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Appropriateness of hydroxyethylcellulose gel as a placebo control in vaginal microbicide trials: A comparison of the two control arms of HPTN 035

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Abstract

Objective—To compare the two control arms of HPTN 035 (a hydroxyethylcellulose (HEC) gel control arm and a no gel control arm) to assess behavioral effects associated with gel use and direct causal effects of the HEC gel on STIs, pregnancy, and genital safety.

Design—Randomized trial with one blinded (HEC gel) and one open label (no gel) control arms.

Methods—HIV-uninfected, sexually active women were randomized into the HEC gel arm (n=771) and into the no gel arm (n=772) in five countries. Participants in the HEC gel arm were instructed to insert the study gel intravaginally <1 hour before each vaginal sex act. Data on sexual behavior, adherence, safety, pregnancy, and STIs were collected quarterly for 12 to 30 months of follow-up.

Results—During follow-up, mean reported condom use in the past week was significantly higher in the no gel arm (81% versus 70%, p<0.001). There were no significant differences, after

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adjusting for this differential condom use, between the two arms in rates of genital safety events, pregnancy outcomes, or STIs, including HIV-1.

Conclusions—In this large randomized trial, we found no significant differences between the no gel and HEC gel arms in rates of genital safety events, pregnancy outcomes, or STIs. These results aid interpretation of the results of previous vaginal microbicide trials that used the HEC gel as a control. The HEC gel is suitable as a control for ongoing and future vaginal microbicide studies.

Keywords

HIV prevention; vaginal microbicide; placebo; women; sexually transmitted infections

INTRODUCTION

The double-blind, placebo-controlled randomized clinical trial (RCT) is the gold standard for establishing the efficacy of investigational products. This study design, through blinding study investigators and participants to product assignments, often maximizes the likelihood of obtaining an unbiased estimate of efficacy. However, to obtain an unbiased estimate of efficacy, the product used as a placebo control must have no effect on the outcomes of interest.

In vaginal microbicide research for prevention of HIV-1 and other sexually transmitted infections (STIs), there are several mechanisms through which a placebo gel could have a protective effect on the outcomes of interest, thereby creating efficacy dilution^{1,2}. First, a placebo gel could have protective effects by virtue of lubricating properties or by serving as a physical barrier to infection. Second, antimicrobial effects from preservatives contained in the placebo gel could have effects on vaginal flora. Finally, presence of a placebo gel in the vagina after ejaculation lowers the concentration of the infecting agent.

To date, vaginal microbicide research for prevention of HIV-1 and other STIs has been limited by a lack of information on the possible protective effects of placebo gels used in clinical trials. The adverse impact of this lack of information on the potential effects of placebo control gels was clearly demonstrated in the UNAIDS sponsored study of the nonoxynol-9 containing gel COL-1492 assessing risk of acquisition of HIV-1³. The placebo used in that study was a bioadhesive gel with all three of the potential mechanisms of actions that could protect against HIV-1 infection^{4,5}. A higher rate of HIV-1 infection was observed in the COL-1492 group of that study compared to the placebo group, a difference which is likely due to a deleterious effect of COL-1492 through epithelial damage with frequent use of N-9⁶. However, part of this difference between the randomized arms could also be due to a possible protective effect of the placebo gel. In the absence of information that inclusion of a no gel arm in that study could have provided, either interpretation is valid.

While there are several reasons that the use of a placebo gel as a control in vaginal microbicides could result in a biased estimate of efficacy, the use of a no gel control arm (“condom only”) also presents difficulties when assessing the effectiveness of a vaginal microbicide product. Women assigned to a gel arm may exhibit different sexual behavior than if they were assigned to a “condom only” arm, perhaps substituting product use for condom use, and this complicates the interpretation of comparisons between the no gel arm and the active product arm^{7–9}.

A hydroxyethylcellulose (HEC) placebo gel has been formulated to minimize any impact – negative or positive – on vaginal mucosa, acquisition of HIV-1 and several other STIs, and pregnancy, and has been proposed as a “universal placebo” for vaginal microbicide trials^{10–14}. However, until the HEC placebo gel was tested *in vivo* in a relevant population

against a no gel arm, it was not possible to assess potential behavioral effects associated with use of the HEC gel, and assess the potential direct causal effects of the HEC gel with respect to multiple outcome measures including acquisition of HIV-1 and other STIs, pregnancy, and genital safety. HPTN 035 was designed with both a no gel control arm and a HEC placebo gel control arm¹. Here we provide a detailed comparison of differences in reported behavior, safety, and effectiveness of these two control arms. This comparison provides information to help interpret the results of previous vaginal microbicide trials using the HEC placebo gel, and to help determine if the HEC placebo gel is a suitable control for ongoing and future vaginal microbicide studies of newly developed products such as the maraviroc and tenofovir combined gel.

