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Population-Level Correlation Between Incidence of Curable Sexually Transmitted Infections and Human Immunodeficiency Virus (HIV)-1 Among African Women Participating in HIV-1 Pre-Exposure Prophylaxis Trials

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Background. Highly efficacious oral pre-exposure prophylaxis (PrEP) is the global standard for human immunodeficiency virus (HIV)-1 prevention, including in clinical trials of novel PrEP agents using active-comparator designs. The analysis assessed whether incident sexually transmitted infections (STIs) can serve as a surrogate indicator of HIV-1 incidence that might occur in the absence of PrEP.

Methods. We analyzed data from 3256 women randomized to placebo groups of oral and vaginal PrEP trials (MTN-003/VOICE and MTN-020/ASPIRE). Regression modeling assessed the correlation between incident individual STIs (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*, each considered separately) and incident HIV-1.

Results. Across 18 sites in 4 countries (Malawi, South Africa, Uganda, Zimbabwe), STI and HIV-1 incidences were high: HIV-1 4.9, *N gonorrhoeae* 5.3, *C trachomatis* 14.5, and *T vaginalis* 7.1 per 100 person-years. There was limited correlation between HIV-1 incidence and incidence of individual STIs: *N gonorrhoeae* ($r = 0.02$, $P = .871$), *C trachomatis* ($r = 0.49$, $P = <.001$), and *T vaginalis* ($r = 0.10$, $P = .481$). The modest association with *C trachomatis* was driven by country-level differences in both *C trachomatis* and HIV-1, with no statistically significant association within countries.

Conclusions. Sexually transmitted infection incidence did not reliably predict HIV-1 incidence at the population level among at-risk African women participating in 2 large PrEP trials.

Keywords. clinical trial design; HIV incidence; sexually transmitted infections; women.

Worldwide, HIV-1 incidence remains highest in Africa, with women disproportionately affected [1], making them a population in great need of new, effective prevention interventions. Simultaneously, many African countries are adopting the use of oral pre-exposure prophylaxis (PrEP) in their national guidelines for persons at risk [2, 3]. The World Health Organization (WHO) recommends oral PrEP as a prevention option for persons at risk for HIV-1 worldwide and advises that PrEP access should be standard of care in future HIV-1 prevention trials.

Thus, how HIV-1 prevention trials are designed, including trials of novel PrEP agents, is being reshaped to adapt to the impact of PrEP expansion [4]. Specifically, because consistent use of oral PrEP is expected to result in substantially lower HIV-1 incidence, the use of HIV-1 incidence as an endpoint indicator in clinical trials could become challenging in studies in which individuals are assigned to either a novel PrEP agent or oral PrEP, if the study populations use PrEP consistently. Having counterfactual, alternative indicators of the HIV-1 incidence that might be expected in the absence of oral PrEP could be valuable to permit efficient evaluation of new prevention strategies, including new PrEP products.

Sexually transmitted infections (STIs) have long been associated with an increased risk of HIV-1 acquisition at the individual level [5], and the synergy between STIs and HIV-1

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acquisition in populations has been observed since the earliest days of the epidemic [6]. One recent analysis found that among men who have sex with men (MSM), there was a reasonable correlation between STI incidence (specifically, incidence of rectal gonorrhea) and incidence of HIV-1 in the absence of PrEP [7]—suggesting that that rectal gonorrhea incidence could be a surrogate for HIV-1 incidence in a novel PrEP trial among MSM. For women, whether STI incidence predicts HIV-1 incidence at the population level is unknown. Although STIs are a well established risk factor for HIV-1 in women, STI incidence is high in many settings in Africa that have a range of prevalences for HIV-1 [8]. Thus, STI incidence may not necessarily predict HIV-1 incidence at the population level. Using data from 2, multi-site, multinational PrEP trials among African women, we explored the correlation between incidence of STIs and incidence of HIV-1.

METHODS

A secondary analysis was conducted using data from 2 independent HIV-1 prevention trials conducted at study sites in sub-Saharan Africa: the MTN-003/VOICE trial and the MTN-020/ASPIRE trial (ClinicalTrials.gov identifiers NCT00705679 and NCT01617096). Detailed methods and results for these studies have been published [9, 10].

