Current Infectious Disease Reports (2019) 21:34
https://doi.org/10.1007/s11908-019-0688-3

FEMALE GENITAL TRACT INFECTIONS (J SOBEL, SECTION EDITOR)

Lessons from Suppressive Therapy and Periodic Presumptive Treatment for Bacterial Vaginosis

Jennifer E. Balkus[1,2,3] · Kayla A. Carter[1] · R. Scott McClelland[1,2,4]

Abstract

Purpose of Review Suppressive therapy and periodic presumptive treatment (PPT) are distinct but related strategies that have been used to reduce the incidence of bacterial vaginosis (BV). Here, we review clinical trial evidence of the effectiveness of suppressive therapy and PPT to reduce BV, and discuss their roles for women who frequently experience symptomatic or asymptomatic BV.

Recent Findings Among women who were recently and successfully treated for symptomatic BV, suppressive therapy with twice-weekly metronidazole gel for 16 weeks reduces the likelihood of recurrent symptomatic BV and is currently recommended by the Centers for Disease Control and Prevention for prevention of recurrent BV. The premise of PPT is to provide regimens used to treat BV at regular intervals to reduce the overall frequency of BV, regardless of symptoms. Three PPT trials were conducted using different routes (oral or intravaginal), doses, and frequencies of administration. Each trial demonstrated a significant reduction in BV over the course 12 months, ranging from a 10 to 45% decrease. PPT regimens that substantially reduce the frequency of BV over time could be evaluated in clinical trials to assess whether a reduced frequency of BV leads to subsequent reductions in BV-associated sequelae. While both suppressive therapy and PPT reduce BV, their impact wanes following cessation of the regimen.

Summary Given the high prevalence of BV globally and burden of adverse reproductive health outcomes among women with BV, there is a critical need for more effective treatments that produce durable shifts in the microbiota towards vaginal health.

Keywords Bacterial vaginosis · Periodic presumptive treatment · Suppressive therapy · Symptomatic · Asymptomatic

Introduction

Bacterial vaginosis (BV) is the most prevalent vaginal infection globally, affecting millions of women each year. It is a polymicrobial condition characterized by a shift from a *Lactobacillus*-dominant vaginal microbiota to one characterized by high concentrations of anaerobic and Gram-negative species [1]. Bacterial vaginosis is a common cause of vaginal complaints and is associated with a range of serious adverse health outcomes including HIV acquisition [2], sexually transmitted infections (STIs) [3–7], preterm birth [8, 9], amnionitis [10], endometritis [10–13], histologic chorioamnionitis [14], and pelvic inflammatory disease (PID) [15, 16]. Among reproductive-aged women, BV prevalence by Nugent score varies from roughly 25–30% in the general population to > 40% in certain sub-groups [17–26]. Current guidelines from the US Centers for Disease Control and Prevention (CDC) recommend first-line treatment with metronidazole or clindamycin for women with symptomatic BV [27]. While

This article is part of the Topical Collection on *Female Genital Tract Infections*

✉ Jennifer E. Balkus
jbalkus@uw.edu

Kayla A. Carter
kaycart@uw.edu

R. Scott McClelland
mcclell@uw.edu

[1] Department of Epidemiology, University of Washington, 1959 NE Pacific Street, Box 357236, Seattle, WA 98195, USA

[2] Department of Global Health, University of Washington, Seattle, WA, USA

[3] Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[4] Department of Medicine, University of Washington, Seattle, WA, USA

Published online: 31 August 2019

these regimens are generally effective at achieving clinical cure [27–29], approximately one-third of women will experience a recurrent episode of BV within 3 months of treatment and more than half will experience a recurrence within 1 year [30]. Women who experience frequent episodes of symptomatic BV report increased psychosocial stress, reduced self-esteem, changes in or avoidance of sexual activity, and physical discomfort [31–33].

A number of factors may contribute to the high rate of BV recurrence, including failure to recolonize with *Lactobacillus* species [34], persistent colonization with BV-associated bacteria [35], formation and persistence of biofilms [36, 37], and potential re-exposure to BV-associated bacteria from sexual partners [38–40]. This high level of recurrence has motivated investigations into alternative approaches to BV treatment and prevention. Several strategies are being assessed to reduce BV recurrence, including use of probiotics (alone or in combination with antibiotics), acidifiers, and biofilm disruptors. Suppressive therapy and periodic presumptive treatment (PPT) using antibiotics are prevention strategies that have demonstrated effectiveness in clinical trials. The goal of suppressive therapy is to reduce the incidence of BV among women who were recently, and successfully, treated for symptomatic BV (i.e., prevent recurrence). The goal of PPT is slightly different, as it relies on providing antibiotic regimens used to treat BV at regular intervals to primarily asymptomatic women (with or without BV) in order to reduce the overall frequency of BV, regardless of symptoms. Given the associations between BV and adverse reproductive health outcomes, PPT regimens that substantially reduce the frequency of BV over time could be evaluated in clinical trials to assess whether a reduced frequency of BV leads to subsequent reductions in BV-associated sequelae. Here, we review clinical trial evidence of the effectiveness of suppressive therapy and PPT to reduce BV, and discuss their roles for women who frequently experience symptomatic or asymptomatic BV.

Antibiotic Approaches to Reduce the Frequency of BV

Our review focuses on four randomized, double-blind, placebo-controlled trials that evaluated the effectiveness of suppressive therapy or periodic presumptive treatment on BV as the primary outcome. Each trial evaluated a different regimen, which was administered at varying intervals. Below, we summarize key characteristics and findings of each trial, with additional details of the trials presented in Table 1 and Fig. 1. While it is not possible to make direct comparisons of regimen efficacy across the four trials given important distinctions in their designs, populations, and outcomes [44], we highlight similarities and differences in their findings and discuss key considerations for the use of suppressive therapy and PPT to reduce BV.