METHODS

Study Design and Procedures

The study was conducted with the understanding and written informed consent of all participants. The trial (NCT00074425) was approved by 11 institutional review boards that oversee research conducted at the eight study sites, as well as regulatory authorities in the USA, South Africa, and Zimbabwe. Details of the HPTN 035 study design and procedures are published elsewhere¹⁵. Briefly, HPTN 035 was a four arm randomized placebo-controlled trial including two active microbicide products (BufferGel and 0.5% PRO2000 Gel), and two control arms (the HEC placebo gel arm and the no gel arm). HIV-negative non-pregnant women at seven sites in Blantyre and Lilongwe, Malawi; Durban and Hlabisa, South Africa; Harare and Chitungwiza, Zimbabwe; Lusaka, Zambia; and Philadelphia USA were randomized (stratified by site) in a 1:1:1:1 ratio to the four arms. Women randomized to a gel arm were instructed to insert one applicator of gel in their vagina up to one hour prior to each episode of vaginal intercourse. Women who became pregnant during follow-up temporarily discontinued gel use while pregnant.

Participants were followed monthly for 12 to 30 months. Pregnancy testing and gel provision were done at monthly study visits, while pelvic examinations, HIV-1 testing, and the collection of data on sexual behavior and adherence were all done quarterly. Testing for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and syphilis was done annually and at study exit; HSV-2 testing was done at enrollment, and at study exit for women testing HSV-2-negative at enrollment.

Laboratory Methods

HIV-1 infection was determined using standardized algorithm explained in detail elsewhere¹⁵. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing was done using urine strand displacement assay (Becton Dickinson ProbeTec). Vaginal fluid wet mount was used to test for trichomoniasis (saline prep), candidiasis (saline and KOH prep) and bacterial vaginosis (saline and KOH prep), and bacterial vaginosis (BV) was defined using Nugent's criteria. Syphilis serologic testing was done using a RPR screening test followed by confirmatory TPHA testing. HSV-2 testing was done using ELISA (Focus Technologies HerpeSelect-2). Finally, pregnancy testing was done using a urine hCG test (Quidel QuickView One Step hCG).

Statistical Methods

All analyses were intent to treat and stratified by site. Sexual behavior during follow-up was compared using the t-test for continuous variables and Chi-square tests for binary variables. Changes in sexual behavior from baseline were tested using the paired t-test. The Cox proportional hazard models were used to compare safety outcomes and pregnancy outcomes. Discrete time Cox Proportional Hazards models were used to compare time to detection of

HIV. For outcomes with recurring events (BV, chlamydia, gonorrhea, trichomoniasis, genital ulcer disease (GUD), and pregnancy), the Andersen Gill Proportional Hazards model with robust variance estimates were used. Mean rates of syphilis were compared using Poisson regression with person years of follow-up as an offset. HSV-2, which was only assessed at study entry and exit, was compared using logistic regression.

To determine the magnitude of differences between the two randomization arms that was independent of condom use, all models of safety, pregnancy, and STI outcomes were adjusted for level of reported condom use (condom use during 85% of last vaginal sex acts during follow-up which was the median reported value).

RESULTS

Study Population Characteristics and Retention

Between February 2005 and September 2008, 771 women were enrolled into the HEC placebo gel arm and 772 into the no gel arm of the trial. Of these, 11 women in the placebo arm and 10 in the no gel arm had no follow-up data. Detailed information on baseline characteristics of these two groups have been presented previously¹⁵. Briefly, mean age at enrollment was 26 years, mean number of vaginal sex acts in the past 7 days was 2.9, and 68% of women reported using a condom during their last sex act. Mean follow-up time was 20.5 months in the no gel arm, and 20.3 months in the placebo arm ($p=0.7$). The no gel arm had an average of 19.2 visits per woman and the HEC placebo gel arm 19.1 visits per woman ($p=0.8$). Retention in HPTN 035 overall was very high (93.6%) and did not differ between the no gel and HEC placebo gel arms (94.0% versus 93.1%, $p=0.3$). Baseline characteristics were similar between the two arms (Table 1).

