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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

Andrew Abaasa[a,*], Gershim Asiki[a], Matthew A. Price[b,c], Eugene Ruzagira[a], Freddie Kibengo[a], Ubaldo Bahemuka[a], Patricia E. Fast[b], Anatoli Kamali[a]

[a] MRC/UVRI, Uganda Research Unit on AIDS, Entebbe, Uganda
[b] International AIDS Vaccine Initiative, New York, USA
[c] University of California at San Francisco, Department of Epidemiology and Biostatistics, San Francisco, USA

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ABSTRACT

Background: Clinical trial participants may differ from the source population due to the demands of trial participation and self-selection, inadvertent selection of a lower-risk group, or both. We investigated the HIV risk status of volunteers in a Simulated Vaccine Efficacy Trial (SiVET) nested within a prospective observational cohort of fisher folks in South Western Uganda.

Methods: Volunteers aged 18–49 years, at high risk for HIV from fishing communities in Masaka district were recruited into an observational cohort and followed quarterly. High risk was defined as a self-report, of at least one of the following in the past three months; sexually transmitted infections, unprotected sex with >1 partner or a new sexual partner, use of recreational drugs, weekly alcohol use, and/or frequent travel. Volunteers who had at least three months of follow-up in the observational cohort were consecutively enrolled in SiVET, administered Hepatitis B vaccine at months (0, 1, 6) and followed-up three days post vaccinations to mimic a vaccine trial schedule. HIV incidence over the next 12 months was compared between SiVET and the observational cohort studies.

Results: Between January 2012 and February 2013, 575 individuals were enrolled in the observational cohort, of whom 282 were enrolled in SiVET between July 2012 and February 2013. Despite similar pattern of reported risk behaviour in both studies, HIV incidence was higher in observational cohort, 11.4 cases/100 PYO [95% CI: 7.4–17.7] compared to 3.8 [95% CI: 2.0–7.0] in SiVET ($p < 0.01$). SiVET volunteers tended to be men, having some education and longer-term residents, all factors that are also associated with lower HIV risk.

Conclusion: We observed a lower HIV incidence in SiVET than in the observational cohort. The two populations differed significantly in demographics but not in reported risk. HIV incidence estimates from observational cohorts must be used with caution to estimate the trial study size.

1. Introduction

Identifying populations with high HIV incidence and adequate study retention is necessary to perform HIV vaccine efficacy trials that have sufficient statistical power [1]. The investigators of the International AIDS Vaccine Initiative (IAVI) network in sub-Saharan Africa have been conducting a number of observational studies to assess the suitability and willingness of potential populations to enrol in future HIV vaccine efficacy trials [2]. Volunteers in these observational cohorts have included discordant couples, members of fishing communities, women at high risk, and men who have sex with men (MSM). In these studies, annual HIV incidence ranged from 1.1 to 10.8 per 100 person years of observation (PYO) with one-year study retention of 75–97% [2] and HIV prevalence ranged from 8.3% to 16.4% [2]. These populations have also expressed a high willingness to enrol in future efficacy trials [3–5]. Other studies in high risk populations in the same region have found HIV prevalence ranging between 6.1%

* Corresponding author at: MRC/UVRI Uganda Research Unit on AIDS, P.O Box 49, Entebbe, Uganda. Tel.: +256 0417 704000.
E-mail addresses: Andrew.Abaasa@mrcuganda.org, andrew.abaasa@yahoo.com (A. Abaasa), gershim@gmail.com (G. Asiki), MPrice@iavi.org (M.A. Price), Eugene.Ruzagira@mrcuganda.org (E. Ruzagira), Freddie.Kibengo@mrcuganda.org (F. Kibengo), Ubaldo.Bahemuka@mrcuganda.org (U. Bahemuka), PFast@iavi.org (P.E. Fast), Anatoli.Kamali@mrcuganda.org (A. Kamali).

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and 37% [6–10] and annual HIV incidence between 4% and 12.6% per 100 PYO [7,11,12]. Microbicide trials among women at high risk of HIV infection identified from sero-discordant relationships residing in areas far from the fishing populations but in the same district observed HIV incidence in the control arm ranging between 3.3 and 4.3 per 100 PYO [13,14]. Although fishing populations have been identified as possible high risk population for future efficacy trials, no trials have been conducted yet in these populations. These populations have unique characteristics such as high mobility and excessive alcohol consumption that may impact on both HIV incidence and study retention during trials [9,11]. In such populations, HIV incidence reported from observational cohorts or feasibility studies is usually used to estimate the required sample size for efficacy trials [12]. However, such data may not reflect the incidence in an efficacy trial because of changes in the eligibility criteria for participation and trial procedures such as risk reduction counselling, mandatory use of contraceptives and condom provision, more frequent visits and the difference in duration between observational studies and efficacy trials. Inadvertent selection of lower risk volunteers into a trial could also play a role [12]. In Uganda [13], Nigeria [15] and Ghana [16] microbicide and a pre exposure prophylaxis (PrEP) [17] trials have shown lower HIV incidence in the control arm than that observed in feasibility cohort studies at the planning stage [12,15–17]. One systematic review [18] reported a number of HIV prevention studies that were unsuccessful or terminated because they found lower HIV incidence and statistical power than what was predicted based on observational data. These underpowered studies expose volunteers to investigational products in experiments of limited clinical value, waste time and financial resources [19,20]. It is important, therefore, to obtain more accurate estimates of the actual incidence that would occur during trial conditions.

