Published in final edited form as:
Sex Transm Infect. 2014 August ; 90(5): 363–369. doi:10.1136/sextrans-2014-051537.

HPTN 035 Phase II/IIb Randomized Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5% PRO 2000 for the Prevention of Sexually Transmitted Infections in Women

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The study was conceptualized and designed by M.B.G., B.R., M.H., B.M., D.C., E.Y., G.R., N.M., K.G., S.H., and S.A.K. Data was analysed and interpreted by M.B.G., B.R., M.H., and S.A.K. M.B.G. had full access to all of the data and takes responsibility for the integrity of the data and accuracy of the data analysis. M.B.G. was responsible for writing the article, and all coauthors contributed to critical revision of the article.

Provenance and peer review
Not commissioned; externally peer reviewed.

Competing Interests:
None of the authors, or their immediate family, has any specified relationships with any companies that might have an interest in the submitted work. Among the remaining members of the HPTN 035 Study Team, A.P. was an employee of, and held equity interest in, Endo Pharmaceuticals Solutions, the owner of PRO 2000. T.M. was an employee of ReProtect that sponsored BufferGel for the study, and R.B., L.S.-T., and S.E. were employed by the NIH, which funded the study.

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Abstract

Objectives—To estimate the effectiveness of candidate microbicides BufferGel and 0.5% PRO 2000 Gel (P) (PRO 2000) for prevention of non-ulcerative sexually transmitted infections (STIs).

Methods—Between 2005 and 2007, 3099 women were enrolled in HIV Prevention Trials Network (HPTN) protocol 035, a phase II/IIb evaluation of the safety and effectiveness of BufferGel and PRO 2000 for prevention of sexually transmitted infections, including *Neisseria gonorrhoeae* (GC), *Chlamydia trachomatis* (CT), and *Trichomonas vaginalis* (TV). Incidences of STIs were determined by study arm, and hazard ratios (HRs) of BufferGel and PRO 2000 versus placebo gel or no gel control groups were computed using discrete time Andersen-Gill proportional hazards model.

Results—The overall incidence rates were 1.6/100 person-years at risk (PYAR) for GC, 3.9/100 PYAR for CT, and 15.3/100 PYAR for TV. For BufferGel versus placebo gel, HRs were 0.99 (95% CI 0.49–2.00), 1.00 (95% CI 0.64–1.57), and 0.95 (95% CI 0.71–1.25) for prevention of GC, CT, and TV respectively. For PRO 2000, HRs were 1.66 (95% CI 0.90–3.06), 1.16 (95% CI 0.76–1.79), and 1.18 (95% CI 0.90–1.53) for prevention of GC, CT, and TV respectively.

Conclusions—The incidence of STIs was high during HPTN 035 despite provision of free condoms and comprehensive risk-reduction counselling, highlighting the need for effective STI prevention programmes in this population. Unfortunately, candidate microbicides BufferGel and PRO2000 had no protective effect against gonorrhoea, Chlamydia, or trichomoniasis.

Keywords

Neisseria gonorrhoeae; *Chlamydia trachomatis*; *Trichomonas*; microbicides; prevention

INTRODUCTION

The World Health Organization (WHO) estimates 328 million new cases of non-ulcerative sexually transmitted infections (STIs; Chlamydia, gonorrhoea, and trichomoniasis) occur every year around the world.[1] Most of these incident infections occur in developing countries where STIs remain a significant public health problem and HIV is hyper-endemic. Those contracting STIs are at high risk for HIV acquisition because they may have recently been exposed to HIV,[2] and the STI represents a biologic agent that increases the individual's susceptibility to HIV. Trials have measured that persons with a non-ulcerative STI have a 3- to 4-fold increased risk of acquiring HIV.[3–5] In HIV negative individuals, STIs increase susceptibility to HIV by recruiting HIV susceptible inflammatory cells to the genital tract and by disrupting mucosal barriers to infection.[3]

With recognition that male-to-female sexual transmission is a major driver of the 21st century HIV-1 epidemic,[6] a new focus in the past decade has been on the development of topical microbicide products for the prevention of HIV-1 that can be used with or without condoms and controlled by the receptive partner.[7] Since vaginal microbicides have the ability to potentially interrupt both HIV as well as STIs, it is important to evaluate their potential efficacy in preventing HIV and STIs independently. In addition, if a microbicide demonstrates effectiveness in preventing HIV, it is useful to see if this impact is dependent or independent of its effects on STIs. Modelling studies predict that a microbicide active against curable STIs with a combined prevalence greater than 10% may substantially contribute to its effect on HIV prevention (by more than half), especially when the microbicide's impact on preventing HIV is modest (i.e. ≤ 50% effectiveness).[8] In the primary analysis of HIV Prevention Trials Network (HPTN) protocol 035, there was suggested benefit of 0.5% PRO 2000/5 Gel (P) (PRO 2000) in HIV prevention; however, a subsequent larger trial failed to confirm this. [910] In this study, we assessed the effectiveness of BufferGel and PRO 2000 in preventing non-ulcerative STI acquisition.

