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ORIGINAL PAPER

Use of Varied Screening Risk Criteria and HIV Incidence in Phase 1 and 2 HIV Vaccine Trials in South Africa

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Abstract

Many early phase HIV prevention studies define HIV risk-related eligibility criteria. We conducted a retrospective review of HIV Vaccine Trials Network (HVTN) Phase 1 and 2 HIV vaccine clinical trials completed in South Africa from 2003 to 2020, evaluating HIV incidence by protocol-defined risk criteria. Comparisons between groups controlled for age, gender and year of trial initiation. Across 12 trials, 1 did not specify risk criteria, and 11 specified various low risk criteria thematically categorized under sexual behaviors, clinical characteristics, and/or drug use behavior. Of the 11 trials, 6 used low sexual risk eligibility criteria standardized by the HVTN in 2009. Of the 1249 participants, median age 23.0 years, 66% were enrolled with the HVTN 2009 standardized low risk criteria, 15% using other sets of low risk criteria, and 19% using no risk criteria. Compared with the standardized low risk criteria group [2.3], HIV incidence per 100 person-years was significantly higher in the non-standardized low risk criteria group [5.0] and in the no risk criteria group [4.8]. In South Africa, cohorts with low HIV incidence can be identified primarily through sexual behavior and clinical characteristics.

Keywords HIV · risk · incidence · criteria

Introduction

Early phase trials bridge pre-clinical science into clinical interventions. [1] Generally, early phase preventive HIV vaccine trials investigate safety and immune responses in individuals at low HIV acquisition risk. The rationale for selecting low risk individuals is because it is unknown if vaccines exacerbate biological risk in behaviorally exposed individuals. It is also a retention consideration: because the effect on HIV disease progression is also unclear, participants who acquire HIV during study are discontinued from vaccinations, and their immunogenicity data post-infection are excluded from analysis.

South Africa has been researching and implementing acceptable, safe and effective HIV prevention methods, but remains the country worst affected by HIV. [2] An estimated 3% of all clinical trial research is conducted in Africa. [3] However, there are scientific reasons supporting the conduct of preventive HIV vaccine research in disease-burdened countries like South Africa. Viral and host differences suggest that it would not necessarily be correct to assume that the safety and efficacy of candidate HIV vaccine regimens would be similar in different regions. A key viral difference is strain diversity: the most prevalent circulating strains in South Africa are of HIV-1 subtype C. [4] Many host-related factors, such as genetics, gender, race, body weight, co-existing conditions or infections that may be regionally specific, are known to contribute to differences in immune responses to various HIV vaccines. [5–8]

The ongoing effort to develop an effective HIV vaccine, the scientific rationale to enroll relevant populations, and the high HIV incidence creates a need amongst researchers to define low risk criteria for eligibility into early phase HIV vaccine trials in South Africa.

