



Changes In Vaginal Flora Associated With Vaginal Microbicides: Cellulose Sulfate and Tenofovir

Justman, J^{1,2};El-Sadr, W^{2,3}; Mayer, K⁴; Maslankowski, L⁵; Hoesley, C⁶;Absalon, J^{2,3}; Gai, F⁷; Mâsse, B.R ⁷; Kwiecien, A⁸; Rooney, J⁹;Soto-Torres,L¹⁰; and the HIV Prevention Trials Network 049 and 050 Study Teams

¹Bronx-Lebanon Hospital Center, NY; ²Columbia University, NY; ³Harlem Hospital Center, NY; ⁴The Miriam Hospital, Brown University, Providence, RI; ⁵University of Pennsylvania, Philadelphia, PA; ⁶University of Alabama at Birmingham; ⁷SCHARP/Fred Hutchinson Cancer Research Center, Seattle, WA; ⁸Family Health International, Arlington,VA; ⁹Gilead Sciences, Inc, Foster City, CA, ¹⁰National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

Jessica Justman, M.D.
Mailman School of Public Health
722 West 168th Street, Room 7
New York, NY 10032 USA
jj215@columbia.edu
212 342 3507 (tel)
212 342 1824 (fax)

Abstract

Background: There is a clear need for vaginal microbicides that will prevent HIV transmission. An important attribute will be the effect of such products on the vaginal flora. We describe the effects of 2 microbicide candidates, cellulose sulfate gel (CS) and tenofovir gel (TFV), on the pH and vaginal flora of sexually abstinent and sexually active HIV- and HIV+ women in 2 completed phase I studies, HIV Prevention Trials Network (HPTN) 049 and HPTN 050.

Methods: Eligibility criteria included negative pregnancy test, normal Pap smear, no sexually transmitted infections in the preceding 6 months, and no vaginal symptoms or discharge. A pelvic examination, including pH measurement, wet mount, and Gram stain of vaginal fluid, were conducted prior to and after 14 days of product use. Both studies included cohorts of sexually abstinent and sexually active women.

Results: We randomized 59 HIV+ women enrolled in HPTN 049 to 6% CS or placebo (KY gel) once or twice a day. Eleven were sexually active. Assignment to CS or placebo was double-blind. The mean vaginal pH was 5.0 at baseline and 5.2 by day 14. Of the 53 women with an available Nugent score, 24 (44%) had bacterial vaginosis at enrollment. By day 14, 17 (71%) of these 23 no longer had bacterial vaginosis. Bacterial vaginosis clearance was similar for CS (89%) and placebo (66%), and did not differ by frequency of gel use or by sexual activity.

We assigned 84 women enrolled in HPTN 050 (60 HIV- and 24 HIV+) to 0.3% or 1% TFV once or twice a day. 60 were sexually abstinent and 24 were sexually active. Mean vaginal pH was 5.0 at enrollment, and 4.9 by day 14. Of the 76 women with an available Nugent score, 30 (39%) had bacterial vaginosis at enrollment. By day 14, 15 (50%) of these 30 women no longer had bacterial vaginosis. Bacterial vaginosis clearance did not differ by gel dose or frequency, or by HIV status or sexual activity level.

Conclusions: Asymptomatic women enrolled in these microbicide studies had a high prevalence of elevated vaginal pH and incidental bacterial vaginosis at enrollment. In both products, clearance of bacterial vaginosis was observed in at least half of those with bacterial vaginosis at baseline, regardless of type of product used, including placebo. There was no substantial change in vaginal pH, suggesting either a dilution effect or a pH-independent effect of the gels. As bacterial vaginosis may act as a co-factor in the heterosexual transmission of HIV, the impact of vaginal microbicides on bacterial vaginosis warrants further study.

Background

- There is a clear need for vaginal microbicides that will prevent HIV transmission.
- An important attribute will be the effect of such products on the vaginal flora.
- Some other microbicides, such as BufferGel, have been associated with a prevalence in BV along with an increase in candidiasis (J. van de Wijgert et al., 2001).

Objective

To measure vaginal flora characteristics before and after 14 days use of 6% CS gel or control gel (HPTN 049) or tenofovir gel (HPTN 050).