Suppressive Therapy

Sobel et al. conducted the first landmark study to assess the impact of long-term therapy to prevent recurrent symptomatic BV, characterized as suppressive therapy [41]. The study population included US women with a history of two or more BV episodes in the past year who currently had symptomatic BV by Amsel's criteria, a measure best suited for characterizing symptomatic BV [45]. Following successful treatment of symptomatic BV with 0.75% intravaginal metronidazole gel nightly for 10 days, women were randomized to 0.75% metronidazole gel or placebo twice per week (nonconsecutive days) for 16 weeks. Women were evaluated every 4 weeks for recurrence of BV. Following completion of treatment, those who had not experienced an episode of recurrent BV were followed for an additional 12 weeks to evaluate any sustained impact after cessation of suppressive therapy. The objective of the trial was to compare the time to BV recurrence by study arm. Following completion of 16 weeks of twice-weekly suppressive therapy, 25.5% of women in the metronidazole arm and 59.1% of women in the placebo arm had a recurrence of symptomatic BV (relative risk [RR] = 0.43; 95% CI = 0.25–0.73). The incidence of BV by Nugent score, a measure that may include symptomatic and asymptomatic BV, was also lower in the intervention arm compared with placebo (RR = 0.66, 95% CI 0.39–1.12). This regimen is currently recommended by the CDC as a treatment approach for women with multiple recurrences of BV [27].

While there was a significant reduction in the frequency of recurrent BV among women in the metronidazole arm, it is worth noting the high incidence of recurrence in both arms, which may be attributable to enrolling a population with a history of recurrent BV. After an additional 12 weeks of follow-up, 51.0% of women in the metronidazole arm had experienced recurrent BV compared with 75.0% placebo women (RR = 0.68; 95% CI 0.49–0.93). Although the frequency of BV was lower among women who received metronidazole suppressive therapy, the effect of the intervention appeared to wane following its cessation.

Period Presumptive Treatment

Others have evaluated PPT regimens in populations with a high burden of both BV and BV-associated sequelae. A randomized clinical trial in Malawi conducted by Taha et al. compared the effect of quarterly dispensation of 0.75% metronidazole gel for five consecutive nights versus placebo gel on BV by Nugent score among both HIV-uninfected and HIV-infected women. The results presented below focus on those for HIV-uninfected women. It was not a requirement for participants to have BV at enrollment to be considered eligible; however, over 45% of HIV-uninfected women had BV by Nugent score at enrollment. The prevalence of BV was

Table 1 Key characteristics of randomized trials of suppressive therapy and periodic presumptive treatment to reduce BV recurrence

Author (years)*	Sites	Population	Intervention	Intervention duration	BV outcome and timing of outcome assessment	Intervention effect	Post-intervention assessment
Sobel et al. [41] (2000–2003)	Seven clinical sites in the USA	157 non-pregnant women with history of 2+ episodes of BV in the prior year who responded to intravaginal treatment with 0.75% metronidazole gel for 5 consecutive nights	Suppressive intravaginal treatment with 0.75% metronidazole gel for 2 nonconsecutive days per week (59 randomized to intervention, 53 randomized to placebo)	Weekly for up to 16 weeks	Primary: Amsel's criteria Secondary: Nugent score BV assessed every 4 weeks	57% reduced risk of BV recurrence by Amsel's criteria at 16 weeks in intervention vs. placebo (RR = 0.43, 95% CI 0.25–0.73) 34% reduced risk of BV recurrence by Nugent score in intervention vs. placebo (RR = 0.66, 95% CI 0.39–1.12)	32% reduced risk of BV recurrence by Amsel's criteria 12 weeks after cessation of study product in intervention vs. placebo (RR = 0.68, 95% CI 0.49–0.73)
Taha et al. [18] (2003–2005)	Blantyre, Malawi	1686 non-pregnant women; 842 HIV-uninfected and 844 HIV-infected	Presumptive intravaginal treatment with 0.75% metronidazole gel for 5 consecutive nights (843 randomized to intervention, 843 randomized to placebo)	Every 3 months for 12 months	Primary: Nugent score BV assessed at study product visits and the month after receipt of study product	HIV-uninfected: 10% reduced risk of BV in intervention vs. placebo (RR = 0.90, 95% CI 0.83–0.97) HIV-infected: 5% reduced risk of BV in intervention vs. placebo (RR = 0.95, 95% CI 0.85–1.01)	Not conducted
McClelland et al. [24] (2003–2006)	Mombasa, Kenya	310 female sex workers who were HIV-1 seronegative, age 18–45, non-pregnant, with no vulvovaginal symptoms	Presumptive monthly single-dose oral treatment with 2 g of metronidazole plus 150 mg fluconazole (155 randomized to intervention, 155 randomized to placebo)	Monthly for 12 months	Primary: Nugent score Secondary: Amsel's criteria BV assessed monthly	45% reduced hazard of BV by Nugent score in intervention vs. placebo (HR = 0.55, 95% CI 0.49–0.63) 49% reduced hazard of BV by Amsel's criteria in intervention vs. placebo (HR = 0.51; 95% CI 0.42–0.62) Increased colonization with both *Lactobacillus* spp. (HR = 1.47, 95% CI 1.19–1.80) and with H_2O_2-producing *Lactobacillus* spp. in intervention vs placebo (HR = 1.63, 95% CI 1.16–2.27)	25% reduced hazard of BV by Nugent score in the 4 months after cessation of study product in intervention arm vs. placebo [42] (HR = 0.75, 95% CI 0.51–1.11)
McClelland et al. [43] (2011–2012)	Mombasa and Nairobi, Kenya; Birmingham, AL, USA	234 women who were HIV seronegative, age 18–45, non-pregnant, sexually active, and had at least one vaginal infection (BV, VVC, or TV)	Presumptive intravaginal treatment with suppositories containing 750 mg metronidazole and 200 mg miconazole used for five consecutive nights (118 randomized to intervention, 116 randomized to placebo)	Monthly for 12 months	Primary: Nugent score Secondary: Amsel's criteria BV assessed every other month	35% reduced risk of BV by Nugent score in intervention vs. placebo (RR = 0.65, 95% CI 0.48–0.87) 19% reduced risk of BV by Amsel's criteria in intervention vs. placebo (RR = 0.81, 95% CI 0.55, 1.19) Increased detection of *L. crispatus* (RR = 1.19, 95% CI 0.91–1.54) and *L. jensenii* (RR = 1.29, 95% CI 0.96–1.73) by quantitative PCR in intervention vs. placebo	Not conducted

