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Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis

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ABSTRACT

BACKGROUND

Bacterial vaginosis affects one third of reproductive-aged women, and recurrence is common. Evidence of sexual exchange of bacterial vaginosis–associated organisms between partners suggests that male-partner treatment may increase the likelihood of cure.

METHODS

This open-label, randomized, controlled trial involved couples in which a woman had bacterial vaginosis and was in a monogamous relationship with a male partner. In the partner-treatment group, the woman received first-line recommended antimicrobial agents and the male partner received oral and topical antimicrobial treatment (metronidazole 400-mg tablets and 2% clindamycin cream applied to penile skin, both twice daily for 7 days). In the control group, the woman received first-line treatment and the male partner received no treatment (standard care). The primary outcome was recurrence of bacterial vaginosis within 12 weeks.

RESULTS

A total of 81 couples were assigned to the partner-treatment group, and 83 couples were assigned to the control group. The trial was stopped by the data and safety monitoring board after 150 couples had completed the 12-week follow-up period because treatment of the woman only was inferior to treatment of both the woman and her male partner. In the modified intention-to-treat population, recurrence occurred in 24 of 69 women (35%) in the partner-treatment group (recurrence rate, 1.6 per person-year; 95% confidence interval [CI], 1.1 to 2.4) and in 43 of 68 women (63%) in the control group (recurrence rate, 4.2 per person-year; 95% CI, 3.2 to 5.7), which corresponded to an absolute risk difference of –2.6 recurrences per person-year (95% CI, –4.0 to –1.2; P<0.001). Adverse events in treated men included nausea, headache, and metallic taste.

CONCLUSIONS

The addition of combined oral and topical antimicrobial therapy for male partners to treatment of women for bacterial vaginosis resulted in a lower rate of recurrence of bacterial vaginosis within 12 weeks than standard care. (Funded by the National Health and Medical Research Council of Australia; StepUp Australian New Zealand Clinical Trials Registry number, ACTRN12619000196145.)

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CME

A Quick Take is available at NEJM.org

Bacterial vaginosis is a dysbiosis of the vaginal microbiota that affects 30% of women worldwide[1,2] and is associated with obstetric and gynecologic sequelae.[2-4] International guidelines recommend metronidazole or clindamycin as first-line treatment for affected women. However, this strategy does not result in sustained cure, with an incidence of recurrence within 3 months exceeding 50%.[5,6]

Efforts to increase the likelihood of cure have been hindered by an incomplete understanding of the pathogenesis of bacterial vaginosis, although epidemiologic and microbiologic data show that it has the profile of a sexually transmitted infection (STI).[7,8] Incident bacterial vaginosis has an incubation period similar to that of bacterial STIs[9] and is associated with new sexual partners,[10-12] whereas the risk of recurrence among women who report sex with a regular partner is double that among women who do not report a regular partner.[6,13,14] Studies show that men may harbor bacterial species associated with bacterial vaginosis in the distal urethra and subpreputial space[15-20] and that the penile microbiota is predictive of a woman's risk of bacterial vaginosis.[19]

Past trials of male-partner treatment did not show an increased incidence of cure, which was interpreted as evidence against sexual transmission.[7] However, most had substantive limitations, including limited statistical power, no assessment of adherence, and the use of single-dose regimens (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[21,22] Moreover, previous trials assessed oral antimicrobial agents alone, which may not be sufficient to clear cutaneous penile carriage of bacterial vaginosis–associated organisms.[15-20,23-28] We performed this randomized, controlled trial (StepUp) to determine whether concurrent oral and topical antimicrobial treatment of male partners of women receiving first-line therapy for bacterial vaginosis, as compared with treatment of the woman only (standard care), reduces the risk of recurrence at 12 weeks.

Methods

Trial Design and Oversight

We enrolled participants from April 2019 through November 2023. Trial sites included two sexual health services and three family-planning services across three Australian states. The protocol was published previously[29] and is available at NEJM.org with the statistical analysis plan. Approval was granted by the Alfred Health Ethics Committee. The trial was funded by the National Health and Medical Research Council, which had no role in trial design, data collection or analysis, or manuscript preparation. The first, second, and last authors had access to all the data and vouch for their completeness and accuracy and for the fidelity of the trial to the protocol.

