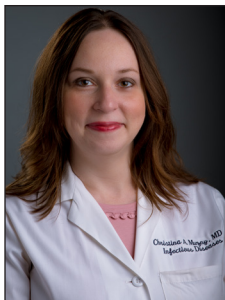


Should Partners of Women with Bacterial Vaginosis be Treated?



Christina Muzny, MD, MSPH
Associate Professor
Division of Infectious Diseases
University of Alabama at Birmingham
Birmingham, Alabama

INTRODUCTION

Bacterial vaginosis (BV) is the most common cause of vaginal discharge and affects nearly 1 in every 3 women in the United States aged 14–49 (21.7 million total).^{1,2} It is associated with multiple adverse outcomes, including preterm birth, pelvic inflammatory disease, and increased risk of acquisition and transmission of a sexually transmitted infections (STIs), including HIV.^{3–8} Among women who have sex with women (WSW), as many as 1 out of 2 have BV.^{2,9} Bacterial vaginosis is more common among women who report new or multiple male sex partners, condomless sex with a male partner, or sex with another woman.¹⁰ In fact, women who identify as lesbian have a 2.5-fold increased likelihood of BV vs heterosexual women.¹¹

BV is characterized by a depletion of lactic acid-producing lactobacilli that comprise the normal vaginal flora and an increase in facultative (*Gardnerella vaginalis*) and strict anaerobes.^{12,13} A clinical diagnosis of BV is made by using Amsel criteria, which require the presence of at least three of four characteristics: a milky white, homogeneous discharge coating the vaginal walls; clue cells visible on wet prep by microscopy (Figure 1); vaginal pH > 4.5; and a positive whiff

test.¹⁴ In research settings, BV is defined by the Nugent score. Scores of 0–3 are graded as lactobacillus-predominant normal vaginal flora, 4–6 as intermediate flora with the emergence of *G. vaginalis*/*Bacteroides* morphotypes, and 7–10 as BV flora with disappearance of lactobacillus species, numerous *G. vaginalis*/*Bacteroides*, and curved gram-variable anaerobic rods.¹⁵ Despite initial cure rates approaching 80%¹⁶ with currently approved BV treatments, 2 out of 3 women experience a recurrence within 6 months of treatment with the 7-day oral metronidazole (MTZ) regimen.¹⁷ One factor that may contribute to BV recurrence is re-infection by a partner with BV.¹⁷

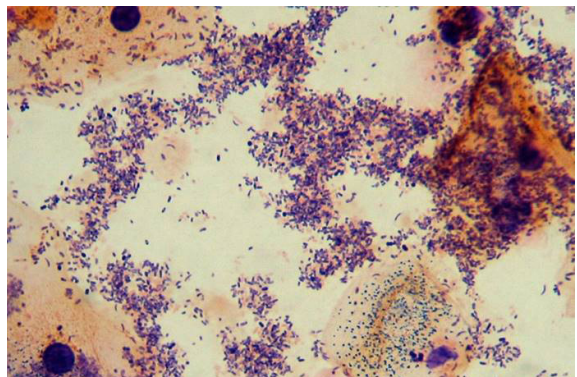


Figure 1. Clue cell on vaginal Gram stain

Although BV is not officially considered a sexually transmitted infection, it has characteristics of an STI and is considered a sexually associated condition.¹⁰ Effective management of treatable STIs requires treatment of current sex partners to prevent re-infection.¹⁸ However, current treatment guidelines do not include treating partners of women with BV,¹ despite epidemiologic data

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indicating that BV-associated bacteria can be sexually transmitted. In this supplement, we will discuss epidemiologic data indicating that BV is an STI and current data regarding partner treatment for women with BV.

EPIDEMIOLOGIC DATA INDICATE BV IS SEXUALLY TRANSMITTED

The notion that BV is sexually transmitted has been investigated for several decades. An early study conducted by Gardner and Dukes in the 1950s demonstrated that BV could be transmitted between women.¹⁹ Healthy women were inoculated with secretions from women with BV; 11/15 (73.3%) of the women subsequently developed BV.

