Effect of consistent condom use on six-month prevalence of bacterial vaginosis varies by baseline BV status

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Abstract

Objectives—Bacterial vaginosis (BV) is a condition characterized by a disturbed vaginal ecosystem which fluctuates in response to extrinsic and intrinsic factors. BV recurrence is common. To explore whether consistent condom use was associated with BV occurrence or recurrence, we compared the effect of condom use on BV prevalence after six months, among women with and without BV at baseline.

Methods—We used data from a randomized controlled trial, conducted among female sex workers in Madagascar during 2000–2001, that assessed the impact of adding clinic-based counseling to peer education on sexual risk behavior and sexually transmitted infection incidence. BV was diagnosed at two time points (baseline and six months) according to modified Amsel criteria. Consistent condom users were women reporting no unprotected sex acts with clients in the past month or non-paying partners in the past year. Adjusted prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated using multivariable regression models.

Results—At baseline, 563 (56%) women had BV. Of those, 360 (72%) had BV at 6 months, compared to 158 (39%) of those without BV at baseline. The adjusted 6-month PR for BV comparing consistent to inconsistent condom users was 0.99 (95% CI: 0.85–1.13) among women with BV at baseline and 0.62 (95% CI: 0.30–0.94) among women without BV at baseline.

Conclusions—Consistent condom use was associated with reduced BV prevalence at 6 months for women who were BV-negative at baseline, but had no effect among women who were BV-positive at baseline. Male condoms appeared to protect against BV occurence, but not BV recurrence.

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INTRODUCTION

Bacterial vaginosis (BV) is the most common cause of abnormal vaginal discharge in women of reproductive age (Hapsari *et al*, 2006). It is characterized by a reduction in vaginal lactobacilli with an associated increase in BV-associated organisms such as Gram-negative and anaerobic bacteria (*Gardenerella vaginalis, Bactroides sp, Provetella sp, Mobiluncus sp*, and *Peptostreptococcus sp*) and genital mycoplasmas (*U. urealyticum* and *M. hominis*) (Hillier *et al*, 1993). BV has been associated with adverse pregnancy outcomes including premature rupture of membranes, premature delivery, low birth weight, and post-partum and post-abortion endometritis (Hillier *et al*, 1995; Kurki *et al*, 1992). Women with BV are also at increased risk of sexually transmitted infections (STIs) (Wiesenfeld *et al*, 2003)), including HIV (Taha *et al*, 1998). However, the cause of the microbial alteration leading to BV is not fully understood.

BV-associated organisms are also found in non-chlamydial non-gonococcal urethritis in men (Workowski & Berman, 2006). In addition, risk factors associated with BV include behaviors that increase STI risk, such as having new or multiple sexual partners (Bradshaw *et al*, 2005), suggesting that BV might be sexually transmitted. However, other factors not known to be associated with sexual activity (vaginal douching, lack of vaginal lactobacilli) have also been linked with BV (Ness *et al*, 2002). Moreover, as many as 25% of girls 14–19 years old in the US have BV, irrespective of sexual experience (Gottlieb *et al*, 2008) and BV may also present as a natural variability associated with menstrual cycle (Morison *et al*, 2005). Thus BV may be acquired through both sexual behaviors and non-sexual factors.

BV can occur as a new acquisition (BV occurrence) or re-emergence of a previous episode (BV recurrence). The two antibiotics used in the recommended first-line therapy (metronidazole and clindamycin (Anonymous, 1998) have imperfect cure rates ranging from 80% – 90% at 1 month (Koumans *et al*, 2002) and recurrence rates as high as 69% in the first year after treatment have been described (Bradshaw *et al*., 2006). In epidemiologic studies it can be difficult to distinguish between BV occurrence and recurrence. This difficulty is exacerbated because a "cured" BV case is simply the normalization of vaginal flora and symptoms rather than the eradication of any particular pathogen (Anonymous, 1998). This lack of differentiation may be the reason behind inconclusive results from studies of BV risk factors, particularly factors associated to the sexual route of BV acquisition. For example, several studies have demonstrated that condoms are protective against BV (Hutchinson *et al*, 2007; Smart *et al*, 2004), whereas others found evidence of effect that condoms prevent BV (Bradshaw *et al*, 2005; Schwebke *et al*, 2004). In addition, treatment of the male sex partners of women with BV has not been beneficial in preventing the recurrence of BV in women (Vutyavanich *et al*, 1993), calling into question whether sexual transmission is a likely route of infection. However, beside the Hutchinson study, all those studies did not clearly differentiate between repeat and first incidence of BV.