Participants

Couples were recruited to the trial as follows. First, premenopausal women were screened. They were eligible if they had symptoms of bacterial vaginosis and met the diagnostic criteria for the condition (presence of at least three of four Amsel criteria[30] and a Nugent score[31] of 4 to 10), had a regular male partner for at least 8 weeks before enrollment, and were receiving first-line antimicrobial treatment (metronidazole 400-mg tablets twice daily for 7 days or, if contraindicated, intravaginal 2% clindamycin cream for 7 nights or intravaginal 0.75% metronidazole gel for 5 nights). The four Amsel criteria are a characteristic homogeneous vaginal discharge, a vaginal pH of more than 4.5, a positive amine test (fishy odor), and the presence of clue cells on microscopic examination. A Nugent score of 0 to 3 represents normal vaginal microbiota, a score to 4 to 6 represents an intermediate state, and a score of 7 to 10 is indicative of bacterial vaginosis. (For details, see the Supplementary Methods section in the Supplementary Appendix.)

Women who met the eligibility criteria were then asked to refer their regular male partner, and the couple was eligible to participate if men could enroll within a week after their partner had enrolled. All the participants needed to be 18 years of age or older, understand sufficient English to provide informed consent, be able to adhere to protocol requirements, not have other partners at enrollment, not be a sex worker, not be known to be living with human immunodeficiency virus infection, and not have contraindications to the antimicrobial agents. Male partners were recruited in accordance with the trial protocol[29] (see the Supplementary Methods section). All the participants provided written informed consent.

Randomization and Treatment

An independent biostatistician created a computer-generated block-randomization sequence, with trial investigators unaware of the sequence. Ran-

domization was stratified according to recruitment site, current use or nonuse of an intrauterine device (IUD), and male circumcision status. (Current use of an IUD has been linked with an increased risk of bacterial vaginosis, as has uncircumcised status.[32-36]) The research nurse logged into the password-protected database (see the Supplementary Methods section), and once essential data had been entered, the next trial-group assignment was displayed.

Couples were randomly assigned in a 1:1 ratio to the partner-treatment group (treatment of the woman and her male partner) or the control group (treatment of the woman only). Male partners who were assigned to partner treatment received metronidazole 400-mg tablets (to be taken twice daily for 7 days) and were instructed to apply a 2-cm-diameter volume of 2% clindamycin cream topically to the glans penis and upper shaft (under the foreskin if the male partner was uncircumcised) twice daily for 7 days. A placebo cream was not used for men owing to concerns that application of any topical cream may alter the composition of the penile microbiome.[29] Treatment was open-label; both researchers and participants knew the group to which the participants had been assigned. Participants were instructed to commence treatment after baseline procedures, and all couples, regardless of assigned group, were counseled to avoid sexual contact during the 7-day treatment period. Couples assigned to the partner-treatment group were asked to synchronize treatment. Couples assigned to the control group were informed that they would be offered male-partner treatment if bacterial vaginosis recurred during the follow-up period.[29]

Questionnaires and vaginal samples for Nugent scoring were collected during clinic visits at baseline and weeks 4 and 12 and at home on day 8 and week 8.[29] At baseline and follow-up, microscopists who were unaware of the trial-group assignments assessed the Nugent score, clue cells, and amine result. At sites without an on-site laboratory, clinicians collected a vaginal smear from women who met three specific Amsel criteria (characteristic discharge, vaginal pH of >4.5, and malodor), which was couriered to the coordinating trial site for Nugent scoring. If the baseline Nugent score was less than 4, women were considered to have screening failure and were not included in the evaluable population.

Women were recalled to the clinic if they reported interim symptoms or if their Nugent score at week 8 was 7 or higher. Amsel and Nugent criteria were assessed at clinic visits. Male partners completed questionnaires at baseline, day 8, and weeks 4, 8, and 12.

OUTCOMES

The primary efficacy outcome was recurrence of bacterial vaginosis, defined by both the presence of at least three Amsel criteria and a Nugent score of 4 to 10, within 12 weeks. Predefined secondary outcomes included recurrence of bacterial vaginosis within 4 weeks, a Nugent score of 7 to 10 within 4 weeks, a Nugent score of 7 to 10 within 12 weeks, and vaginal microbiota outcomes[29] (Table S2). Treated women and men were provided with a questionnaire that captured adherence and adverse events. The questionnaire included a list of symptoms known to be associated with metronidazole and clindamycin and also allowed for spontaneous reporting.

