2–0.8)], occupation [work in restaurant/bar/hair salon: 3.1(1.3–7.4) compared to being engaged in small-scale business], other factors are shown in Table 5. In $SiVET_1$ cohort, only duration lived at the current location [> 1 year: 0.5 (0.3–0.9)] was independently associated with dropout.

FSW

Factors independently associated with dropout in the non-$SiVET_2$ cohort included religion [Muslim: 0.6 (0.3–0.9)], marital status [married: 2.2 (1.1–5.6) compared to single never married] and having sex under influence of alcohol [sometimes: 0.4 (0.2–0.8) compared to never]. In $SiVET_2$ cohort, factors independently associated with dropout included age [25–34 years: 0.6 (0.3–0.9), 35 or more years: 0.3 (0.1–0.7) all compared to 18–24 years] and duration lived at the current location [> 1 year: 0.4 (0.2–0.7)], other factors are shown in Table 5.

Discussion

We investigated how participant dropout rate from the Simulated HIV Vaccine Efficacy Trial (SiVET) differs from the observational cohort within which SiVET was nested. We compared participant dropout rate in SiVET to that in non-SiVET cohort adjusted to align over a set duration of time in two distinct key populations in Uganda. We found that the dropout rate in the SiVET cohort was nearly half that in the non-SiVET cohort. When stratified by the study population, the difference in dropout rate between SiVET and non-SiVET cohorts was generally similar though the dropout rates in either cohort were higher in the FSW population.

The results of this comparative analysis suggest that even when participants are drawn from the same population and followed up for the same duration of time, the selection criteria into efficacy trial and/or trial environment could cause a difference in trial dropout rate. Much as the observational cohorts were the recruitment source for the SiVETs, participants who joined SiVETs differed in significant ways from those who did not. SiVET recruited fewer females, young participants (< 25 years), not educated, working in restaurants/bar/hair salon, single and never married and those that had lived at the current location for a shorter duration (1 year or less). These participant characteristics have been previously associated with high attrition from observational cohorts in these [9, 11, 15] and other populations [25, 26]. Furthermore, these participant characteristics have also been previously associated with high risk of HIV

Table 2 Baseline characteristics of the participants in the non-SiVET and SiVET cohorts in FF and FSW populations in Uganda 2012–2017

Variables	FF($N = 565$)			FSW($N = 960$)		
	non-SiVET$_1$ ($n = 283$)	SiVET$_1$ ($n = 282$)	p -value	non-SiVET$_2$ ($n = 670$)	SiVET$_2$ ($n = 290$)	*p*-value
	Total (%)	Total (%)		Total (%)	Total (%)	
Sex			< 0.01			na
Male	137 (48)	205 (73)		na	na	
Female	146 (52)	77 (27)		670 (100)	290 (100)	
Age group (years)			0.01			< 0.01
18–24	127 (45)	88 (31)		304 (45)	85 (29)	
25–34	115 (41)	127 (45)		289 (43)	143 (49)	
35+	41 (14)	67 (24)		77 (12)	62 (22)	
Tribe			0.02			0.04
Baganda	114 (40)	128 (45)		295 (44)	153 (53)	
Banyankole	50 (18)	31 (11)		109 (16)	32 (11)	
Banyarwanda	69 (24)	54 (19)		40 (6)	20 (7)	
Other	50 (18)	69 (25)		226 (34)	85 (29)	
Education			0.04			< 0.01
None	35 (12)	19 (6)		272 (41)	16 (6)	
Primary	190 (67)	211 (75)		282 (42)	149 (51)	
Secondary+	58 (21)	52 (19)		116 (17)	125 (43)	
Marital status			0.17			0.01
Single never married	86 (30)	84 (30)		240 (36)	68 (24)	
Married	125 (44)	143 (51)		42 (6)	18 (6)	
Single ever married	72 (26)	55 (19)		388 (58)	204 (70)	
Religion			0.86			0.96
Christian	216 (76)	217 (77)		507 (76)	219 (76)	
Muslim	67 (24)	65 (23)		163 (24)	71 (24)	
Occupation			< 0.01			0.02
Fishing/fish related[b]	124 (44)	169 (60)		0 (0)	0 (0)	
Small scale business	59 (21)	73 (26)		17 (3)	11 (4)	
Work in restaurant/bar/hair salon	65 (23)	23 (8)		196 (29)	111 (38)	
Sex work	0 (0)	0 (0)		452 (67)	165 (57)	
Other[a]	35 (12)	17 (6)		5 (1)	3 (1)	
Duration lived at the current location (years)			< 0.01			< 0.01
0–1	96 (34)	48 (17)		222 (33)	51 (18)	
> 1	187 (66)	234 (83)		448 (67)	239 (82)	
Illicit drug use			0.29			0.79
No	254 (90)	245 (87)		132 (20)	55 (19)	
Yes	29 (10)	37 (13)		538 (80)	235 (81)	

SiVET- Simulated Vaccine Efficacy Trial, N-Total sample size, n-Sub study sample size, %-Percent, *na*- Not applicable, p-value compares SiVET to non-SiVET stratified by population

[a]Peasant farmer, house wife

[b]Drying fish, salting or smoking fish

Table 3 Dropout in non-SIVET and SIVET cohorts, FF and FSW populations, Uganda 2012–2017

Population	non-SiVET		SiVET		Rate ratio (95%CI)
	C/PYO	Rate-R_2 (95%CI)	C/PYO	Rate-R_1 (95%CI)	R_1/ R_2
FF	93/335	27.8 (22.7–34.0)	46/322	14.3 (10.7–19.0)	0.51 (0.37–0.71)
FSW	132/376	35.1 (29.6–41.6)	55/227	24.2 (18.6–31.6)	0.69 (0.50–0.96)
Overall	225/711	31.6 (27.8–36.1)	101/549	18.4 (15.1–22.4)	0.58 (0.46–0.73)

FF- Fisherfolk, *FSW* -Female sex worker, *C*- cases of dropout, *PYO*- person years of observation, *SiVET*- Simulated Vaccine Efficacy Trial

acquisition in these populations [9, 15, 16, 19] and other HIV at-risk populations [27, 28].

SiVET cohorts' lower dropout rate could also be attributable to the enhanced follow up procedures. SiVET cohorts' participants were reminded of their next scheduled clinic visit at least 2 days in advance, and were picked by a trial staff on a motor cycle or vehicle if they needed help to access the clinic for their visits. Enhanced strategies to keep participants in follow up have been previously associated with high retention in follow up [29]. Furthermore, SiVET participants had four more clinic visits to complete trial procedures and adherence counselling. Regular study clinic visits have been associated with improved study outcomes and completion [30]. More clinic visits resulted in more HIV risk reduction counselling and other free Health care services in the SiVET cohort than non-SIVET cohort and a lower HIV incidence observed in this group [8].

The results suggest a number of factors were independently associated with dropout from the SiVET and non-SiVET cohorts including age, gender, occupation, marital status, duration lived at the current location, having sex while drunk, having multiple sexual partners, mobility, condom use with a new sexual partner, and genital sores/ulcer disease. These have previously been associated with more non-study completion in the key populations [6, 15, 20, 27, 31] and other populations [3, 32]. A surprising finding was that in FF and FSW non-SiVET cohorts, the rate of dropout among Muslims was statistically significantly lower than that among Christians. Though not statistically significant, a similar result was observed in the SiVET cohorts. While there is no clear explanation to this, Muslims have been indicated to be less likely to migrate [33] and over 90% of the dropouts were either uncontactable, lost to follow up or missed the last visit.

The commonest reasons for dropping out of the SiVET and non-SiVET cohorts were lost to follow up, being uncontactable and missing the last visit without giving investigators an opportunity to ascertain the actual reasons. Missing study visits has been associated with migration [11, 34]. Similarly, participants that migrate have been previously associated with increased risk of HIV infection because of high-risk sexual behaviours among those that move [11, 34]. SIVET cohort recruited more of the participants that had lived at the current location for more than 1 year. This could partly explain the lower drop out observed in SiVET cohort in this analysis and the lower HIV incidence in SiVET previously published [8]. Recruitment strategies aimed at avoiding participants that move could improve retention but screen out those likely to seroconvert. Therefore, researchers planning HIV vaccine efficacy trials in these populations need strategies aimed at retaining participants likely to be mobile, to minimize dropout rates and maximize HIV incidence.

Our study strengths included large sample size, two distinct key populations, aligning both SiVET and non-SiVET cohorts to the same duration of follow up in a concurrent period and participants being seen by the same study staff. Furthermore, participants were allowed a run in period of at least 3 months participation in the source cohort, mimicking a screening enrolment time lag in an actual HIV vaccine efficacy trial. Results from SiVETs suggest that with enhanced strategies, these populations could be enrolled and retained in HIV vaccine efficacy trials.

The limitations of this comparative analysis include, SiVET cohorts were likely to screen and enroll participants that came on time for their three - eighteen months visit in the source cohort. This could have filtered participants likely to come on time and completing study follow up visits beyond that seen in non-SiVET cohorts. This could have inadvertently decreased dropout in SiVETs compared to non-SiVET cohorts. Furthermore, although participants screened for HIV vaccine efficacy trials are required to have a run in period before actual recruitment, as it was done in SiVETs, it is unlikely that this will be up to three to eighteen months. The procedures in the SiVET and non-SiVET cohorts were conducted by the same study staff and were not blinded. This could have led to differential handling of follow up efforts to ensure that participants return for follow up. SiVET cohort participants were fully informed that the vaccine being administered has no effect on their risk of HIV infection but prevents against Hepatitis B infection. This could have led to participants continued attendance to enjoy enhanced health care services. Nonetheless, in an actual

Table 4 Dropout by participant characteristics in the non-SiVET and SiVET cohorts in FF and FSW populations, Uganda 2012–2017

Variables	FF(N = 565)					FSW(N = 960)				
	non-SiVET$_1$ (n = 283)			SiVET$_1$ (n = 282)		non-SiVET$_2$ (n = 670)			SiVET$_2$ (n = 290)	
	Total (%)	C/PYO	Rate	C/PYO	Rate	Total (%)	C/PYO	Rate	C/PYO	Rate
Sex										
Male	342 (60)	47/165	28.6	32/236	14.6	–	–	–	–	–
Female	223 (40)	46/170	27.0	14/86	16.2	960 (100)	132/376	35.1	55/227	24.2
Age group (years)										
18–24	215 (38)	45/150	30.0	16/103	15.6	389 (41)	66/162	40.9	22/64	34.4
25–34	242 (43)	35/135	26.0	25/144	17.3	432 (45)	52/163	31.9	27/111	24.3
35+	108 (19)	13/50	26.0	5/75	6.7	139 (14)	14/52	27.0	6/52	11.6
Tribe										
Baganda	242 (43)	43/128	33.7	22/146	15.0	448 (47)	58/177	32.8	30/118	25.4
Banyankole	81 (14)	17/62	27.3	4/36	11.2	141 (15)	25/60	41.7	5/26	19.6
Banyarwanda	123 (22)	20/86	23.1	6/62	9.7	60 (6)	8/19	42.1	5/16	31.5
Other	119 (21)	13/59	22.1	14/78	17.9	311 (32)	41/120	34.1	15/67	22.3
Education										
None	54 (9)	12/32	38.0	2/23	8.7	288 (30)	54/151	35.7	3/11	27.6
Primary	401 (71)	64/229	27.9	34/241	14.1	431 (45)	56/157	35.7	30/118	25.4
Secondary+	110 (20)	17/74	22.9	10/58	17.3	241 (25)	22/68	32.3	22/98	22.4
Marital status										
Single never married	170 (30)	33/97	34.1	19/99	19.2	308 (32)	52/132	39.5	11/58	18.9
Married	268 (47)	39/151	25.8	20/160	12.5	60 (6)	11/24	46.1	5/12	40.9
Single ever married	127 (23)	21/87	24.1	7/63	11.1	592 (62)	69/221	31.2	39/157	24.9
Religion										
Christian	433 (77)	78/244	32.0	35/247	14.1	726 (76)	106/277	38.3	42/170	24.7
Muslim	132 (23)	15/91	16.4	11/75	14.7	234 (24)	26/99	26.2	13/57	22.7
Occupation										
Fishing/fish related[b]	293 (52)	42/151	27.7	24/193	12.4	–	–	–		
Small scale business	132 (23)	14/73	19.1	15/82	18.1	28 (3)	3/13	23.0	1/9	10.8
Work in restaurant/bar/hair salon	88 (16)	31/61	50.5	5/27	18.6	307 (32)	35/118	29.6	19/87	21.7
Sex work	–	–	–	–	–	617 (64)	93/243	38.3	34/128	26.6
Other[a]	52 (9)	6/49	12.2	2/19	10.6	8 (1)	1/2	44.4	1/2	44.0
Duration lived at the current location (years)										
0–1	144 (25)	38/104	36.7	13/53	24.4	273 (28)	41/129	31.8	19/37	51.2
> 1	421 (75)	55/231	23.8	33/269	12.3	687 (72)	91/247	36.8	36/190	19.0
Illicit drug use										
No	499 (88)	84/298	28.1	38/278	13.7	187 (20)	31/63	49.5	8/43	18.6
Yes	66 (12)	9/37	24.6	8/44	18.1	773 (80)	101/314	32.2	47/184	25.5

FF -Fisherfolk, *FSW*- Female sex worker, *C*- cases of dropout, *PYO*- person years of observation, *SiVET*- Simulated Vaccine Efficacy Trial
[a]Peasant farmer, house wife
[b]Drying fish, salting or smoking fish

HIV vaccine efficacy trial, participants have to be informed that the vaccine being administered is not yet known to prevent against HIV infection. Even with these limitations, our comparative analysis gives a rare opportunity of estimating dropout rate in trials nested within source cohorts adjusting them to reflect the same duration of follow up in the same period and populations.

Table 5 Unadjusted and adjusted factors associated with dropout in the non-SiVET and SiVET in FF and FSW, Uganda (2012–2017)

Variables	Fisherfolks (N = 565)				Female Sex Workers (N = 960)			
	non-SiVET$_1$ (n = 283)		SiVET$_1$ (n = 282)		non-SiVET$_2$ (n = 670)		SiVET$_2$ (n = 290)	
	uRR (95%CI)	aRR (95%CI)	uRR (95%CI)	aRR (95%CI)	uRR (95%CI)	aRR (95%CI)	uRR (95%CI	aRR (95%CI)
Sex								
Male	1	1	1	1	na	na	na	na
Female	0.9 (0.6–1.4)	**0.5 (0.3–0.9)**	1.2 (0.7–2.1)	0.8 (0.4–1.7)				
Age group (years)								
18–24	1	1	1	1	1	1	1	1
25–34	0.8 (0.6–1.4)	0.8 (0.5–1.3)	1.1 (0.7–1.9)	1.4 (0.8–2.4)	0.8 (0.5–1.2)	0.8 (0.5–1.4)	0.7 (0.4–1.2)	**0.6 (0.3–0.9)**
35+	0.8 (0.5–1.6)	0.8 (0.4–1.5)	0.4 (0.2–1.1)	0.5 (0.2–1.4)	0.7 (0.3–1.3)	0.7 (0.3–1.5)	0.3 (0.2–0.8)	**0.3 (0.1–0.7)**
Tribe								
Baganda	1		1		1		1	
Banyankole	0.8 (0.5–1.4)		0.7 (0.3–1.9)		1.3 (0.7–2.2)		0.8 (0.3–2.0)	
Banyarwanda	0.7 (0.4–1.2)		0.6 (0.3–1.5)		1.2 (0.5–3.1)		1.3 (0.5–3.2)	
Other	0.6 (0.4–1.2)		1.2 (0.7–2.1)		1.1 (0.7–1.7)		0.8 (0.5–1.6)	
Education								
None	1		1		1	1	1	
Primary	0.7 (0.4–1.4)		1.6 (0.5–5.7)		0.9 (0.6–1.6)	1.4 (0.8–2.2)	0.9 (0.3–3.1)	
Secondary+	0.6 (0.3–1.3)		2.0 (0.5–7.6)		0.9 (0.5–1.6)	1.2 (0.6–2.4)	0.8 (0.2–2.7)	
Marital status								
Single never married	1		1		1	1	1	1
Married	0.8 (0.5–1.2)		0.6 (0.4–1.1)		1.2 (0.5–2.6)	**2.2 (1.1–5.6)**	2.2 (0.7–6.4)	**4.0 (1.3–11.8)**
Single ever married	0.7 (0.4–1.2)		0.5 (0.3–1.3)		0.8 (0.5–1.2)	0.9 (0.6–1.6)	1.3 (0.7–2.5)	**2.2 (1.1–4.6)**
Religion								
Christian	1	**1**	1		1	**1**	1	
Muslim	0.5 (0.3–0.9)	**0.4 (0.2–0.8)**	1.1 (0.6–1.9)		0.7 (0.4–1.1)	**0.6 (0.3–0.9)**	0.9 (0.5–1.7)	
Occupation								
Small scale business	1	1	1		1		1	
Fishing/fish related[b]	1.5 (0.8–2.6)	1.5 (0.8–2.8)	0.7 (0.4–1.2)		–		–	
Work in restaurant/bar/hair salon	2.6 (1.4–5.0)	**3.1 (1.3–7.4)**	1.1 (0.5–2.4)		1.3 (0.4–4.6)		2.0 (0.3–14.4)	
Sex work	–	–	–		1.7 (0.5–5.8)		2.5 (0.4–17.1)	
Other[a]	0.6 (0.2–1.7)	0.8 (0.3–2.3)	0.6 (0.2–2.3)		1.9 (0.1–25.6)		4.1 (0.3–61.2)	
Duration lived at the current location (years)								
0–1	1	1	1	1	1	1	1	1
> 1	0.6 (0.4–0.9)	0.8 (0.5–1.3)	0.5 (0.3–0.9)	**0.5 (0.3–0.9)**	1.2 (0.8–1.8)	1.3 (0.8–2.1)	0.4 (0.2–0.6)	**0.4 (0.2–0.7)**
Illicit drug use								