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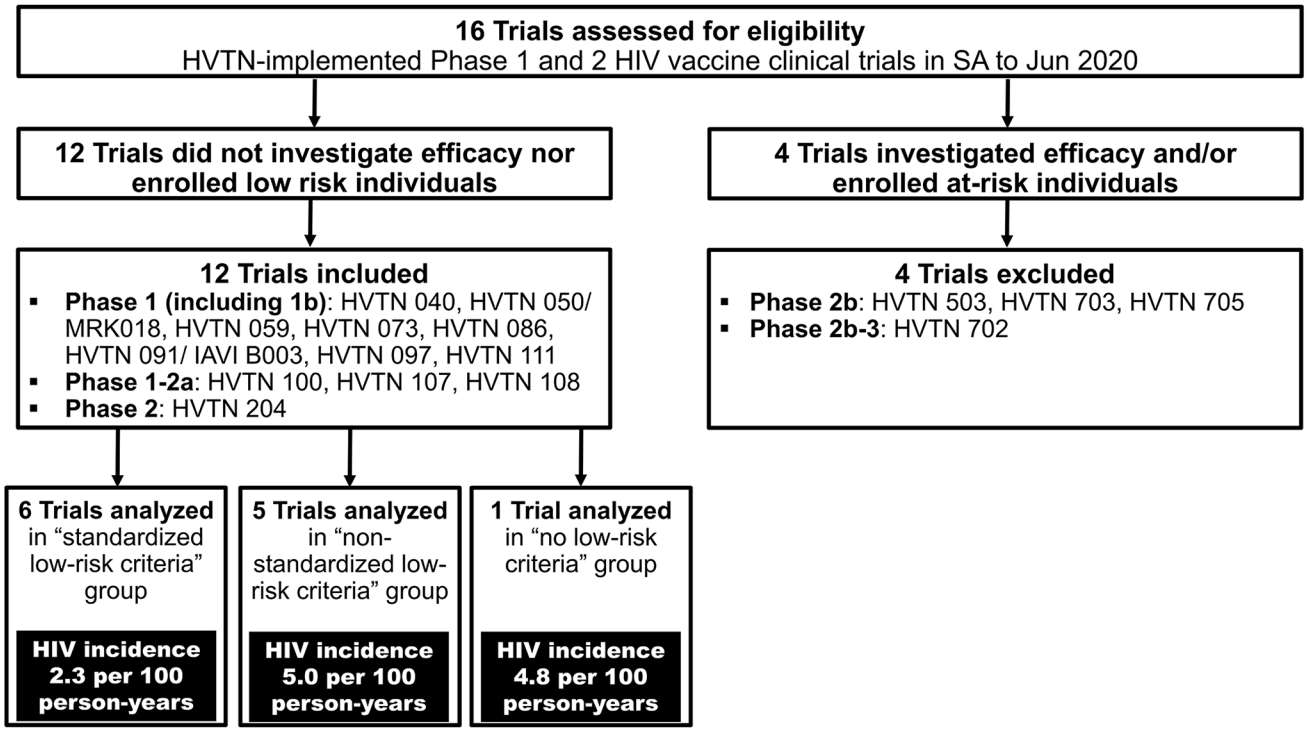

Fig. 1 Selection of Phase 1 and 2 HIV vaccine trials for analysis, and HIV incidence by risk criteria

In prevention research, the term 'low risk' has been used when an individual is deemed to have a small chance of being exposed to or acquiring HIV. Much of the work in the field of HIV risk criteria has pertained to identifying individuals at high risk, often to inform patient care, such as evaluations for eligibility for pre-exposure prophylaxis. [9, 10] Less is published about low risk criteria. Because risk factors for HIV acquisition differ by setting, early phase preventive HIV vaccine trials have defined low risk sexual behavior criteria variably. Beyond its use in HIV vaccine research, low risk criteria could also inform early phase research for prevention of HIV and other sexually transmitted infections.

Here, we describe the evolution of the eligibility criteria to define low-risk behavior in Phase 1 and 2 preventive HIV vaccine trials conducted with the HIV Vaccine Trials Network (HVTN) in South Africa. We measure HIV incidence in these trials, as a way of evaluating whether the low-risk behavior criteria applied at trial enrolment were, indeed, able to identify trial cohorts with low HIV incidence. In 2009, the HVTN standardized low risk criteria for their South African Phase 1 and 2 trials: not having a sexually transmitted infection, and being either sexually abstinent, in a mutually monogamous relationship with a known HIV-uninfected partner, or with one partner believed to be HIV-uninfected with whom condoms were used regularly in the preceding 12 months. We measure differences in HIV incidences in trial cohorts enrolled with the various stipulated HIV risk criteria.

Methods

We conducted a retrospective review of all completed HVTN-implemented Phase 1 and 2 HIV vaccine clinical trials conducted in South Africa until June 2020 (Fig. 1). We included all Phase 1 trials (i.e. Phase 1, Phase 1a, and Phase 1b). For Phase 2 trials, we included Phase 2a trials. We excluded Phase 2b trials because they sought to enroll individuals at risk for HIV acquisition. For trials named only as Phase 2, we included them if their objectives were not about vaccine efficacy.

From the protocols and trial guidance documents, we collated the eligibility criteria related to HIV risk (Table 1). Two authors coded the criteria in categories and resolved differences by discussion until consensus was reached.

From the trial databases, we collated the year that each trial began, the number of participants enrolled in South Africa, the trial follow up time and HIV outcomes. Data were pooled to form a metadata with the variables of participant number, date of enrolment, date of the final visit, age, gender and HIV results. A variable was created to distinguish between trials which followed the HVTN 2009 standardized low risk criteria versus trials which followed

Table 1 Summary of HIV risk criteria stipulated for enrolment into HVTN Phase 1 and 2 preventive HIV vaccine clinical trials conducted in South Africa (Unless specified, time periods refer to the 12 months before enrolment.) [(+) symbolises inclusion criteria and (–) symbolises exclusion criteria.]