These candidate microbicides have promising preclinical data in support of their potential impact on non-ulcerative STIs. BufferGel was designed to exploit the natural defence against cervicovaginal infections found in acidic vaginal fluid[1112] by maintaining an acidic pH in the vagina despite the presence of an alkaline ejaculate and was shown effective against *Neisseria gonnorrhoeae* (GC) and *Chlamydia trachomatis* (CT) *in vitro* and in some[13–15] but not all animal models.[1516] PRO 2000, a naphthalene sulfonate polymer, which has minimal effect on vaginal pH, was designed to block attachment and entry of STIs and HIV into host cells. Preclinical studies of PRO 2000 demonstrated *in vitro* and *in vivo* efficacy against GC and CT but not *Trichomonas vaginalis* (TV).[131718]

METHODS

Ethics approval

The trial (clinicaltrials.gov number NCT00074425) was approved and overseen by local ethics committees and institutional review boards at each study site.

Study Population

This study was conducted at 8 sites: Blantyre and Lilongwe, Malawi; Durban and Hlabisa, South Africa; Lusaka, Zambia; Chitungwiza and Harare, Zimbabwe; and Philadelphia, U.S.A. Women eligible for enrolment into study included HIV negative women 18 years or older in general good health, who had at least one episode of vaginal intercourse in the 3 months preceding enrolment, and who were willing and able to provide informed consent and locator information. Women who were latex allergic, had used intravenous drugs in the preceding 12 months, had on average more than 2 sexual episodes per day in the 2 weeks preceding screening, had safety laboratory abnormalities, were recently pregnant or planned to become pregnant during the study, or had deep epithelial disruption on pelvic examination, were excluded.

Study Procedures

During screening, women were tested for cervical/vaginal infections, including GC and CT strand displacement assay (SDA) on urine samples and TV by microscopic evaluation of vaginal fluid (i.e., wet prep). Women diagnosed with active infection by these, or other, STIs at the time of screening were treated per WHO guidelines[19] and were not enrolled unless treatment was completed and all symptoms had resolved within 30 days of obtaining informed consent for screening.

Women enrolling into the study were randomly assigned in equal proportions to one of four study arms [BufferGel vaginal gel, PRO 2000 vaginal gel, hydroxyethylcellulose (HEC) placebo vaginal gel, or no gel/condoms only]. Randomization was stratified by site, and the three gel groups were double-blinded while the no gel group was open label. All study gels were similar in appearance and were packaged in pre-filled, identical vaginal applicators. Women assigned to a gel arm were educated and instructed to insert one applicator of gel intravaginally ≤1 hour before each episode of vaginal intercourse, were given condoms and risk-reduction counselling, and were informed to contact study staff with questions or adverse events (AEs). Participants answered behavioural questionnaires during one-on-one interviews at enrolment and quarterly to assess number of partners, frequency and type of sex, use of condoms, adherence to study product, and any social harms resulting from study involvement. Medical evaluation included monthly visits and quarterly physical examination including pelvic examination and AE determination. All issues of reproductive health were addressed within the study facilities, including syndromic treatment for documented STIs. Study gels were held in the case of pregnancy or HIV seroconversion.

Laboratory Procedures

Quarterly laboratory procedures included saline wet mount of the vaginal smear, which was examined on site for the presence of motile TV. Specificity for TV by wet mount is approximately 100%, with a sensitivity of 51 to 66%, as compared to 70 to 85% by culture.[20] Local referral laboratories for each site performed Bectin Dickinson Probe Tec ET GC and CT SDA from urine on individuals annually, at study exit, and as clinically indicated among participants with suspected cervicitis/vaginitis. Diagnostic test of cure following treatment was not performed. The BD Probe Tec ET urine assay has a specificity of more than 97% and a sensitivity of 80% as compared with culture methods.[21] Additional laboratory procedures included evaluation for Candidiasis, bacterial vaginosis (BV), syphilis, type 2 herpes simplex virus, chancroid, and HIV. Clinical and laboratory staff at all sites underwent proficiency testing for on-site testing per protocol prior to study initiation and were subject to periodic review by DAIDS Clinical Site Monitoring Group for quality assurance.