Methods

- Eligibility criteria included: adult sexually abstinent and active women, with negative pregnancy test, normal Pap smear, no sexually transmitted infections in the preceding 6 months, no vaginal symptoms or discharge, enrollment in either of two Phase I vaginal microbicide studies (HPTN 049 and 050)
- Procedures: pelvic examination, including pH measurement, wet mount, and Gram stain of vaginal fluid, at baseline and 14 days after product use.
- Two BV definitions:
 - modified Amsel's criteria (pH >4.5, presence of clue cells, and + whiff test)
 - Nugent's criteria (gram stain score >6, slides read in a central lab)
- Data were analyzed using frequency distributions stratified by product and by arm of study
- McNemar's chi square test was used to detect differences in pH and BV prevalence between groups

HPTN 049 Schema

Design: Multicite, Phase I, double blind, randomized, controlled, frequency escalation study with 14 days of product exposure and follow-up.

Population: HIV-infected women (sexually abstinent and sexually active)

Regimen: Women applied 3.5 mL of either 6% cellulose sulfate gel or a control gel intravaginally once or twice daily for 14 intermenstrual days, as follows:

Study Cohort	CS n	Control n	Frequency of Use
1: Sexually Abstinent	12	12	Once Daily
2: Sexually Abstinent	12	12	Twice Daily
3: Sexually Active	5	6	Once Daily

HPTN 050 Schema

Design: Multicite, Phase I, dose and frequency escalation study

Population: HIV- and HIV+ women (sexually abstinent and sexually active)

Regimen: Women applied gel intravaginally once or twice daily for 14 intermenstrual days

Cohort	Description	N	Dose	Frequency
A ₁	HIV-/abstinent	12	0.3%	once daily
A ₂	HIV-/abstinent	12	1.0%	once daily
A ₃	HIV-/abstinent	12	0.3%	twice daily
A ₄	HIV-/abstinent	12	1.0%	twice daily
B	HIV+/active	12	1%	twice daily
C	HIV+/abstinent	12	1%	twice daily
D	HIV+/active	12	1%	twice daily

Table 1: Baseline Characteristics

	HPTN 049		HPTN 050	
	CS (n = 29)	Placebo (n = 30)	CS (n = 30)	Tenofovir (n = 54)
Age				
< 20	3	3	10	14
21-40	18	42	17	41
> 40	8	28	10	29
Race				
Black	17	59	20	67
White	6	21	6	28
Other	7	24	7	23
Ethnicity/Latino Origin	6	21	4	13
HIV infected	29	100	30	100
CD4 count				
<350	29	100	29	97
350-500	0	0	0	3
>500	0	0	0	11*
HIV-RNA				
<2000 c/mL	22	76	22	73
>2000 c/mL	7	24	8	27
On ART	18	62	22	73
STD history	5	17	8	27
Sexually active	5	17	6	20

*Only HIV-infected participants (cohorts C & D) had CD4 counts and HIV-RNA assays

Table 2: Vaginal characteristics before and after use of microbicide gel

	Day 0		Day 14		Day 0		Day 14	
	CS (n = 29)	Placebo (n = 30)	CS (n = 30)	Placebo (n = 26)	Tenofovir (n=30)	Tenofovir (n = 54)	n	n
Vaginal pH								
<4.5	8	28	10	33	4	15	9	28
>4.5	21	2	20	67	21	84	21	78
Whiff test +	7	24	6	28	0	1	3	19
Clue cells >20%	4	14	5	17	1	4	2	8
BV, mod Amsel	4	14	5	17	0	1	3	16
BV, Nugent	9	31	15	58	2	7	6	28
C. albicans	0	0	0	3	11	2	8	5
Z. vaginalis	0	0	0	0	0	0	0	0

Conclusions:

- These asymptomatic, highly selected women had a high prevalence of elevated vaginal pH and incidental BV at baseline.
- After 2 weeks of intravaginal CS, placebo or tenofovir:
 - Clearance of BV was observed in over half of the cases.
 - There was no significant change in vaginal pH
 - There was no increase in the prevalence of candidiasis
- These findings are of interest because BV may act as a co-factor in the heterosexual transmission of HIV.
- The ameliorative effect of microbicide gel on BV may be a dilutional effect or other pH-independent effect.

Figure 1: No effect of gel on vaginal pH

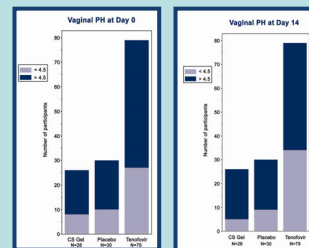


Figure 2: Reduction in BV prevalence after 14 days of gel use including placebo gel