Table 5 Unadjusted and adjusted factors associated with dropout in the non-SiVET and SiVET in FF and FSW, Uganda (2012–2017) *(Continued)*

Variables	Fisherfolks (N = 565)				Female Sex Workers (N = 960)			
	non-SiVET$_1$ (n = 283)		SiVET$_1$ (n = 282)		non-SiVET$_2$ (n = 670)		SiVET$_2$ (n = 290)	
	uRR (95%CI)	aRR (95%CI)	uRR (95%CI)	aRR (95%CI)	uRR (95%CI)	aRR (95%CI)	uRR (95%CI	aRR (95%CI)
No	1		1		1	1	1	
Yes	0.8 (0.4–1.7)		1.3 (0.7–2.5)		0.7 (0.4–1.1)	0.6 (0.3–0.9)	1.4 (0.7–2.9)	
Alcohol use								
Never	1		1		1		1	
Rarely	1.4 (0.9–2.1)		0.8 (0.5–1.3)		1.1 (0.6–2.1)		1.2 (0.6–2.4)	
Daily	0.9 (0.4–2.3)		0.4 (0.1–1.4)		1.4 (0.8–2.3)		1.8 (0.9–3.7)	
Sex while drunk								
Never	1	1	1	1	1		1	
Sometimes	0.9 (0.6–1.5)	**0.6 (0.3–0.9)**	1.2 (0.7–2.0)	1.3 (0.8–2.3)	1.5 (0.8–2.8)		1.3 (0.7–2.1)	
Frequently	1.1 (0.6–1.9)	0.7 (0.4–1.3)	0.3 (0.1–1.2)	0.4 (0.1–1.5)	1.3 (0.1–14.1)		2.3 (0.8–6.8)	
Genital discharge								
Yes	1		1		1		1	
No	0.8 (0.5–1.1)		1.2 (0.7–2.1)		0.8 (0.5–1.3)		0.7 (0.4–1.2)	
Genital ulcer/sores								
Yes	1		1		1		1	1
No	0.9 (0.6–1.3)		1.1 (0.7–1.9)		0.9 (0.2–1.6)		0.5 (0.3–0.9)	**0.5 (0.3–0.9)**
Number of sexual partners								
0–1	1	1	1	1	1	1	1	
2+	1.9 (1.3–2.9)	**1.7 (1.1–2.6)**	0.7 (0.4–1.3)	0.7 (0.4–1.3)	0.7 (0.4–1.5)	0.6 (0.3–1.4)	1.0 (0.4–2.5)	
New sexual partner								
No	1		1		1		1	
Yes	2.0 (1.1–3.9)		2.0 (1.2–3.6)		1.2 (0.5–2.8)		0.9 (0.5–1.9)	
Condom use with new sexual partner								
Never	1		1		1	1	1	
Sometimes	1.2 (0.7–1.9)		1.1 (0.6–1.9)		0.4 (0.2–0.7)	**0.4 (0.2–0.8)**	0.2 (0.1–0.9)	
Always	0.9 (0.6–1.6)		0.9 (0.4–2.1)		0.7 (0.5–1.2)	0.7 (0.4–1.2)	0.4 (0.1–1.9)	
Away[c]								
Yes	1	1	1	1	–		1	1
No	1.7 (1.1–2.5)	**2.0 (1.3–3.1)**	1.2 (0.7–2.0)	1.2 (0.7–2.1)			0.8 (0.5–1.4)	0.7 (0.4–1.3)

uRR- Unadjusted risk ratio, *aRR*- adjusted risk ratio, *CI*- Confidence interval, *%-Percent*, *SiVET*- Simulated Vaccine Efficacy Trial, *na*- not applicable, *bold*- statistically significant adjusted results
[a]Peasant farmer, house wife
[b]Drying fish, salting or smoking fish
[c]being away from home for ≥ 2 nights per/week

Conclusion

In conclusions, HIV Vaccine Efficacy Trial's inclusion-exclusion criteria and possibly some degree of bias in procedures, selected volunteers with characteristics different from those in the source population and not recruited. These in combination with trial environment and enhanced retention strategies reduced dropout rate from a trial in mobile populations. In HIV high-risk populations where no HIV prevention or simulation trials have been previously conducted to provide data for planning HIV vaccine efficacy trials, the dropout rate in observational cohort could be a useful tool. However, this rate might have to be decreased by 40% as observed in the SiVET cohorts in these key populations. Evidence further suggests that the decrease in dropout varied by population, 50% in FF and 30% in FSW. Entire results from these studies suggest that FF and FSW could be good populations for actual HIV vaccine efficacy trials because of the already known high HIV incidence and lower dropout rates in a trial setting as seen in the SiVETs.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; aRR: Adjusted Rate Ratio; CI: Confidence Interval; FF: Fisherfolk; FSW: Female Sex Worker; HIV: Human Immunodeficiency Virus; IAVI: International AIDS Vaccine Initiative; LSHTM: London School of Hygiene and Tropical Medicine; MA: Massachusetts; MRC: Medical Research Council; OBC: Observational Cohort; PYO: Person Years of Observation; RR: Rate Ratio; SiVET: Simulated Vaccine Efficacy Trial; UK: United Kingdom; uRR: Unadjusted Rate Ratio; USA: United States of America; USAID: United States Agency for International Development; UVRI: Uganda Virus Research Institute; WA: Washington

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Authors would like to acknowledge the study teams and participants.

Authors' contributions

AA: Lead Author, drafted initial manuscript draft, carried out data management for OBC_1 and both SiVETs, data analysis and interpreted the data. JT: contributed to data analysis and interpreted the data. SN: contributed to data analysis and interpreted the data. YM: contributed to the design of the $SiVET_2$ protocol, study coordination (OBC_2 and $SiVET_2$). PK: directed the implementation of both OBCs and SiVETs. PEF: contributed to the design of both SiVETs and OBC_1, and interpreted the data. MP: contributed to the design of both SiVETs and OBC_1 and interpreted the data. All authors critically commented and provided revisions to the manuscript. The authors have approved this final version for submission.

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Availability of data and materials

The MRC/UVRI and LSHTM Uganda Research Unit operates an open data access and has a data sharing policy accessible at https://www.mrcuganda.org/publications/data-sharing-policy. The policy summarizes the conditions under which data collected by the Unit can be made available to other bona fide researchers, the way in which such researchers can apply to have access to the data and how data will be made available if an application for data sharing is approved. Should any other researchers need to have access to the data from which this manuscript was generated, the processes to access the data are well laid out in the policy. The corresponding and other co-author emails have been provided and they could be contacted anytime for further clarifications and/or support to access the data.

Ethics approval and consent to participate

The Uganda Virus Research Institute (UVRI) Research and Ethics Committee (GC127, GC/127/14/04/454, GC/127/12/04/22 and GC127/12/06/01) and the Uganda National Council for Science and Technology (MV834, HS364 and HS1584) approved the conduct of both observational cohorts and SiVETs. Furthermore, the London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee (LSHTM14588) approved the concept leading to this comparative analysis. Written informed consent was obtained from each participant before enrolment into the observational cohort and SiVET.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Chapter Seven: Comparison of HIV risk behaviours between clinical Trials and observational cohorts in Uganda

7.1 Research in context

Key populations such as Fisher-folks (FF) on the shoreline of Lake Victoria and female sex workers (FSW) in Kampala, Uganda have higher HIV risk behaviours, hence higher HIV incidence than the general populations (23, 25, 27). This makes them attractive for the conduct of anticipated HIV vaccine efficacy trials. However, no HIV prevention trials have been conducted in these key populations to provide trial specific context baseline data. Available information on trial targeted outcomes in these key populations come from observational cohorts. Previous HIV prevention trials have shown lower HIV incidence during participant follow up in trials compared to that obtained from the underlying observational cohort data from the same populations prior to the trial onset. Some of these trials were prematurely terminated due to loss of statistical power (38, 39, 42). One of the key reasons advanced for the diminished HIV incidence was that participants had lower HIV risk behaviours due to rigorous HIV risk-reduction measures in trials (38). Participants that joined the trials reported higher increases in condom use, fewer numbers of sexual partners and fewer sex acts compared to the baseline.

7.2 Trials Simulating HIV vaccine efficacy trials in FF and FSW in Uganda

Two Simulated HIV Vaccine Efficacy Trials (SiVETs) nested within observational cohorts of Female Sex Workers and Fisher-folks subpopulations in Uganda were conducted and are described in previous chapters of this thesis. The data from these SiVETs were used to estimate participant response to HIV risk reduction measures by way of comparing HIV risk behaviours at baseline and at the end of follow up. These were further compared between the observational cohort and the nested simulation trial in the same population. The detailed methods and results are provided in the manuscript draft below.

7.3 Key findings

Results suggest that in both SiVETs and source observational cohorts, the proportion of participants with high-risk HIV behaviour decreased over the one-year follow-up with greater decreases in SiVETs. Overall, 72.2% (95% Cl: 68.0% - 76.0%) of the participants in SiVETs experienced a decrease in high-risk behaviour compared to 54.0% (95% Cl: 50.1% - 57.8%) in

the source observational cohorts. The decrease in high-risk behaviour was lower among Female Sex Workers than Fisher-folks; conversely, the difference between SiVET and source observational cohort was greatest in the FSW population. Further details are indicated in the publication below.

7.4 Implications for anticipated HIV vaccine efficacy trial in these key populations

Conduct of SiVETs in these key populations could mean that investigators recruiting participants into clinical trials from observational cohorts in these or similar populations need to consider the likely effect of reduction in HIV risk behaviours on likelihood of seroconversion and the trial statistical power.

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Student ID Number	lsh133215	**Title**	Mr
First Name(s)	Andrew Max		
Surname/Family Name	Abaasa		
Thesis Title	Using observational cohort data from Key populations to plan HIV intervention studies		
Primary Supervisor	Jim Todd		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	AIDS & Behavior		
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If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not Applicable (NA)		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I participated in the conceptualization of the Simulated HIV Vaccine Efficacy Trial (SiVET) concept, drafting of the studies documents (protocol, standard operating manuals and procedures, case report and consent forms), conduct of the studies (data management and cleaning). I headed the data management team for both observational cohorts (performing data management tasks and statistical analysis). I aggregated the datasets from the different observational cohorts and SiVETs, carried out statistical analysis, drafted the initial manuscript and interpreted the study findings.

SECTION E

Student Signature	Abaasa
Date	20 May. 2020

Supervisor Signature	Todd
Date	21st May 2020

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ORIGINAL PAPER

Comparison of HIV Risk Behaviors Between Clinical Trials and Observational Cohorts in Uganda

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Abstract
Many key populations have high-risk behaviors for HIV infection making them suitable for HIV vaccine efficacy trials. However, these behaviors may change when participants enroll into a trial. We used HIV simulated vaccine efficacy trials (SiVETs) nested within observational cohorts of fisherfolks and female sex workers in Uganda to evaluate this difference. We screened observational cohort participants for enrolment into SiVETs, until 572 were enrolled. Those not enrolled (n = 953) continued participation in the observational cohorts. We determined risk behaviors at baseline and at 1 year, assigned a numeric score to each behavior and defined composite score as the sum of reported behaviors. We compared changes in scores over 12 months. Both observational cohorts and SiVETs saw a significant decrease in score but greatest in the SiVETs. Investigators recruiting for trials from these populations should consider the likely effect of reduction in risk behaviors on incident HIV infection and trial statistical power.

Keywords HIV · Risk behavior · Trials · Observational · Cohorts

Introduction

According to UNAIDS, 1.8 million new HIV infections occurred globally in 2017, 66% of which were in Sub Saharan Africa (SSA) [1]. Available HIV prevention methods have had limited effect in curbing new HIV infections in SSA because of poor adherence and/or lack of access [2]. Three possible long-term hopes for controlling the HIV pandemic are an effective and affordable HIV vaccine [3], a long-acting drug [4], and antibody injection [5]. Successful efficacy trials will need populations with high HIV incidence and SSA is likely to be a key destination for many such trials. However, many SSA countries suffer from generalized HIV epidemics [6, 7], and although the HIV incidence is below 1% per annum [8], the HIV prevalence in the general population in Uganda has consistently remained above 5% [1]. In such a setting, trials may not be conducted in the general population but population sub groups.

Occupational subpopulations, such as Fisherfolks (FF) and female sex workers (FSW), are suitable for HIV vaccine efficacy trials [9–12]. The incidence of HIV is much higher in these subpopulations, with incidence rates as high as 11 per 100 persons at risk in Uganda [9–14]. These groups have shown high willingness to participate in HIV prevention research [15, 16] and have good retention in study follow up [17, 18]. However, most incidence and retention information comes from observational cohorts, and trials often have lower HIV incidence than observational cohorts drawn from the same population [9, 19, 20]. In 2007/8, lower than expected HIV incidence led to the premature termination of three microbicides trials in West Africa [20–22].

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Two key reasons have been put forward to explain the reduced HIV incidence in trials. First, an inclination for participants to reduce risky behaviors due to vigorous trial HIV risk-reduction measures. Second, there may be important differences between participants who join clinical trials and those that do not [20–22]. In such trials, participants have reported increased condom use, fewer sexual partners, and fewer sex acts compared to their baseline behavior.

To our knowledge, no HIV efficacy trials to date have completed follow up among FF on the shoreline of Lake Victoria nor among FSW in Kampala. Observational studies in FF and FSW in Uganda have shown very high HIV risk behaviors and genital infections [12, 17, 23–25]. HIV incidence in these groups has also been high [12, 14]. As an ethical requirement, conduct of HIV vaccine efficacy trials requires that participants receive HIV behavioral risk reduction messages/measures and this is likely to decrease the proportion of participants who engage in high-risk behavior.

Composite sets of HIV risk components have been previously used in cohorts of serodiscordant couples in seven African countries [26] and Men who have sex with men in China [27], Kenya [28] and Brazil [29], to generate HIV risk scores. In these studies, a lower risk score was associated with 20 to 85% [26, 29] lower HIV incidence. The composite score allowed for more precise predictive capability of risk on HIV incidence, than individual predictors [26].

Since 2008, the International AIDS Vaccine Initiative (IAVI) in collaboration with MRC/UVRI and LSHTM Uganda research Unit have run cohorts of FF and FSW [10, 11, 17, 18, 24]. Beginning July 2012, HIV simulated vaccine efficacy trials (SiVETs) (designed to mimic an HIV vaccine efficacy trial using a commercially licensed Hepatitis B vaccine) were nested within both cohorts [9, 13]. Results from these studies have shown a 50% reduction in HIV incidence in the simulation trials compared to the cohorts in which they were nested, despite the fact that the licensed vaccine has no effect on HIV infection [9, 13].

We use data from the two observational cohorts and the nested SiVETs to: (i) determine the proportion of participants with decreased composite risk score at end of follow up, (ii) compare the decrease in composite risk score between the SiVET and the observational cohorts and (iii) determine baseline factors associated with decrease in composite risk score.

Methods

Study Design

Data presented in this paper come from two observational cohorts, OBC_1 (Jan 2012–Apr 2015) in FF and OBC_2 (Apr 2008–Apr 2017) in FSW, and two HIV simulated vaccine efficacy trials, $SiVET_1$ (Jul 2012–Apr 2014) nested in OBC_1 and $SiVET_2$ (Aug 2014–Apr 2017) nested in OBC_2.