Statistical Methods

The statistical rationale for the study design and sample size have been presented elsewhere;[22] the primary analysis was intent-to-treat including all women with non-zero follow-up time. Incidence rates for GC, CT, and TV were calculated as the number of incident events (allowing for multiple events per participant) divided by the total person-years at risk (PYAR). Results were calculated as number of events/100 PYAR. Two

controls, a placebo gel and a no gel comparator were utilized during this study to confirm that the near-neutral pH HEC placebo gel had no impact on risk of infection.[23] The primary analysis of this study was a comparison of the effectiveness of BufferGel and PRO 2000 versus placebo gel; however, the candidate microbicides were also compared to the no gel study group.

For each STI and study site, incidence rates were computed by study group as well as overall. The 95% confidence intervals (95% CI) around these estimates were calculated based upon methods for recurrent outcomes.[24] Because women with STIs and other genital infections (and their partners) received treatments regarded to be effective at all sites, any infection detected during the follow-up periods was considered a new infection. Risk of STI acquisition by study arm was then determined by calculating hazard ratios (HRs) comparing the hazard of acquiring an STI while in the BufferGel or PRO 2000 groups to the hazard of acquiring an STI while in the placebo gel or no gel groups, using discrete time Andersen-Gill proportional hazards model. Self-reported sexual risk behaviour data was collected at baseline and each quarterly follow-up visit. All data analysis was performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Of 5888 women screened for eligibility, 3101 (53%) were enrolled in the study. Of these, 443 were from Blantyre, 600 from Lilongwe, 704 from Durban, 350 from Hlabisa, 320 from Lusaka, 260 from Chitungwiza, 224 from Harare, and 200 from Philadelphia. Fourteen women were excluded because of acute HIV infection at the time of enrolment (n=12) or duplicate enrolment (n=2). The remaining 3087 women were analysed by intention to treat for each study group as follows: 775 in BufferGel, 769 in PRO 2000, 771 in placebo gel, and 772 in no gel/condoms only.[10] Overall, 2,889 (94%) women successfully completed the study, with similar rates across the four study groups (range: 93%–94%; p = 0.9). Individuals with no follow-up time (n=37) were excluded from analysis; those 3050 contributing at least some time in follow-up, including the 2889 (94%) finishing study and 161 (5%) lost to follow-up, were included in the primary intent-to-treat analysis and completed a median of 1.8 years follow-up during study from February 2005 to September 2008.

Baseline characteristics did not significantly differ between the four treatment arms including age, education, marriage, cohabitation, sexual behaviour, and baseline prevalence of non-ulcerative STIs (GC, CT, TV) identified at each site during screening (Table 1) as well as pelvic exam findings and safety laboratory measures (data not shown). Certain characteristics varied significantly by site, such as condom use and report of ever having had anal sex. At enrolment, the proportion of women reporting condom use during their last vaginal sex act ranged from 52%–87% among study sites but was similar within the four treatment groups (range: 67%–69%). 46% of participants at the Philadelphia site reported a history of engaging in anal sex compared to only 0.3% – 4.1% of women within the African sites.

Gel groups and the no gel/condoms only group were counselled identically in a comprehensive fashion and encouraged to use condoms at each sexual encounter. 600,672 male condoms were distributed among study participants. Reported condom use at last vaginal sex ranged from 73% to 76% during the first 12 months. Self-reported condom use during the last sexual act was similar in the three gel arms, but higher in the no gel arm (71.7% vs 80.7%, $p<0.0001$). Reported gel use at last sex was 81% (range: 75–94% across the sites) and was not significantly different between the three gel groups (range 80.6%–81.5%). Overall, women reported gel use in conjunction with condoms during study follow-up in 61.3% of sex acts. Gel products were used in 69.1% of last sex acts in which a condom was not used, among those in the three gel arms. Gel acceptability was high, and 99% of women stated at study exit that they would use a microbicide gel if it were found effective. The safety profiles of both BufferGel and PRO 2000 were excellent.[10]