Assuming that sexual factors are associated only with the initial BV acquisition but not with re-emergence of a persistent episode, analyzing the association between condom use and a single, heterogeneous outcome capturing all types of BV cases could lead to an underestimation of the importance of condom and therefore of the sexual route in BV acquisition.

In this secondary data analysis, we examined the effect of consistent condom use on BV risk at six months. We hypothesized that repeat BV is more likely due to a re-emergence of a persistent, existing BV infection rather than acquisition of a new case of BV, and therefore that consistent condom use was more likely to have a stronger protective effect on women who were BV-negative at baseline than on women who were BV-positive at baseline.

METHODS

Data and procedures

We used data from a randomized controlled trial (RCT), conducted among female sex workers (FSWs) in Madagascar in 2000–2001, that was designed to assess the impact of adding clinic-based counseling to peer education on sexual risk behavior and STI incidence (Feldblum *et al.*, 2005; Hoke *et al.*, 2007). Self-identified active FSWs (n=1,000), age 16 or older, with no signs of pregnancy, were individually randomized to receive condom counseling by peer educators (peer-only arm), or peer counseling plus clinic-based counseling (peer+clinic). Participants were followed for 18 months in two public dispensaries in the capital city, Antananarivo, and in the principal port city, Tamatave. The details of the randomization process and the main findings from the intervention have been published elsewhere (Feldblum *et al.*, 2005; Hoke *et al.*, 2007).

The study had two phases: an initial phase (from baseline through 6 months) during which only male condoms were available, and a second phase when both male and female condoms were promoted. The analyses presented here used data from the first 6 months of the study only. After enrollment, each study participant returned to the clinic every 2 months for follow-up visits. At each visit, data on sexual activity and condom use were collected through face-to-face interviews. In addition, at the baseline and 6-month visits, one clinician at each study site examined participants and collected specimens for laboratory testing (Feldblum et al., 2005). After examination, all participants were treated presumptively for gonococcal and chlamydial infection with ciprofloxacin (500 mg orally in a single dose) and azithromycin (1 g orally in a single dose). Treatment was given one week later for syphilis (benzathine penicillin, three doses of 2.4 million units IM at 1-week intervals for latent syphilis of unknown duration, one dose for early syphilis), candidiasis (nystatin, one ovule (100 000 IU) per night for 10 consecutive nights), and trichomoniasis and BV (metronidazole, 2 g orally in a single dose) as needed.

Variable definition

Outcome—This analysis uses BV data from two time points: baseline and 6 months. BV was classified according to modified Amsel criteria (Workowski & Berman, 2006). Women were BV-positive if at least three of the following criteria were met: pH of the vaginal fluid

>4.5, homogenous vaginal discharge, clue cells on microscopic examination, or a positive amine test (the "whiff" test).

Exposure—In the RCT, condom use was measured differently for clients (paying sex partners) and non-paying partners. For clients, participants were asked at each visit (once every two months) the number of sex acts they had had with clients over the preceding 30 days and how many of those acts were protected by condoms. For non-paying partners, this information was asked for the preceding 12 months. Women who reported no unprotected sex with clients at all 3 follow-up visits (2, 4, and 6 months) and no unprotected sex with non-paying partners in the past 12 months at the 6-month visit were classified as consistent condom users. All other participants were classified as inconsistent users.

We also assessed several potential confounding factors, including age, study site, randomization group, marital status (married/cohabiting, single (with or without a steady partner), and widowed/separated/divorced), average number of sex partners in the week preceding each of the 3 follow-up visits, and vaginal cleansing practices (use of water only vs. use of water plus other products).