Description of Cohorts

Observational Cohorts Before SiVETs

Eligible Fisherfolks (HIV negative, aged 18–49 years, at high risk of HIV infection) were enrolled into OBC_1 at a clinic located in Masaka town (100 km Southwest of Kampala, the capital of Uganda) about 50 km inland from the fishing communities on Lake Victoria. High risk was defined as any one of: multiple or casual sexual partners; presence of a sexually transmitted infection; non-condom use with causal partner; and alcohol use). Enrolled participants were primarily scheduled for quarterly HIV counselling and testing (HCT) and six-monthly HIV behavioral risk assessment. OBC_2 enrolled eligible female sex workers (HIV negative, aged 18–49 years) at a clinic located in Kampala city about 2 km from the city center. The follow up schedules and reason (HIV incidence and creating a pool of participants to enroll in future HIV prevention trials) for establishing this cohort were similar to those of OBC_1, except that HIV behavioral risk assessment in this cohort was done annually. Details of both cohorts have been previously reported [11, 13, 17, 24, 30].

SiVET Cohorts

From July 2012, participants that had spent between 3 and 18 months in follow up in OBC_1 were screened for eligibility (Table 1) and enrolled into $SiVET_1$. In addition to the procedures in OBC_1, participants in $SiVET_1$ were administered a commercially licensed hepatitis B vaccine (ENGERIX-BTM GlaxoSmithKline Biologicals Rixensart, Belgium) following the standard schedule of 0, 1 and 6 months mimicking an actual HIV vaccine efficacy trial with extra follow up visits (Fig. 1). Similar procedures were followed to establish $SiVET_2$, nested within OBC_2. In both SiVETs, data were collected on risk factors, including sexual behaviors at enrolment, 6 and 12 months. The primary purpose of SiVET was to determine study participants' retention at 12 months of follow up in a trial environment. Details of both SiVETs have been previously reported [9, 13, 30].

Non-SiVET Cohorts (Observational Cohorts in the SiVET Concurrent Period)

Non-$SiVET_1$ in FF and non-$SiVET_2$ in FSW cohorts comprised of participants in the respective OBCs that either failed the SiVET screening procedure (Table 1 and Fig. 1) or who were not enrolled because the SiVET had reached its target sample size. In both non-SiVET cohorts, data were

Table 1 Screening and enrolment eligibility criteria for SiVETs and non-SiVETs cohorts

SiVET cohort	Non-SiVET cohort
Inclusion	*Inclusion*
At least 3 and no more than 18 months of follow up in the OBC_1 or OBC_2	At least 3 months and no more than 18 months of follow up in OBC_1 or OBC_2
HIV-1 negative and willing to undergo HIV testing	Still in active follow up in the OBCs
Age 18 to 49 years	HIV-1 negative and willing to undergo HIV testing
Able and willing to provide written informed consent	
Able and willing to provide adequate locator information including physical address	
Willing and able to return for follow-up clinic visits	
Intending to reside in study area for at least 1 year	
Willing to undergo pregnancy testing	
Not breastfeeding and no intent for pregnancy in the next year	
Willing to use effective contraception during the study and at least 3 months after the last vaccination	
Exclusion	*Exclusion*
History of severe allergic reaction to any substance	HIV positive
An acute or chronic illness	
Contraindication for Hepatitis B vaccine	
Participation in another clinical trial	
Hepatitis B positive (only $SiVET_2$)	

SiVET simulated vaccine efficacy trial, *OBC* observational cohort

collected on sexual behaviors at enrolment, 6 months (only non-$SiVET_1$) and 12 months.

HIV Risk Components Score

We defined a composite risk score for each participant taking account of the following: alcohol consumption; use of alcohol prior to sex; number of sexual partners; starting a new sexual relationship recently; condom use; and presence of genital discharge and/or disease, with scoring as shown in Table 2. A higher score indicates higher risk components. We used the difference in this composite score between baseline and end of follow up (12 months) as a measure of change in risk components [29], where a positive value indicates an increase in high-risk behavior.

Data Management and Statistical Methods

The data from non-SiVET cohorts were entered and managed in MS Access 2003 (Microsoft Corporation, Redmond, WA), and from SiVET cohorts in OpenClinica 3.5 (Waltham, MA). All data were analyzed in Stata 14.0 (Stata Corp, College Station, TX, USA). We excluded from analysis participants who did not return for at least one HIV risk assessment follow-up visit. We summarized baseline characteristics using frequencies and percentages and compared them between non-SiVET and SiVET cohorts in the same population with chi-square tests. Bar graphs were used to display (i) the proportion of participants reporting each risk component at baseline and at 12-month follow up and (ii) the proportion of participants for each reported risk component who experienced a decrease in their risk score from that reported at baseline. We categorized the score difference into a binary variable, 1 for decreased risk component (difference < 0) and 0 otherwise (difference ≥ 0). The proportion of participants with decreased risk component was estimated as the number with difference < 0 divided by the total number of participants in the analysis expressed as a percentage. We estimated the mean and median of the composite risk scores at baseline and at 12 months stratified by non-SiVET and SiVET cohort as well as the study population. We fitted linear regression models stratified by the study population to determine the relationship of risk score at 12 months with study (non-SiVET vs SiVET) or other baseline characteristics adjusted for baseline risk score. After bivariable analyses, a multivariable model was fitted. In the multivariable model, factors were removed from the model using a backward elimination algorithm retaining any factors which remained significant predictor of dropping risk score ($p \leq 0.05$) or which caused a change in the regression coefficient of 20% or more (i.e., suggesting they were a confounding factor). Sex, age group and study cohort (SiVET and non-SiVET) were included a priori. We preferred linear models to Poisson or negative binomial because the data under consideration did not have any zero or skewed scores. However, we further fitted Poisson models in a supplementary analysis and similar results were observed, Supplementary Table 6.

Two sensitivity analyses were performed: one, stratifying the fisherfolk population by gender; the other comparing the primary outcome between non-SiVET participants (those not screened because of SiVET recruitment accrual) to (a) SiVET screen failures and (b) SiVET.

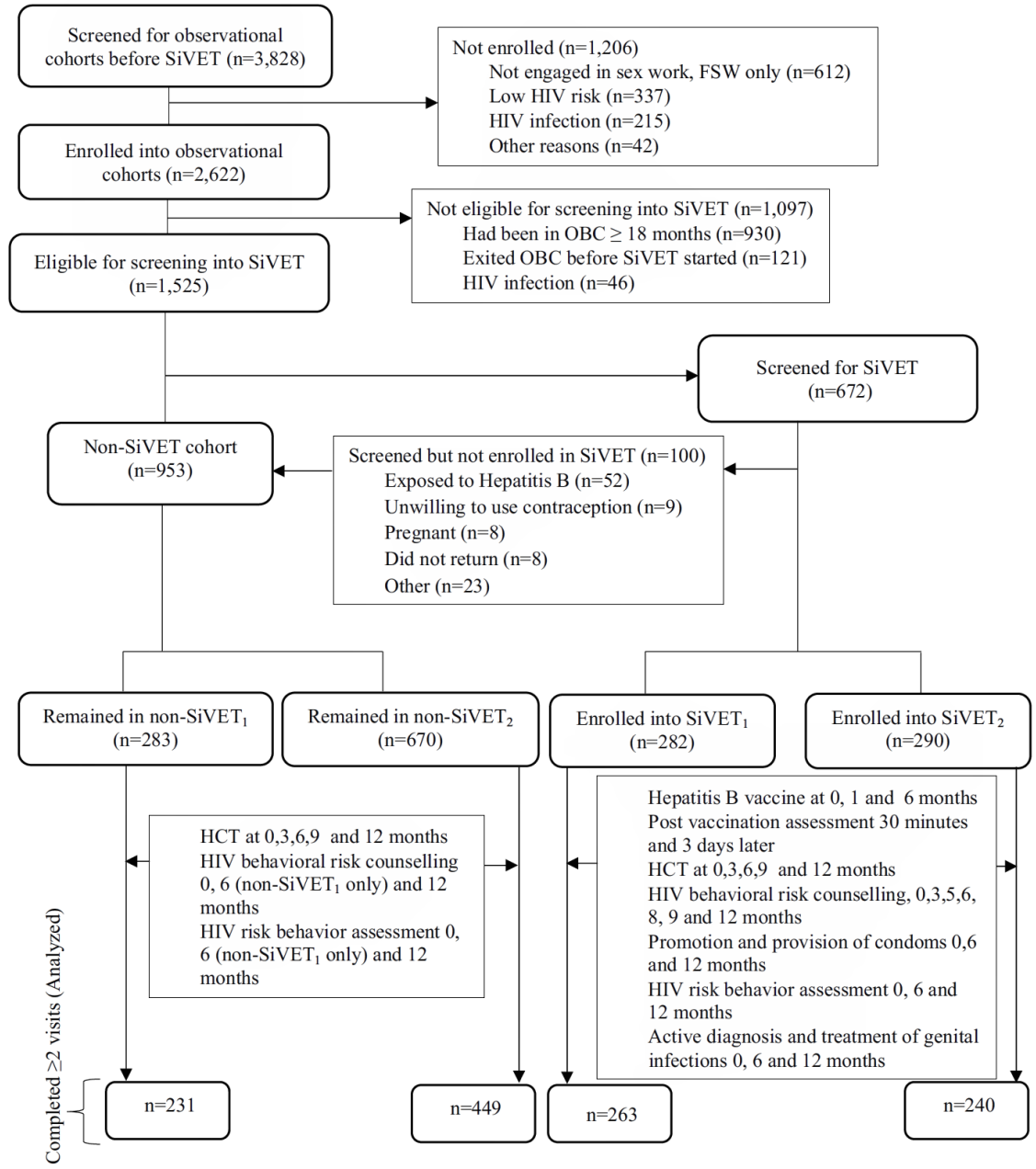


Fig. 1 Study profile for participants screened and enrolled in SiVET cohorts and those remaining in the non-SiVET cohorts in the FF and FSW populations, Uganda

Table 2 HIV risk reduction measures and risk score determination in the non-SiVET and SiVET cohorts in the key populations, Uganda

Risk reduction measure	Study cohort		Assessment question	Component score
	SiVET	non-SiVET		
HIV counselling and testing	Yes	Yes	HIV test results[a]	na
Counselling on alcohol consumption	Yes	No	Alcohol consumption (last 3 months)[a]	Never (0) Sometimes (1) Weekly (2) Daily (3)
Counselling on having sex under influence of alcohol	Yes	No	Having sex under influence of alcohol (last 3 months)[a]	Never (0) Sometimes (1) Frequently (2) Always (3)
Counselling on the number of sexual partners	Yes	Yes	Number of sexual partners (last 3 months)[a]	None (0) One (1) Two (2) Three (3) ≥Four (4)
Counselling on having new (casual) sexual partners	Yes	Yes	Number of new sexual partner besides the regular (last 3 months)[a]	None (0) One (1) Two (2) Three (3) ≥Four (4)
Promotion and provision of condoms	Yes	No (provided on request)	Condom use with a new sexual partner (last 3 months)[a]	No new partner (0) Always (1) Frequently (2) Sometimes (3) Never (4)
Active diagnosis and treatment for genital discharge (GD)	Yes	Symptomatic treatment	Presence of genital discharge[a]	No (0) Yes (1)
Active diagnosis and treatment for genital ulcer disease (GUD)	Yes	Symptomatic treatment	Presence of genital ulcer/sores[a]	No (0) Yes (1)
Total least score = 0 while the maximum worst score = 20				

na not applicable, *SiVET* simulated vaccine efficacy trial

[a]Schedule indicated in Fig. 1

Results

Screening, Enrolment and Follow Up

In total, 3828 volunteers were screened and 2622 (68%) enrolled into observational cohorts before SiVETs, Fig. 1. At the start of the SiVET period, 1525 (58%) of those enrolled into the original observational cohorts were eligible for screening into SiVETs, 672 (44%) were consecutively screened until 572 (85%) were enrolled. This analysis includes data from the 1183 participants who completed at least one follow-up behavior assessment visit: 231 (81.6%) of the participants in the non-$SiVET_1$ cohort, 449 (65.1%) non-$SiVET_2$, 263 (93.3%) $SiVET_1$ and 240 (82.8%) $SiVET_2$ (Fig. 1).

Baseline Characteristics of the Analyzed Participants

FF population: From the counts and percentages, compared to the non-$SiVET_1$ cohort, the $SiVET_1$ cohort had more men (73% vs 50%), more participants aged 35+ years (25% vs 14%), more participants engaged in fishing or related occupations (59% vs 45%) and more participants who had lived at their current location for more than 1 year (83% vs 70%).

FSW population: From the counts and percentages, compared to the non-$SiVET_2$ cohort, the $SiVET_2$ cohort had more participants aged 35+ years (24% vs 14%), more with secondary or higher education (44% vs 17%), and more participants who had lived at the current location for one or more years (85% vs 65%). See Table 3 for more details.

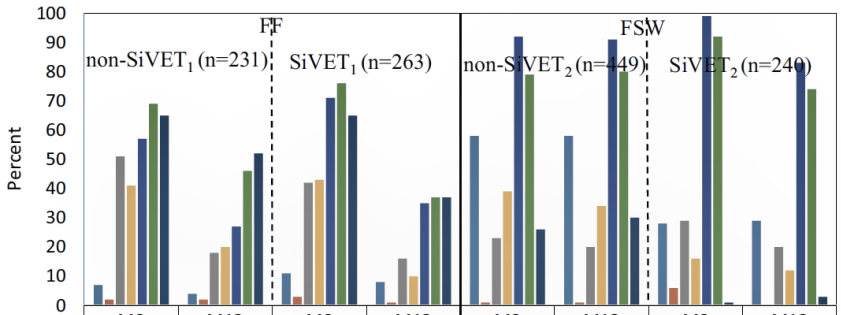
Table 3 Baseline characteristics of participants in the non-SiVET and SiVET cohorts in the key populations in Uganda, counts, percentages and chi-squared test

Variable	Total (%)	FF (N = 494)			FSW (N = 689)		
		Non-SiVET1 n (%)	SiVET1 n (%)	p-value	Non-SiVET2 n (%)	SiVET2 n (%)	p-value
Overall	1183 (100)	231 (100)	263 (100)		449 (100)	240 (100)	
Sex				< 0.01			
Male	306 (26)	115 (50)	191 (73)		–	–	
Female	877 (74)	116 (50)	72 (27)		449 (100)	240 (100)	
Age (years)				0.01			< 0.01
18–24	440 (37)	104 (45)	79 (30)		191 (43)	66 (28)	
25–34	522 (44)	94 (41)	119 (45)		193 (43)	116 (48)	
35+	221 (19)	33 (14)	65 (25)		65 (14)	58 (24)	
Ethnicity				0.02			0.07
Baganda	544 (46)	94 (41)	121 (46)		204 (45)	125 (52)	
Banyankole	170 (14)	40 (17)	27 (10)		76 (17)	27 (11)	
Banyarwanda	150 (13)	59 (26)	53 (20)		21 (5)	17 (7)	
Other	319 (27)	38 (16)	62 (24)		148 (33)	71 (30)	
Religion				0.36			0.98
Christian	899 (76)	172 (74)	205 (78)		340 (76)	182 (76)	
Muslim	284 (24)	59 (26)	58 (22)		109 (24)	58 (24)	
Education				0.12			< 0.01
None	237 (20)	25 (11)	17 (6)		182 (41)	13 (5)	
Primary	666 (56)	156 (67)	197 (75)		191 (42)	122 (51)	
Secondary+	280 (24)	50 (22)	49 (19)		76 (17)	105 (44)	
Marital status				0.24			0.01
Single never married	359 (31)	67 (29)	75 (29)		158 (35)	59 (25)	
Married	275 (23)	104 (45)	135 (51)		24 (5)	12 (5)	
Single ever married	549 (46)	60 (26)	53 (20)		267 (60)	169 (70)	
Occupation				< 0.01			0.22
Small scale business	147 (12)	54 (23)	70 (27)		13 (3)	10 (4)	
Fishing/related	259 (22)	104 (45)	155 (59)		–	–	
Hotel/bar/hair saloon	298 (25)	41 (18)	22 (8)		144 (32)	91 (38)	
Sex work	425 (36)	–	–		289 (64)	136 (57)	
Other	54 (5)	32 (14)	16 (6)		3 (1)	3 (1)	
Duration (years) in community				< 0.01			< 0.01
0–1	306 (26)	70 (30)	44 (17)		156 (35)	36 (15)	
> 1	877 (74)	161 (70)	219 (83)		293 (65)	204 (85)	
Illicit drug use				0.53			0.95
No	572 (48)	207 (90)	231 (88)		87 (19)	47 (20)	
Yes	611 (52)	24 (10)	32 (12)		362 (81)	193 (80)	