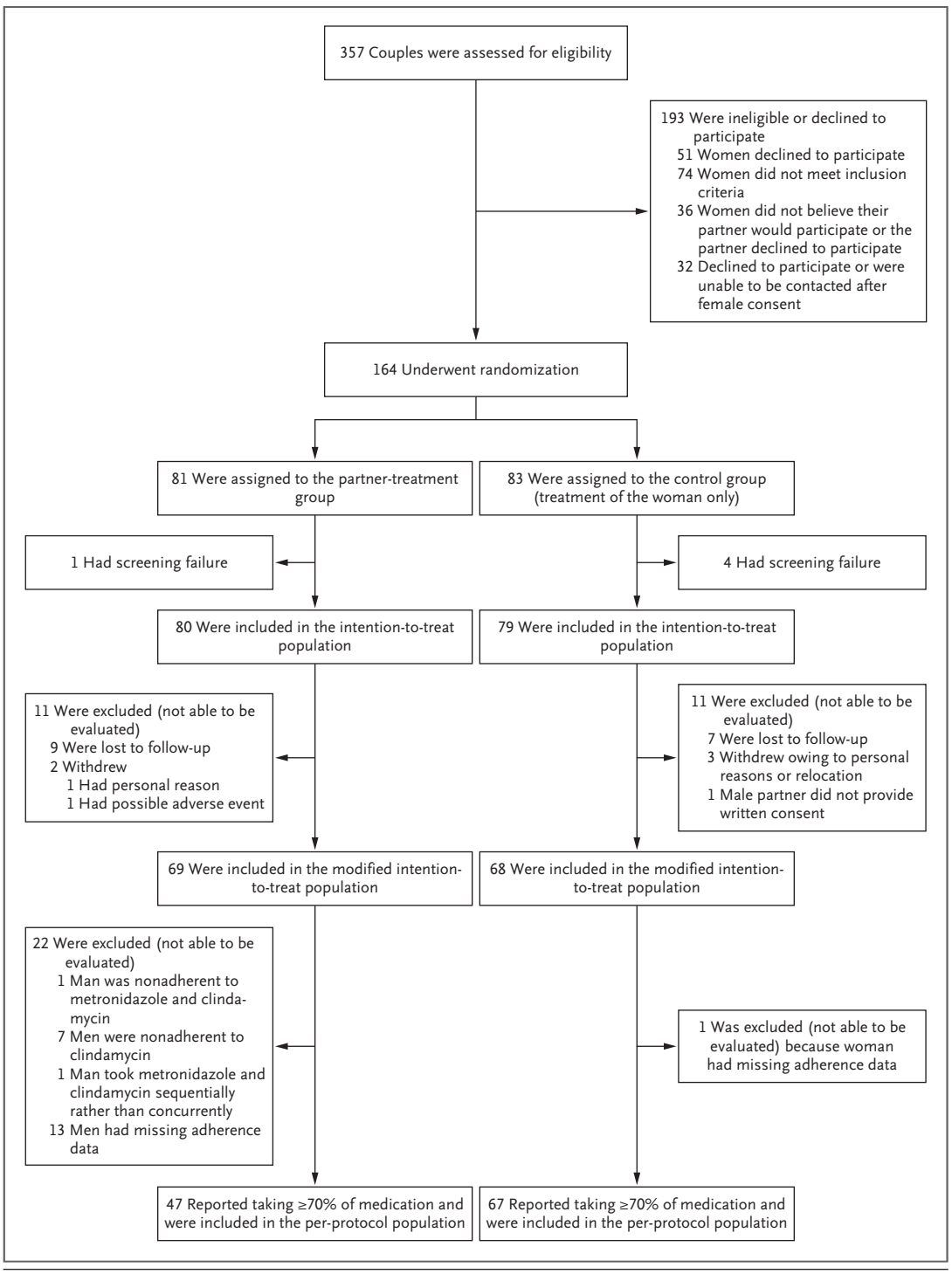
PROTOCOL REVISION

A revision to the trial protocol[29] occurred owing to the coronavirus disease 2019 (Covid-19) pandemic. From March 2020 through 2022, there were extended lockdowns, movement restrictions, and Covid-19 isolation rules. Seven women who were unable to attend the clinic collected vaginal samples at home and returned them by mail to the trial site. For these women, recurrence was defined by a Nugent score of 4 or higher with clue cells on microscopic examination.