Statistical analysis

Prevalence ratios (PR) assessing the effect of consistent condom use on BV risk at 6 months were calculated among women with and without BV at baseline. Prior to multivariable modeling, we first examined the bivariate association between consistent condom use and BV at six months. We used the Mantel-Haenszel test of homogeneity to assess if the crude effect of consistent condom use on BV differed by baseline BV status.

The odds ratio was not an appropriate choice for the measure of effect because our outcome (BV) was very common (57.5%) (Altman *et al.*, 1998). Binomial models did not converge. To estimate the adjusted PRs and their confidence intervals, the method recently proposed by Localio *et al.* (Localio *et al.*, 2007) was used. Standard errors, estimated using bootstrap methods, were used to calculate the 95% confidence intervals (CI) for the adjusted PRs.

Prior knowledge and bivariate analyses were used to select variables that were included in the initial model. We also included an interaction term between BV at baseline and consistent condom use in the initial model, to allow computation of the effect of consistent condom use on BV at 6 months in each stratum of baseline BV status. We used likelihood ratio tests (LRT) to assess the contribution of the interaction term to the fit of the model. The significance level for the test of homogeneity and the LRT for the interaction term was α=0.10 (Kleinbaum & M., 2002). To arrive at the most parsimonious model that captured the effect of consistent condom use on 6-month BV risk, we used a manual, backward elimination, change-in-estimate strategy to eliminate covariates that did not substantially affect the effect estimate (the change-inestimate criterion was 10%). Regardless of the change in the effect estimate, we retained two additional variables in the final multivariable model – use of hormonal contraception and vaginal cleansing practices – because of *a priori* hypotheses about their role in BV risk.

RESULTS

Of the 1,000 women that were randomized at baseline, 901 (90%) returned for the 6-month visit. By design, 50% of participants were from Antananarivo and 50% from Tamatave. Participants were also equally split between the two randomization groups (Table 1). At baseline 65% of women were single, and the mean age was 28 years. Half reported more than six paying sexual partners a week. During at least one of the three follow-up visits, 25% of women reported using hormonal contraception, 62% reported having had sex with a non-paying partner within the past week, and all reported vaginal cleansing. Most (68%) women reported using water only for vaginal cleansing.

BV was highly prevalent among study participants. At baseline, 563 women (56%) had BV and virtually the same percentage of BV-positives was observed at 6 months (57%). Fifty four women (6%) were classified as consistent condom users over the six-month follow-up. In bivariate analyses, 360 participants (72%) who had BV at baseline were again BV-positive at 6 months, compared to 158 (39%) of those without BV at baseline who were BV-positive at 6 months. Participants who were younger, single, used a product other than water for vaginal cleansing, used no hormonal contraception, from Tamatave, or with BV at baseline were less likely to use condoms consistently and more likely to be diagnosed with BV at 6 months. In addition, women who reported a non-paying sexual partner in the past week were less likely to be diagnosed with BV at 6 months. The unadjusted PR for BV at the 6-month visit comparing consistent to inconsistent condom users was 0.60 (95%CI: 0.41, 0.86) among all women, 0.98 (95% CI: 0.72, 1.33) among women with BV at baseline, and 0.46 (95% CI: 0.23, 0.90) among those without BV at baseline. The Mantel-Haenszel test for homogeneity of the PRs by baseline BV status was significant (p=0.01) (Table 2).

In the initial multivariable model including BV at baseline, the interaction term between BV at baseline and consistent condom use, and all potential confounders, the LRT for the interaction term met our criteria for significance (see Methods) (p=0.08). The final multivariable model adjusted for use of hormonal contraception, age, average number of paying sex partner in the past week, and vaginal cleansing practices. The adjusted PR for the effect of consistent condom use on BV at six months was 0.70 (95%CI: 0.38, 1.01) among all women, 0.98 (95% CI: 0.85, 1.13) among women with BV at baseline, and 0.62 (95% CI: 0.30, 0.94) among those without BV at baseline (Table 2).

DISCUSSION

BV was very common among study participants, consistent with previous observations in Madagascar that sexual and reproductive tract infections are highly prevalent among women seeking primary care for genitourinary infections and highest among female sex workers (Behets et al., 2001; Behets et al., 2005). Only 6% of participants were classified as consistent condom users during the 6-month follow-up period. This low level of condom use matches the high rates of STIs described in other reports from this trial (Feldblum et al., 2005; Hoke et al., 2007).