Gel Use, Sexual Behavior, and Condom Use

Adherence to gel use in the HEC placebo gel arm was high with gel use reported 81.4% of last vaginal sex acts. Similar levels of gel use were also reported during vaginal sex acts in the past week. The mean reported number of sex partners, mean reported number of vaginal sex acts, and mean reported number of anal sex acts were all similar between the two arms during follow-up (Table 2).

The no gel arm reported significantly higher condom use during follow-up compared to the HEC placebo gel arm. Specifically, 47% of women in the HEC placebo gel arm reported high condom use (defined as using a condom during 85% of last vaginal sex acts), compared to 59% of women in the no gel arm ($p<0.001$). In addition, this differential reported condom use was fairly consistent throughout the 30 months of the study (Figure 1).

To further assess changes in behavior during follow-up in the HEC gel arm and the no gel arm, baseline reported sexual behavior was compared to reported sexual behavior during follow-up. There was not a significant change from baseline in the reported number of sex partners in either arm ($p=0.1$ for the HEC placebo arm, and $p=0.9$ for the no gel arm), and women in both arms reported fewer vaginal sex acts during follow-up compared to baseline ($p=0.007$ for the HEC placebo arm, and $p<0.001$ for the no gel arm). However, there were differences between the two arms in the change from baseline in reported condom use. While the HEC placebo arm did not have a significant change from baseline in reported condom use (mean increase from baseline in the percentage of vaginal sex acts reported to be protected by a condom of 1.58% ($p=0.4$)), the no gel arm had a significant increase from baseline in reported condom use (mean increase from baseline in the percentage of vaginal sex acts reported to be protected by a condom of 15.1% ($p<0.001$)).

Safety

The incidence rates of safety outcomes during follow-up in the two arms are presented in Table 3. The overall incidence of deep epithelial disruption, defined as lesions penetrating into and exposing the sub-epithelial tissue and possibly blood vessels, was similar in the HEC placebo gel arm and the no gel arm (1.93 versus 1.48 per 100 person years), although there was limited statistical power to assess this endpoint. There was not a significant difference between the two arms in the percentage of women with at least one pelvic exam finding, the percentage of women experiencing at least one grade 3 or higher adverse event, and the rate of adverse pregnancy outcomes between the two arms, although statistical power for the pregnancy outcomes was limited (Table 3). Results were similar after adjustment for differential condom use during follow-up (data not shown).

STDs, Genital Tract Conditions, and Pregnancy

There was no difference in the rate of acquisition of HIV-1 in the two arms (Hazard Ratio (HR)=0.97, 95% Confidence Interval (CI): (0.66, 1.44)) (Table 4). There were also no differences in the rates of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, bacterial vaginosis, trichomoniasis, genital ulcer disease, syphilis, HSV-2, and pregnancy (Table 4). Results were similar after adjusting for differential condom use (data not shown).

DISCUSSION

HPTN 035 is the only large scale vaginal microbicide effectiveness study designed with women randomized to either the HEC placebo gel or no gel. This design provides a unique opportunity to compare sexual behavior and safety measurements during follow-up in these two control arms, and to assess the activity of the HEC placebo gel against HIV-1 and other STIs. In this RCT, we found no significant differences between the HEC placebo gel and the no gel arms in the rates of genital adverse events, pregnancy outcomes or STIs, including HIV-1. However, there were significantly higher rates of condom use during follow-up in the no gel arm. After controlling for this differential condom use, results were similar to the unadjusted results.

Our finding of a higher rate of reported condom use in the no gel arm has been seen in other STI prevention studies using a “no product” or “condom use alone” arm as a control⁷⁻⁹. This phenomenon is thought to mainly occur through “product substitution” or “condom migration” in which women in an intervention arm substitute using the intervention product for condoms while, at the same time, women in the condom use only arm maintain high rates of condom use¹⁶. In HPTN 035, we did not see evidence of condom migration (i.e., a decrease in reported condom use from baseline rates in the HEC placebo gel arm). Rather, we saw reported rates of condom use remain relatively stable from baseline through follow-up in the HEC placebo gel arm, and an increase from baseline in reported rates in the no gel arm, plausibly because of intensive counseling regarding condom use during the trial, but also plausibly due to reporting bias. Regardless of the cause, the phenomenon of differential condom use between arms has been postulated as one reason most HIV/STI prevention trials using an open label “condom use alone” arm as a control have not yielded a positive estimate of efficacy^{17,18}.