STATISTICAL ANALYSIS

We estimated that a sample size of 290 couples (145 per group) would provide 80% power to detect a 40% lower incidence of recurrence of bacterial vaginosis in the intervention group than in the control group, assuming an incidence of recurrence in the control group of 40% over a period of 12 weeks (two-sided alpha, 5%).[29] Assuming a 15% loss to follow-up, we aimed to recruit 342 couples (171 per group). An interim analysis of cumulative recurrence and recurrence rates according to group, to be viewed in a blinded fashion by an independent data and safety monitoring board, was scheduled to occur when 150 randomly assigned couples had completed the trial requirements.[29] A conservative Peto–Prentice stopping rule ($P<0.001$) could be applied if one group was statistically inferior to the other according to the Pearson chi-square test or the log-rank test.

The primary analysis was a modified intention-



to-treat analysis.[37] The evaluable population for the modified intention-to-treat analysis included all the women who underwent randomization, passed screening, received at least one treatment dose, and were assessed for recurrence according to both Amsel criteria and Nugent score (primary outcome). Data for participants lost to follow-up without recurrence were censored at their last visit. (Guidelines for handling missing data are provided in the Supplementary Methods section.)

Figure 1 (facing page). Enrollment, Treatment, and Follow-up.

Eligibility criteria for women included a diagnosis of symptomatic bacterial vaginosis, a regular male partner for at least 8 weeks before enrollment, and treatment with a first-line antimicrobial regimen. All the participants needed to be 18 years of age or older, be able to adhere to protocol requirements, and not have other partners at enrollment. In couples assigned to the partner-treatment group, the male partner received oral and topical antimicrobial treatment. In couples assigned to the control group, the male partner received no treatment. In the partner-treatment group, one couple withdrew after reporting a possible adverse event during the treatment period by means of a short-message-service text; however, they did not respond to multiple contact attempts. Investigators therefore could not determine what the adverse event was, if it was an adverse event, or what medication may have been responsible. Women were eligible to be included in the modified intention-to-treat population (primary analysis) if they took at least one dose of treatment and attended at least one clinic visit for assessment.

The cumulative recurrence rates per person-year and Poisson 95% confidence intervals were determined according to randomization group. A Kaplan–Meier survival curve was used to summarize cumulative recurrence according to group, and hazard ratios were derived from Cox regression models to express time-to-event treatment effects. Time-dependent analysis showed evidence of nonproportional hazards after 12 weeks. Therefore, we performed post hoc analyses of restricted mean survival time, truncating follow-up at 12 weeks (84 days). For these analyses, the treatment effect is presented as a between-group difference in the restricted mean survival time in days until recurrence (partner-treatment group minus control group), and positive values indicate a decreased risk in the partner-treatment group.

We assumed a priori that data were missing completely at random. To assess the effect of missing data, we also performed two post hoc analyses of the primary outcome in which we imputed missing week 12 data in participants lost to follow-up as either cure or treatment failure. A preplanned per-protocol analysis removed nonadherent couples (defined as either member taking <70% of doses). Analyses were also planned according to IUD use or nonuse and circumcision status. Additional sensitivity and secondary analyses were conducted (see the Supplementary Methods section).[37]

We summarized adherence and adverse events (expected or prespecified events and other, unsolicited events) according to randomization group for women, as well as for men who reported taking at least one treatment dose. Analyses were conducted with the use of Stata software (version 17.0). Secondary outcome results are reported as point estimates and 95% confidence intervals. We did not adjust the widths of the confidence intervals for results of secondary or subgroup analyses for multiplicity, and they should not be used in place of hypothesis testing.

RESULTS

PARTICIPANTS

Of 357 couples assessed for eligibility, 164 underwent randomization: 81 were assigned to the partner-treatment group and 83 to the control group (Fig. 1 and Table S3). The trial was stopped by the data and safety monitoring board at the interim analysis of the first 150 couples (October 2023) because of the inferiority of standard care. Participant characteristics at baseline were generally balanced between the two groups, with some minor differences (Table 1 and Tables S4 and S5). After randomization, 27 couples (12 in the partner-treatment group and 15 in the control group) were ineligible for the primary analysis. Eleven couples (7 in the partner-treatment group and 4 in the control group) who did not complete the week 12 visit attended at least one post-treatment assessment and were eligible for the primary analysis. Therefore, the primary analysis included 69 couples in the partner-treatment group and 68 couples in the control group.