Alternative definitions of consistent condom use were considered: (1) condom use at last sex with a client at each of the 3 follow-up visits, (2) condom use in all sex acts with clients in the past 30 days at each of the 3 follow-up visits, (3) condom use at last sex with a client and last sex with a non-paying partner, at each of the 3 follow-up visits, and (4) consistent condom as defined above. Condom use was low in general ranging from 66% with definition (1) to 6% with definition (4). With each of these definitions, we detected no effect of condom use on BV prevalence at 6 months among women with BV at baseline. However, among women without BV at baseline, we saw a protective effect of condom use on BV at 6 months for all 4 definitions. But the magnitude of the strength of the protective association between condom use and 6-month BV prevalence increased as the total number of sex acts covered by the definition increased (results not shown).

Consistent condom users were women who reported no unprotected sex with clients at all the 3 follow-up visits (2, 4, and 6 months) and with non-paying partners in the past 12 months at the 6-month visit. While this definition does not cover all sex acts during the follow-up period, it reduces possible measurement error by shortening the period over which women were asked to remember their sexual behavior. Nevertheless, because participants were asked to report both the total number of sex acts they had had over a 30-day period and, out of these, the number when condoms were used, it is possible that some misreporting occurred (recall bias). It is also possible, given that participants were actively counseled to use condoms, that some may have overstated the number of acts in which they used condoms (social desirability bias). We expect that bias resulting from recall error or social desirability, which we hypothesize would lead to an overestimate of condom use, is likely to be nondifferential with respect to the outcome (BV status at 6 months), and therefore our observed estimates may be biased toward the null. However, given the large difference in 6-month BV risk between BV-positive and BV-negative women at baseline, we do not think that bias is likely to explain our results.

In both unadjusted and multivariate analyses, the effect of consistent condom use was different depending on women's baseline BV status. Among women negative for BV at baseline, women who reported using condoms consistently had a significantly lower risk of acquiring BV after 6 months. In contrast, consistent condom use did not appear to have any effect among those with BV at baseline. These findings suggest that, among those with BV at baseline, BV recurrence is not likely to be a new acqustion from a male partner. Our results for women without BV at baseline agree with previous studies that suggest that consistent condom use reduces BV risk (Hutchinson *et al.*, 2007), and provide additional evidence that at least some BV can be acquired sexually (and hence consistent condom use is an effective mean to prevent it). The finding that consistent condom use had no effect on the risk of repeat BV is also consistent with a study of BV recurrence among Australian women. Those authors reported no association between BV recurrence and women's reported number of male sex partners or condom use (Bradshaw *et al.*, 2006).

We note that although our results fit both with our *a priori* hypothesis about the role of condom use on BV and with the sparse prior literature on this topic, these findings alone cannot determine whether recurrent BV is simply a reemergence of an existing condition or acquisition of a new one through a non-sexual transmission route. BV may be best described

as a disturbed ecosystem with resilience fluctuating in response to various extrinsic and intrinsic factors (sexual activity, hygiene, host factors, contraceptive choices, *etc.*). Therefore classifying a woman as BV-negative at baseline in this study (one time point) may represent misclassification, and given the 6-month interval between the two BV assessments, it is difficult to assess accurately whether BV as detected at the 6-month visit was incident or prevalent. However, any misclassification is likely to be nondifferential with respect to the exposure (condom use), and any bias would push our estimate toward the null. In addition, though our findings in women without BV at baseline suggest that BV might be acquired through sexual route, studies of the dynamic of BV associated organisms in both male and female sex partners are needed to confirm this observation.