Incidence of STIs varied substantially by location (Table 2). Hlabisa, the site with the highest incidence of HIV, had the highest incidence rates of GC, CT and TV. Among study clinics, incidence of GC trended similarly to incident HIV, whereas CT and TV did not. Overall, 82 cases of GC were diagnosed in 76 women over 5115 person-years (incidence rate: 1.6 cases/100 PYAR; 95% CI: 1.2–2.0). Incident GC rates were lowest at the U.S. site (0.2 cases/100 PYAR; 95% CI: −0.3–0.8) and highest at the Durban and Hlabisa sites (2.0 cases/100 PYAR; 95% CI: 1.2–2.9 and 3.0 cases/100 PYAR; 95% CI: 1.4–4.6, respectively). Participants in the PRO 2000 arm had the highest incidence rate of GC (2.2 cases/100 PYAR; 95% CI: 1.3–3.0) but it was not statistically different from the other treatment groups, overall or by site, as indicated by overlapping 95% confidence intervals with incidence rates among the BufferGel, placebo or no gel arms (Figure 1A).

Cases of CT occurred 198 times in 180 women during 5115 person-years follow-up for an overall incidence of 3.9 cases/100 PYAR (95% CI: 3.3–4.4) at all sites. Incident CT was more common in Hlabisa (10.3 cases/100 PYAR; 95% CI: 7.6–13.0) and Durban (6.4 cases/100 PYAR; 95% CI: 4.9–7.9) as compared to the remaining sites (Table 2). Incidence of CT by treatment group was not different (Figure 1B).

TV was diagnosed 792 times in 521 women during 5177 person-years of follow-up for an overall event rate of 15.3 cases per 100 PYAR (95% CI: 13.9–16.7) for all sites. Rates were highest in Hlabisa (33.6 cases/100 PYAR; 95% CI: 28.0–39.1) and Philadelphia (25.7 cases/100 PYAR; 95% CI: 18.9–32.5). Incidence at the remaining sites were statistically significantly lower than in Hlabisa. All remaining sites' rates but Lilongwe's were lower compared to the Philadelphia site's rate (Table 2). Estimates of TV were not statistically different among treatment groups (Figure 1C).

To examine the impact of study products on incidence of non-ulcerative STIs, HRs for STI acquisition were calculated for BufferGel and PRO 2000 as compared to either placebo gel or no gel controls (Table 3). HRs for acquiring GC, CT, or TV in the BufferGel group, as compared to the placebo gel group, were 0.99, 1.00 and 0.95, with 95% CIs crossing 1.0 in all cases, indicating no effect on STIs by BufferGel. HRs for acquisition of STIs when BufferGel was compared to the no gel control group were also not statistically significant, with 95% CI of HRs crossing 1.0 for each group. Among those in the PRO 2000 arm, there

was a tendency toward higher acquisition of GC as compared to the placebo gel group (HR 1.66; 95% CI: 0.90–3.06) and the no gel group (HR 1.45; 95% CI: 0.78–2.70) but neither finding was statistically significant. The HRs for acquisition of CT and TV among those in the PRO 2000 group as compared to the placebo gel group were 1.16 (95% CI 0.76, 1.79) and 1.18 (95% CI 0.90, 1.53), respectively, demonstrating no efficacy of PRO 2000 against these organisms. Similarly, no statistical differences were seen when comparing the PRO 2000 group with the no gel group, with all 95% CIs crossing 1.0. Finally, the HRs for incident GC, CT and TV for individuals in the placebo gel group were compared to those in the no gel group. No statistically significant differences were found among these comparisons.

DISCUSSION

Neither BufferGel nor PRO 2000 demonstrated a statistically significant protective effect against any of the three non-ulcerative STIs when compared to placebo gel or no gel controls in this study. While HPTN 035 primary findings suggested benefit toward decreased risk of HIV acquisition among women randomized to PRO 2000 (no effect among those using BufferGel), this result was subsequently not confirmed in a larger trial.[9,10] In this study, we went further to suggest that these two microbicides were also not effective in blocking male-to-female sexual transmission of bacterial and protozoan pathogens.