OUTCOMES

Primary Analysis

Recurrence of bacterial vaginosis within 12 weeks was observed in 24 of 69 women (35%) in the partner-treatment group (recurrence rate, 1.6 per person-year; 95% confidence interval [CI], 1.1 to 2.4) and in 43 of 68 women (63%) in the control group (recurrence rate, 4.2 per person-year; 95% CI, 3.2 to 5.7) (Table 2 and Fig. 2). The mean time until recurrence was 73.9 days in the partner-treatment group and 54.5 days in the control group (difference in restricted mean survival time, 19.3 days; 95% CI, 11.5 to 27.1; P<0.001). These findings corresponded to an absolute risk difference of –2.6 recurrences per person-year (95% CI, –4.0 to –1.2) and a lower risk of recurrence among

Table 1. Baseline Characteristics of All Randomly Assigned Participants Who Fulfilled Eligibility Criteria for the Trial.*

Characteristic	Partner-Treatment Group (N=80)	Control Group (N=79)
Female participants		
Age at randomization — yr	28.5±6.6	30.9±7.5
Participant-reported ethnic background, grouped according to WHO region — no./total no. (%)		
Region of the Americas	9/80 (11)	4/77 (5)
South-East Asian Region	3/80 (4)	1/77 (1)
European Region	20/80 (25)	28/77 (36)
Western Pacific†	44/80 (55)	37/77 (48)
Mixed ethnic background	4/80 (5)	7/77 (9)
Current IUD use — no. (%)‡	22 (28)	26 (33)
Median no. of previous diagnoses of bacterial vaginosis (IQR)§	3 (1–5)	3 (1–5)
Median no. of male sexual partners during lifetime (IQR)	15 (7–24)	15 (8–30)
Median no. of female sexual partners during lifetime (IQR)	0 (0–2)	0 (0–4)
Median duration of sexual relationship with regular male partner (IQR) — mo	14 (6–36)	14 (6–37)
Median no. of times per month reporting vaginal sex with regular male partner (IQR)	12 (8–16)	8 (4–16)
Always uses condom with regular male partner for vaginal sex — no./total no. (%)	2/78 (3)	4/75 (5)
Clinical findings at enrollment		
Vaginal pH >4.5 — no./total no. (%)	77/79 (97)	74/76 (97)
Characteristic homogeneous vaginal discharge — no. (%)	77 (96)	76 (96)
Fishy odor or positive amine test — no. (%)	75 (94)	74 (94)
Presence of clue cells visualized on wet mount — no./total no. (%)	76/80 (95)	70/78 (90)
Nugent score of 4–6 — no. (%)¶	11 (14)	10 (13)
Nugent score of 7–10 — no. (%)¶	69 (86)	69 (87)
Male participants		
Age at randomization — yr	31.1±8.7	34.2±8.0
Uncircumcised — no. (%)‡	64 (80)	63 (80)
Participant-reported ethnic background, grouped according to WHO region — no./total no. (%)		
Africa Region	1/72 (1)	1/69 (1)
Region of the Americas	4/72 (6)	7/69 (10)
European Region	22/72 (31)	24/69 (35)
Eastern Mediterranean Region	2/72 (3)	1/69 (1)
Western Pacific†	38/72 (53)	33/69 (48)
Mixed ethnic background	5/72 (7)	3/69 (4)
Median no. of female sexual partners during lifetime (IQR)	18 (10–40)	20 (10–40)

* Plus–minus values are means ±SD. In couples assigned to the partner-treatment group, the woman received first-line antimicrobial treatment for bacterial vaginosis and the male partner received oral and topical antimicrobial treatment. In couples assigned to the control group, the woman received first-line antimicrobial treatment and the male partner received no treatment. Percentages may not total 100 because of rounding. IQR denotes interquartile range, IUD intrauterine device, and WHO World Health Organization.
† Included are four Aboriginal or Torres Strait Islander participants (two women and two men).
‡ Randomization was stratified according to current IUD use or nonuse and male circumcision status.
§ Overall, 87% of the participants reported a previous diagnosis of bacterial vaginosis.
¶ Gram's staining of the vaginal smear was used to determine the Nugent score. A score of 0 to 3 represents normal vaginal microbiota, a score of 4 to 6 represents an intermediate state, and a score of 7 to 10 is indicative of bacterial vaginosis.