We did not perform a test of cure among women treated for BV at the baseline visit. The high frequency of BV at 6 months among women with BV at baseline (72%) compared to the substantially lower frequency among women without BV at baseline (39%) may suggest that oral metronidazole, administered in single dose (as was the recommended treatment at the time this study was implemented (Anonymous, 1998), might not be sufficient to eradicate BV-associated pathogens. This interpretation is consistent with findings from a recent study designed to determine the efficacy of the current standard treatment with oral metronidazole for 1 week in the eradication of the bacterial vaginosis biofilm (a complex aggregation of microorganisms marked by the excretion of a protective and adhesive matrix) (Swidsinski *et al.*, 2008). That study reported that although all patients initially recovered from their symptoms, treatment cessation brought about a consistent resurgence of a dense and active bacterial biofilm on the vaginal mucosa, primarily consisting of *Gardnerella vaginalis* and *Atopobium vaginae*. However, the study did not follow participants long enough to see whether symptoms reappeared or not.

In conclusion, our results show that though consistent condom use had a protective effect on the 6-month prevalence of BV among BV-negative women at baseline, it had no effect on the 6-month prevalence of BV among women who were classified as BV-positive at baseline.

Acknowledgments

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Table 1

Distribution of consistent condom use, bacterial vaginosis (BV) at six months, and selected covariates by baseline BV status among female sex workers (FSWs) in Madagascar

	Baseline BV status					
	Positive		Negative		overall	
Variables	N*	Percentage	N*	Percentage	N*	Percentage
Bacterial vaginosis at 6 months						
Yes	360	72.1	158	39.3	518	57.5
No	139	27.9	244	60.7	383	42.5
Consistent condom use						
Yes	17	3.4	37	9.2	54	6.0
No	482	96.6	365	90.8	847	94.0
Marital status						
Married or cohabiting	55	9.9	62	14.2	117	11.8
Single with or without steady boyfriend	411	73.7	233	53.4	644	64.8
Widowed/separated/divorced	92	16.5	141	32.3	233	23.4
Hormonal contraception						
Yes	92	18.4	132	32.8	224	24.9
No	407	81.6	270	67.2	677	75.1
**Mean number of clients in the past **7 days (SD)[†]*	499	7.13 (5.1)	402	7.66 (5.7)	901	7.37 (5.4)
Non-paying sex partner in the past week						
Yes	286	57.3	272	67.7	558	61.9
No	213	42.7	130	32.3	343	38.1
Randomization group[†]						
Peer + clinic counseling	263	46.7	237	54.2	500	50.0
Peer only counseling	300	53.3	200	45.8	500	50.0
Site[†]						
Antananarivo	367	65.2	133	30.4	500	50.0
Tamatave	196	34.8	304	69.6	500	50.0
Bacterial vaginosis at baseline[†]						

Variables	Baseline BV status							
	Positive		Negative		overall			
	N*	Percentage	N*	Percentage	N*	Percentage		
Yes					563	56.3		
No					437	43.7		
Age in years: Mean (SD) [†]	561	28.17 (7.9)	437	28.38 (8.5)	901	28.26 (8.13)		
Use water only for vaginal cleansing								
Yes	294	58.92	273	67.9	567	37.1		
No	205	41.08	129	32.09	334	62.9		

*
Of the 1000 female sex workers (FSWs) randomized at baseline, 901 returned for 6-month visit. SD = sample standard deviation.

**
Mean number of clients reported for the 7 days preceding each of the 3 follow-up visits.

[†]
measured at baseline

Table 2

Crude and adjusted effects of consistent condom use on bacterial vaginosis (BV) at 6 months, stratified by baseline BV status among FSWs in Madagascar[†].

BV at baseline	Crude PR[*]	95% CI	Adjusted PR[**]	95% CI
Yes	0.98	(0.72 – 1.33)	0.99	(0.85 – 1.13)
No	0.46	(0.23 – 0.90)	0.62	(0.30 – 0.94)
Overall	0.60	(0.41 – 0.86)	0.70	(0.38 – 1.01)

[*]
P-value for Mantel-Haenszel homogeneity test = 0.01, FSWs = female sex workers

[**]
adjusted for use of hormonal conception, age, average number of paying sex partners in the past week, use of water only for vaginal cleansing.

[†]Data from the 901 women who returned for the 6-month visit was used in this analysis.

The adjusted Prevalence ratio (PR) was obtained by fitting a logistic model and using the parameter estimate to calculate the risk in each exposure group and a bootstrap method was used to calculate the 95% confidence interval (CI)