Strengths of this analysis include that HPTN 035 was a multinational, randomized, placebo-controlled, clinical trial evaluating candidate microbicides BufferGel and PRO 2000 for the capacity to reduce sexually transmitted infections. STI prevalence in participants at screening (0.7% GC, 3.5% CT, 7.3% TV) was similar to that anticipated, based on preparatory study HPTN 055 in Hlabisa and Durban, South Africa, and Lusaka, Zambia,[25] and during HPTN 035, these STIs occurred at rates of 1.6, 3.9, and 15.3 per 100-person years (GC, CT, and TV, respectively). Reported uptake of gel products was adequate (81% in all groups by self-report), and no risk compensation was identified as a result of gel usage as compared to the no gel group. Evidence for this includes that while the three gel arms were somewhat less likely to report using condoms than the no gel arm, there was no evident effect on non-ulcerative STI acquisition, as indicated by incidence of STIs among those in the placebo gel arm as compared to no gel control.[26]

The study did have limitations. Firstly, non-culture methods were used for assessment of outcomes. While we believe sensitivity of detection was adequate for determination of incident infections, the measurement of STIs may have been fewer, as compared to culture methods, or other modalities (e.g., direct swab), resulting in an underestimate of the number of infections and potentially reduce statistical power to observe a treatment effect. Additionally, it is possible that some of the studied STIs may have been treated unintentionally by receipt of antimicrobials for non-reproductive indications during the intervening time between assessments. We do believe however that this was a rare event, as the majority of all care was received within study clinics. Throughout, the overall reported use of condoms at last vaginal sex was 74% (range 51%–77%), but it is very likely that self-reported condom use was an overestimate of actual use, and probable that the residual unprotected sexual acts remained sufficient to account for the STI transmissions. Low

uptake of condoms in some of these communities and reasons for this have been previously identified highlighting the limitation of using condoms for STI and HIV prevention in women in many African communities[25] since women may not be able to negotiate their use with male partners.[27] Reported condom use was higher in the no gel group compared to the gel arms (81% vs. 72%), but this modest difference in self-reported condom use did not correlate with a decreased incidence of STIs in the no gel group.

The discordance between the results of this clinical trial and preclinical evaluations could be interpreted in two ways. First, these data could suggest that *in vitro* assays and animal model studies may overestimate the effectiveness of these agents when used vaginally within the context of sexual exposure. An alternative hypothesis is that the products were somewhat effective, but that actual adherence to product was lower than that reported by study participants, which minimized the power to detect a difference in the rates of incident STIs. Other prevention trials among similar populations, which have evaluated adherence by drug levels, suggest more modest levels of adherence despite high measures of adherence by self-report.[28] HPTN 035 measured adherence only through self report through one-on-one interviews, which is a methodology with greater susceptibility to social desirability bias than measurement by drug levels, or applicator biomarkers, such as used in other studies of microbicides,[29] or other modalities such as audio computer assisted self interview (ACASI).[30]

Though GC was less common at the U.S. site, Philadelphia had CT and TV rates similar to the women enrolled in the African sites. Among African sites, those in South Africa, especially, had high rates of non-ulcerative STIs. The tendency toward higher rates of non-ulcerative STIs among women enrolled from South Africa sites compared to those seen in other African countries paralleled the higher risk of HIV observed at sites in South Africa in this study. Additionally, antibiotic resistance in GC, which was increasing in prevalence during the time of study,[31] may have contributed to differences between centres, although not to the randomized comparison in treatment groups.

Given the high prevalence, cost, and morbidity associated with non-ulcerative STIs and the lack of effective prevention modalities, an effective microbicide would become an important tool to reduce the burden of STIs. Though BufferGel and PRO 2000 microbicide gels were accepted by users and shown to be safe,[10] neither was found effective at preventing non-ulcerative STIs. While recent trials have focused on pre-exposure prophylaxis using antiretroviral therapy to prevent HIV transmission, it remains important to keep the research pipeline flowing for the development and testing of specific and broadly acting compounds that will be effective against these important pathogens, because of their high morbidity, as well as their potential impact on combination HIV prevention.

Acknowledgments

The HPTN 035 (www.mtnstopshiv.org/studies/62) study team includes the following: Sponsors: US National Institutes of Health: R Black, L Soto-Torres, S Estep; Endo Pharmaceuticals Solutions Inc.: A Profy; ReProtect: T Moench; Protocol Chair: SA Karim; Blantyre, Malawi: T Taha, N Kumwenda, B Makanani, S Hurst, C Nkhoma, E Kachale; Durban and Hlabisa, South Africa: G Ramjee, R Govinden, N Coumi, N Dladla-Qwabe, S Ganesh, N Morar; Harare, Zimbabwe: ZM Chirenje, N Padian, A van der Straten, T Magure, M Mlingo, N Mgodi; Lilongwe, Malawi: I Hoffman, F Martinson, T Tembo, L Chinula, T Mvalo; Lusaka, Zambia: G Parham, M Kapina, C Reid,

M Kasaro, A Brahmi; Philadelphia, USA: L Maslankowski, J Prince, N Tustin, S Whittington, E Yu; Coordinating Centre: W Cates, A Coletti, K Gomez, R White; Statistical Centre: M Cianciola, C Kelly, C Miller, B Mâsse, B Richardson, T Fleming; Network Laboratory: S Hillier, E Piwowar-Manning, L Rabe.