*Years the study was conducted

BV bacterial vaginosis, *VVC* vulvovaginal candidiasis, *TV Trichomonas vaginalis*, *RR* relative risk, *HR* hazard ratio, *CI* confidence interval

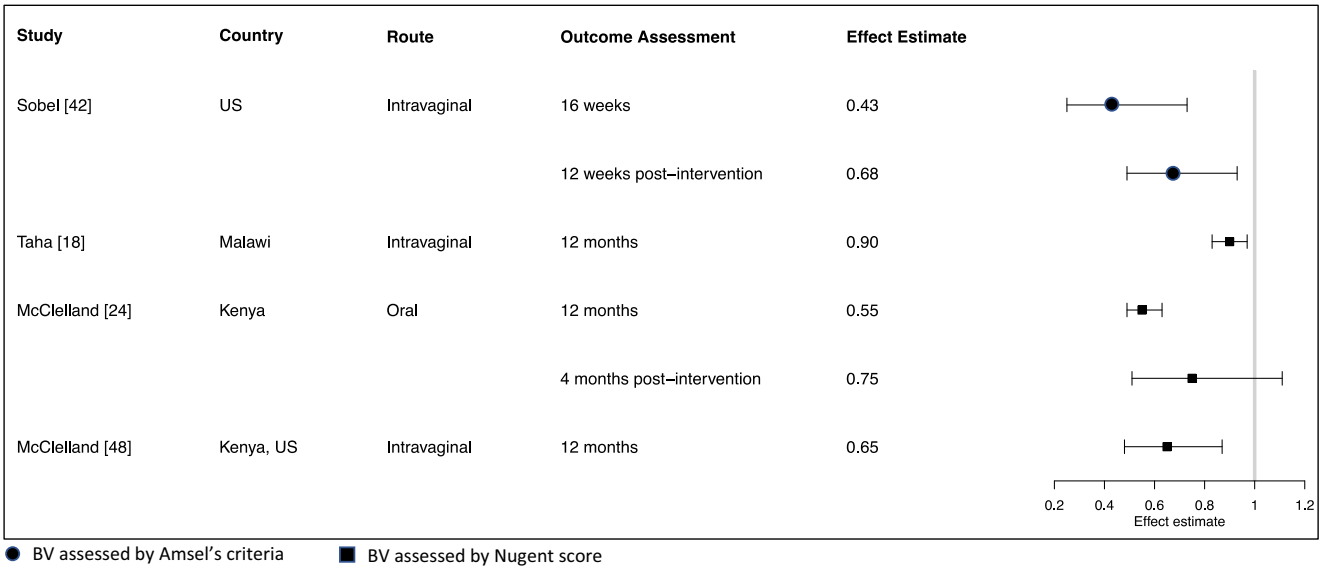

Fig. 1 Forest plot of effect estimates from clinical trials of suppressive therapy and periodic presumptive treatment

evaluated at quarterly visits, when study product was dispensed, and at each month following receipt of study product. Among HIV-uninfected women in the active arm, the prevalence of BV was lower in the month following receipt of study product compared with the prevalence at the quarterly visit at which treatment was dispensed. However, BV prevalence tended to be slightly higher at the next quarterly visit, indicating recurrence.

Over the course of the year, the prevalence of BV decreased in the active arm from 46% at baseline to 25% at the last study visit; conversely, the prevalence of Nugent score 0–3 increased from 37% at baseline to 56% at the last study visit. Interestingly, a similar trend was observed in the placebo arm, with 47% of women having prevalent BV at baseline compared with 29% at the last study visit. Overall, the intervention decreased the frequency of BV over the course of a year; however, given the parallel decreases observed in the placebo arm, the effect of the intervention was modest (RR = 0.90; 95% CI 0.83–0.97). The authors speculated that the placebo gel may have had an antimicrobial effect, which could have contributed to the decreased prevalence of BV in the placebo arm. It is also possible that other components of trial participation, such as dispensation of open-label treatment for symptomatic BV or changes in BV-associated risk behaviors such as intravaginal practices and condomless sex (Hawthorne effect), may have impacted BV frequency over the course of follow-up. Although the intervention effectively reduced the frequency of BV, the impact was not substantial and the prevalence of BV appeared to rebound following treatment. While quarterly PPT may minimize patient burden compared with more frequently administered regimens, it appears that this interval of PPT may not be sufficient to promote sustained changes in the vaginal microbiota.