FF Fisherfolk, *FSW* female sex worker, *SiVET* simulated vaccine efficacy trial

Risk Indicator Characteristics at Baseline and 12 Months

Reported participant behavior/characteristics at baseline and 12 months are shown in the bar graph, Fig. 2. For the FF population, the baseline components were broadly comparable between the non-SiVET$_1$ and SiVET$_1$ cohorts, except for the proportion of participants reporting more than one sexual partner, which was higher in the SiVET$_1$ (71%) compared to the non-SiVET$_1$ (57%). At 12 months of follow up, the two groups were largely similar, except for having genital ulcer/sores (20% vs 10%), reporting new sexual partners (46% vs 37%) and non-condom use with new sexual partner (52% vs 37%) that were all higher in non-SiVET$_1$ compared to SiVET$_1$. Similarly, in the FSW population the baseline components were comparable



M-Month of follow up	M0	M12	M0	M12	M0	M12	M0	M12
Daily alcohol use (%)	7	4	11	8	58	58	28	29
Alcohol use before sex (%)	2	2	3	1	1	1	6	0
Genital discharge (%)	51	18	42	16	23	20	29	20
Genital ulcer/sores (%)	41	20	43	10	39	34	16	12
>1 sexual partners (%)	57	27	71	35	92	91	99	83
Having a new sexual partner (%)	69	46	76	37	79	80	92	74
Non condom use with new partner (%)	65	52	65	37	26	30	1	3

Fig. 2 Proportion of risk component measures at baseline and 12 months in the non-SiVET and SiVET cohorts among the key populations in Uganda

Table 4 Risk score at baseline and 12 months of follow up stratified by study cohort and population (means and medians)

Population	Study	Risk score at baseline				Risk score at 12 months			
		Mean	SD	Median	IQR	Mean	SD	Median	IQR
FF	Non-$SiVET_1$	7.7	3.9	8	5–10	5.1	3.6	4	2–7
	$SiVET_1$	8.8	3.6	9	6–11	4.8	3.2	5	2–7
FSW	Non-$SiVET_2$	8.7	2.7	9	7–10	8.5	2.5	9	7–10
	$SiVET_2$	11.4	3.1	9	8–13	9.5	3.8	10	7–12

FF Fisherfolk, *FSW* female sex worker, *SiVET* simulated vaccine efficacy trial, *SD* standard deviation, *IQR* interquartile range

between the non-$SiVET_2$ and $SiVET_2$ populations, except for reported daily alcohol use (58% vs 28%), genital ulcer/sores (39% vs 16%) and non-condom use with new sexual partner (26% vs 1%) that were all higher in the non-$SiVET_2$ (Fig. 2). At 12 months of follow up, the differences between non-$SiVET_2$ and $SiVET_2$ seen at baseline remained.

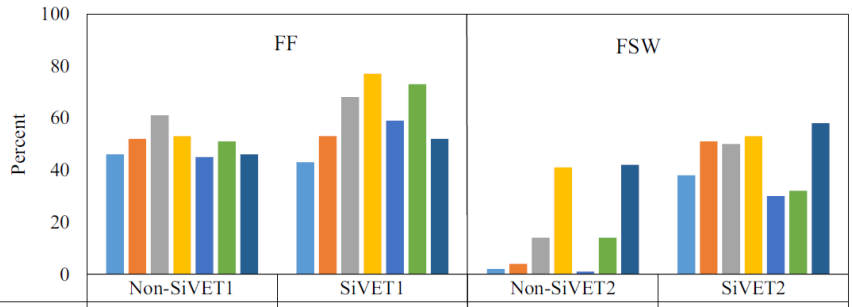
Composite Risk Score

The composite risk scores for each cohort, and stratified by study population, are shown by means and medians in Table 4. In both cohorts, the mean risk score was higher in the SiVET than the corresponding non-SiVET at baseline; in the FF population, this situation had reversed in the 12 months of follow up.

Decrease in Risk Score Between Baseline and 12 Months of Follow-Up

Overall, 170 (73.6%) of the participants in the non-$SiVET_1$ and 214 (81.4%) in the $SiVET_1$ cohort in the FF population experienced a decrease in risk score ($p=0.038$). Similarly, 197 (43.9%) of the participants in the non-$SiVET_2$ compared to 149 (62.1%) in $SiVET_2$ cohort in the FSW population experienced a decrease in risk score, $p<0.001$.

The bar graph, Fig. 3 shows the proportion of participants whose individual component risk scores at 12 months decreased from that at baseline. In the FF population, there was generally a large decrease, of 40% or more, in the risk score for all components in both non-$SiVET_1$ and $SiVET_1$. The difference between non-$SiVET_1$ and $SiVET_1$ cohorts were observed mainly in the



	Non-SiVET1	SiVET1	Non-SiVET2	SiVET2
Daily alcohol use (%)	46	43	2	38
Alcohol use before sex (%)	52	53	4	51
Genital discharge (%)	61	68	14	50
Genital ulcer/sores (%)	53	77	41	53
>1 sexual partners (%)	45	59	1	30
Having a new sexual partner (%)	51	73	14	32
Non condom use with new partner (%)	46	52	42	58

Fig. 3 Proportion of participants with decrease in the score of a given risk component measure between baseline and 12 months among the key populations in Uganda

proportion with decreased genital ulcer/sores (53% vs 77%) and those reporting new sexual partners (51% vs 73%).

In the FSW population there were generally smaller decreases (typically less than 15%) in the risk score in the non-$SiVET_2$ for most components except for genital ulcer/sores and non-condom use with a new sexual partner that declined by about 40%. On the other hand, the decreases in risk score were over 30% for all components in the $SiVET_2$ cohort. Comparing non-$SiVET_2$ to $SiVET_2$, the proportion of decreased risk score were higher in $SiVET_2$ for all components.

Regression Analysis of Risk Score at 12 Month

Table 5 shows the results of linear regression models comparing non-SiVET to corresponding SiVET cohort at 12 months of follow up adjusted for baseline risk score and other factors shown in the table. Overall, in the FF population, the predicted mean risk score for $SiVET_1$ at 12 months was 0.63 points lower (95% CI – 1.18 to – 0.08, p = 0.024) than for non-$SiVET_1$ after adjustment for factors shown in Table 5. In FSW it was 0.10 points lower (95% CI – 0.58 to 0.39, p = 0.692) for $SiVET_2$ than non-$SiVET_2$ after adjusting for factors shown in Table 5. In the FF population, the predicted mean risk score for females was 1.65 points lower (95% CI – 2.24 to – 1.05, p < 0.001) than males.

Results of the sensitivity analyses

Linear regression models comparing non-SiVET participants (not screened because of SiVET recruitment accrual) to SiVET and SiVET screen failures and adjusting for the factors in Table 5 were applied separately to each of the two subpopulations. Compared to the non-SiVET participants in the FF population; the predicted mean risk score was 0.75 points lower (95% CI – 1.31 to – 0.20, p = 0.004) in SiVET participants, and 1.94 lower (95% CI – 3.60 to – 0.29, p = 0.021) in SiVET screen failures. Similarly, in the FSW compared to non-SiVET participants, the predicted mean risk score was 0.05 points lower (95% CI – 0.57 to 0.46, p = 0.836) in SiVET participants but 0.52 points higher (95% CI – 0.27 to 1.32, p = 0.198) in the SiVET screen failures.

In a further sensitivity analysis of the adjusted linear regression models stratified by sex in the FF population, comparing non-SiVET participants to SiVET ones, the predicted mean risk score for SiVET was 1.24 points lower (95% CI – 2.01 to – 0.48, p = 0.002) for the men and 0.67 points lower (95% CI – 1.41 to – 0.08, p = 0.080) for the women. All results and adjustment risk factors are shown in Supplementary Table 7.

Discussion

In this paper, we compared behaviors of people recruited into simulated HIV vaccine efficacy trials with people who remained in the observational cohorts in which the trials

Table 5 Unadjusted and adjusted factors associated with decrease in risk score among key populations in Uganda, linear regression models results

Variable	FF (N = 494)				FSW (N = 689)			
	Uncoef (95%CI)	p-value	aCoef (95%CI)	p-value	Uncoef (95%CI)	p-value	aCoef (95%CI)	p-value
Study								
Non-SiVET	Ref		Ref		Ref		Ref	
SiVET	−0.63 (−1.18 to −0.08)	0.024	−0.92 (−1.47 to −0.37)	0.001	−0.10 (−0.58 to 0.39)	0.692	−0.12 (0.63 to 0.38)	0.625
Sex								
Male	Ref		Ref		–	–	–	–
Female	−1.55 (−2.11 to −0.98)	< 0.001	−1.65 (−2.24 to −1.05)	< 0.001				
Age (years)								
18–24	Ref		Ref		Ref		Ref	
25–34	0.25 (−0.36 to 0.86)	0.425	0.09 (−0.51 to 0.69)	0.764	0.09 (−0.38 to 0.56)	0.697	0.09 (−0.41 to 0.59)	0.729
35 +	−0.23 (−0.99 to 0.52)	0.544	−0.24 (−0.99 to 0.50)	0.522	0.07 (−0.54 to 0.69)	0.810	0.14 (−0.52 to 0.79)	0.686
Ethnicity								
Baganda	Ref		Ref		Ref			
Banyankole	0.65 (−0.20 to 1.50)	0.132	0.43 (−0.40 to 1.25)	0.310	−0.26 (−0.89 to 0.36)	0.412		
Banyarwanda	−0.26 (−0.96 to 0.45)	0.478	−0.14 (−0.83 to 0.55)	0.694	−0.09 (−1.04 to 0.86)	0.849		
Other	0.39 (1.13 to 2.55)	0.300	0.22 (−0.50 to 0.93)	0.553	0.35 (−0.14 to 0.83)	0.159		
Religion								
Christian	Ref				Ref			
Muslim	−0.31 (−0.96 to 0.33)	0.337			−0.01 (−0.51 to 0.49)	0.968		
Education								
None	Ref				Ref			
Primary	−0.10 (−1.09 to 0.89)	0.842			0.26 (−0.25 to 0.77)	0.317		
Secondary +	−0.55 (−1.67 to 0.57)	0.337			−0.15 (−0.72 to 0.43)	0.614		
Marital status								
Single never married	Ref				Ref		Ref	
Married	−0.42 (−1.07 to 0.22)	0.197			−1.03 (−2.03 to −0.04)	0.042	−1.15 (−2.17 to −0.14)	0.026
Single ever married	−0.29 (−1.05 to 0.47)	0.456			0.003 (−0.46 to 0.46)	0.989	−0.14 (−0.65 to 0.37)	0.599
Occupation								
Small scale business	Ref				Ref		Ref	
Fishing/related	0.64 (−0.03 to 1.31)	0.060			–		–	
Hotel/bar/salon	−0.37 (−1.30 to 0.56)	0.434			−0.59 (−1.80 to 0.62)	0.339	−0.56 (−1.78 to 0.66)	0.368
Sex work					−0.21 (−1.40 to 0.97)	0.726	−0.16 (−1.35 to 1.04)	0.798
Other	−0.48 (−1.50 to 0.55)	0.360			−1.33 (−3.87 to 1.21)	0.304	−1.27 (−3.82 to 1.27)	0.326
Duration (years) in community								

Table 5 (continued)

Variable	FF (N = 494)				FSW (N = 689)			
	Uncoef (95%CI)	p-value	aCoef (95%CI)	p-value	Uncoef (95%CI)	p-value	aCoef (95%CI)	p-value
0–1	Ref				Ref		Ref	
> 1	0.41 (−0.24 to 1.05)	0.217			0.30 (−0.17 to 0.77)	0.213	0.31 (−0.18 to 0.80)	0.209
Illicit drug use								
No	Ref		Ref		Ref			
Yes	1.06 (0.19–1.94)	0.017	0.78 (−0.07 to 1.63)	0.073	−0.29 (−0.82 to 0.24)	0.288		

FF Fisherfolk, *FSW* female sex worker, *SiVET* simulated vaccine efficacy trial, *CI* confidence interval, *Uncoef* unadjusted linear regression model coefficient, *aCoef* adjusted linear regression model coefficient, *p value* statistical significance, *Ref* reference category

were nested. The cohorts consisted of fisherfolks and female sex workers in Uganda. We found that the proportion of participants whose composite HIV risk score decreased was higher among participants who enrolled in SiVETs. Generally, the proportion of participants with decreased risk score were lower among FSW than FF; conversely, the difference between SiVET and non-SiVET cohorts was greatest in the FSW population. The results from the linear regression analysis suggested that participation in a SiVET was independently associated with a decrease in composite risk score in both populations; however, there was only good statistical evidence for this among FF. This result is consistent with previous trials, which reported participants' engagement in lower HIV risky behaviors during trial follow up beyond that observed in the source population [20–22].

In the FF population, women were more likely than men to report a decrease in HIV risk behaviors. Literature shows that women in Sub Saharan Africa [31] have better health seeking behaviors and they could have been more likely to respond to the HIV risk reduction measures provided in these cohorts.

Although the observational cohorts were the recruitment source for the SiVETs, screening and enrollment was consecutive and not random; thus participants' baseline characteristics between SiVET and non-SiVET cohorts differed in some important ways in both populations. SiVETs recruited more men ($SiVET_1$ in FF), more participants aged 35 or over, more educated participants ($SiVET_2$ in FSW) and more people who had lived in the community for longer than 1 year. Previous studies have highlighted the significant selection differences between clinical trials and source population and its effect on the trial outcomes [19–21, 32].

Clinical trials of active interventions have shown a 50% to 78% reduction in HIV incidence in the control arm compared to that predicted from the source population [20–22]. This led to many of these trials ending early due to futility. Similarly, previous publications from these SiVETs [9, 13] in FF and FSW populations have indicated a 40% to 50% reduction in HIV incidence in those recruited into the trial compared to the source population, even though the Hepatitis B vaccine used in the SiVETs had no effect on HIV susceptibility.

It is possible that consecutive screening and enrolment into SiVET included more of the participants that were likely to report on time for study visits and adhere to HIV risk reduction measures. The engagement with less risky behaviors might lower the risk for HIV infection in intervention trials for reasons unrelated to the product being tested. In the FF population, individual HIV risk components generally decreased between baseline and 12 months, more so in the SiVET cohorts. More notable was a decrease in 'condomless' sex with a new sexual partner. This was more marked in the SiVET, about 43% decrease as opposed to 20% in non-SiVET cohort. Though not documented at interim clinic visits, SiVET participants had more access to condoms because of the more clinic visits.

On the other hand, in the FSW population, there were marginal decreases in individual reported risk behavior in the SiVET cohort and very minimal to none in the non-SiVET cohort. This could be associated with the occupational demands of sex work as the livelihood of 100% of these cohort participants depended on high-risk behavior. Unlike the FF population, the FSW population was comprised of females and only male condoms were provided for use with male sexual clients. Literatures in Africa shows that, females have limited power in relationships to demand condom use [33]. Furthermore, studies in female sex workers population in Africa [34] and elsewhere [35–37] have shown that 'condomless' sex attracted more pay. This could hamper decreases in 'condomless' sex with new or other causal sexual partners as seen in this population.

Our analysis has a number of strengths that included a reasonable sample size, two distinct key populations in which SiVET and non-SiVET cohorts were aligned to a set duration of time. Both SiVET and corresponding non-SiVET cohorts' participants were seen at the same

clinic by the same study staff under standardized study procedures. All staff were trained on both studies, and study visits and conduct were done per Standard Operating Procedures to assure data were collected in a systematic manner. Our comparative analysis is not without limitations, however. SiVET cohorts were more likely to screen and enroll participants that reported on time for their 3 to 18 months source cohort clinic visit. It is possible that timely participants are also more inclined to take up the HIV behavioral risk reduction measures or are otherwise more compliant with study instructions. The study procedures in the SiVET and non-SiVET cohorts were not blinded. However, at the time of the conduct of SiVETs, the primary aim was not to compare SiVET to non-SiVET participants and if there were any differences in the conduct of study procedures, they were likely modest unconscious biases, and are unlikely to have affected the outcomes considered in this analysis. Participants were encouraged to take more condoms in case their stock was finished before the next scheduled clinic visits and we did not document the data on condom demands on visits that HIV risk behavior assessment was not scheduled. This could have helped explain the more marked increase in condom use with a new sexual partner seen in the SiVETs cohort because participants in this cohort had more of such visits. Notwithstanding these limitations, our comparative analysis gives a rare opportunity of estimating the likely drop in HIV risk components in trials nested within source cohorts in two distinct key populations.

