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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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\textbf{Abstract}

\textbf{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.

\textbf{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.

\textbf{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).

\textbf{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.

\textbf{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 (Fish-erfolks, FF) shoreline and female sex workers (FSW) in Kampa-lata.

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
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 was 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.

2. Methods

2.1. Study design

We use data from two longitudinal observational cohorts in Uganda (observational cohort one (OBSC1) in FF, Feb 2009–Apr 2015 and observational cohort two (OBSC2) 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 (SIVET1, Jul 2012–Apr 2014) and SIVET2 (Aug 2014–Apr 2017) were nested within OBSC1 and OBSC2 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. Obsc1

Eligible participants (Table 1) were enrolled into OBSC1 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 OBSC1 details are previously described [9,12,13]. From Jul 2012 to Apr 2014, FF attending the OBSC1 clinic were assessed for eligibility (Table 1) for enrolment into SIVET1.

2.2.2. Obsc2

Similarly, eligible participants (Table 1) were enrolled into OBSC2 at MRC/UVRI and LSHTM clinic in Kampala with similar assessments and follow up schedules as OBSC1 above. The OBSC2 details have been previously described [7]. Similarly, from Aug 2014 to May 2016, FSW attending the quarterly clinic visits in OBSC2 were assessed for eligibility for enrolment into SIVET2 (Table 1).

2.2.3. SIVET1

Eligible participants (Table 1) were enrolled into SIVET1 (nested in OBSC1 in the FF population) and had their follow up visits in SIVET1 synchronized with their source OBSC1 participants clinic visits for HIV and behavioral risk assessment. In addition to their OBSC1 procedures, they were further administered a commercially licensed Hepatitis B vaccine (ENGEXIX-B™ GlaxoSmithKline Biologicals Rixensart, Belgium) following the standard schedule of 0, 1

Table 1

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<tr>
<th>Period</th>
<th>OBSCs pre SIVETs</th>
<th>Inclusion</th>
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<tr>
<td>(i)</td>
<td></td>
<td>HIV negative and willing to undergo HIV testing</td>
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<td>(ii)</td>
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<td>Age 18–49 years</td>
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<td>(iii)</td>
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<td>Able and willing to provide written informed consent</td>
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<th>Non-SIVETs concurrent period</th>
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<td>Inclusion</td>
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<td>HIV positive</td>
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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 SiVET1 protocol. Upon completion of SiVET1 follow up, participants were followed-up under OBSC1 procedures only, for another 12 months (post-SiVET1).

2.2.4. SiVET2

Similar procedures as in SiVET1 above were followed to establish SiVET2, though this was nested in OBSC2 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, Matsuhiada, Matsu-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 OBSC2, 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
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

Fig. 1. Study profile for participants screened and enrolled Pre, during and post SiVET in two key populations in Uganda.
83.8% in SiVETs vs. 76.4% in non-SiVET cohorts in the concurrent period (ii), p < 0.01.

In the OBSC1, compared to those that were not eligible for screening into SiVET1, 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 72.5%, p < 0.001 but were otherwise similar in terms of other characteristics. Similarly, in the OBSC2, compared to those that were not eligible for screening into SiVET2, 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 SiVET1 (FF) and SiVET2 (FSW) compared to those in the source population who were not recruited into the SiVETs (non-SiVET1 and non-SiVET2) in the same period (ii). In the FF population, compared to SiVET1, non-SiVET1 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 SiVET2, non-SiVET2 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 greater in the FF population than FSW population. HIV incidence was greater
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 PYAR 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 underestimation of 22% of the expected number of study participants (633 in each arm) to show the RR of 0.30, with a significance of 5% and power of 80%.

Our study strengths included an adequate follow up period in 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).

After adjusting for age and male sex, the difference in the HIV incidence was 0.4 (95% CI 0.3 to 0.5) per 100 PYAR per arm. This was higher than the 0.3 (95% CI 0.1 to 0.4) per 100 PYAR difference in the 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.

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 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 rigorous 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 (counseling 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).
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, and both SIVETs, data analysis and interpreted the data. YM: contributed to the design of the SIVET1 protocol, study coordination (OBSC, and SIVET1). MP: contributed to the design of both SIVETs and OBSC1, and interpreted the data. PEF: contributed to the design of both SIVETs and OBSC2, 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.

References