McClelland et al. evaluated the impact of monthly 2 g metronidazole plus 150 mg of fluconazole versus placebo for 1 year in a cohort of HIV-uninfected women in Kenya [24]. Both regimens were administered orally as directly observed therapy. Given the high rate of vaginal candidiasis following BV treatment [41, 46] and associations between vulvovaginal candidiasis (VVC) and HIV acquisition [19], the antifungal was included as part of the intervention regimen to reduce the incidence of VVC. Similar to the study by Taha et al., participants were not required to have BV to enroll in the trial; however, 34% of women had BV by Nugent score at enrollment. Participants were evaluated for BV monthly and at the end of 1 year, the incidence of BV in the intervention arm was 198.6 per 100 person-years versus 326.4 per 100 person-years in the placebo arm (hazard ratio [HR] = 0.55; 95% CI 0.49–0.63). Results were similar when the incidence of clinical BV by Amsel's criteria was assessed (HR = 0.51; 85% CI 0.42–0.62). In addition, both the overall detection of *Lactobacillus* species by culture and the detection of H_2O_2-producing *Lactobacillus* species on tetramethylbenzidine agar were higher in the intervention arm compared with placebo (Table 1). Effects of this intervention were similar in a secondary analysis restricted to the subset of women with BV at enrollment [47]. In summary, this trial successfully reduced the frequency of BV and increased *Lactobacillus* species detection over the course of a year. However, in subsequent analyses that assessed BV incidence in the 4-month period following completion of the trial, no sustained effect of the intervention was observed [42].

As CDC and World Health Organization (WHO) guidelines shifted to primarily recommend multi-day antibiotic regimens due to their higher effectiveness in treating single episodes of BV [48], McClelland et al. conducted a second PPT

trial among Kenyan and US women that evaluated a co-formulated monthly regimen of high-dose vaginal suppositories containing 750 mg of metronidazole and 200 mg of miconazole used nightly for 5 consecutive nights each month versus placebo [43]. In contrast to the trial by Taha et al. and the first trial by McClelland et al., the vaginal suppository PPT trial enrolled women with a confirmed vaginal infection at screening (BV, VVC, or *Trichomonas vaginalis*). Women were followed for 12 months and the presence of BV by Nugent score was evaluated every other month. At enrollment, 35% of participants had BV by Nugent score (all were asymptomatic at their enrollment visit per eligibility criteria for the trial). The intervention reduced the proportion of visits with BV compared with placebo (21% vs 33%, RR = 0.65; 95% CI 0.48–0.87) and also reduced the proportion of visits with detection of BV-associated bacteria (BVAB1, BVAB2, *Atopobium vaginae*, *Leptotrichia/Sneathia*, and *Megasphaera* spp.) using highly sensitive quantitative PCR assays [49]. The intervention effect was similar when restricted to women who reported ≥ 80% adherence to study product. The sustained effect of the intervention following completion of the study was not evaluated.

Considerations for Suppressive Therapy and PPT

Route of Administration and Potential Side Effects

With any regimen, it is important to consider the route of administration for its potential impact on dose, effectiveness, acceptability, and side effects. There are certainly advantages and disadvantages related to the different routes of administration. Single-dose oral PPT results in the fewest doses and, in the context of clinical trials, oral PPT can be evaluated as directly observed therapy, ensuring a clear estimate of adherence. However, the higher frequency of systemic side effects, particularly nausea, is a disadvantage of oral PPT compared with intravaginal regimens [24]. In addition, the impact of systemic drug exposure is of particular concern for oral PPT, as high cumulative systemic doses of metronidazole have been associated with peripheral neuropathy [50].

Intravaginal products, including low-dose 0.75% metronidazole gel and high-dose (typically 500–750 mg) metronidazole suppositories, may be advantageous over oral regimens, as drug is concentrated locally in the vaginal fluid, reducing systemic exposure [51] and the likelihood of associated toxicity [52]. However, intravaginal regimens are not without side effects, and women assigned to the active arm of the suppressive therapy trial reported more frequent episodes of pain (head, lower back, abdominal, and leg) compared with women in the placebo arm [41]. In addition, both low-dose and high-dose intravaginal PPT regimens are more complex, requiring a higher number of doses to be administered at specific intervals. There are no direct comparisons of low-dose and high-dose intravaginal metronidazole for treatment of symptomatic BV or PPT; thus, it is uncertain if the high-dose regimen would result in greater efficacy as compared with lower dose vaginal regimens.

One additional concern related to extended use of both oral and vaginal metronidazole treatments for suppressive therapy and PPT is post-antibiotic vaginal candidiasis [41, 46]. In the suppressive therapy trial, vaginal candidiasis was the most commonly reported AE and was significantly more common among women in the intervention arm compared with placebo (43.1% vs 20.5%, $P = 0.02$). In contrast, symptomatic vaginal candidiasis was reported in less than 5% of participants in the trial by Taha et al. Trials of monthly oral and intravaginal PPT included an antifungal as part of the PPT regimen and evaluated the effect of PPT on the frequency of vaginal candidiasis. In both trials, the frequency of vaginal candidiasis was slightly lower in the PPT arm compared with placebo, but the differences were not statistically significant. Women receiving PPT may benefit from co-administration with an antifungal to reduce the frequency of post-metronidazole candidiasis; however, this approach has not been evaluated with suppressive therapy or other PPT regimens. Despite the challenges associated with oral and intravaginal regimens, it is important that both routes of administration are available as some women may prefer one method over the other.