Populations and Procedures

Both trials were multi-site, double-blind, placebo-controlled randomized trials enrolling healthy, sexually active, HIV-1 seronegative, reproductive age women at risk of HIV-1 acquisition. Additional eligibility criteria were being nonpregnant, not breastfeeding, and willing to use effective contraception during study participation. In general, the major difference between the trials were the differing study products being investigated.

The VOICE study was conducted from September 2009 to August 2012 and tested the safety and effectiveness of daily use of either an antiretroviral tablet (tenofovir disoproxil fumarate [TDF]) alone or in combination with emtricitabine (FTC) or a vaginal gel (tenofovir [TFV], 1% gel) among women aged 18 to 40 years. The study enrolled 5029 women from 15 clinical research sites in Uganda, South Africa, and Zimbabwe. Participants were randomized to the tablet or the vaginal gel regimen and then to active or placebo within those groups, with study follow-up from a minimum of 12 months to 34 months.

ASPIRE was conducted between August 2012 and June 2015 and tested the safety and effectiveness of a vaginal ring containing the dapivirine for reducing the risk of HIV-1 infection when used by women for 1 month at a time. ASPIRE enrolled 2629 women aged 18 to 45 years and was conducted at 15 clinical research sites in Malawi, Uganda, South Africa, and Zimbabwe, 11 of which were sites that had previously participated in VOICE. Participants were randomized into active or placebo vaginal ring groups, with study follow-up from a minimum of 12 months to 31 months.

Ethical Review

The VOICE and ASPIRE studies were approved by the Institutional Review Boards associated with each study site. Women provided written informed consent.

Study Procedures

At each monthly visit, pregnancy testing, study product management procedures, behavioral evaluations for HIV-1/STI risk reduction, and protocol adherence were conducted. Comprehensive HIV-1 prevention services were provided for each participant, which included behavioral risk reduction counseling, partner HIV-1 testing, STI testing, and treatment including partner treatment, provision of free male or female condoms, and referral of partner for medical male circumcision and HIV-1 treatment as appropriate. Sexually transmitted infections were managed per local guidelines or current WHO guidelines as part of study procedures; however, there was no test for cure after treatment was given.

At baseline in both trials, women were screened for curable STIs (syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*) and treated before enrollment. After enrollment, scheduled STI testing was done annually in VOICE and semiannually in ASPIRE for all participants and at the final visit in both trials, with additional testing in both studies testing when clinically indicated. Testing for *N gonorrhoeae* and *C trachomatis* was performed on urine samples using strand displacement amplification (by BD Probe Tec ET; Becton Dickinson, Franklin Lakes, NJ) in VOICE and by nucleic acid amplification testing (Cepheid's GeneXpert System) in ASPIRE. Syphilis serologic testing was done in both studies, but incidence was low (<1 per 100 person-years in both trials) and thus was not included in the present analysis. Vaginal fluid swabs collected during pelvic examinations were used to conduct the OSOM *Trichomonas* rapid test for diagnosis of *T vaginalis* in both studies. Sexually transmitted infections diagnosed during follow-up were treated using local national standard regimens.

In both trials, HIV-1 seronegative status was confirmed at the time of enrollment and HIV testing was performed at all subsequent monthly visits. Testing was done by 2 rapid blood-based tests done in parallel; positive results were confirmed by assessment of HIV-1 ribonucleic acid (RNA) and Western blot, and all incident HIV-1 infections were confirmed by an endpoint committee.

Statistical Methods

Data from the 3 placebo arms across the 2 trials (VOICE placebo oral tablet, VOICE placebo vaginal gel, and ASPIRE placebo vaginal ring, analyzed separately) were analyzed, to remove any effect on HIV-1 acquisition of the active PrEP products.

Because the intention of the analysis was to assess the correlation between population-level incidence of STIs and HIV-1, not individual-level risk, each site in each placebo arm was considered a data point. Analyses were limited to the modified intention-to-treat populations of the 2 studies (ie, excluding participants who were HIV-1 infected at baseline as demonstrated by subsequent HIV-1 RNA polymerase chain reaction testing of archived samples) who had at least 1 STI test done post-baseline.

Incidence rates at each site were calculated as the number of incident events (allowing for multiple events per participant for STIs) divided by the total person-years at risk. Each positive test was considered as an incident event, because the study procedures mandated treatment and STI therapies have known high cure rates.