Table 2. Primary and Secondary Analyses of Recurrence of Bacterial Vaginosis (Primary Outcome).*

Analysis and Population	Partner-Treatment Group				Control Group				Absolute Risk Difference (95% CI)	Hazard Ratio (95% CI)†	Difference in RMST (95% CI)‡
	No. with Recurrence/ Total No. (%)	Person-Yr	Recurrence Rate per Person-Yr (95% CI)	RMST	No. with Recurrence/ Total No. (%)	Person-Yr	Recurrence Rate per Person-Yr (95% CI)	RMST			
				days				*days*			*days*
Primary analysis											
Modified intention-to-treat population§	24/69 (35)	14.7	1.6 (1.1 to 2.4)	73.9	43/68 (63)	10.1	4.2 (3.2 to 5.7)	54.5	−2.6 (−4.0 to −1.2)	0.37 (0.22 to 0.61)	19.3 (11.5 to 27.1)¶
Secondary analyses‖											
Intention-to-treat population											
Missing data imputed as cure**	24/80 (30)	20.6	1.2 (0.8 to 1.7)	75.7	44/79 (56)	14.3	3.1 (2.3 to 4.1)	58.8	−2.0 (−3.0 to −0.9)	0.39 (0.24 to 0.64)	17.0 (10.0 to 23.9)
Missing data imputed as treatment failure**	44/80 (55)	20.4	2.2 (1.6 to 2.9)	75.0	59/79 (75)	14.2	4.1 (3.2 to 5.4)	58.1	−2.0 (−3.2 to −0.8)	0.45 (0.30 to 0.67)	16.9 (9.9 to 23.9)
Per-protocol population††	15/47 (32)	10.0	1.5 (0.9 to 2.5)	72.9	42/67 (63)	10.0	4.2 (3.1 to 5.7)	54.7	−2.7 (−4.2 to −1.2)	0.35 (0.19 to 0.64)	18.2 (9.4 to 27.0)

* Recurrence of bacterial vaginosis was defined by both the presence of at least three of four Amsel criteria and a Nugent score of 4 to 10 within 12 weeks. The four Amsel criteria are a characteristic homogeneous vaginal discharge, a vaginal pH of more than 4.5, a positive amine test (fishy odor), and the presence of clue cells on microscopic examination. During the coronavirus disease 2019 (Covid-19) pandemic, the Australian state of Victoria enacted strict government-enforced lockdown measures and isolation rules, which limited nonessential movement and reduced clinical capacity at clinical services. These measures commenced in March 2020 and extended for prolonged periods to the end of 2022. During this time, the protocol was revised to allow seven female participants who were unable to attend a clinical assessment of bacterial vaginosis to be included in the primary outcome. Four returned a vaginal smear for microscopy that had a Nugent score of 0 to 3, and two had an intermediate Nugent score (4 to 6). None of these six had clue cells present, so their trial end point was defined as no recurrence of bacterial vaginosis for the primary outcome. One person had a Nugent score of 7 and clue cells were present under microscopy, so the participant's trial end point was defined as recurrence of bacterial vaginosis. A sensitivity analysis that excluded persons whose participation was affected by the Covid-19 pandemic did not affect the primary outcome (hazard ratio, 0.37; 95% CI, 0.22 to 0.62).

† The hazard ratios were calculated with the use of Cox regression models.

‡ Shown is the between-group difference in days until recurrence, as calculated by the restricted mean survival time (RMST) method.

§ The primary analysis was a modified intention-to-treat analysis, excluding women who did not return for a post-treatment assessment for bacterial vaginosis. This population included all the women who had undergone randomization, were not deemed to have screening failure, received at least one dose of treatment, and underwent testing for clinical cure. If a participant attended the week 4 visit without bacterial vaginosis but was subsequently lost to follow-up, the week 4 data constituted the participant's trial end point and result (i.e., censored at this point).

¶ $P<0.001$.

‖ The widths of the confidence intervals for secondary analyses are not adjusted for multiplicity and should not be used for hypothesis testing.

** Two intention-to-treat analyses included all the participants who had undergone randomization. For those who were lost to follow-up, data missing at week 12 were imputed as cure or treatment failure.

†† The per-protocol analysis excluded nonadherent couples, defined as those taking less than 70% of all prescribed doses. If a participant attended the week 4 visit without bacterial vaginosis but was subsequently lost to follow-up, the week 4 data constituted the participant's trial end point and result (i.e., censored at this point).