Patient Burden and Adherence

As highlighted above, the frequency of administration and the number of doses are important considerations for suppressive therapy and PPT use that may impact adherence. Qualitative data on women's experiences with treatment for recurrent BV are limited. One study conducted among Australian women who experienced recurrent BV reported that most women interviewed disliked taking antibiotics, especially on a regular basis (dispensed as part of standard BV treatment), and many complained about the side effects [32]. Of the suppressive therapy and PPT regimens evaluated, the duration under study ranged from 16 weeks to 12 months, which may be a challenge for some women. Reported adherence to PPT regimens in clinical trials was generally high, indicating the acceptability of these regimens, with the highest levels of adherence observed with regimens that were used less often. Self-reported adherence to quarterly vaginal gel was high, with 93–97% of women reporting adherence to the study regimen [18]. The study of single-dose oral PPT employed directly observed treatment and achieved 92% adherence in both study arms [24]. In the vaginal suppository PPT trial, participants were considered adherent if they reported using 80% of the total possible number of vaginal suppositories. This level of adherence was achieved by 75% participants in the intervention arm and 81% participants in the placebo arm [43]. Data on adherence was not reported for the Sobel et al. trial [41]. To

date, only suppressive therapy has been recommended by the CDC to prevent recurrent symptomatic BV. For women with three or more episodes of BV in the last year who may be candidates for suppressive therapy [53], this suppressive regimen should be considered as first-line. For women unable to adhere to the twice-weekly intravaginal regimen, alternative dosing schedules or an oral single-dose regimen might be considered based on individual preferences.

Potential Antimicrobial Resistance

With prolonged exposure to antibiotics in the context of suppressive therapy and PPT, it is critical to consider issues of antimicrobial resistance [54]. Studies assessing the impact of routine antibiotic treatment for BV on bacterial isolates reported high levels of resistance (> 50%) following clindamycin therapy, whereas resistance to metronidazole was rare (< 1%) [55]. Emerging data suggest that *Gardnerella vaginalis*, which is commonly detected among women with BV [56, 57], may contribute to recurrence via reduced susceptibility to metronidazole. Several studies have identified multiple clades of *G. vaginalis* [58–60], two of which have been demonstrated to have resistance to metronidazole [61]. Metatranscriptomic analysis of the vaginal microbiota of women who failed to respond to BV treatment suggests that *G. vaginalis* genes that contribute to repair of DNA damage caused by the antibiotics are upregulated. This genetic variation within *G. vaginalis* subspecies may contribute to the lack of treatment response in some women [62]. It is unclear whether such antibiotic resistance is present at initial colonization versus acquired or activated following repeated metronidazole exposure. Antibiotic resistance following suppressive therapy or PPT has not been evaluated; thus, the impact of these regimens on the development of resistance is uncertain and should be assessed.

The Roles of Suppressive Therapy and PPT to Reduce BV

Suppressive therapy and PPT are treatment approaches that have both successfully reduced the frequency of BV. Among women with symptomatic BV and a history of recurrent BV, suppressive therapy with twice-weekly metronidazole gel for 16 weeks resulted in a significant reduction in incident symptomatic BV. This regimen has become the cornerstone of treatment for women with recurrent BV. Importantly, the 0.75% metronidazole gel used in this suppressive regimen is available globally [27]. Among asymptomatic women (both with and without BV by Nugent score), reductions in the frequency of BV were demonstrated with monthly and quarterly PPT, with larger reductions observed in trials of monthly PPT (both oral and intravaginal). While the oral PPT regimen (2 g metronidazole) is available globally, high-dose intravaginal metronidazole/miconazole suppositories are not currently available in the USA, and the availability of high-dose intravaginal metronidazole products varies by country.

In contrast to suppressive therapy, which seeks to delay time to recurrence of symptomatic BV, the objective of PPT is to decrease the number of occurrences of BV with the hope that reductions in BV may lead to lower risk of BV-associated sequelae. This hypothesis has not been explicitly tested in a phase III clinical trial. However, preliminary data suggest that intravaginal metronidazole regimens may reduce the incidence of certain STIs [63, 64]. Women randomized to monthly high-dose intravaginal metronidazole suppositories had lower incidences of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Mycoplasma genitalium* compared with women in the placebo arm [64]. In a second study by Schwebke et al., women randomized to twice-weekly metronidazole gel for 6 months experienced fewer episodes of BV as well as fewer STIs (outcome = time to first STI [*C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, herpes simplex virus, or PID]) compared with women receiving standard of care [63]. In the context of this review of suppressive therapy and PPT, it is notable that the study by Schwebke et al. utilized the twice-weekly regimen previously evaluated as suppressive therapy, but targeted asymptomatic women using a PPT approach. These findings highlight that while the goals of suppressive therapy and PPT are distinct, the regimens may be interchangeable in some circumstances. Future trials that directly compare different suppressions and PPT regimens for both symptomatic BV and prevention of BV-associated sequelae would be helpful for guiding both clinical and public health practices.

A notable limitation of both suppressive therapy and PPT with the regimens tested to date is the lack of a sustained effect following cessation of the regimen. Recent evidence suggests that pre-treatment colonization with certain bacteria, including *Megasphaer*a type 2 and BV-associated bacteria (BVAB) type 2, may predict BV recurrence [65, 66]. The impact of pre-treatment colonization was evaluated in women receiving monthly high-dose metronidazole intravaginal PPT [43]. Despite receiving effective monthly PPT, women in the intervention arm that were colonized with BVAB1 or *Leptotrichia*/*Sneathia* at baseline had more BV detected during follow-up compared with women without detectable concentrations of these bacteria [67]. Given the associations between pre-treatment colonization and BV frequency/recurrence, additional research is needed to better define which women will benefit most from currently available regimens and which may require alternative treatments to effect sustained changes in the vaginal microbiota [68].