Scatterplots with loess curves were generated to visually assess association between incidence of STIs and HIV-1 acquisition in the placebo groups of the VOICE and ASPIRE trials with loess (moving average) curves and least squares linear fits provided to visualize relationships. Each clinical site in each study randomized group represented 1 data point. Pearson's correlation (r) was calculated to assess the strength of the linear relationship between HIV-1 incidence and STI incidence. All statistical analyses were performed using R v4.0.2 software.

RESULTS

Study Population

In VOICE, a total of 5029 women (median age was 24 years; interquartile range, 21 to 29) were enrolled: 1007 in the oral TDF arm, 1003 in the oral TDF-FTC arm, 1009 in the oral placebo arm, 1007 in TFV gel arm, and 1003 in placebo gel arm. In ASPIRE, a total of 2629 women (median age was 26 years; interquartile range, 22 to 31) were enrolled: 1313 in the active dapivirine vaginal ring arm and 1316 in the placebo arm. Included in this analysis were 3256 women enrolled in the 3 placebo arms from the 2 trials across 18 sites in 4 countries (Malawi, South Africa, Uganda, Zimbabwe) who had at least 1 STI test done post-baseline. Characteristics of participants generally were consistent with a population at risk for HIV-1 and STIs (Table 1).

Human Immunodeficiency Virus-1 and Sexually Transmitted Infection Incidence

In ASPIRE, the 1306 women randomized to placebo were followed for a total of 2135 person-years. Human immunodeficiency virus-1 incidence was 4.5 per 100 person-years (95% confidence interval [CI], 3.7 to 5.5). In VOICE, 980 women who were randomized to oral placebo were followed for a total of 1307 person-years; similarly, 970 women randomized to vaginal gel placebo were followed for a total of 1030 person-years. The oral placebo arm HIV-1 incidence was 4.6 (95% CI, 3.5–5.9), and the vaginal gel placebo arm HIV-1 incidence was 6.8 (95% CI, 5.3–8.6). In both studies, HIV-1 incidence differed strongly by country, with the highest incidence in South Africa.

In both studies, STI rates were high, with *C trachomatis* the most commonly detected. The STI incidences per 100 person-years in VOICE oral placebo, VOICE gel placebo, and ASPIRE placebo groups were as follows: *N gonorrhoeae* incidences were 3.3 (95% CI, 2.4–4.5), 3.1 (95% CI, 2.1–4.4), and 7.5 (95% CI, 6.4–8.8). *Chlamydia trachomatis* incidences were 15.1 (95% CI, 13.1–17.4), 12.0 (95% CI, 10.0–14.3), and 15.4 (95% CI, 13.8–17.2). *Trichomonas vaginalis* incidences were 7.1 (95% CI, 5.7–8.8), 6.2 (95% CI, 4.8–8.0), and 7.1 (95% CI, 6.3–7.9).

Correlation of Human Immunodeficiency Virus- Incidence and Sexually Transmitted Infection Incidence

There was limited correlation between HIV-1 incidence and the incidence of individual STIs (Figure 1), with generally low

Table 1. Characteristics of Participants at Baseline by Placebo Randomization Group in the VOICE and ASPIRE Trials

Characteristic	VOICE Oral Placebo *N* = 980	VOICE Gel Placebo *N* = 970	ASPIRE Placebo Vaginal Ring *N* = 1306
Age (year), median (range)	24 (18–40)	24 (18–40)	26 (18–45)
Earns own income, no. (%)	576 (59)	553 (57)	577 (44)
Currently married, no. (%)	204 (21)	212 (22)	544 (42)
≥2 male sex partners in the past 3 months, no./total no. (%)	234/971 (24)	184/960 (19)	223 (17)
Condom use during last vaginal sex, no./total no. (%)	717/843 (85)	708/854 (83)	722 (55)
Anal sex in the previous 3 months, no./total no. (%)	171/970 (17)	168/954 (18)	28 (2)
Contraception method, no. (%)			
Injectable	681 (69)	699 (72)	732 (56)
Oral pills	228 (23)	210 (22)	143 (11)
STIs			
Neisseria gonorrhoeae, no. (%)	33 (3)	35 (4)	51 (4)
Chlamydia trachomatis, no. (%)	124 (13)	123 (13)	137 (10)
Trichomonas vaginalis, no. (%)	66 (7)	50 (5)	90 (7)

Abbreviations: STI, sexually transmitted infection.