Protocol number	Sexual behavior	Clinical characteristic	Drug use behavior
HVTN 040, HVTN 059	(-) Sexual contact (vaginal or anal) with HIV infected partner(s), or with > 4 partners of opposite sex, or with partner(s) who have injected drugs (-) Woman exchanged sex for drugs or money (-) Man had anal sex with > 1 male partner in last 6 months	(-) Self-reported syphilis, gonorrhea, non-gonococcal urethritis, chlamydia, pelvic inflammatory disease	(-) Crack or intravenous drug use
HVTN 050/ MRK018	(-) Unprotected or protected penile-anal or penile-vaginal sexual contact with an HIV infected partner in last 6 months (-) Exchanged sex for money, drugs or gifts in last 6 months (-) Protected penile-anal or penile-vaginal sexual contact with > 4 partners in last 6 months (-) Unprotected penile-anal or penile-vaginal sexual contact with > 1 partner in last 6 months	(-) History of, treatment for or diagnosis with a new sexually transmitted disease in last 6 months	(-) Alcohol abuse in last 2 years (-) Crack or intravenous drug use (-) Received injections of questionable sterility
HVTN 204	Nil standardized criteria stipulated		
HVTN 073	Nil standardized criteria stipulated	Nil standardized criteria stipulated	(-) Cocaine or methamphetamine
HVTN 091/ IAVI B003	(+) Sexually abstinent (+) Two or fewer mutually monogamous relationships with partners not known to be HIV infected who did not use illicit drugs (+) Two or fewer partners believed to be HIV-uninfected and who did not use illicit drugs and with whom he/she regularly used condoms for vaginal and anal intercourse (+) Two or fewer partners not known to be HIV-infected, did not use illicit injection drugs and with whom the volunteer used condoms for sexual intercourse (-) Unprotected sexual intercourse with a known HIV-infected person, a partner known to be at high risk of HIV infection or a casual partner (i.e., no continuing established relationship) (-) Engaged in sex work for money or drugs (-) Three or more sexual partners	(-) Syphilis, gonorrhea, non-gonococcal urethritis, HSV-2, chlamydia, pelvic inflammatory disease, trichomonas, mucopurulent cervicitis, epididymitis, proctitis, lymphogranuloma venereum, chancroid, or hepatitis B	(-) Frequent excessive daily alcohol use or frequent binge drinking or chronic marijuana or any other use of use of illicit drugs
HVTN 086, HVTN 097, HVTN 100, HVTN 111, HVTN 108, HVTN 107	Within last 12 months: (+) Sexually abstinent (+) In a mutually monogamous relationship with a partner with a known HIV-uninfected status (+) Had one partner believed to be HIV-uninfected with whom he/she regularly used condoms for vaginal and anal intercourse	(-) Syphilis, gonorrhea, chlamydia, trichomoniasis, active HSV lesions, chancroid, pelvic inflammatory disease, genital sores or ulcers, cervicitis, genital warts of the labia minora, vagina, or cervix, or any other symptomatic genital warts	HVTN 086 only (-) Excessive daily alcohol use or frequent binge drinking or chronic marijuana abuse or any other use of illicit drugs

low risk criteria other than the standardized risk criteria, and those which did not stipulate any risk criteria.

Median and interquartile ranges (IQR) were determined for continuous measures overall and by the risk criteria groupings. The medians were compared between criteria by quantile regression controlling for gender and the year the trial was initiated; age was included in the follow-up time comparison. Proportions were compared by logistic regression controlling for age, gender and year of trial initiation as appropriate. HIV incidence per 100 person-years was determined by dividing the number of HIV infections by total person-time. The hypothesis of no difference in HIV incidence between criteria was tested using Poisson regression modelling controlling for gender and age with follow-up

Table 2 Phase 1 and 2 preventive HIV vaccine clinical trials conducted by the HVTN in South Africa