The absence of a sustained effect of both suppressive therapy and PPT highlights the urgent need for better interventions that promote shifts in the vaginal microbiota that can be maintained in the absence of any intervention. As new strategies to prevent BV recurrence emerge, including probiotics

and biofilm disruptors [69, 70], it will be important to assess the impact of suppressive therapy and PPT when combined with these new approaches to evaluate the potential for higher levels of effectiveness.

Conclusions

Suppressive therapy is an important tool to prevent recurrence of symptomatic BV among women who experience frequent episodes of BV. Periodic presumptive treatment reduces the frequency of BV among women who are asymptomatic but at risk for both BV and BV-associated sequelae. However, the effect of both suppressive and PPT regimens has generally been modest, and none of these regimens appear to provide a sustained effect following cessation of treatment. Given the high burdens of both recurrent symptomatic BV and adverse reproductive health outcomes among women with BV (regardless of symptoms), there is critical need for more effective treatments that produce durable shifts in the microbiota towards vaginal health.

Compliance with Ethical Standards

Conflict of Interest JEB has received honoraria for consulting from BD and Lupin Pharmaceuticals. RSM currently receives research funding from Hologic/Gen-Probe and has received honoraria for consulting from Lupin Pharmaceuticals.

All other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Hillier S. Bacterial Vaginosis. In: Holmes KKSP, Stamm W, Piot P, Wasserheit J, Corey L, Cohen M, Watts D, editors. Sexually transmitted diseases. New York: McGraw-Hill; 2008.
2. Atashili J, Poole C, Ndumbe PM, Adimora AA, Smith JS. Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. AIDS. 2008;22:1493–501.
3. Brotman RM, Klebanoff MA, Nansel TR, Yu KF, Andrews WW, Zhang J, et al. Bacterial vaginosis assessed by gram stain and diminished colonization resistance to incident gonococcal, chlamydial, and trichomonal genital infection. J Infect Dis. 2010;202:1907–15.
4. Balkus JE, Richardson BA, Rabe LK, Taha TE, Mgodi N, Kasaro MP, et al. Bacterial vaginosis and the risk of trichomonas vaginalis acquisition among HIV-1-negative women. Sex Transm Dis. 2014;41:123–8.
5. Lokken EM, Balkus JE, Kiarie J, Hughes JP, Jaoko W, Totten PA, et al. Recent bacterial vaginosis is associated with acquisition of mycoplasma genitalium. Am J Epidemiol. 2017;186:194–201.
6. Cherpes TL, Meyn LA, Krohn MA, Hillier SL. Risk factors for infection with herpes simplex virus type 2: role of smoking, douching, uncircumcised males, and vaginal flora. Sex Transm Dis. 2003;30:405–10.
7. Tamarelle J, Thiebaut ACM, de Barbeyrac B, Bebear C, Ravel J, Delarocque-Astagneau E. The vaginal microbiota and its association with human papillomavirus, chlamydia trachomatis, Neisseria gonorrhoeae and mycoplasma genitalium infections: a systematic review and meta-analysis. Clin Microbiol Infect 2018.
8. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med. 1995;333:1737–42.
9. Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent associations of bacterial vaginosis and Chlamydia trachomatis infection with adverse pregnancy outcome. JAMA. 1986;256:1899–903.
10. Watts DH, Krohn MA, Hillier SL, Eschenbach DA. Bacterial vaginosis as a risk factor for post-cesarean endometritis. Obstet Gynecol. 1990;75:52–8.
11. Haggerty CL, Hillier SL, Bass DC, Ness RB. Bacterial vaginosis and anaerobic bacteria are associated with endometritis. Clin Infect Dis. 2004;39:990–5.
12. Watts DH, Eschenbach DA, Kenny GE. Early postpartum endometritis: the role of bacteria, genital mycoplasmas, and Chlamydia trachomatis. Obstet Gynecol. 1989;73:52–60.
13. Hillier SL, Kiviat NB, Hawes SE, Hasselquist MB, Hanssen PW, Eschenbach DA, et al. Role of bacterial vaginosis-associated microorganisms in endometritis. Am J Obstet Gynecol. 1996;175:435–41.
14. Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. N Engl J Med. 1988;319:972–8.
15. Larsson PG, Platz-Christensen JJ, Thejls H, Forsum U, Pahlson C. Incidence of pelvic inflammatory disease after first-trimester legal abortion in women with bacterial vaginosis after treatment with metronidazole: a double-blind, randomized study. Am J Obstet Gynecol. 1992;166:100–3.
16. Haggerty CL, Totten PA, Tang G, Astete SG, Ferris MJ, Norori J, et al. Identification of novel microbes associated with pelvic inflammatory disease and infertility. Sex Transm Infect. 2016;92:441–6.
17. Peebles K, Velloza J, Balkus JE, McClelland RS, Barnabas RV. High global burden and costs of bacterial vaginosis: a systematic review and meta-analysis. Sex Transm Dis. 2019;46:304–11.
18. Taha TE, Hoover DR, Dallabetta GA, Kumwenda NI, Mtimavalye LAR, Yang LP, et al. Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. AIDS. 1998;12:1699–706.
19. van de Wijgert JH, Morrison CS, Cornelisse PG, et al. Bacterial vaginosis and vaginal yeast, but not vaginal cleansing, increase HIV-1 acquisition in African women. J Acquir Immune Defic Syndr. 2008;48:203–10.
20. Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001–2004 National Health and Nutrition Examination Survey data. Obstet Gynecol. 2007;109:114–20.
21. Martin HL Jr, Nyange PM, Richardson BA, et al. Hormonal contraception, sexually transmitted diseases, and risk of heterosexual transmission of human immunodeficiency virus type 1. J Infect Dis. 1998;178:1053–9.
22. Martin HL Jr, Richardson BA, Nyange PM, et al. Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. J Infect Dis. 1999;180:1863–8.
23. van de Wijgert JH, Morrison CS, Brown J, et al. Disentangling contributions of reproductive tract infections to HIV acquisition in African Women. Sex Transm Dis. 2009;36:357–64.
24. McClelland RS, Richardson BA, Hassan WM, et al. Improvement of vaginal health for Kenyan women at risk for acquisition of