Funding

HPTN 035 was funded by the US National Institutes of Health (NIH). The study was designed and implemented by HIV Prevention Trials Network (HPTN) and Microbicides Trials Network (MTN). HPTN (U01AI46749) and MTN (U01AI068633) were supported by the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Development, and National Institute of Mental Health. HPTN was also funded by National Institute of Drug Abuse. The study products were provided free of charge by Endo Pharmaceuticals and ReProtect, Inc. The US Agency for International Development provided funding for manufacturing of BufferGel. The Statistical Center was supported by NIAID (UO1AI068615).

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KEY MESSAGES

- HPTN 035, a randomized controlled trial of 3099 women, identified high rates of non-ulcerative STIs among women in eight international sites, despite intensive risk-reduction counselling.
- The impact of condom use in the three gel arms, versus the no gel control arm, had no evident effect on non-ulcerative STI acquisition.
- Vaginal microbicides BufferGel and 0.5% PRO 2000 showed no significant effect for the prevention of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis*.

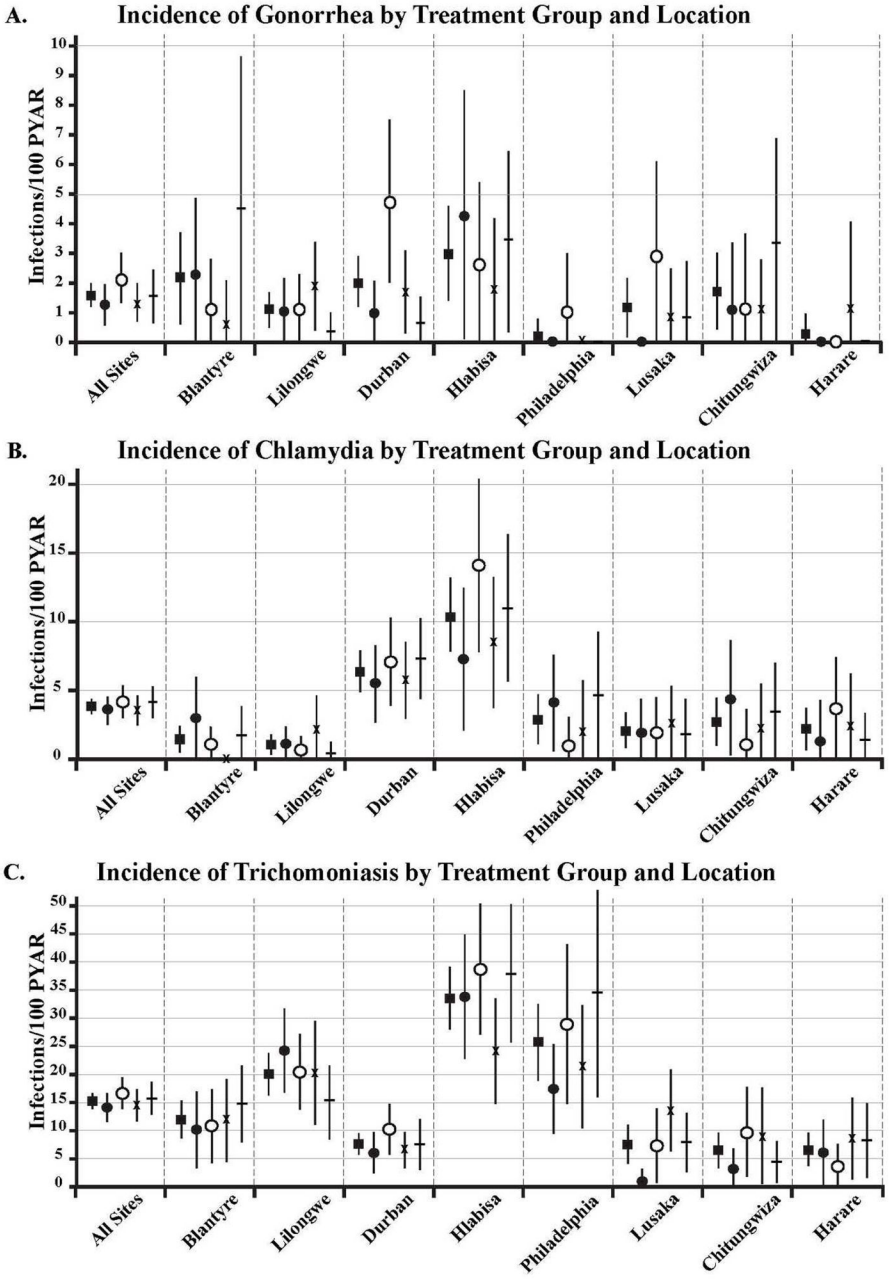

Figure 1. Incidence rates of non-ulcerative STIs by treatment group and location

Incidence rates are calculated as the number of new infections per 100 person-years at risk (PYAR) for incident Gonorrhoea (A), Chlamydia (B), and Trichomoniasis (C). Incidence rates are indicated by treatment group including: all groups combined (■), BufferGel (●), PRO 2000 (○), Placebo Gel (✖), and No Gel/Condoms Only (−), and 95% confidence intervals are shown as vertical lines. For each STI, incidence rates at all sites combined are presented first, followed by rates of infection at each site.