In conclusion, results from both key populations suggest that participation in both studies positively affected risk-taking behavior, and in some cases, this was more pronounced in a "Simulation trial" conducted alongside an observational study aligned to the same duration of time. Previous publications from these populations have shown lower HIV incidence in SiVET cohorts compared to non-SiVET cohorts even when aligned to the same duration of follow up. Other studies have also shown lower HIV incidence in the trial control arm compared to that predicted from observational data at the trial on set. Therefore, it is likely that participants who join trials are mostly those likely to respond to HIV risk reduction measures beyond what is seen in source population or the general population. While the more than half drop in the HIV risk score in FF and one third in FSW participating in SiVETs is of great public health importance, investigator-recruiting participants into clinical trials from observational cohorts in these key populations need to consider the likely effect of reduction in HIV risk components on likelihood of seroconversion and the trial statistical power. Taking the results of this analysis and previous publications on HIV incidence from these SiVETs and non-SiVET cohorts, it is encouraging that these key populations could still be suitable for HIV vaccine efficacy and other HIV prevention trials.

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Author Contributions AA: Lead Author, drafted initial manuscript draft, carried out data management, analysis and interpretation. SN contributed to data analysis and interpretation. YM: contributed to the design of the $SiVET_2$ protocol, study coordination (Observational cohort in FSW and $SiVET_2$), MP: contributed to the design of both SiVETs and the observational cohort in FF and interpreted the data, PEF: contributed to the design of both SiVETs and the observational cohort in FF and interpreted the data. PK: directed the implementation of both observational cohorts and SiVETs. JT contributed to data analysis and interpretation. All authors critically commented, provided revisions to the manuscript and approved the final version for submission.

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Data Availability The MRC/UVRI and LSHTM Uganda Research Unit encourages open data access and has a data sharing policy accessible at https://www.mrcuganda.org/publications/data-sharing-policy. The policy summarizes the conditions under which data collected by the Unit can be made available to other bona fide researchers, the way in which such researchers can apply to have access to the data and how data will be made available if an application for data sharing is approved. Should any other researchers need to have access to the data from which this manuscript was generated, the processes to access the data are well laid out in the policy. The corresponding and other co-author emails have been provided and they could be contacted anytime for further clarifications and/or support to access the data.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Ethical Approval The Uganda Virus Research Institute (UVRI) Research and Ethics Committee (GC127, GC/127/14/04/454, GC/127/12/04/22 and GC127/12/06/01) and the Uganda National Council for Science and Technology (MV834, HS364 and HS1584) approved the conduct of non-SiVET and SiVET cohorts in both key populations. The London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee (LSHTM14588) approved the proposal leading to this comparative analysis.

Informed Consent We obtained written informed consent from each participant before enrolment into the non-SiVET and SiVET cohorts.

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Chapter 8: Discussion

8.1 Introduction

The planning of HIV vaccine efficacy trials in the fisher-folk (FF) and female sex workers (FSW) populations in Uganda will require accurate estimation of the trial targeted outcome components and other key elements. These will include (a) HIV incidence in the control (placebo) arm, (b) retention, (c) reliable contraceptives use to prevent pregnancy and (d) the expected reduction in HIV incidence due to vaccination (treatment effect). This thesis covers components/elements (a) to (c). The common practice (source of these components/elements) includes adopting these from previous efficacy trials in the target population.

8.2 Estimation of HIV efficacy trial control arm HIV incidence in FF or FSW in Uganda

To date, no HIV vaccine efficacy or other prevention trials have completed follow up in the FF on the shore of Lake Victoria or FSW population in Kampala, Uganda. Therefore, data on assumed HIV incidence in the control arm of anticipated HIV vaccine efficacy trial will have to come from historical observational or pilot cohorts in these key populations.

8.3 Challenges of using observational studies HIV incidence to plan efficacy trials

Extrapolation of observational data to plan efficacy trials is complicated and needs to be done with caution to minimize selection bias. Observational data on HIV incidence may not accurately estimate that in an efficacy trial because of the differences in selection criteria and the highly controlled trial environment. Efficacy trials select participants who fulfill the trial inclusion criteria including among others; willingness to attend all trial clinic visits, if female accepting reliable contraceptives use in the duration of follow, and conforming to the use of HIV risk reduction measures provided. Such selection requirement many include into trial participants with HIV risk profile different from those excluded. This may affect HIV incidence in the trial adopted from observational data, even in absence of an effective investigational product.

8.4 Simulated vaccine efficacy trials

A simulated vaccine efficacy trial is a trial which mimics an actual efficacy trial but uses a commercially licensed vaccine instead of an experimental one. It is conducted in the same manner as an actual efficacy trial in all other respects. The concept of simulation trials has been previously

used in a population where no baseline data was available to aid planning of trials (67). Similarly, this concept was used in the FF and FSW populations in Uganda, primarily to provide accurate data on participant retention in a vaccine efficacy trial specific context. Data from these simulation trials was used to investigate these PhD questions/objectives. (a) how HIV incidence in a simulation trial might differ from that in observational cohorts, in which the trials were nested in the FF and FSW populations in Uganda, (b) use of reliable contraceptives by female participants, (c) participant retention in follow up and (d) participant response to other HIV risk reduction measures.

8.5 HIV incidence in vaccine efficacy trials in FF and FSW in Uganda

The first key step in planning HIV vaccine efficacy trial in these populations is accurate estimation of HIV incidence in the control (placebo) arm. To provide such data for FF on the shoreline of Lake Victoria and FSW in Kampala, Uganda, the HIV incidence observed in simulation trials was compared to that seen in observational cohorts in the same population in the three time periods: pre-trial, concurrent, and post-trial. Results suggested that HIV incidence in the simulation trials was lower than that in the observational cohorts in the pre-trials and the trials concurrent period but tended to be similar to that in the observational cohorts in the 12 months post-trials period.

Table 5: HIV incidence pre, during and post simulation trial and stratified by the study population

	Pre-trials	Concurrent		Post-trials
		Observational data	Simulation trials data	
Target population	Incidence (95%CI)	Incidence (95%CI)	Incidence (95%CI)	Incidence (95%CI)
Fisher-folk	4.9 (3.9-6.2)	8.3 (5.6-12.4)	3.8 (2.0-7.1)	4.1 (2.3-7.3)
FSW	4.0 (2.9-5.5)	4.1 (2.5-6.7)	3.2 (1.5-6.6)	3.4 (1.8-6.5)
Overall	4.5 (3.8-5.5)	5.9 (4.3-8.1)	3.5 (2.2-5.6)	3.7 (2.5-5.8)

FSW: Female sex work, CI: Confidence Interval

The difference in HIV incidence between the source observational cohort and simulation trial was highest in the Fisher-folks population.

8.6 Likely reasons for lower incidence in the simulation trials

The reasons for the lower incidence in the Simulation trial as opposed to observational studies could be (1) selection differences at enrolment, (2) different environment in that the trial encouraged the participants to engage in HIV prevention, (3) follow-up differentials (retention),

and (4) Chance (not covered in this thesis). These may not be mutually exclusive. The reasons (1-3) correspond to the three papers presented in chapters 4, 6 and 7.

8.6.1 Selection differences at enrolment

Results in these papers suggest differences in the participants' characteristics between those who joined the simulation trials and those that did not. The observational cohorts in FF and FSW populations were the participants' recruitment source for the simulation trials in these key populations, however, participants that entered trials differed from those that did not in some important ways. The proportions of participants with characteristics (male (FF only), age >25 years, with some formal education and more than one year in community) previously associated with lower risk of HIV acquisition (27, 28, 30, 66, 79-82) were higher in the simulation trials. The differences in volunteer characteristics between clinical trials and source populations and their effect on HIV incidence are previously highlighted (39, 64).

8.6.2 Trial environment

Reduction in HIV incidence in the trials could also be attributed to the controlled environment of the trial. This has previously been associated with more than a 50% reduction (from that seen in the underlying cohort) in HIV incidence in the control arm during follow up (38, 39, 42). These trials were prematurely terminated. The investigators attributed the reduction in incidence to participants' vigorous response to HIV risk reduction measures and inclination to safer HIV risk behaviours during follow up. In our simulation trials, we provided a wide range of HIV risk reduction measures including HIV counseling and testing, counselling on concurrent multiple sexual partners, condom use, faithfulness to one partner, provided free condoms, actively diagnosed and treated sexually transmitted and other genital infections. While participants in the observational cohorts also received these interventions, the frequency of their provision was lower, they only received condoms on request and no active diagnosis and treatment for STIs and other genital infections was done. As presented in chapter 7, we observed greater decreases in HIV risk behaviours in the simulation trials compared to observational cohorts in both key populations. These HIV risk reduction measures, when applied to an HIV vaccine efficacy trial planned in these key populations, could lower the risk of HIV infection during participant follow up even in the

absence of an effective HIV vaccine. If their effect on HIV incidence is not carefully adjusted for at the trial planning stage, it could diminish statistical power.

8.6.3 Follow up differentials (retention)

Our simulation trials aimed at providing context-specific information on trial dropout for FF and FSW populations. In these simulation trials, we found that the dropout rate in the trials was nearly half that in the source observational cohorts in the same population and aligned to the same duration. The lower dropout rate in the trials could be attributed to the enhanced follow up procedures. Simulation trials participants were reminded of their next scheduled clinic visit at least two days in advance, and were picked up by a trial staff on a motor cycle or vehicle if they needed help to access the clinic for their visits. Such strategies in trials have been previously associated with high retention during follow up among the Fisher-folks (83) and other populations (84). Furthermore, Literature shows that participants at higher risk of HIV infection are also more likely to dropout of longitudinal studies which could lead to inaccurate estimation of HIV incidence in the underying population (33, 85).

Similar differences in dropout between non-SiVET and SiVET were observed when the analysis considered time to dropout approach. The plot of a Kaplan Meier gave extra evidence that most of the study participant dropout happened either early in the study or later on during follow up. Early dropout from the study could affect study internal validity and factors leading to early or mid-study dropout might be different from those associated with late dropout. Early study dropout (baseline dropout) may be associated with a passive resistance to participation by those who find it difficult to refuse outright. On the otherhand, late study attrition may be associated with individual participant experiences with the study including among others having suffered an adverse event. Both early and late dropout negatively affect the trial statistical power. Either stage of trial dropout could led to having lower number of person time of follow up required to evaluate the treatment effects between active and control arms with greater effects linked to early dropout.

8.6.4 Access to pre exposure prophylaxis (PrEP)

PrEP is new HIV prevention modality that is now a standard part of HIV prevention trials. We were not able to assess PrEP access in the SiVETs and it is unlikely that participants in these communities accessed PrEP. PrEP provision in HIV vaccine efficacy trials anticipated in these

communities will likely further push HIV incidence rates down, calling for increases in the trial size. Given how compliance with PrEP has been so problematic (86), it is unclear how much HIV incidence might drop (i.e., how good PrEP uptake and compliance will be); some PrEP trials (87) and programmes (88-90) have shown very high compliance with PrEP being associated with HIV incidence rates plummeting. Figuring out how to implement this in the African context (specifically among FF and FSW), would certainly impact trial size and planning.

8.7 Impact of these findings on planning for an HIV vaccine efficacy trial

Putting the observed results in the context of an actual HIV vaccine efficacy trial, the results overall suggested that using HIV incidence and retention from observational studies to plan an HIV vaccine efficacy trial as opposed to using simulation trial incidence and retention would underestimate the trial sample size by about one-quarter and achieve a statistical power of 68%. When stratified by the source population, the underestimation of the study size was highest in the Fisher-folk population. The simulation trials in both key populations provided a benchmark HIV incidence and retention that could be a useful aid when planning HIV vaccine efficacy trials in these and similar populations.

8.8 Reliable contraceptives use

The other key element in planning HIV vaccine efficacy trial is the adequate use of reliable contraceptives by female participants to avoid pregnancy during follow up. HIV vaccine efficacy trials take months from recruitment to completion of follow up and women could become pregnant and have to withdraw. More withdrawals than anticipated could affect trial statistical power. Use of reliable contraceptives in trials to prevent the foetus from exposure to investigational products whose effects are unknown has become a key inclusion criterion (61). This requirement could make it difficult to recruit women into HIV vaccine efficacy trials in FF and FSW populations because of cultural beliefs and myth about contraceptives in Africa (91-99).

Completed HIV vaccine efficacy trials have shown low baseline reliable contraceptives use with limited data on uptake during follow up and high incidence of pregnancy (55). In these simulation trials in the FF and FSW in Uganda, we found that only one in every two women were using a reliable contraceptives method at baseline, and this improved to nine in every ten women at the end of follow up as a result of promotion and provision of reliable methods. Acceptance to use of

reliable contraceptives was a key inclusion criterion in our simulation trials unlike in previous HIV vaccine efficacy trials. Furthermore, in the FSW population, pregnancy affects the source of livelihood hence the huge motivation to use reliable contraceptives beyond that seen in the fisher-folks or previous trials that recruited women from the general population.

There is a perception that women in these key population may be difficult to recruit into longitudinal studies where use of reliable contraceptives is key (100, 101). However, in our SiVETs, 80% of the screened women were enrolled and only under 2% of the women were excluded because of unwillingness to use a reliable contraceptive method. Accurate messaging and meeting the unmet need of contraceptives in these key populations could have played a role. Accurate information about contraception has been associated with improved contraceptives uptake in the previous HIV prevention trial recruiting HIV serodiscordant couples (51). More interesting, we are only aware of eleven women who became pregnant during follow up and seven of these were on reliable contraceptive methods. Four of the seven were on injectable DMPA and had delayed an injection by about a month; while three used pills. The challenge with use of pills in trials is previously documented (102). In these previous trials, women using pills had a pregnancy rate more than three times higher than average, mainly attributed to poor adherence.

8.9 Study strengths

Strengths of this study include: large sample sizes; two distinct key populations in different geographical locations; aligning both the simulation trial and observational cohort to the same duration of follow up in a concurrent period; and same study staff attending to the participants in both studies (simulation trial and source observational cohort in a given population). Additionally, promotion and provision of reliable contraceptives in the context of HIV vaccine efficacy trial, counselling women on the importance of reliable contraceptives use and providing them with a method of their choice. Lastly, we allowed a run-in period of at least three months participation in the source cohort mimicking a screening enrolment time lag in an actual HIV vaccine efficacy trial.

8.10 Study limitations

Although HIV vaccine efficacy trials in these key populations will be expected to have a participant run in period, it might not be up to three months. Selection bias (inform of self-selection

or the study teams recruiting into the simulation trials mostly participants that came on time for their source observational cohort visits) could have played a role in the participant recruitment. This could have led to selection of participants mostly from low HIV risk groups such as long-term residents and those easier to keep in follow up. Even then, actual HIV vaccine efficacy trials anticipated in these populations are expected to recruit participants that confirm availability for follow up in the trial duration and presenting for recruitment in a given screening-enrolment window period when results of screening are still valid. Simulation trials participants were fully informed that the vaccine being administered has no effect on their risk of HIV infection but prevented acquisition of hepatitis B virus. This could have enhanced continued trial attendance in a country where the burden of Hepatitis B is high (103). Nonetheless, in an actual HIV vaccine efficacy trial, participants are expected to be informed of accurate information about the candidate product. Notwithstanding these limitations, these studies provided for the first time a rare opportunity for estimating HIV vaccine efficacy trial targeted outcomes in a trial specific context in two distinct key populations in Uganda.

8.11 Conclusion

In summary, we observed in our cohorts that individuals in FF and FSW populations that volunteer to join trials are different from those that do not. This difference together with trial environment lead to lower HIV incidence in the trials even in absence of an effective investigational product. Promotion and provision of reliable contraceptives and counselling on their use more than double the proportions of women using them during trial follow up from that recorded at baseline. Enhanced retention strategies improve retention of volunteers in these highly mobile populations. Lastly, HIV risk reduction measures provided in the simulation trials decreased the proportion of participants engaging in high HIV risk behaviours. Interestingly, the HIV incidence in these key populations remains high, in an era of wide spread use of antiretroviral treatment, and while reduced in the simulation trials, it is still suitable for actual HIV vaccine efficacy and other intervention trials in these and similar key populations.