human immunodeficiency virus type 1: results of a randomized trial. J Infect Dis. 2008;197:1361–8.
25. McClelland RS, Richardson BA, Graham SM, et al. A prospective study of risk factors for bacterial vaginosis in HIV-1-seronegative African women. Sex Transm Dis. 2008;35:617–23.
26. Fettweis JM, Brooks JP, Serrano MG, Sheth NU, Girerd PH, Edwards DJ, et al. Differences in vaginal microbiome in African American women versus women of European ancestry. Microbiology. 2014;160:2272–82.
27. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep. 2015;64:1–138.
28. Oduyebo OO, Anorlu RI, Ogunsola FT. The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. Cochrane Database Syst Rev 2009:CD006055.
29. Koumans EH, Markowitz LE, Hogan V, Group CBW. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. Clin Infect Dis. 2002;35:S152–72.
30. Bradshaw CS, Morton AN, Hocking J, Garland SM, Morris MB, Moss LM, et al. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. J Infect Dis. 2006;193:1478–86.
31. Bilardi JE, Walker S, Temple-Smith M, McNair R, Mooney-Somers J, Bellhouse C, et al. The burden of bacterial vaginosis: women's experience of the physical, emotional, sexual and social impact of living with recurrent bacterial vaginosis. PLoS One. 2013;8:e74378.
32. Bilardi J, Walker S, McNair R, Mooney-Somers J, Temple-Smith M, Bellhouse C, et al. Women's management of recurrent bacterial vaginosis and experiences of clinical care: a qualitative study. PLoS One. 2016;11:e0151794.
33. Payne SC, Cromer PR, Stanek MK, Palmer AA. Evidence of African-American women's frustrations with chronic recurrent bacterial vaginosis. J Am Acad Nurse Pract. 2010;22:101–8.
34. Mitchell C, Manhart LE, Thomas K, Fiedler T, Fredricks DN, Marrazzo J. Behavioral predictors of colonization with Lactobacillus crispatus or Lactobacillus jensenii after treatment for bacterial vaginosis: a cohort study. Infect Dis Obstet Gynecol. 2012;2012:706540.
35. Marrazzo JM, Thomas KK, Fiedler TL, Ringwood K, Fredricks DN. Relationship of specific vaginal bacteria and bacterial vaginosis treatment failure in women who have sex with women. Ann Intern Med. 2008;149:20–8.
36. Swidsinski A, Mendling W, Loening-Baucke V, et al. An adherent Gardnerella vaginalis biofilm persists on the vaginal epithelium after standard therapy with oral metronidazole. Am J Obstet Gynecol. 2008;198(97):e1–6.
37. Swidsinski A, Mendling W, Loening-Baucke V, Ladhoff A, Swidsinski S, Hale LP, et al. Adherent biofilms in bacterial vaginosis. Obstet Gynecol. 2005;106:1013–23.
38. Liu CM, Hungate BA, Tobian AA, et al. Penile microbiota and female partner bacterial vaginosis in Rakai, Uganda. mBio. 2015;6:e00589.
39. Zozaya M, Ferris MJ, Siren JD, Lillis R, Myers L, Nsuami MJ, et al. Bacterial communities in penile skin, male urethra, and vaginas of heterosexual couples with and without bacterial vaginosis. Microbiome. 2016;4:16.
40. Vodstrcil LA, Walker SM, Hocking JS, Law M, Forcey DS, Fehler G, et al. Incident bacterial vaginosis (BV) in women who have sex with women is associated with behaviors that suggest sexual transmission of BV. Clin Infect Dis. 2015;60:1042–53.
41. Sobel JD, Ferris D, Schwebke J, Nyirjesy P, Wiesenfeld HC, Peipert J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. Am J Obstet Gynecol. 2006;194:1283–9.
42. Balkus JE, Jaoko W, Mandaliya K, Richardson BA, Masese L, Gitau R, et al. The posttrial effect of oral periodic presumptive treatment for vaginal infections on the incidence of bacterial vaginosis and Lactobacillus colonization. Sex Transm Dis. 2012;39:361–5.
43. McClelland RS, Balkus JE, Lee J, et al. Randomized trial of periodic presumptive treatment with high-dose intravaginal metronidazole and miconazole to prevent vaginal infections in HIV-negative women. J Infect Dis. 2015;211:1875–82.
44. Kim H, Gurrin L, Ademi Z, Liew D. Overview of methods for comparing the efficacies of drugs in the absence of head-to-head clinical trial data. Br J Clin Pharmacol. 2014;77:116–21.
45. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74:14–22.
46. Ferris DG, Litaker MS, Woodward L, Mathis D, Hendrich J. Treatment of bacterial vaginosis: a comparison of oral metronidazole, metronidazole vaginal gel, and clindamycin vaginal cream. J Fam Pract. 1995;41:443–9.
47. Mochache V, McClelland RS, Balkus JE. Periodic presumptive treatment for women with prevalent vaginal infections: secondary analysis of data from a randomized controlled trial. Sex Transm Dis. 2014;41:453.
48. World Health Organization (WHO). Guideline for the management of sexually transmitted infections. Geneva: WHO; 2003. p. 1–91.
49. Balkus JE, Srinivasan S, Anzala O, Kimani J, Andac C, Schwebke J, et al. Impact of periodic presumptive treatment for bacterial vaginosis on the vaginal microbiome among women participating in the preventing vaginal infections trial. J Infect Dis. 2017;215:723–31.
50. Goolsby TA, Jakeman B, Gaynes RP. Clinical relevance of metronidazole and peripheral neuropathy: a systematic review of the literature. Int J Antimicrob Agents. 2018;51:319–25.
51. Cunningham FE, Kraus DM, Brubaker L, Fischer JH. Pharmacokinetics of intravaginal metronidazole gel. J Clin Pharmacol. 1994;34:1060–5.
52. Hanson JM, McGregor JA, Hillier SL, Eschenbach DA, Kreutner AK, Galask RP, et al. Metronidazole for bacterial vaginosis. A comparison of vaginal gel vs. oral therapy. J Reprod Med. 2000;45:889–96.
53. Sobel J. Bacterial vaginosis: treatment. www.uptodate.com; Accessed 1 July 2019 2019; Last updated Feb 21, 2019.
54. Doron S, Davidson LE. Antimicrobial stewardship. Mayo Clin Proc. 2011;86:1113–23.
55. Beigi RH, Austin MN, Meyn LA, Krohn MA, Hillier SL. Antimicrobial resistance associated with the treatment of bacterial vaginosis. Am J Obstet Gynecol. 2004;191:1124–9.
56. Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. N Engl J Med. 2005;353:1899–911.
57. Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SSK, McCulle SL, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci U S A. 2011;108(Suppl 1):4680–7.
58. Ahmed A, Earl J, Retchless A, Hillier SL, Rabe LK, Cherpes TL, et al. Comparative genomic analyses of 17 clinical isolates of Gardnerella vaginalis provide evidence of multiple genetically isolated clades consistent with subspeciation into genovars. J Bacteriol. 2012;194:3922–37.
59. Balashov SV, Mordechai E, Adelson ME, Gygax SE. Identification, quantification and subtyping of Gardnerella vaginalis in noncultured clinical vaginal samples by quantitative PCR. J Med Microbiol. 2014;63:162–75.
60. Cornejo OE, Hickey RJ, Suzuki H, Forney LJ. Focusing the diversity of Gardnerella vaginalis through the lens of ecotypes. Evol Appl. 2018;11:312–24.