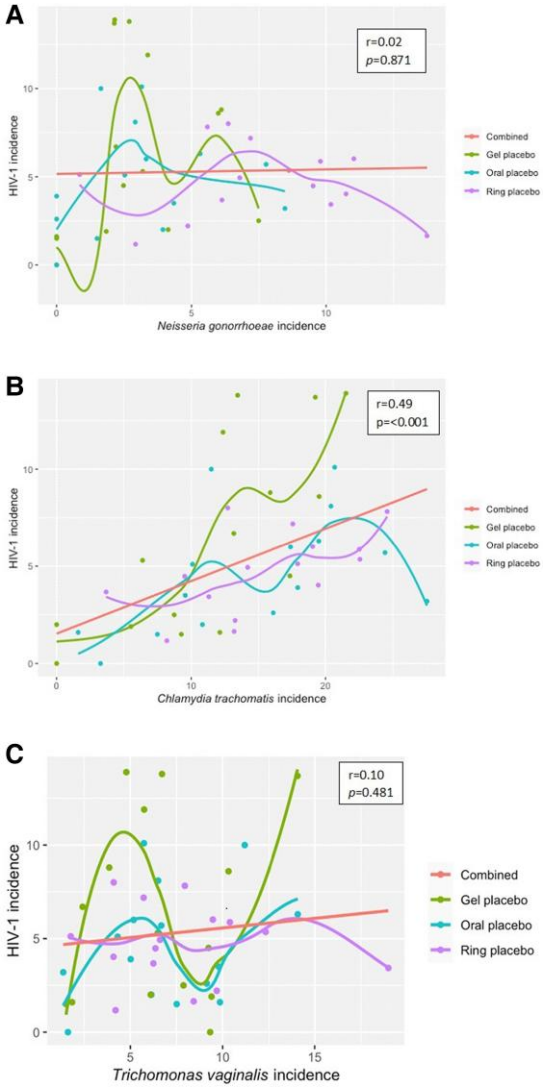

Figure 1. Graphical depiction of the association between incidences of curable sexually transmitted infections (STIs) and human immunodeficiency virus (HIV)-1, in the placebo groups of the VOICE and ASPIRE trials. Each panel represents 1 STI, with incidence depicted along the x-axis: *(A) Neisseria gonorrhoeae, (B) Chlamydia trachomatis, (C) Trichomonas vaginalis*, for each, HIV-1 incidence is depicted along the y-axis. Each clinical site in each study represents one date point: green = VOICE vaginal gel placebo, blue = VOICE oral placebo, purple = ASPIRE placebo. Corresponding colored lines represent moving averages (loess) of association between STI and HIV-1 incidences. Red lines represent overall relationship by linear regression. R values are from regression models.

correlation coefficients. For *N gonorrhoeae* ($r = 0.02$, $P = .871$) and *T vaginalis* ($r = 0.10$, $P = .481$), virtually no association was detected, whereas with regards to *C trachomatis* infection, a modest relationship to HIV-1 incidence was detected ($r = 0.49$, $P = <.001$). Further analysis suggested that relationship was largely driven by between-country differences in incidences of both *C trachomatis* and HIV-1, with incidences of both infections being high in South Africa (Figure 2); when limited to South African sites, the correlation between *C trachomatis*

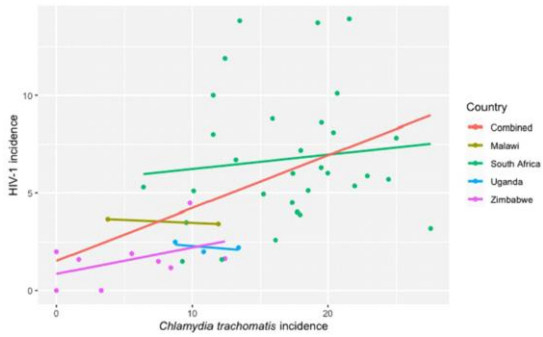

Figure 2. Graphical depiction of the correlation between incidences of *Chlamydia trachomatis* and human immunodeficiency virus (HIV)-1, grouped by country. Each clinical site in each study represents one date point, date points are color-coded by country: yellow green = Malawi, green = South Africa, blue = Uganda, purple = Zimbabwe, red = combined countries. Corresponding colored lines represent regression depiction of association between *C trachomatis* and HIV-1 incidences within each country, generally showing limited association.

and HIV-1 incidences was weak ($r = 0.11$, $P = .55$). To explore the potential effect of differences in the frequency of STI testing between ASPIRE and VOICE, analyses were repeated for each trial considered separately; results were similar to the overall findings (data not shown).