Protocol number	Phase	Year that trial began	Number enrolled in South Africa	Median (IQR) age in years of South African participants	Number of males (%)	Median (IQR) follow up time in weeks per South African participant	Number of HIV infections
HVTN 040	1	2003	24	25.5 (22.5–31.0)	13 (54%)	55.5 (53.9–56.6)	1
HVTN 050/ MRK018	1	2005	17	25.0 (23.0–30.0)	9 (53%)	53 (52-102.7)	6
HVTN 059	1	2005	26	25.0 (22.0–31.0)	13 (50%)	36.5 (25.7–41.0)	0
HVTN 204	2	2006	240	24.0 (21.0–29.0)	108 (45%)	53.9 (52.1–56.1)	13
HVTN 073	1	2009	36	21.5 (20.0–25.0)	20 (56%)	173.6 (54.9-179.9)	0
HVTN 086	1	2011	185	23 (20.0–26.0)	89 (48%)	41.4 (40.0-43.2)	5
HVTN 091/ IAVI B003	1	2011	81	23.0 (21.0–27.0)	36 (44%)	16.0 (16.0–16.0)	2
HVTN 097	1b	2013	100	21.0 (20.0–25.0)	51 (51%)	58.1 (57.3–58.7)	0
HVTN 100	1–2	2015	252	23.0 (21.0–27.0)	143 (57%)	68.3 (65.2-134.9)	10
HVTN 111	1	2016	76	24.0 (21.0–27.0)	36 (47%)	54.0 (53.0-55.3)	0
HVTN 107	1-2a	2017	80	25.0 (22.0–27.0)	30 (38%)	78.9 (75.0-80.6)	4
HVTN 108	1-2a	2017	132	24.0 (21.0–28.0)	76 (58%)	53.9 (50.8–56.0)	4
Totals			**1249**	**Overall median 23.0 (21.0–27.0)**	**624 (50%)**	**Overall median 54.6 (43.7–63.9)**	45

time as an offset variable and a log link function. Model fit for incidence rate comparison was assessed using the scaled deviance and Pearson Chi-Square fit statistics. Statistical analyses were conducted using SAS Enterprise Guide 7.15 (SAS Institute, Cary, NC, USA).

This study was approved by the University of the Witwatersrand Human Research Ethics Committee. Participants provided informed consent voluntarily and in writing for their respective clinical trials.

Results

Risk Criteria

For twelve Phase 1 and 2 preventive HIV vaccine clinical trials conducted by the HVTN in South Africa, we categorized the eligibility low risk criteria as none, sexual behaviors, clinical characteristics, and/or drug use (Table 1). The indicators for sexual behavior included abstinence, a low number of uninfected or non-drug-using sexual partners, use of barrier protection, and not engaging in transactional sex. The indicator for clinical characteristics was the lack of sexually transmitted diseases.

The risk criteria of the earliest protocols (HVTN 040 and HVTN 059), initiated between 2003 and 2005, differ in two obvious ways from the standardized criteria used in protocols from 2011 onward (HVTN 086, HVTN 097, HVTN 100, HVTN 111, HVTN 108 and HVTN 107). First, the limit in the number of sexual partners became more stringent over time: the earliest protocols excluded participants on the basis of having more than 4 partners, while the latter protocols included participants who had no partner or one HIV-uninfected partner. Second, the constraint on the use of drugs was dropped over time: the earliest protocols excluded participants using certain illicit drugs, but the latter protocols – with the exception of HVTN 086 – did not stipulate this.

The age eligibility range began at 18 years old for all protocols, and ended at 60 years for HVTN 040; 50 years for HVTN 050/MRK018, HVTN 059, HVTN 204 and HVTN 091/IAVI B003; 45 years for HVTN 073 and HVTN 086; and 40 years for HVTN 097, HVTN 100, HVTN 111, HVTN 107 and HVTN 108. All protocols specified exclusion of individuals who had active syphilis, and pregnant women. All protocols except HVTN 204 specified exclusion of individuals with hepatitis B or hepatitis C infection.

Participant Demographics

The twelve trials enrolled 1249 participants in total, following them for a median of 54.6 (IQR: 43.7–63.9) person-weeks. The overall median age of participants was 23.0 years (IQR: 21.0–27.0). The proportions of males (50%, 624/1249) and females (50%, 625/1249) were similar.

Approximately 66% (825/1249) had been enrolled with the HVTN 2009 standardized low risk criteria, 15% (184/1249) had been enrolled using other sets of low risk criteria and 19% (240/1249) using no risk criteria. HVTN 204 (n = 240) enrolled the highest number of participants. Those enrolled in HVTN 040 (25.5 years, IQR: 22.5–31.0) had the highest median age. HVTN 073 had the longest median follow-up time (173.6 weeks, IQR: 54.9-179.9) (Table 2).