The positive safety profile of the HEC placebo gel seen in HPTN 035, along with the lack of any large effects on HIV/STI incidence, help interpret the findings of previous vaginal microbicide trials using the HEC placebo as a control. Recently, four Phase III randomized double-blind, placebo-controlled HIV prevention trials using the HEC placebo gel as a control have reported results^{12-14,19}. Two of these studies, one assessing 1.0% C31G (SAVVY) gel and one assessing Cellulose Sulphate gel, were halted early and reported a

trend for a higher rate of HIV incidence in women randomized to the active gel arm ^{12,14}. The results from HPTN 035 provide additional evidence to suggest that this apparent increased risk of HIV was likely not due to a highly protective effect of the HEC placebo gel. The findings also suggest that the efficacy observed in the CAPRISA 004 trial [18] was due to the tenofovir and not due to a harmful placebo.

It has been argued that the ideal design RCT of a vaginal microbicide for STI prevention would contain both a placebo control arm and a no gel arm ¹. In such a trial, the comparison of the microbicide with the placebo control arm provides estimates of the antimicrobial effects of the microbicide, while comparison of the microbicide with the no gel arm allows assessment of “real world” effectiveness, which includes physical barrier effects, lubrication effects, effects on vaginal flora, and effects on risk behavior, including condom use. While these considerations may be applicable, with limited resources for HIV/STI prevention research, designing every large RCT of a vaginal microbicide with two control arms, thereby substantially increasing the size and cost of the trial, is not feasible. The results of HPTN 035 indicate that in the presence of high adherence to study product, future and ongoing studies do not require both control arms. Microbicide trials designed to use the HEC placebo gel as their lone control arm have not limited their ability to produce a valid result or their statistical power to detect an effective method of HIV/STI prevention.

The main strength of our study is the study design – an RCT with women randomized to two control arms. Other strengths include the high rates of retention in both control arms, high reported adherence to gel in the HEC placebo gel arm, and frequent collection of behavioral data to aid interpretation of the results. However, the main weakness of the study is also the design – HPTN 035 was not designed as an equivalence trial for the two control arms. Thus, while the hazard ratio comparing the rates of HIV-1 acquisition in the two arms was near unity, the 95% confidence interval ranged from 0.66 to 1.44, highlighting the inability of this study to determine equivalence of these two control arms. However, for some of the safety endpoints (e.g., pelvic exam findings), and some of the STI endpoints (e.g., bacterial vaginosis and Trichomoniasis) we had high power to see fairly small effects, and for most other STIs, including HIV, we had high power to rule out large differences between the two arms. Other weaknesses include the open label nature of the no gel arm, and the reliance on self reported data on sexual risk behavior and adherence.

There are many challenges in the design of, conduct of, and interpretation of results from HIV prevention trials ²⁰. Just one of these challenges is the choice of an appropriate control arm. In this large RCT, we found no significant differences between the no gel and HEC placebo gel arms in rates of genital safety events, pregnancy outcomes, or STIs. These results aid interpretation of the results of previous vaginal microbicide trials that used the HEC gel as a control, and suggest that the HEC gel is a suitable control for future and ongoing vaginal microbicide studies, including antiretroviral containing microbicides such as the newly developed maraviroc and tenofovir combined gel.

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Figure 1. Reported Percent Condom Use by Arm Over Time Since Enrollment

Dark solid line is the mean for the placebo group, light solid lines are 95% upper and lower confidence interval limits for the placebo group. Dark dashed line is the mean for the no gel arm, light dashed lines are 95% upper and lower confidence interval limits for the no gel arm.