8.12 Recommendations

- HIV incidence and dropout in the SiVETs in these and similar key populations where no previous efficacy trials have been conducted should be used to estimate sample size for future HIV vaccine efficacy trials.
- In similar populations where there is no SiVET data or data from previous efficacy trials, we recommend use of observed incidence and dropout in observational data but decreasing this incidence and dropout by 25% and 40% respectively to accommodate for the likely lower incidence and dropout in trials.
- To improve study completion in these populations, an investigator needs a phone contact of a participant's neighbor or someone that knows about a participant's whereabout at all times. This will help to improve participant tracing.
- Helping participants to access the trial clinic by way of providing physical transport using motor cycle or motor vehicle will improve trial completion in these key populations.
- We recommend use of FF and FSW populations in Uganda as source populations for HIV vaccine and other efficacy trials targeting women because of the high screening-enrolment ratio, high reliable contraceptives uptake and use, and low pregnancy incidence.
- In the FF and FSW and similar key populations, it is not necessary to put women on reliable contraceptives for atleast three months before screening for trial enrolment instead these should happen concurrently.

8.13 Future work

Further work planned in these observational cohorts and SiVETs includes using propensity score matching to segregate the effect of the difference in participant characteristics between SiVET and non-SiVET on HIV incidence from that of trial environment.

Appendix One: LSHTM Ethical Approval Notification

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Observational / Interventions Research Ethics Committee

Mr Andrew Abaasa
LSHTM
13 November 2017
Dear Mr. Andrew Abaasa

Study Title: Using observational cohort data from Key populations to plan HIV intervention studies
LSHTM Ethics Ref: 14588

Thank you for your application for the above research project, which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion
Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Local Approval	GHWP UVRIREC approval	21/09/2007	1.0
Consent form	IAVI_VPS ICD	17/05/2012	4.0
Local Approval	SiVET TWO UVRIREC approval	07/01/2014	1.2
Consent form	SiVET Nested in GHWP ICD	07/03/2014	1.0
Consent form	GHWP ICD	09/03/2015	1.2
Local Approval	IAVI_VPS & nested SiVET one approvals	22/09/2016	2.0
Protocol / Proposal	Andrew Abaasa proposal	01/10/2017	1.0
Investigator CV	Andrew Abaasa CV	30/10/2017	1.0

After ethical review
The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study. At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk. Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Appendix Two: Studies information sheets and informed consents

INFORMED CONSENT FOR SCREENING/ENROLLMENT INTO THE A SIMULATED VACCINE EFFICACY TRIAL AMONG WOMEN OF GOOD HEALTH WOMEN PROJECT IN KAMPALA

Information sheet and consent form for screening and enrolment into a simulated vaccine efficacy trial among women of Good Health Women Project in Kampala

Title: Participation In a simulated vaccine efficacy trial among women of Good Health Women Project in Kampala

1. Why is this study being done?

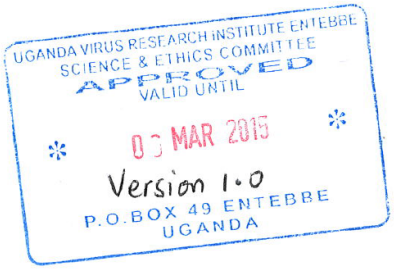
MRC/UVRI collaboration with the International AIDS Vaccine Initiative (IAVI), has been conducting HIV Vaccine Preparatory Studies since 2004 to determine the suitability of communities in Uganda for future HIV vaccine efficacy trials. We have interesting results showing that it may be feasible for some communities to participate in future HIV vaccine studies. However, we would like to further learn if communities can participate in studies that mimic actual HIV vaccine studies. This will provide useful information which will allow us plan how best to work with these communities in actual HIV vaccine trials when the vaccines become available. In this study, volunteers will be receive vaccination for hepatitis B at designated time points and followed for one year. Hepatitis B is a virus which infects the liver and can cause long term damage to the liver. It is acquired through sexual intercourse, needle injuries, from mother to baby, the same way HIV is transmitted. A vaccine to prevent hepatitis B is available and registered for use. Since we still do not have an HIV vaccine available for HIV vaccine efficacy trials yet, we will use the Hepatitis B vaccine to mimic an HIV vaccine efficacy trial. This vaccine may also help to protect you against hepatitis B infection.

2. Why have I been chosen to take part in the study?

You have been selected because you live or work in Makindye/Rubaga division and you have regularly been participating in the MRC/UVRI Research for six months or more. Though you have been participating in other on- going research we ask you to familiarize yourself with this new study, and ask any questions you have.

3. What will happen to me if I decide to take part in the study?

You can choose to take part in the study or not. If you choose not to take part in the study, there is no problem. If you choose to take part, you will sign your name or make your thumb print mark on 2 copies of this informed consent document to confirm that you voluntarily agree to take part in this study. One copy will be given to you and one will be kept at the MRC/UVRI Uganda Research Unit on AIDS at Kampala. If you do not wish to keep your copy, it will be kept for you at the research centre in a secure place. You may bring a person with you to help you understand the study and to witness that you understand and agree with participating in the study. We are requesting your participation in a study involving blood samples as well as medical information. Your blood samples contain genes which we will study. Your genes are made up of DNA which serves as the "instruction book" for the cells that make up our bodies. Your samples and medical information will help us study how genes interact with other factors that influence how your body responds to vaccination.



Soura Dot.
[redacted]
07.03.14

If you qualify for the study, you will undergo the following procedures:

Study screening and enrolment:

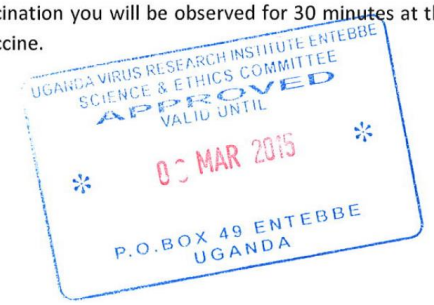
- At the first visit, study staff will assess your eligibility for the study. You will also be asked questions about behaviours that may increase your chance of catching HIV. If you refuse or fail to join the study, reasons for this will be documented.
- About 3 table spoons of blood will be drawn from a vein in your arm.
- Your blood will be tested for HIV and for evidence of hepatitis infection. If any of thse tests shows evidence of infection you will be counselled about their results. If your test results show that you are not infected with HIV, you may be eligible to enrol into this study.

If your test results show that you are infected with HIV at screening:

- You will be given counselling on HIV, what this means for sexual partner or partners and family members, and how to avoid giving HIV to others in future.
- You will be asked about your health. An examination may be done to find out if you have any medical problems. You may be asked about any illnesses you have had in the past three months.
- Your blood may be tested to find out what your blood counts are, how your liver and kidneys are functioning and your CD4 count. An additional ½ table spoon of blood will be requested from you for these tests. These results will be provided to you so that you can discuss with MRC/UVRI doctors within our clinic here at Kampala.
- You will be offered additional care if necessary. If you are pregnant, you will be offered care and your baby and enrolled into the "Elimination of Mother to Child Transmission" (PMTCT) program where you may get medicines that can help prevent your baby from getting HIV.
- You would not be enrolled into this study.

If you are not infected with HIV and do enrol in this study

- Study staff will ask you where you live and how to contact you. If you move, you will be asked to update this information. The staff may use this information to remind you of study visits. If you miss a visit, the study staff will try to contact you by telephone if you have access to one or by visiting your home or place of work if you permit it. They will try to contact you through the people whose names you have provided. If they talk to these people they will not tell them why they are trying to reach you.
- At study entry and every 6 months, you will be asked some questions about behaviours that may increase your chance of catching HIV. Study staff will explain the questions to you so that you can understand them better.
- A simulated vaccine trial will be described to you and you will be asked questions about your willingness to participate in such a trial. This will be done study entry.
- At study entry you will be asked about your health and you will also have a full medical examination.
- At study entry, month 1 and month 6, you will receive an injection of hepatitis B vaccine.
- After each vaccination you will be observed for 30 minutes at the clinic to see how you react to the vaccine.



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- You will also be requested to come to the clinic 3 days following each vaccination to assess any reactions to the vaccine.
- At each follow up visit, about ½ tablespoons of blood will be drawn from your arm.
- Your blood will be tested for HIV and the rest will be stored for additional studies.
- You will be asked to provide a urine sample for a pregnancy test. You should receive these results before each vaccination. You will also have family planning counselling and started on a contraceptive method of your choice.
- You are encouraged to come to the clinic anytime you have a fever or other common infection as soon as possible.
- If you complete 12 months of follow up in or withdraw from the study you will revert to follow up within the Good Health Women Project.
  Your blood that is stored will only have a number on it and not your name so that no one, other than study staff will know who you are. Your blood may be stored for up to 10 years.

If you acquire HIV infection during your participation in this study

- You will be given counselling on HIV, what this means for your sexual partner or partners and family members, and how to avoid giving HIV to others in future. If you wish, your partner and/or family members can have counselling with you.
- About ½ tablespoons of blood will be collected. The blood will be tested to find out what your blood counts are, how your liver and kidneys are functioning and your CD4 cell count. We will discuss these results with you and decide whether you require starting treatment for HIV/AIDS.

4. Can I decline to be in the study or decline to give blood or Urine?

It is up to you whether or not to take part in the study. You can withdraw from the study or decide not to give blood at any time without giving a reason. This will not affect the standard medical care that you are entitled to.

5. Are there any benefits to me from being in the study?

During the discussion of your results, you will receive lifestyle advice or be linked to treatment that may improve your health. The information about you will help the MRC/UVRI, IAVI and other researchers to plan better preventive HIV vaccine trials. You will receive a vaccine against the Hepatitis B virus. This will protect you from acquiring Hepatitis B infection if you are not already immune or do not currently have Hepatitis B infection.

6. What risks can I expect from being in the study?

If you take part in the study, the risks to you are very slight. Most of the study questions are general in nature, but there are some that are personal and may make you feel uncomfortable. You are free to refuse to answer any questions. However, in order to obtain good results from the study, it is important that you attempt to answer all questions if possible. If you give blood, the risks to you are small. You may get some slight bruising where the blood is taken from your arm. If you have any discomfort, bleeding or swelling at the site, please contact our study staff or your health worker. All research team members are trained to protect your privacy and all information you share will be kept

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secret. You may develop soreness and redness at the injection site. The vaccine we will be providing in this study is licensed for use in adults and is safe and effective. However, rarely, some people develop a mild fever and a flu-like illness for a few days after the injection. All vaccines have rare side effects worse than this and this is an approved and widely used vaccine. We will ask you to report these feelings if you get them.

7. How will the information and blood/urine I give in the study be kept private?

Everything we talk about will be kept secret to the extent allowed by the law. Your results will be kept secret to the extent allowed by the law. To protect your privacy, we will use a code number to identify you and all information about you, including your blood samples. We will put a study number, not your name, on the blood or urine tubes. We will keep these records and samples securely locked. Your name or any other facts that might point to you will not appear when we present this study or publish its results.

Your records and samples will then be securely archived in Uganda for future research studies. This future research may be done by us or by other research teams working in Uganda or other countries. Only your information, blood samples and results which do not have your name or identifiable information will be stored and shared with other research teams.

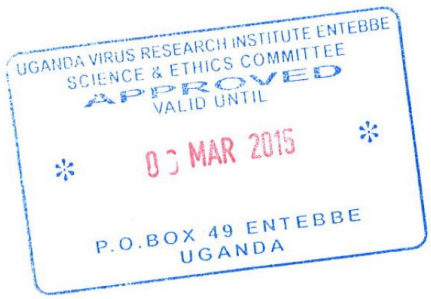
8. Whom can I ask if I have questions about the study?

If you have any questions about the study, you can call Dr. Anatoli Kamali, the Principal Investigator at 0772 422 765.

If you have a medical problem related to the study procedures, please contact Dr Yunia Mayanja, Dr Gertrude Namale on Tel: 0414 269 715 at the MRC/UVRI Uganda Research Unit clinic on Plot 616 Block 12 Kyadodo, Mengo, Kampala.

Nurse/Counselors are available at the MRC/UVRI Uganda Research Unit clinic on Plot 616 Block 12 Kyadodo, Mengo, Kampala and can be reached on Tel: 0414 269 715.

If you have a question about your rights as a research subject you should contact ~~Mr. Tom Lutalo~~, the Chairman of the Uganda Virus Research Institute Science and Ethics Committee (UVRI SE) on Tel:0414 320776 at the UVRI, Entebbe.



Sora dr. [redacted]
07.03.14

INFORMED CONSENT DOCUMENT

A simulated vaccine efficacy trial among women of Good Health Women Project in Kampala

I, (name of volunteer) .....

Of (address) .....

agree to take part in the research project entitled: "A simulated preventive HIV Vaccine trial among women of Good Health Women Project in Kampala Uganda"

I have been told in detail about all the procedures in the study and know what is required of me. I understand and accept the requirements. I understand that I am taking part in the study freely and that I can stop being part of this study at any time and for any reason. If I stop taking part, the legal rights that I have will not be affected.

□ By ticking this box, I agree that my specimens may be stored and sent to other expert laboratories for possible future testing to help in research for AIDS vaccines. No additional tests will be performed without the approval of the Ethics Committee.

Volunteer:

Signature/Thumb Print: .....

Date: |__|__|/|__|__|__|/|__|__|__|__| Time: |__|__|: |__|__| (24 hours)

Person Obtaining Consent:

I have explained the nature, demands and foreseeable risks of the above study to the volunteer:

Print Name:..... Signature: .....

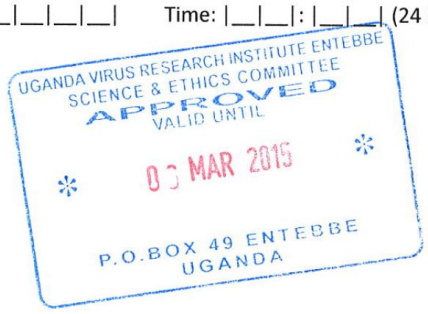
Date: |__|__|/|__|__|__|/|__|__|__|__| Time: |__|__|: |__|__| (24 hours)

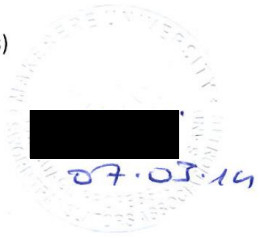
Witness: (if volunteer was not able to read and understand the Consent Information Sheet and Informed Consent Document)

I affirm that the Informed Consent Document has been read to the volunteer, and he/she understands the study and I have witnessed the volunteer's consent to study participation.

Print Name:..... Signature: .....

Date: |__|__|/|__|__|__|/|__|__|__|__| Time: |__|__|: |__|__| (24 hours)





Informed Consent Form (English)

The Good Health for Women Project (GHWP) - studies on the epidemiology and prevention of HIV and other diseases in a cohort of high risk women and their male regular partners in Kampala.

Institution: MRC/UVRI Uganda Research Unit on AIDS
Po Box 49 Entebbe

Principal Investigators: Dr Anatoli Kamali,
MRC/UVRI Uganda Research Unit on AIDS

Prof Janet Seeley
MRC/UVRI Uganda Research Unit on AIDS

This Informed Consent Form has two parts:

- **Information sheet (to share information about the research with you)**
- **2 Certificates of consent (for signatures if you agree to take part in the study)**

PART I. Information sheet

I am X..... working for MRC/UVRI Uganda Research Unit on AIDS at the Mengo clinic in Kampala. We are doing research on HIV/AIDS and other diseases. I am going to give you information and invite you to be part of this research. If there are words that you do not understand, please ask me to stop as we go through the information and I will take time to explain. You will be given a copy of this form to keep but if you do not want to take it with you, we shall keep your copy for you. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research or have someone of your choice read it to you. If you decide not to take part now or to withdraw from the study later, you will still be able to attend the health services offered by our clinic.

What is the reason for doing this study?

Many people in Uganda, especially women, are infected with HIV. Most of them have been infected by having unprotected sex with an HIV positive partner. Besides HIV, there are other infections that are sexually transmitted, shortly called STIs. The best known STIs are syphilis and gonorrhoea, but there are several others.

Why are these STIs so important? First of all, they may cause a lot of discomfort (vaginal discharge, vaginal itching, burning sensations or painful ulcers) although some dangerous STI may not cause symptoms at all. If untreated, they may cause severe damage to the female reproductive tract leading to infertility. Secondly, in pregnant women STIs may lead to miscarriage, severe diseases in the new born or even death of the mother and the child. Finally and very important, having an STI increases the chances of getting infected with HIV or of infecting others with HIV.

The risk to get infected with HIV and/or STIs increases with the number of sexual partners and the number of unsafe sex acts. Condoms are very effective to protect, if used correctly and consistently. However for women working in the entertainment sector, it may sometimes be difficult to convince men to use condoms. We want to find out how many of the women working in this area are infected with HIV or other STIs, how often unsafe sex acts take place and whether regular genital examination and treatment in the clinic, health education and counselling would help to decrease the number of new infections over time.