Table 1

Baseline characteristics of participants by site, and overall.

	All Sites (n=3087)	Blantyre, Malawi (n=441)	Lilongwe, Malawi (n=596)	Durban, South Africa (n=702)	Hlabisa, South Africa (n=346)	Philadelphia, USA (n=200)	Lusaka, Zambia (n=319)	Chitungwiza, Zimbabwe (n=260)	Harare, Zimbabwe (n=223)
Variable	**Mean (SD) or # (%)**								
Age	26.3 (6.2)	25.9 (5.3)	27.3 (6.3)	25.2 (4.5)	25.3 (5.9)	35.5 (9.9)	23.0 (3.5)	25.8 (4.4)	26.9 (4.5)
Some secondary school	1944 (63%)	134 (30%)	97 (16%)	654 (93%)	271 (78%)	197 (99%)	140 (44%)	245 (94%)	206 (92%)
Married	1926 (62%)	421 (95%)	592 (99%)	131 (19%)	30 (9%)	28 (14%)	258 (81%)	249 (96%)	217 (97%)
Living with partner	2102 (68%)	418 (95%)	590 (99%)	275 (39%)	36 (10%)	62 (31%)	257 (81%)	247 (95%)	217 (97%)
>1 partner in past 3 months	99 (3%)	1 (<1%)	1 (<1%)	27 (4%)	3 (1%)	55 (28%)	10 (3%)	1 (<1%)	1 (<1%)
Number of vaginal sex acts in past week	2.9 (2.5)	3.4 (2.4)	2.7 (2.2)	2.3 (2.0)	1.9 (2.6)	2.4 (2.6)	2.6 (2.3)	5.0 (2.8)	4.2 (2.0)
Number using condom at last vaginal sex	2095 (68%)	228 (52%)	330 (55%)	540 (77%)	215 (62%)	122 (61%)	246 (77%)	225 (87%)	189 (85%)
Ever had anal sex	140 (5%)	3 (1%)	4 (1%)	29 (4%)	1 (<1%)	91 (46%)	8 (3%)	3 (1%)	1 (<1%)
Number using hormonal contraception	2123 (69%)	318 (72%)	461 (77%)	414 (59%)	163 (47%)	19 (10%)	275 (86%)	253 (97%)	220 (99%)
STI at screening:									
Gonorrhoea	22 (1%)	7 (2%)	2 (<1%)	5 (1%)	4 (1%)	0 (0%)	2 (1%)	1 (<1%)	1 (<1%)
Chlamydia	108 (3%)	3 (1%)	2 (<1%)	46 (7%)	26 (8%)	5 (3%)	10 (3%)	10 (4%)	6 (3%)
Trichomoniasis	225 (7%)	27 (6%)	67 (11%)	36 (5%)	51 (15%)	5 (3%)	21 (7%)	16 (6%)	2 (1%)
BV (Nugent ≥7)	1154 (37%)	152 (34%)	213 (36%)	273 (39%)	134 (39%)	94 (47%)	120 (38%)	91 (35%)	77 (35%)

Table 2

Incidence rates of HIV, Gonorrhoea, Chlamydia, and Trichomoniasis per site, and overall.