Table 1

Baseline Characteristics by Arm

Variable	HEC Gel Mean (95% CI) or % (n) N=771		No Gel Mean (95% CI) or % (n) N=772	
Age (years)	26.6	(26.1, 27.0)	26.3	(25.9, 26.7)
Married	63%	(485)	63%	(484)
Contraceptive use				
Oral contraceptive pills	19%	(147)	20%	(151)
Medroxyprogesterone acetate	49%	(381)	47%	(363)
Other/None	32%	(243)	33%	(258)
Number of sex partners in past 3 months	1	(1, 1)	1	(1, 1)
Had sex in past 7 days	84%	(650)	88%	(676)
Number of vaginal sex acts in past 7 days	2.8	(2.6, 2.9)	3.0	(2.9, 3.2)
Anal sex in past 7 days	1%	(5)	1%	(5)
Percentage of vaginal sex in past week with a condom	69%	(66%, 72%)	66%	(63%, 70%)
Condom used at last sex act	69%	(533)	67%	(520)
Ever had anal sex	5%	(37)	5%	(42)

Table 2

Follow-up Sexual Behavior by Arm

Variable	HEC Gel Mean (95% CI) or % (n) N=759	No Gel Mean (95% CI) or % (n) N=756	P-value
Mean number of sex partners in 3 months prior to visit	1 (1, 1)	1 (1, 1)	0.2
Mean number of vaginal sex acts in past 7 days	2.6 (2.5, 2.7)	2.7 (2.6, 2.9)	0.1
Any anal sex during follow-up	2% (18)	2% (18)	1.0
Mean percentage of vaginal sex in past week with a condom *	70% (68%, 73%)	81% (80%, 83%)	<0.001
Mean number of visits at which condom use was reported at last sex act	4.5 (4.3, 4.7)	5.2 (5.0, 5.3)	<0.001
Used a condom during ≥85% of last vaginal sex acts	47% (354)	59% (449)	<0.001

* Among those reporting any vaginal sex in the past week (n=731 in placebo arm, n=740 in no gel arm).

Table 3

Safety Outcomes During Follow-up by Arm

Variable	Incidence per 100 person years (number of cases/PYs) or % (n/sample size)		RR or OR (95% CI)
	HEC Gel	No Gel	
At least one pelvic exam finding	60% (457/758)	59% (452/760)	1.03 (0.84, 1.27)
Deep epithelial disruption	1.48 (19/1286)	1.93 (25/1298)	0.77 (0.39, 1.52)
At least one grade 3 or higher adverse event [*]	6.7% (52/771)	9.2% (71/772)	0.71 (0.49, 1.04)
Premature live birth	0.22 (3/1341)	0.52 (7/1358)	0.44 (0.11, 1.68)
Spontaneous abortion or fetal death/still birth	2.16 (29/1341)	2.65 (36/1358)	0.82 (0.49, 1.36)

^{*} Most common grade 3 or higher adverse events were metrorrhagia (n=6 in placebo (P), n=7 in no gel (NG)), decreased hemoglobin (n=2 (P), n=5 (NG)), anemia (n=3 (P), n=4 (NG)), spontaneous abortion (n=3 (P), n=3 (NG)), prolonged prothrombin time (n=2 (P), n=3 (NG)), and malaria (n=3 (P), n=2 (NG)).

Table 4

STDs, Genital Tract Conditions and Pregnancy Testing During Follow-up by Arm

Condition	Incidence per 100 person years (number of cases/PYs)		RR (95% CI)
	HEC Gel	No Gel	
HIV-1	3.91 (51/1305)	4.02 (53/1318)	0.97 (0.66, 1.44)
<i>Chlamydia trachomatis</i>	3.62 (46/1272)	4.16 (53/1275)	0.85 (0.56, 1.30)
<i>Neisseria gonorrhoeae</i>	1.34 (17/1272)	1.57 (20/1275)	0.83 (0.43, 1.61)
Bacterial vaginosis	161 (2068/1286)	160 (2077/1296)	1.01 (0.88, 1.15)
Trichomoniasis	14.46 (186/1286)	15.87 (206/1298)	0.91 (0.68, 1.20)
GUD	1.79 (23/1286)	3.16 (41/1298)	0.55 (0.30, 1.03)
Syphilis	0.94 (12/1277)	1.01 (13/1282)	0.94 (0.43, 2.07)
HSV-2 *	7.43 (53/714)	7.14 (48/672)	1.05 (0.69, 1.59)
Pregnancy	9.91 (133/1341)	12.22 (166/1358)	0.82 (0.65, 1.02)

* Person years for incident HSV-2 analysis are lower because only women negative for HSV-2 at baseline were tested for HSV-2 at study exit.