DISCUSSION

In this analysis among women from multiple African countries participating in an HIV-1 prevention trial but not using active oral or vaginal PrEP, STI incidence was high and differed substantially across countries but was not strongly correlated with HIV-1 incidence. These results suggest that STI incidence is unlikely to be a robust counterfactual marker of HIV-1 incidence for future trials of HIV-1 prevention interventions in cis women, including new PrEP trials.

Whether STIs can be an indicator for HIV-1 acquisition in populations at risk for HIV-1 could be valuable for planning future clinical trials of PrEP agents, such as for a noninferiority designed trial testing a novel PrEP agent compared with an established PrEP agent. In such a trial, HIV-1 incidence might be expected to be low in both randomized groups, because both would be receiving active PrEP. Thus, a high STI incidence, rather than HIV-1 incidence itself, could indicate high ongoing sexual risk of HIV-1, but only if STI incidence and HIV-1 incidence were known to be correlated. In addition, using alternative indicators of HIV-1 risk, like STIs, may permit more cost-effective trials with smaller sample populations. It is unfortunate that our data do not support curable STIs as an indicator of HIV-1 incidence in African women. There was a modest association with *C trachomatis* that was driven by country-level differences in both *C trachomatis* and HIV-1—essentially, *C trachomatis* and HIV-1 were both high in South Africa and both were lower elsewhere, so the correlation was

driven by country not by an inherent correlation between the STI and HIV-1. Thus, this STI has limited utility as a counterfactual tool in a South African prevention trial.

An analysis similar to the one we conducted, focused on studies globally among MSM not using PrEP, showed a strong correlation between the incidence of rectal *N gonorrhoeae* infection and HIV-1 incidence [7]. For MSM, rectal exposure is thought to be the principal route of HIV-1 exposure, thus a correlation between rectal STI incidence and HIV-1 incidence suggests a robust counterfactual relationship; for women, the analogous predictor would be cervicovaginal STIs, as measured in the present analysis, because vaginal exposure is the principal route of HIV-1 acquisition. We analyzed 8 studies and created a predictive regression model that could predict HIV-1 acquisition in populations with varying incidences of rectal *N gonorrhoeae* infection. One potential limitation of that analysis was that several of the studies included were conducted before widespread use of antiretroviral treatment for HIV-1 prevention or use of oral PrEP at the community level, and thus results may not be fully relevant to contemporary HIV-1 risk. In addition, the relationship between curable STIs and HIV-1 may be different for MSM versus women. Our analysis did not establish a similar correlation within the population of heterosexual women between curable STIs and HIV-1 acquisition.

Sexually transmitted infections as an individual risk factor for HIV-1 acquisition in heterosexual women has been well established in numerous published articles [11–15]. Other evaluations from HIV-1 prevention trials have found that STIs can be used for predicting HIV-1 risk for individuals through prediction tools, in combination with other risk factors. Our results do not refute those prior findings but instead reflect analyses operating at the population versus individual level. Other potential counterfactual measures of HIV-1 incidence are being evaluated, including assessing recent HIV-1 infections using antibody avidity approaches among individuals screening for HIV-1 prevention trials, short-duration prospective cohorts to directly measure HIV-1 incidence in a population, using concurrent or near-contemporary historical HIV-1 incidence in populations from similar geographies, using standardized risk scoring tools to predict incident HIV-1 based on baseline demographics and risk behaviors, and back-calculating HIV-1 risk reduction and background incidence based on PrEP adherence measures [4, 16, 17].

Our findings should be interpreted in the context of limitations. The 2 trials we analyzed did not conduct test of cure for STIs, which makes it difficult to differentiate new infections from reinfections or treatment failures. Data were limited to 4 countries within sub-Saharan Africa with varying HIV-1 incidences that may not be generalizable to all heterosexual women in the region; however, the trial sites were highly representative of the types of clinical trial sites that would be used for clinical trials of novel PrEP, vaccine, and other HIV-1 prevention strategies.

CONCLUSIONS

In summary, in this population of women in Africa having a high incidence STI, acquisition of STIs were not predictive of HIV acquisition and cannot be used as surrogates of HIV risk. Other counterfactual strategies will be needed to establish expected HIV-1 incidence in populations participating in next-generation PrEP clinical trials.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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