There are diseases that are starting to affect our communities as a result of poor diet, lack of exercises, smoking and excessive alcohol use. These are called non-communicable diseases and we shall study risk factors for these illnesses at this clinic.

Why have especially you been invited to participate in this study?
You have been invited because you are working in the entertainment sector and living in an area in or around Kampala where we have clinical services.

What exactly will happen if you accept to take part?
We will ask you to come to the clinic every three months even if you do not feel sick. For each visit you will need to spend about 4 hours at the clinic.

At the first visit we will take your personal contact details and ask you how we can reach you if we need to find you urgently. Because we respect your privacy we will never visit you at your home if you don't allow us to do so.

At each visit you will be asked for a urine sample and a pregnancy test will be performed.

After that you will receive counselling for an HIV test. We will ask you to give a small amount of blood (two tablespoons). This blood will be tested for HIV and syphilis at the clinic and the rest stored for future studies. If the test is negative we will tell you that you are not HIV infected. In case you are HIV positive, you will have a chance to talk with counsellors about how you feel, what can be done for you and how you can avoid spreading HIV. We shall talk to you about antiretroviral drugs (ARV) which are drugs that will not cure from HIV but will slow down the infection so as to prolong and improve the quality of your life. All women who are enrolled into this clinic and test HIV positive are eligible to start (ARVs). We shall counsel you to start and adhere to ARVs which are available at the clinic and provided free of charge. HIV testing and care will be provided for your children below 18 years. HIV positive children below 15 years are all eligible to start ARVs and will be supported to start and adhere to treatment.

Then we will ask you to take place on an examination bed for a gynaecological examination: the examining doctor or nurse will first inspect your external private parts for any signs of STI (for example warts), and then will place a small instrument inside your vagina to look inside your vagina and at your uterus mouth for any signs of STI (e.g. discharge or ulcers) or cancer of the cervix. You will be treated free of charge for all the STI we have found when we examine you. You will be offered free condoms at each follow-up visit.

Once a year, we will ask you some personal questions about your sexual life, sexual behaviour and use of alcohol and other substances.

Will I experience any possible risks and/or discomforts?
You may feel some discomfort, weakness and dizziness or faint after the blood draw. You may get redness, pain, swelling, bruising or infection on the arm where we collect the blood. However I would like to reassure you that the clinicians and nurses of our team are well trained and will collect your blood specimens with great care, trying to make you feel as comfortable as possible.
You may feel some discomfort during the vaginal examination; you may also feel shy, or feel worried when you are talking about your sexual life and HIV. A trained counsellor will help you to discuss any feelings you may have and to answer your questions.

How long does this study take?
The study will last for 4 years. We will ask you to stay in this study for as long as you can.

What if you get pregnant during the study time?

You will not be excluded from the study if you are pregnant or become pregnant during the study. You will be offered antenatal care at the clinic and informed where to obtain delivery services. In case you need treatment for STI or other illnesses during your pregnancy,we will only provide drugs that are known to be harmless to you and the baby. If you are HIV positive and beocome preganant, you will be counselled to enrol for the Elimination of Mother to Child Transmission of HIV (EMTCT) program, and will be helped to start ARV drugs to protect your unborn child.

How will I benefit from joining this research?
During each visit you will be systematically examined for STI, whether you have complaints or not. At each visit you will receive free treatment for any diagnosed infections. If you have any complaints or signs in between the appointments we will examine and treat you at the clinic. We will also provide free primary health care for your children under five years old.

At each visit we will explain to you the importance of having safe sex with your partners and you will offered condoms free of charge. The research will help to understand the health problems and needs faced by women like you. This may help to convince politicans and health care managers that special services may be needed for women working in such occupations.

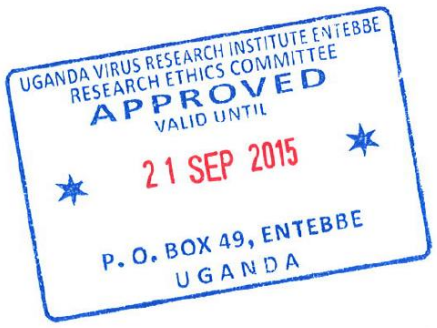
Can you withdraw from the study at any time?
You can withdraw from the study at any time without loosing access to health care and benefits that you are entitled to.

How confidential is the information you give us and who else will know about the results of your blood and genital examinations?
We shall do everything possible to keep the information about you confidential while you are in the study. Only staff involved in this project (medical staff in the clinic, and collaborators who put all data on the computer) will know about the information you gave and they will be instructed not to share the information with people outside the team. We will not put your name on the blood samples, but a number, so no laboratory staff will know your results.

Who should you contact for more information?
1. Dr Anatoli Kamali (Principal Investigator)
   0417 704000/ 0414 272953

2. Prof Janet Seeley
   0417 704000/ 0414 272953

3. Chair of UVRI-REC
   0414 321 962



PART II a - Written Consent for giving personal information and taking blood samples at regular intervals.

►*I have read the information sheet or it has been read to me. I have had the opportunity to ask questions about it and the questions that I have asked have been answered to my satisfaction. I accept voluntarily to participate in this research and understand that I have the right to withdraw from the research at any time and that this will not in any way affect access to health care offered by the clinic.*

Participant's signature (or thumbprint if illiterate)	Print name	date

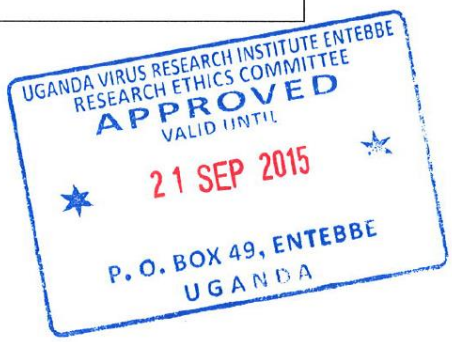
►*I have witnessed the accurate reading of the consent form to the potential participant and individual had the opportunity to ask questions. I confirm that the individual has given informed consent freely.*

Note: *the witness must be literate, should be selected by the participant and should have no connection to the research team.*

Witness' signature	Print name	date

► *I have accurately read or witnessed the accurate reading of the consent form to the potential participant and the individual has had the opportunity to ask questions. I confirm that the individual has given informed consent freely.*

Researchers' signature	Print name	date



PART II b - Consent for storage of blood samples for later studies other than genetic studies

►*I have read the information sheet or it has been read to me. I have had the opportunity to ask questions about it and the questions that I have asked have been answered to my satisfaction. I consent voluntarily that my blood samples may be stored at the laboratory of the MRC for later studies, possible HIV infection and possible tests related to HIV disease and non-communicable diseases. I understand that I have the right to withdraw this consent at any time and that this will not in any way affect access to health care offered by the clinic.*

Participant's signature (or thumbprint)	Print name	date

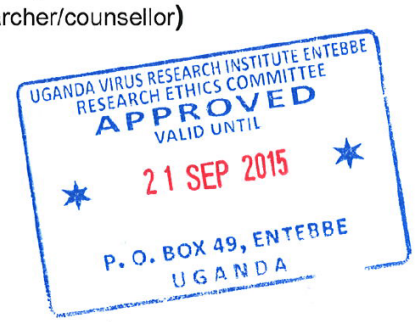
►*I have witnessed the accurate reading of the consent form to the potential participant and individual had the opportunity to ask questions. I confirm that the individual has given informed consent freely.*
Note: the witness must be literate, should be selected by the participant and should have no connection to the research team.

Witness' signature	Print name	date

► *I have accurately read or witnessed the accurate reading of the consent form to the potential participant and the individual has had the opportunity to ask questions. I confirm that the individual has given informed consent freely.*

Researchers' signature	Print name	date

A copy of this Informed Consent Form has been provided to participant ..... (Initialled by the researcher/counsellor)



MRC/UVRI UGANDA RESEARCH UNIT ON AIDS - MASAKA
PROTOCOL B OPEN COHORT STUDY

INFORMED CONSENT FOR SCREENING/ENROLLMENT INTO THE MAIN STUDY (IAVI OPEN B COHORT)

Title: A Prospective, Open cohort, Observational Study to Determine HIV incidence in Preparation for future Preventive HIV Vaccine Clinical Trials

Reason for this Study

Over 40 million people worldwide are infected with human immunodeficiency virus (HIV), the virus that causes AIDS. New people are being infected every day. Many experts believe that a HIV vaccine may help prevent HIV infection or keep people healthier for longer even if they become infected. Right now there is no vaccine that does this.

This research study aims to find how many people will become infected with HIV while they are receiving regular HIV counseling to reduce their risks for becoming infected and testing for HIV.

Background

The International AIDS Vaccine Initiative (IAVI), the Sponsor of this study, is an international, scientific, non-profit organization, whose mission it is to ensure the development of a safe and effective, preventive vaccine against HIV and to make sure that if such a vaccine is found, those who need it most will get it. The study will also help the MRC/UVRI Uganda Research Unit on AIDS and IAVI to prepare for the testing of HIV vaccines in the future. However, this study does not involve an HIV vaccine.

This document provides information about the study for you. If you wish, it can also be read to you. You may bring a person with you to help you understand the study and to witness that you understand and agree with participating in the study. One copy of this document will be given to you and one will be kept at the MRC/UVRI Uganda Research Unit on AIDS Masaka clinic in a safe and secure place. If you do not wish to keep your copy, it will be kept at this site for you.

Your participation is of your own free will. You may decide to stop being part of the study at any time. You will not lose any rights or benefits you normally have if you do not join the study or if you leave the study.

Study Volunteers

This study will enroll up to 400 male and female volunteers 18 – 49 years old, who qualify for the study and who agree to be in the study.

MRC/Uganda Virus Research Unit on AIDS | C/O Uganda Virus Research Institute | Plot 51- 59 Nakiwogo Road - Entebbe | P.O Box 49 Entebbe | Tel: +256 (0) 417 704000 | +256 (0) 312 262910/1 | +256 (0) 752 731733
Email: mrc@mrcuganda.org | Website: www.mrcuganda.org

MRC/UVRI UGANDA RESEARCH UNIT ON AIDS - MASAKA
PROTOCOL B OPEN COHORT STUDY

Duration of the Study
If you join this study, you will have at least 5 scheduled study visits at this research center for up to 12 months. At your last scheduled study visit you may be asked to continue in the study, and the decision to continue with the study at that time will be up to you and the study team.

WHAT WILL HAPPEN IN THE STUDY

If you decide to join this study, after you read, discuss and sign or mark this form, this is what will happen:

Study screening and enrolment:

- At the first visit, study staff will assess your eligibility for the study. You will be asked questions such as your age and how you learned about the study. You will also be asked questions about behaviors that may increase your chance of catching HIV. If you refuse or fail to join the study, reasons for this will be documented.
- About ½ table spoon of blood will be drawn from a vein in your arm.
- Your blood will be tested for HIV. In most cases you will receive the result on the same day in less than one hour. Occasionally the blood will have to be sent for a second test and you should receive the result in 1-2 weeks. If your test results are still not clear, you will be asked to return and be tested again.
- If your test results show that you are not infected with HIV, you may be eligible to enroll into this study.

If your test results show that you are infected with HIV at screening:

- You will be given counseling on HIV, what this means for sexual partner or partners and family members, and how to avoid giving HIV to others in future. If you wish, your partner and/or family members can have counseling with you.
- You will be asked about your health. An examination may be done to find out if you have any medical problems. You may be asked about any illnesses you have had in the past three months.

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Email: mrc@mrcuganda.org | Website: www.mrcuganda.org

- Your blood may be tested to find out what your blood counts are, how your liver and kidneys are functioning and your CD4 count. For these tests an additional ½ table spoon of blood will be requested from you. These results will be provided to you so that you can discuss them with your doctor.

- You will be referred for additional care if necessary. If you are a woman infected with HIV and you are pregnant, you will be referred to care for you and your baby and to the "Prevention of Mother to Child Transmission" (PMTCT) program where you may get medicines that can help prevent your baby from getting HIV.

If you enroll in this study:

- Study staff will ask you where you live and how to contact you. If you move, you will be asked to update this information. The staff may use this information to remind you of study visits. If you miss a visit, the study staff will try to contact you by telephone if you have access to one or by visiting your home or place of work if you permit it. They will try to contact you through the people whose names you have provided. If they talk to these people they will not tell them why they are trying to reach you. You will be asked about your health and you will also have a full medical examination.

- You will be asked some questions about behaviors that may increase your chance of catching HIV. Study staff will explain the questions to you so that you can understand them better.

- A hypothetical HIV vaccine trial will be described to you and you will be asked questions about your willingness to participate in such a trial. This will be done at study entry or at the month 3 or 6 visits. At each follow up visit, about ½ tablespoon of blood will be drawn from your arm.

- Your blood will be tested for HIV and the rest will be stored for additional studies. In most cases you will receive the result on the same day in less than one hour. Occasionally the blood will have to be sent for a second test and you should receive the result in 1-2 weeks. If your test results are still not clear, you will be asked to return and be tested again. If your test results show that you are not infected with HIV, you will be told when to return for the first follow up visit.

- There is a small chance that even if your test says you do not have HIV, you may be in the very early period of HIV infection. This period can last up to three months after you have become infected HIV.

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- You will be asked about your health. An examination may be done to find out if you have any medical problems. You may be asked about any illnesses you have had in the past three months.

- You are encouraged to come to the clinic anytime you have an STI or have a fever that is not malaria or other common infection as soon as possible so that you can be tested for HIV.

- At the first and one year visits (and if you ever get a sexually transmitted disease (STI), your blood will be tested for syphilis. You will get the test results as soon as they are available. You will receive treatment if you need it, or you will be referred for care.

If your tests results show that you have HIV infection at a follow up visit

- You will be given counseling on HIV, what this means for your sexual partner or partners and family members, and how to avoid giving HIV to others in future. If you wish, your partner and/or family members can have counseling with you.

- You will be asked questions about how and when you think you may have become infected with HIV.

- About ½ tablespoon of blood will be collected. The blood will be tested to find out what your blood counts are, how your liver and kidneys are functioning and your CD4 cell count. These results will be provided to you so that you can discuss them with your doctor.

- If you are a woman infected with HIV and you are pregnant, you will be referred to care for you and your baby and to the "Prevention of Mother To Child Transmission" (PMTCT) program where you may get medicines that can help prevent your baby from getting HIV.

Storing your Blood (for enrolled volunteers)

Your blood that is stored will only have a number on it and not your name so that no one, other than study staff will know who you are. Your blood may be stored for up to 10 years.

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MRC/UVRI UGANDA RESEARCH UNIT ON AIDS - MASAKA
PROTOCOL B OPEN COHORT STUDY

Your stored blood will be used to check that tests in the laboratory are done with very high standards. With the approval of the Ethics Committee, some of your stored blood may be sent to other expert research laboratories, for special research testing related to HIV, or for other diseases or germs common in the area where you live.

If you get HIV during the study, some of your stored blood may be tested for HIV using special tests. No other tests will be done without the permission from the Ethics Committee. You will not get the results of these tests as they are research tests

Risks and/or Distress

Taking blood from the arm causes pain. Sometimes bruising can occur where the needle goes into your arm. You may feel dizzy or faint, but this is not common.

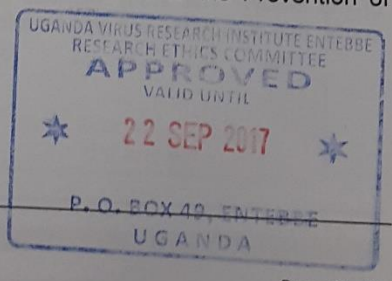
You may become embarrassed, worried, or anxious when discussing sex, ways to protect against HIV and your test results. You may become worried or anxious while waiting for your HIV test results. A trained counselor will help you with any feelings or questions you may have.

We will protect your privacy during and after the study. However, it is possible that others may learn of you being in the study and think you have caught HIV. This may lead to stigma and problems, like having trouble getting or keeping a job, or even not being accepted by your family or community. The studies at this site enroll all kinds of people. Some have HIV and some do not. This may decrease the chance of people knowing about your health.

Benefits

You may benefit by being in the study. You will receive regular counseling and medical examinations. As part of counseling, you will be given information about how to reduce your risk of becoming infected with HIV and you will receive regular HIV testing. If you wish, your partner and/or family members can have counseling with you.

If you become infected with HIV during the study, tests will be done on your blood, to find out about your general health, and your CD4 counts. These results will be very helpful to you and your doctor for your care. You will also be referred for counseling and care for HIV. You or others may benefit in the future from information learned in this study. You may get some satisfaction from being part of research on HIV. If you are a woman, and you become pregnant and catch HIV, you will be referred for prenatal care and to the Prevention of Mother To Child Transmission of HIV program.