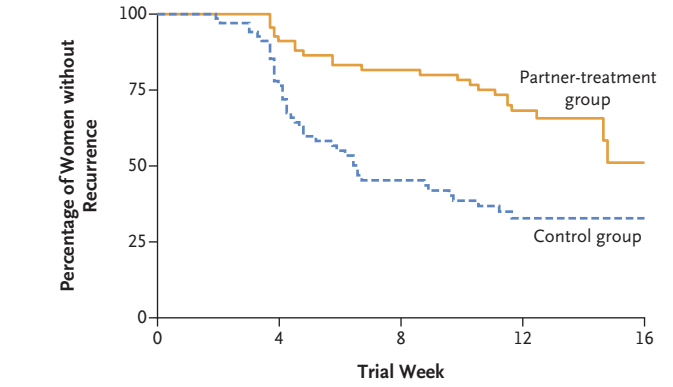


Figure 2. Kaplan–Meier Curves for Time to Recurrence of Bacterial Vaginosis (Modified Intention-to-Treat Population).

women in the partner-treatment group than among those in the control group over 12 weeks (hazard ratio, 0.37; 95% CI, 0.22 to 0.61).

Secondary Analyses

The results of the secondary and sensitivity analyses supported the results of the primary analysis (Table 2, Tables S6 and S7, and Fig. S1). In the intention-to-treat analyses, when missing week 12 data were imputed as cure, the recurrence rate was 1.2 per person-year (95% CI, 0.8 to 1.7) in the partner-treatment group and 3.1 per person-year (95% CI, 2.3 to 4.1) in the control group (risk difference, –2.0; 95% CI, –3.0 to –0.9). When missing week 12 data were imputed as treatment failure, the recurrence rate was 2.2 per person-year (95% CI, 1.6 to 2.9) in the partner-treatment group and 4.1 per person-year (95% CI, 3.2 to 5.4) in the control group (risk difference, –2.0; 95% CI, –3.2 to –0.8). These analyses indicated that our results were robust with respect to missing data. In the per-protocol population, the recurrence rate was 1.5 per person-year (95% CI, 0.9 to 2.5) in the partner-treatment group and 4.2 per person-year (95% CI, 3.1 to 5.7) in the control group (risk difference, –2.7; 95% CI, –4.2 to –1.2).

When the primary outcome was stratified according to IUD use or nonuse and circumcision status, there was no evidence of different treatment effects across strata (Table S8). There were no associations between recurrence and contraceptive or sexual practices (Table S9).

ADHERENCE

Adherence data were available for all 69 women and 56 of 69 men in the partner-treatment group and for 67 of 68 women in the control group. All the female participants took at least 70% of their prescribed medication (Table S10). Among male participants, 8 of 56 (14%) reported taking less than 70% of doses of prescribed medications, with men missing more doses of clindamycin than metronidazole (Table S11). Sensitivity analyses showed that the lowest recurrence rate of 1.3 per person-year (95% CI, 0.7 to 2.6) was among partners of men who were 100% adherent to treatment (Table S12).

ADVERSE EVENTS

Data on adverse events were available for 68 of 69 women and 56 of 69 men in the partner-treatment group and for 65 of 68 women in the control group. The percentages of women who reported adverse effects did not differ substantially between the partner-treatment and control groups (59% and 57%, respectively); nausea, headache, and vaginal itch were most common (Table 3). Adverse events were reported by 26 of 56 men (46%) who received partner treatment and returned the post-treatment questionnaire; these included nausea, headache, and metallic taste. Redness or irritation of penile skin was uncommon (4 participants) (Table 3). No serious adverse events were reported.

DISCUSSION

In this multicenter, randomized trial, the addition of oral and topical antimicrobial therapy for male partners, at the time that their female partner was treated for bacterial vaginosis, resulted in a significantly lower recurrence rate over a period of 12 weeks than the recommended practice of treating women only. Secondary and sensitivity analyses supported these findings.

Our trial population had a high burden of risk factors for recurrence.[7,13,33,35] Most women (87%) had a history of bacterial vaginosis and an uncircumcised male partner (80%), and nearly a third used an IUD. To our knowledge, the only other trial in the past several years to show reduced recurrence involved a lactobacillus live biotherapeutic product, administered intravaginally weekly for 11 weeks after antimicrobial therapy (risk ratio at 12 weeks, 0.66; 95% CI, 0.44 to 0.87), although this trial was not conducted exclusively in women with a regular partner.[38]

Table 3. Adverse Events Reported by Participants Receiving Treatment.