STI	All Sites (n=3087)	Blantyre, Malawi (n=441)	Lilongwe, Malawi (n=596)	Durban, South Africa (n=702)	Hlabisa, South Africa (n=346)	Philadelphia, USA (n=200)	Lusaka, Zambia (n=319)	Chitungwiza, Zimbabwe (n=260)	Harare, Zimbabwe (n=223)
HIV									
Number seroconversions	**194**	**26**	**16**	**57**	**58**	**2**	**18**	**9**	**8**
IR* [95% CI]	3.7 [3.2, 4.2]	3.7 [2.4, 5.4]	1.4 [0.8, 2.3]	4.6 [3.5, 6.0]	9.1 [6.9, 11.8]	0.5 [0.1, 1.7]	4.1 [2.4, 6.5]	2.5 [1.1, 4.6]	2.5 [1.1, 4.9]
Gonorrhoea									
Number with ≥1 infection	76	12	12	22	17	1	5	6	1
Total number infections	82	15	12	24	18	1	5	6	1
IR* [95% CI]	1.6 [1.2, 2.0]	2.2 [0.6, 3.7]	1.1 [0.5, 1.7]	2.0 [1.2, 2.9]	3.0 [1.4, 4.6]	0.2 [−0.3, 0.8]	1.2 [0.2, 2.2]	1.7 [0.4, 3.0]	0.3 [0.0, 1.0]
Chlamydia									
Number with ≥1 infection	180	9	10	71	54	10	9	10	7
Total number infections	198	10	12	76	62	12	9	10	7
IR* [95% CI]	3.9 [3.3, 4.4]	1.4 [0.5, 2.4]	1.1 [0.3, 1.8]	6.4 [4.9, 7.9]	10.3 [7.6, 13.0]	2.9 [1.1, 4.7]	2.1 [0.8, 3.4]	2.8 [1.1, 4.5]	2.2 [0.6, 3.8]
Trichomoniasis									
Number with ≥1 infection	521	59	138	66	126	63	30	19	20
Total number infections	792	83	224	93	208	106	33	24	21
IR* [95% CI]	15.3 [13.9, 16.7]	12.0 [8.6, 15.4]	20.1 [16.3, 23.8]	7.7 [5.7, 9.6]	33.6 [28.0, 39.1]	25.7 [18.9, 32.5]	7.6 [4.7, 10.4]	6.5 [3.3, 9.7]	6.6 [3.6, 9.6]

*Incidence Rate (per 100 person-years follow-up).

Table 3

Risk of acquisition of STIs by treatment arm.

	BufferGel n=775	**PRO 2000 n=769**	**Placebo Gel n=771**	**No Gel n=772**
Gonorrhoea				
# cases	17	28	17	20
PYAR	1271	1297	1272	1275
IR* (95% CI)	1.34 (0.6, 2.0)	2.16 (1.3, 3.0)	1.34 (0.7, 2.0)	1.57 (0.7, 2.5)
HR+ (95% CI) vs. Placebo	0.99 (0.49, 2.00)	1.66 (0.90, 3.06)	REF	NA
HR+ (95% CI) vs. No Gel	0.88 (0.43, 1.80)	1.45 (0.78, 2.70)	0.83 (0.43, 1.61)	REF
Chlamydia				
# cases	45	54	46	53
PYAR	1271	1297	1272	1275
IR* (95% CI)	3.54 (2.4, 4.7)	4.16 (3.0, 5.4)	3.62 (2.5, 4.7)	4.16 (3.0, 5.3)
HR+ (95% CI) vs. Placebo	1.00 (0.64, 1.57)	1.16 (0.76, 1.79)	REF	NA
HR+ (95% CI) vs. No Gel	0.88 (0.57, 1.35)	0.97 (0.65, 1.46)	0.85 (0.56, 1.30)	REF
Trichomoniasis				
# cases	180	220	186	206
PYAR	1285	1308	1286	1298
IR* (95% CI)	14.01 (11.4, 16.6)	16.82 (14.0, 19.6)	14.46 (11.6, 17.3)	15.87 (13.0, 18.8)
HR+ (95% CI) vs. Placebo	0.95 (0.71, 1.25)	1.18 (0.90, 1.53)	REF	NA
HR+ (95% CI) vs. No Gel	0.87 (0.66, 1.14)	1.06 (0.82, 1.38)	0.91 (0.68, 1.20)	REF

*Incidence Rate (per 100 person-years follow-up).

+Hazard ratio from discrete time Andersen-Gill proportional hazards model.