61. Schuyler JA, Mordechai E, Adelson ME, Sobel JD, Gygax SE, Hilbert DW. Identification of intrinsically metronidazole-resistant clades of Gardnerella vaginalis. Diagn Microbiol Infect Dis. 2016;84:1–3.
62. Deng ZL, Gottschick C, Bhuju S, Masur C, Abels C, Wagner-Dobler I. Metatranscriptome analysis of the vaginal microbiota reveals potential mechanisms for protection against metronidazole in bacterial vaginosis. mSphere. 2018;3.
63. Schwebke JR, Desmond R. A randomized trial of metronidazole in asymptomatic bacterial vaginosis to prevent the acquisition of sexually transmitted diseases. Am J Obstet Gynecol. 2007;196:517 e1–6.
64. Balkus JE, Manhart LE, Lee J, Anzala O, Kimani J, Schwebke J, et al. Periodic presumptive treatment for vaginal infections may reduce the incidence of sexually transmitted bacterial infections. J Infect Dis. 2016;213:1932–7.
65. Hilbert DW, Smith WL, Paulish-Miller TE, Chadwick SG, Toner G, Mordechai E, et al. Utilization of molecular methods to identify prognostic markers for recurrent bacterial vaginosis. Diagn Microbiol Infect Dis. 2016;86:231–42.
66. Bradshaw CS, Tabrizi SN, Fairley CK, Morton AN, Rudland E, Garland SM. The association of Atopobium vaginae and Gardnerella vaginalis with bacterial vaginosis and recurrence after oral metronidazole therapy. J Infect Dis. 2006;194:828–36.
67. Balkus J, Srinivasan S, Andac C, et al. Impact of baseline vaginal bacterial colonization on subsequent development of bacterial vaginosis among women receiving periodic presumptive treatment for vaginal infections. Presented at the Infectious Dieseases Society of Obstetrics and Gynecology, Philadelphia, PA, 2018 2018.
68. Sobel JD, Kaur N, Woznicki NA, Boikov D, Aguin T, Gill G, Akins RA Prognostic indicators of recurrence of bacterial vaginosis. J Clin Microbiol 2019;57.
69. Marrazzo JM, Dombrowski JC, Wierzbicki MR, Perlowski C, Pontius A, Dithmer D, et al. Safety and efficacy of a novel vaginal anti-infective, TOL-463, in the treatment of bacterial vaginosis and vulvovaginal candidiasis: a randomized, single-blind, phase 2, controlled trial. Clin Infect Dis. 2019;68:803–9.
70. Hemmerling A, Harrison W, Schroeder A, Park J, Korn A, Shiboski S, et al. Phase 2a study assessing colonization efficiency, safety, and acceptability of Lactobacillus crispatus CTV-05 in women with bacterial vaginosis. Sex Transm Dis. 2010;37:745–50.