A wealth of more recent epidemiologic data also support the exchange of vaginal bacterial species between WSW.^{9,11,20–22} Among monogamous female couples, vaginal Gram stains have been found to be 95% concordant.⁹ In addition, genital *Lactobacillus* strains, particularly *L. crispatus*, are shared between female sexual partners.²³ Similarly, an investigation of *G. vaginalis* diversity found that the vaginal flora was concordant among 87% of female couples.¹¹

The risk of BV in women is directly related to exposure to a partner with BV.²⁰ Among 21 monogamous female couples, the likelihood of a partner having BV was 19.7 times greater ($P < 0.008$) if the index woman had BV.²⁰ High levels of concordance in BV status between female sexual partners have been reported in several studies, including concordance in BV status ranging from 81%–95% among female couples across four studies.^{9,20–22}

Adding to the body of evidence that BV is sexually transmitted is that BV-associated bacteria can be found on the penis and urethra of men, particularly men who have female partners with BV.^{24–28} A study of the genital microbiota in uncircumcised men from Uganda found that men with more diverse genital microbiota were more likely to be colonized with BV-associated

bacteria and more likely to have female sexual partners with BV.²⁶ Further, a cross-sectional study that compared the genital microbiota of monogamous heterosexual couples in the United States confirmed that the penile skin of male partners of women with BV is colonized with several of the same bacteria that are strongly associated with BV.²⁷ This study also found that the penile microbiota of male partners were significantly more similar to the vaginal microbiota of their female sexual partner compared to those of non-partners. Heterosexual monogamous sexual partners have also been found to harbor the same strains of *G. vaginalis*.²⁹ These studies

support the hypothesis that BV-associated bacteria are exchanged during sexual intercourse.

Despite the extensive epidemiological evidence supporting the concept that BV is sexually transmitted, current CDC Sexually Transmitted Disease (STD) Treatment Guidelines only recommend treatment for symptomatic women with BV and not for partners of women with BV.¹

- A wealth of epidemiological evidence supports the sexual transmission of BV.
- Currently, the CDC STD Treatment Guidelines do not recommend treating partners of women with BV.
- The majority of prior partner treatment trials conducted in the 1980s–1990s used outdated treatment regimens and had methodological limitations.
- More rigorous partner treatment trials in the current era are needed, including trials with female partners.

PARTNER TREATMENT STUDIES

Partner treatment is not currently recommended for women with BV in the most recent CDC STD Treatment Guidelines. This guidance is based on 6 studies conducted in the 1980s and 1990s.^{30–36} (Table 1). No significant benefit from partner treatment with antibiotics was observed in 5 of the studies.^{31–35} Only one study, by Mengel et al, in 1989 found benefits from partner treatment: Women whose male sexual partners were treated were significantly more likely to not have BV, based on vaginal Gram stain, at 2 and 5 weeks, and were more likely to report resolution in any of their BV symptoms at 8 weeks.³⁶

Although the results from these studies suggest that little benefit is derived from treating male sexual partners of women with BV, all 6 studies had methodological limitations. Many of the BV treatment regimens in these studies are now

considered suboptimal. Three of the studies had substantial dropout rates, small treatment groups, or both.^{31,33,36} All 6 studies used only Amsel criteria for diagnosis and did not include the more rigorous Nugent score for BV diagnosis.¹⁵ Additionally, Mengel et al presented results graphically and did not state effect sizes.