Table 3 Comparison of South African Phase 1 and 2 preventive HIV vaccine clinical trials by risk criteria and comparison of incidence controlling for gender and age with follow-up time as an offset variable

	Low risk criteria stipulated using the HVTN 2009 standardized low risk criteria	Low risk criteria stipulated with criteria other than the HVTN 2009 standardized low risk criteria	No risk criteria specified	p-value comparing standardized versus other non-standardized criteria (Wald χ^2)	p-value comparing standardized versus no risk criteria (Wald χ^2)
HVTN trials 2003–2020	HVTN 086, HVTN 097, HVTN 100, HVTN 111, HVTN 108, HVTN 107	HVTN 040, HVTN 059, HVTN 050/ MRK018, HVTN 073, HVTN 091/ / IAVI B003	HVTN 204	N/A	N/A
N	825	184	240	N/A	N/A
Females (%)	400/825 (48.5%)	93/184 (50.5%)	132/240 (55.0%)	0.1244 (2.36)	0.9030 (0.0148)
Median age in years	23.0 (IQR: 21.0–27.0)	24.0 (IQR: 21.0–27.0)	24.0 (IQR: 21.0–29.0)	0.6360 (0.22)	0.99 (0.0)
Median follow up in weeks	57.0 (IQR: 45.1–66.6)	29.9 (IQR: 16.0-55.1)	53.9 (IQR: 52.1–56.1)	**< 0.0001 (57606.7)**	**0.0015 (10.1)**
HIV infections, n (%)	23/825 (2.8%)	9/184 (4.9%)	13/240 (5.4%)	0.1327 (2.26)	0.0964 (2.76)
HIV incidence /100 person-years (CI)	2.3 (95% CI: 1.5–3.5)	5.0 (95% CI: 2.6–9.6)	4.8 (95% CI: 2.8–8.3)	**< 0.0001 (20.6)**	**< 0.0001 (15.2)**

Incident HIV Infections

Across all the trials, 45 HIV infections were reported, resulting in an overall HIV incidence of 3.1 (95% CI: 2.3–4.2) per 100 person-years. Table 3 shows comparisons by criteria types of the proportion of females, age, follow-up time, HIV infections and incidence [11–13]. Controlling for age and gender, the median follow-up time was significantly higher in the standardized criteria group compared to the non-standardized (57.0 weeks, IQR: 45.1–66.6 vs. 29.9 weeks, IQR: 16.0-55.1; $p < 0.0001$, Wald $\chi^2 = 57606.7$) and in the no risk criteria group (57.0 weeks, IQR: 45.1–66.6 vs. 53.9 weeks, IQR: 52.1–56.1; $p = 0.0015$, Wald $\chi^2 = 10.1$). HIV incidence was significantly higher in the low risk criteria [5.0 (95% CI: 2.6–9.6) versus 2.3 (95% CI: 1.5–3.5), $p < 0.0001$, Wald $\chi^2 = 20.6$] and no risk criteria [4.8 (95% CI: 2.8–8.3) versus 2.3 (95% CI: 1.5–3.5), $p < 0.0001$, Wald $\chi^2 = 15.2$] groups compared with the standardized low risk criteria group.

When HVTN 050/MRK018 data were excluded from the non-standardized low-risk criteria group, the HIV incidence rate was 2.7 (95% CI: 2-3.7), similar to the standardized low-risk criteria group (p-value = 0.714, Wald $\chi 2 = 0.13$) but lower than the no risk criteria group (p-value = 0.0036, Wald $\chi 2 = 8.46$).

Discussion

Our study found that, even in South Africa which had high HIV prevalence (20%) and incidence (1.72 per 100 person-years in 2012), [2, 14, 15] early phase HIV vaccine trials were able to enroll cohorts which experience low HIV incidence by assessing eligibility with standardized low HIV risk criteria. When the standardized criteria were applied, HIV incidence was 2.3 per 100 person-years. When criteria other than the standardized risk criteria were specified for eligibility, HIV incidence was 5.1 per 100 person-years, similar to applying no risk criteria (4.8 per 100 person-years).