Variable	Women in the Partner-Treatment Group (N=69)	Women in the Control Group (N=68)	Men Receiving Partner Treatment (N=69)*
Adherence data available — no. of participants			
No	1	3	13
Yes	68	65	56
Adverse events — no. of participants/total no. (%)†			
None	28/68 (41)	28/65 (43)	30/56 (54)
Any	40/68 (59)	37/65 (57)	26/56 (46)
Systemic adverse events — no. of participants/total no. (%)			
Nausea	14/68 (21)	14/65 (22)	8/56 (14)
Vomiting	1/68 (1)	1/65 (2)	0/56
Metallic taste	6/68 (9)	5/65 (8)	4/56 (7)
Headache	11/68 (16)	14/65 (22)	7/56 (12)
Local genital adverse events — no. of participants/total no. (%)			
Vaginal irritation	11/68 (16)	7/65 (11)	—
Vaginal itch	16/68 (24)	15/65 (23)	—
Redness of penile skin	—	—	2/56 (4)
Irritation of penile skin	—	—	4/56 (7)
Other adverse events — no. of participants‡			
White discharge or intermittent vaginal discharge	1	1	—
Diarrhea	1	1	0
Mood swings	1	0	0
Suspected thrush	2	3	0
Reflux	0	1	0
Stomach pain or discomfort	1	1	0
Tonsillitis	0	0	1
Arm aches	0	0	1
Dry mouth or bad breath	0	2	2
Loss of appetite	0	0	1
Brain fog and fatigue	2	2	1
Insomnia, difficulty sleeping	0	1	1
Vaginal dryness	1	0	—
Mild penile itchiness	—	—	1

* The day 8 questionnaire was returned by 56 of 69 men (81%) in the partner-treatment group and 57 of 68 men (84%) in the control group (treatment of the woman only). Although men in the control group completed a day 8 questionnaire on behavioral and sexual practices, they were not asked about adherence or adverse events and are not included in the table.
† Participants could select from a prespecified list of expected adverse events.
‡ Participants also had the option to list other, unsolicited adverse events.

Unlike previous trials of male-partner treatment, which used only oral antimicrobial therapy, our trial targeted male carriage of bacterial vaginosis–associated organisms at both the penile urethra[20,23,39] and penile skin, including the subpreputial space.[19,33] The trial findings align with microbiologic evidence from our pilot studies, which showed that oral and topical antimicro-

bial therapy favorably altered the microbiota composition at both penile sites[16,17] and was associated with lower-than-expected rates of recurrence in women. Adverse events that were related to clindamycin cream were uncommon, with only four men reporting mild penile irritation. Systemic adverse events that were reported are known to be associated with oral metronidazole and were no different from those reported by women. Adherence to treatment in men was high, with adherence to clindamycin slightly lower than to metronidazole. As in the most recent partner-treatment trial,[28] recurrence rates were lowest in women whose male partners were highly adherent to antimicrobial therapy; however, adherence bias might also explain these results.

Nearly a third of the female participants used an IUD, which is a known risk factor for bacterial vaginosis.[32,34,35] Results did not differ substantially according to the use or nonuse of an IUD or according to male circumcision status. Our trial was not powered to explore the association between these factors and recurrence, and secondary analyses did not identify additional practices or behaviors that contributed to recurrence.

Some limitations should be considered. The population largely included participants attending one sexual health service. Sexual health center attendees may reflect a higher-risk population, which may affect the generalizability of the findings (Table S13). However, many women were first-time clinic attendees, and a third referred themselves from the community. The distribution of different ethnic groups was representative of urban Australia, although there were few Aboriginal or Torres Strait Islander women. The trial was stopped early at the interim analysis because of a significant difference between the two groups. This stoppage occurred at a small sample size because high rates of recurrence were observed, probably owing to a high burden of risk factors. To reduce the risk of untreated partners undermining the intervention, only women in monogamous relationships were eligible. Few couples (nine) reported sex with an additional partner during the trial; it is possible that some did not disclose concurrent partners. Treated men were asked specifically about adverse events; we do not have data on the occurrence of adverse events in the control group. Finally, participants and clinicians in the trial were aware of the trial-group assignments, but the laboratory staff and microscopist assessing the primary outcome were not.

Our trial showed that treating male partners with a week of oral metronidazole and topical clindamycin, together with treatment of women, resulted in a lower rate of recurrence of bacterial vaginosis within 12 weeks than treatment of the woman alone.

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