To our knowledge, there is no data that have compared HIV incidence in an observational cohort to that in an efficacy trial using the fishing populations that are potentially being considered for future trials. In this analysis, we compared HIV incidence in a longitudinal HIV vaccine preparedness observational cohort to that in a Simulated Vaccine Efficacy Trial (SiVET) nested within the cohort. These two studies were part of collaboration between the Medical Research Council/Uganda Virus Research Institute (MRC/UVRI) Uganda Research Unit on AIDS and the International AIDS Vaccine Initiative (IAVI) to prepare for future vaccine efficacy trials.

2. Methods

2.1. Study population

We used data from an observational fishing cohort and from a nested Simulated Vaccine Efficacy Trial (SiVET) to compare HIV incidence between the two studies in rural South-Western Uganda. The observational cohort was established to estimate annual HIV incidence and maintain a pool of volunteers for possible recruitment into future efficacy trials. Enrolment for the observational cohort was between January 2012 and February 2013. The SiVET study mimicked an HIV vaccine efficacy trial using a licensed Hepatitis B vaccine as a proxy for an HIV vaccine to assess retention and willingness to participate in future trials. Enrolment into the SiVET started in July 2012; and ended in February 2013 when the estimated sample had been accrued. In this analysis, we included observational cohort volunteers that had been enrolled by the date SiVET completed enrolment. We included data for every volunteer from the 3 month visit date to 12 months later. Each volunteer in the two studies contributed at most 12 months of follow up data or to the point they were last seen or tested HIV positive, if that was shorter.

2.2. Observational cohort procedures

Volunteers in the observational cohort were recruited from fishing communities located about 40 km from the MRC/UVRI research site in Masaka town by trained fieldworkers. Fieldworkers visited each household on the lakeshore, offered HIV counselling and testing (HCT). Male and female adults aged (18–49 years) identified as HIV negative through HCT were screened for high risk of acquiring HIV. High risk was defined as a self-report of any of the following in the previous three months: sexually transmitted infections (STIs), unprotected sex with more than one or a new sexual partner, use of recreational drugs and/or at least weekly alcohol use, and absence from home for at least three consecutive nights per week. Eligible volunteers and at high risk were referred to the MRC/UVRI study clinic for enrolment and subsequent quarterly follow up visits. At the clinic, interviewer-administered case report forms were used to record locator details (physical location and phone contacts), demographics, risk behaviour characteristics, and medical assessments. Medical assessments and HCT were repeated every 3 months. HIV risk was assessed every 6 months and at annual visit, volunteers whose risk profile had changed to low risk were withdrawn from the cohort. Volunteers were reminded by phone call and followed by a home visit if they missed their clinic appointments. Cohort volunteers were considered as lost to follow up and withdrawn from the cohort if they failed to attend two sequential follow up visits. A lost to follow up volunteer was readmitted into the cohort if they came back to the study clinic and still fulfilled the eligibility criteria.

2.3. SiVET procedures

When volunteers presented for their 3 month visits in the observational cohort, they were assessed for recruitment into SiVET. SiVET inclusion criteria included; having spent at least three months in the observational cohort, no contraindications for Hepatitis B vaccine and, if female, willingness to use contraception until 3 months after the last vaccination. Recruitment was stopped at accrual of the estimated sample size when 291 had been screened and 282 enrolled. Of the nine volunteers screened and not enrolled, three were pregnant, two refused to consent and four did not show up for enrolment (Fig. 1). Volunteers in SiVET continued with their procedures and schedules in the parent observational cohort. SiVET visits were synchronised with observational cohort visits. In addition to the parent observational cohort procedures and schedules SiVET volunteers were administered a licensed Hepatitis B vaccine (ENGERIX-B^{TM} GlaxoSmithKline Biologicals Rixensart, Belgium,) following the standard schedule of 0, 1 and 6 months, akin to what might happen in an HIV vaccine trial. At each vaccination visit, volunteers were kept in the clinic for observation of reactogenicity events for at least 30 min after vaccination and asked to return to the clinic after 3 days for further review. Each volunteer was followed for 12 months aligned to the period SiVET was conducted.

2.4. Laboratory methods

Rapid HIV testing was performed by Determine (Alere, Medical Co., Ltd, Matsuhidai, Matsudo-shi, Chiba, Japan) and all positive specimens were confirmed by two ELISA tests (Vironostika HIV Uni-Form II plus 0 microelisa system, Biomerieux, Boxtel, The Netherlands and Murex HIV-1.2.0, Murex, Biotech Limited, Dartford, UK). A western blot was performed if ELISA results were discordant.