In our analysis, standardization of risk criteria was significantly associated with reduced HIV incidence. In trials stipulating the HVTN 2009 standardized low risk criteria, median age was significantly younger and median trial follow up was significantly longer. The effect of criteria standardization on HIV incidence is explained by the application of existing national epidemiological knowledge on HIV risk factors. Although the age criteria for the protocols permitted a large range (the smallest range was 18–40 years, stipulated in five trials), it is interesting that the median age of enrolled participants was within a small, young, range. As evidenced by the inter-quartile range, half of the participants were aged 21–27 years. It is possible that trial investigators may have applied younger age to avoid exclusion by other criteria for age-related comorbidities. However, it is also possible that trial investigators may have used age as a consideration of risk, especially for men who are known to have lower HIV incidence at a younger age.

An individual's perception of their own risk for HIV acquisition may not always equate to HIV outcomes, so the use of risk factor assessments may be helpful. There is extensive scientific literature about factors that place individuals at high risk for HIV acquisition: biological (for example, women, uncircumcised males, sexually transmitted infections) [16–18] or behavioral (for example, multiple sexual partners, unprotected sex, [19, 20] alcohol before sex and sexual violence) [21, 22]. Our paper categorized factors which were used to identify low risk individuals in South Africa: sexual behaviors, clinical characteristics, and/or drug use behaviors.

Common to all protocols was the procedure of risk reduction counselling and HIV testing during visits, conducted using US Centers for Disease Control and Prevention (CDC) or local guidelines. The CDC recommends that clients in low prevalence settings be screened for HIV risk to decide whether a person should be referred for HIV testing. Individuals at risk, who should be considered for testing, are those who use injection drugs, have unprotected intercourse with a partner suspected to be infected, multiple sexual partners, sexually transmitted disease, hepatitis, tuberculosis, fever or illness of unknown cause, or an infection related to a weak immune system. [23]

In South Africa, country estimates of HIV incidence are based on cross-sectional data, which is unlike our data measured directly by longitudinal follow up. The country estimates and our measurements differ because of reasons including different sampling approaches and methods of estimation. Country data shows that HIV incidence amongst 15–49 year olds in 2012 was 1.72 per 100 person-years and in 2017 was 0.79 per 100 person-years. [14, 15]

Could low risk criteria be refined further to improve the identification of individuals who do not have HIV acquisition outcomes? As the prevention field evolves, it would be worthwhile investigating whether medical male circumcision and use of pre-exposure prophylaxis should be considered as low risk criteria. Male circumcision has been proven to reduce HIV acquisition risk durably. [24] Oral pre-exposure prophylaxis effectiveness has been variable, ostensibly by adherence: low among South African women but high among men who have sex with men MSM in developed countries. [25] Additionally, to standardize further, there could be quantifiable limits placed on how often condoms should be used in order to be considered "regularly".

The first key limitation to our analysis is a bias that would be challenging to quantify: sites may have customized their own additional criteria in accordance with community epidemiology. Secondly, although the exact product used in HVTN 050/MRK 018 was not tested for efficacy, it evaluated an Adenovirus 5 vaccine that was similar, except for two gene inserts, to a vaccine that later showed, in two HIV vaccine trials, an increased risk of HIV acquisition among some sub-groups. [11] To adjust for this possible confounder in a sub-analysis, we removed the HVTN 050 data from its non-standardized low risk group, and found that HIV incidence decreased, but was still lower than if no risk criteria were specified. Finally, during the years of the trials, the national introduction of prevention methods, such as couples counselling, male circumcision and pre-exposure prophylaxis, may have also reduced HIV incidence in later trials.

In conclusion, in South Africa lower risk cohorts can be identified successfully through sexual behavior, clinical characteristics and drug use behavior defined in the HVTN 2009 standardized low risk criteria.

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Authors' Contributions FL conceived the idea. FL and KO contributed to study design. FL and KO wrote the first draft of the manuscript. FL and KO analyzed the data. VOM collated risk data. MA performed data validation. All authors edited the manuscript with important intellectual content, and approved it.

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Data Availability Data will be made publicly available at the public-facing HVTN website (https://atlas.scharp.org/).

Code Availability not applicable.

Declarations

Conflict of Interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics Approval and Consent to Participate This study was approved by the University of the Witwatersrand Human Research Ethics Committee. Participants provided informed consent voluntarily and in writing for their respective clinical trials.

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