In addition to untreated partners contributing to BV recurrence, lack of adherence to treatment among partners may also play an important role in recurrence of BV in women. Lack of partner adherence to treatment could attenuate the potential therapeutic benefit of the treatment in men. Among the 6 trials assessing partner treatment, 2 of the trials reported adherence among the men participating. In the trial by Vutyavanich et al, 4 men in the tinidazole group and 2 men in the placebo group were reported by their female partners as refusing medication.³⁴ In the study by Colli et al, nonadherence was 19% (27 men of 139 randomized) and did not differ by treatment arm.³⁵

NEXT STEPS

Epidemiological data strongly suggest that BV is sexually transmitted. However, prior partner treatment studies have not shown a significant effect. These studies had multiple methodological limitations and were conducted 20–30 years ago. Needed are more recent, rigorous partner treat-

ment trials using currently approved medications for BV treatment.

The acceptability and tolerability of treating women and men for 7 days with MTZ 400 mg orally twice daily, plus 2% clindamycin cream topically to the penile skin of the men twice daily, were assessed in a pilot study (n=16) of women with recurrent BV and their regular male sexual partner.³⁷ Completed in 2018, it showed a decrease in the prevalence and abundance of BV-associated bacteria in the penile microbiota immediately following treatment at day 8. An ongoing phase 3, double-blind, placebo-controlled study is randomizing male partners of women with recurrent BV to treatment with MTZ 500 mg twice daily for 7 days or placebo.³⁸ It aims to compare the rates of recurrent BV among women whose partners were or were not treated (NCT02209519).

Results from the ongoing phase 3 study treating male partners of women with recurrent BV will help determine whether male partner treatment can effectively reduce BV recurrence in women. Female partner treatment trials of WSW with recurrent BV are also needed.

Furthermore, less complex treatment regimens such as that of single-dose secnidazole 2 g,^{39,40} recently FDA-approved for the treatment of BV, may help to improve adherence among partners. ♦

Study, year	N	Treatment of Women	Treatment of Men	Comparator	Primary Outcome
Swedberg et al, 1985 ³¹	64	Oral MTZ 2 g single dose or oral MTZ 500 mg BID x 7 days	Oral MTZ 2 g single dose or oral MTZ 500 mg BID x 7	Standard of care	Culture negative for <i>G. vaginalis</i> and improved vaginal symptoms at 21 days: 68% vs 64% (RR=1.06; 95% CI: 0.74-1.52)
Vejtorp et al, 1988 ³²	106	Oral MTZ 2 g on days 1 and 3	Oral MTZ 2 g on days 1 and 3	Placebo	Clinically diagnosed BV at 5 wks: 25% vs 29% (RR=0.85; 95% CI: 0.45-1.61)
Mengel et al, 1989 ³⁶	98	Oral MTZ 2 g single dose or Oral MTZ 500 mg BID x 7 days	Oral MTZ 2 g single dose	Placebo	Symptoms and clinical cure of BV at 2, 5, and 8 wks: BV on vaginal Gram stain at 2 and 5 wks. No point estimates reported.
Moi et al, 1989 ³³	190	Oral MTZ 2 g on days 1 and 3	Oral MTZ 2 g on days 1 and 3	Placebo	Relapse of clinically diagnosed BV at 12 wks: 21.1% vs 15.8% (RR=1.33; 95% CI: 0.73-2.44)
Vutyavanich et al, 1993 ³⁴	106	Oral TIN 2 g single dose	Oral TIN 2 g single dose	Placebo	Clinical cure rate of BV at 4 wks: 71.6% vs 63.2% (RR=1.13; 95% CI: 0.95-1.35)
Colli et al, 1997 ³⁵	139	2% clindamycin vaginal cream qhs x 7 days	Clindamycin 150 mg orally QID x 7 days	Placebo	Clinically diagnosed BV recurrence at 12 wks: 31.9% vs 30.0% (RR= 1.06; 95% CI: 0.65-1.75)

Table 1. Adapted from Mehta et al³⁰; BID, 2 times daily; CI, confidence interval; MTZ, metronidazole; qhs, at bedtime; QID, 4 times daily; RR, risk ratio; TIN, tinidazole

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