MRC/Uganda Virus Research Unit on AIDS | C/O Uganda Virus Research Institute | Plot 51- 59 Nakiwogo Road - Entebbe | P.O Box 49 Entebbe | Tel: +256 (0) 417 704000 | +256 (0) 312 262910/1 | +256 (0) 752 731733
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If you have any medical problems that need treatment that is not available at the clinic, we will refer you to another clinic or hospital. This study will not cover costs for care at the place of referral.

You will also learn about HIV infection, HIV vaccines and research during the study.

Injuries
We do not expect you to suffer any injury as a result of participating in this study, but if you do, the MRC/UVRI Uganda Research Unit on AIDS will give you the necessary treatment for your injuries without charge. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

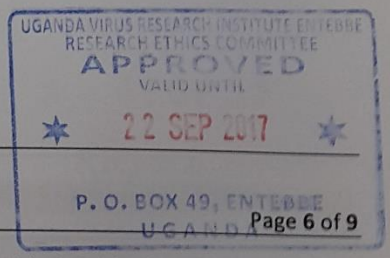
Taking you out of the Study
You may be removed from the study without your consent for the following reasons:

- You are not able to or do not attend study visits or complete the study visits
- If the study is stopped
- You do not want to have HIV testing or receive your HIV test results
- Other reasons in the judgment of the investigator

What happens if you do not join the study?
There may be other HIV studies going on that you may join. If you wish, we will tell you about the other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish. If you choose not to join this study, this will not affect the care you get at other places.

New information
You will be told about any important new information during the study. You will be told when the results of the study may be available, and how to learn about them.

Supervision of the study
The conduct of the study will be supervised by the Principal Investigator. All study information will be regularly checked by independent monitors and experts who are not part of the study. The study will also get approval of the Ethics Committee before the study starts; this committee will also be informed when any big changes are made to the study.



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MRC/UVRI UGANDA RESEARCH UNIT ON AIDS - MASAKA
PROTOCOL B OPEN COHORT STUDY

Costs to You

There is no cost to you for being in the study. You will receive 5000 Ush for each study visit you complete. This payment is to cover the time spent in the clinic. You will also receive money to cover your transport expenses to and from the clinic for each study visit according to the prevailing transport rates.

Confidentiality

Being in the study, all information collected about you, your blood and results of all tests will be identified by a special number and not your name. All papers containing your name will be locked away safely and will only be available to the study staff. Apart from the study staff that you meet, others from National or international government bodies that ensure correct conduct of research, members of the Ethics Committee, study monitors, auditors, Government or regulatory inspectors, and representatives of the Sponsor (IAVI) will check the study papers to make sure that the study was conducted properly. They all have to keep your information private and safe.

Contact Numbers

If you have any questions about the study, you can call Dr. Anatoli Kamali, the Principal Investigator at 04814 21211.

If you have a medical problem related to the study procedures received during HIV testing, please contact Dr Freddie Kibengo, Dr. Ubaldo Bahemuka or Dr. Eugene Ruzagira on Tel: 04814 21211 at the MRC/UVRI Uganda Research Unit clinic on Plot 2-5 Ntikko Road, Masaka town.

Nurse/Counselors are available at the MRC/UVRI Uganda Research Unit clinic on Plot 2-5 Ntikko Road, Masaka town and can be reached on Tel: 04814 21211.

If you have a question about your rights as a research subject you should contact Mr. Tom Lutalo, the Chairman of the Uganda Virus Research Institute Science and Ethics Committee (UVRI SE) on Tel:0414 320776 at the UVRI, Entebbe.

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MRC/UVRI UGANDA RESEARCH UNIT ON AIDS - MASAKA
PROTOCOL B OPEN COHORT STUDY

INFORMED CONSENT DOCUMENT

OPEN COHORT

I, (name of volunteer)……

Of (address) ……

AGREE TO TAKE PART IN THE RESEARCH PROJECT ENTITLED: A PROSPECTIVE, OPEN COHORT, OBSERVATIONAL STUDY TO DETERMINE HIV INCIDENCE IN PREPARATION FOR FUTURE PREVENTIVE HIV VACCINE CLINICAL TRIALS

I have been told in detail about all the procedures in the study and know what is required of me. I understand and accept the requirements. I understand that I am taking part in the study freely and that I can stop being part of this study at any time and for any reason. If I stop taking part, the legal rights that I have will not be affected.

□ By ticking this box, **I agree** that my specimens may be stored and sent to other expert laboratories for possible future testing to help in research for AIDS vaccines. No additional tests will be performed without the approval of the Ethics Committee.

□ By ticking this box, **I do not agree** that my specimens may be stored and sent to other expert laboratories for possible future testing to help in research for AIDS vaccines.

Volunteer:

Signature/Thumb Print: ……

Date: |__|__|/|__|__|__|/|__|__|__|__|Time: |__|__|: |__|__| (24 hours)

Person Obtaining Consent:

I have explained the nature, demands and foreseeable risks of the above study to the volunteer:

Print Name:…… Signature:……

Date: |__|__|/|__|__|__|/|__|__|__|__|Time: |__|__|: |__|__| (24 hours)

Witness: (if volunteer was not able to read and understand the Consent Information Sheet and Informed Consent Document)

UGANDA VIRUS RESEARCH INSTITUTE ENTEBBE
RESEARCH ETHICS COMMITTEE
APPROVED
VALID UNTIL
22 SEP 2017
P. O. BOX 49, ENTEBBE

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I affirm that the Informed Consent Document has been read to the volunteer, and he/she understands the study and I have witnessed the volunteer's consent to study participation.

Print Name:..... Signature:.....

Date: |__|__|/|__|__|__|/|__|__|__|__|Time: |__|__|: |__|__| (24 hours)

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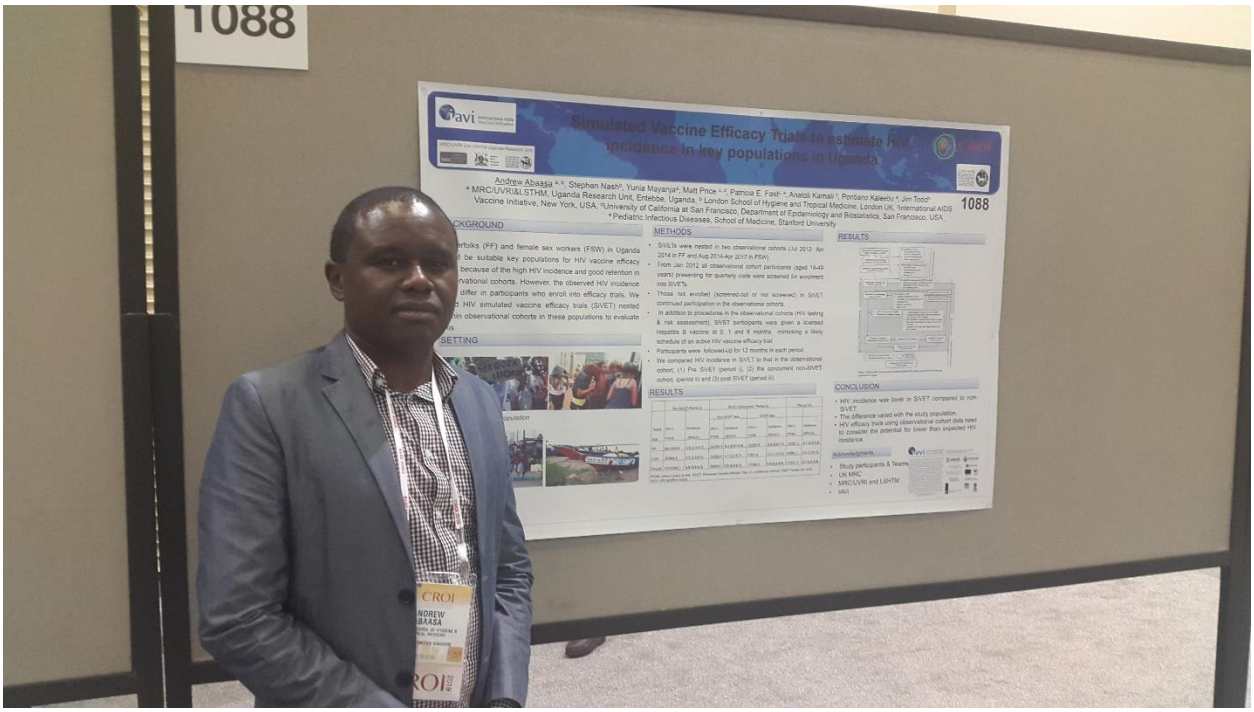
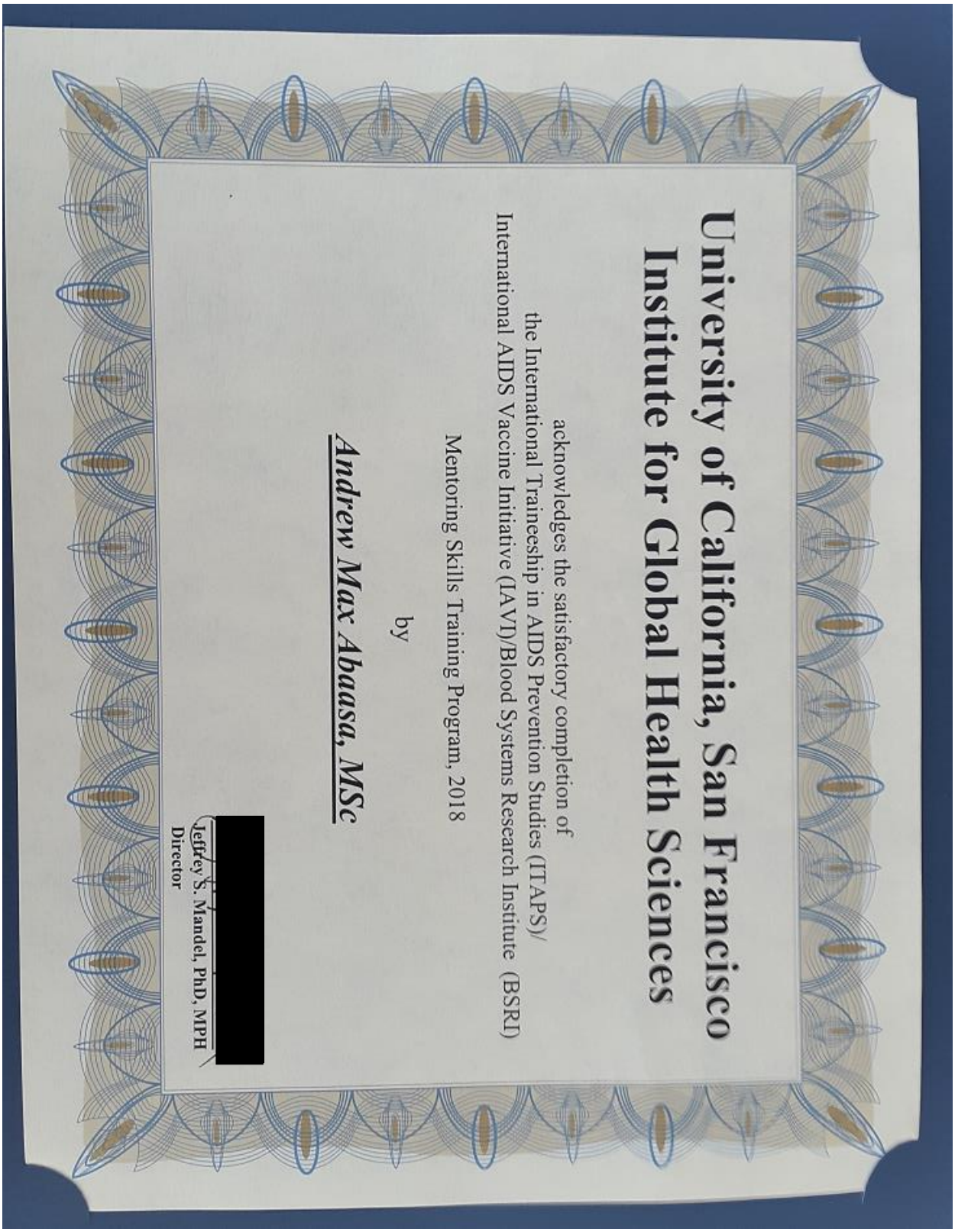
Appendix Three: PhD related conference presentations



Appendix Four: Awarded Training certificates



University of California, San Francisco
Institute for Global Health Sciences

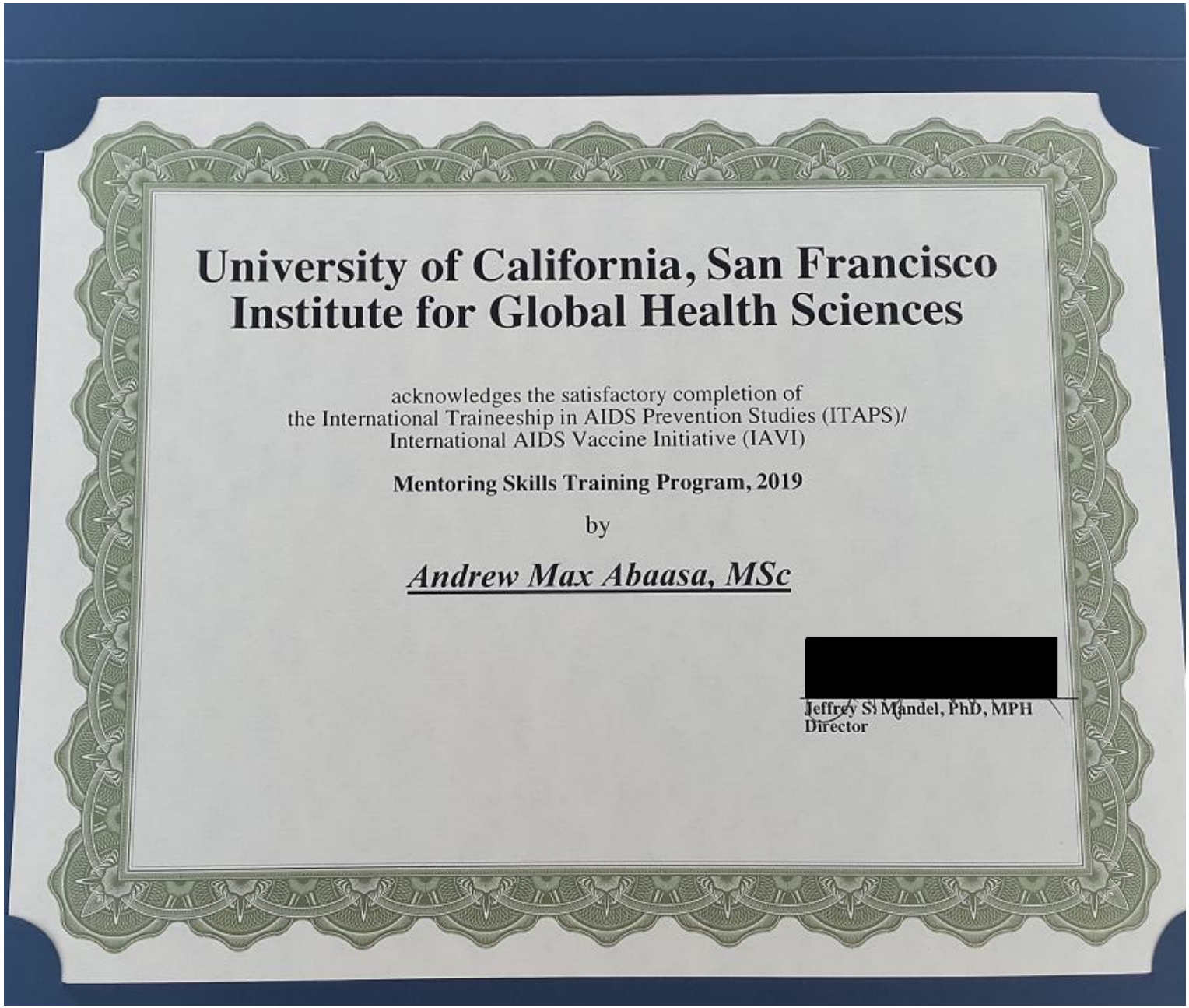
acknowledges the satisfactory completion of
the International Traineeship in AIDS Prevention Studies (ITAPS)/
International AIDS Vaccine Initiative (IAVI)/Blood Systems Research Institute (BSRI)

Mentoring Skills Training Program, 2018

by

Andrew Max Abaasa, MSc

[redacted]
Jeffrey S. Mandel, PhD, MPH
Director



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Director

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