Systematic Review of Randomized Trials of Treatment of Male Sexual Partners for Improved Bacteria vaginosis Outcomes in Women

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Running Title: Systematic Review of Male Treatment for BV

Abstract (254 words)

Background: Bacterial vaginosis (BV) affects 10-30% of women and recurs in 15-30% within 3 months after treatment. BV is not considered an STI and treatment of the male sexual partner is not recommended. This recommendation is based on the results of 6 randomized controlled trials (RCT) of male partner treatment for reducing BV recurrence, which did not find a uniformly beneficial effect. These results are incongruous with epidemiologic and microbiologic data suggesting a sexually transmissible component of BV. In light of this disconnect, the 6 RCTs of male treatment were reviewed to assess validity.

Methods: Trials are summarized according to CONSORT guidelines. Absolute differences and risk ratios (RRs) with binomially obtained 95% confidence intervals (CIs) were estimated. Post-hoc power analyses determined the probability of rejecting the null hypothesis for observed relative effect sizes and for the smallest relative effect size detectable with $\geq$80% power.

Results: Each of the 6 RCTs had significant flaws: randomization methods were either overtly deficient or insufficiently reported; 5 RCTs used sub-optimal treatment regimens in women; adherence to treatment in women was not reported in any trial and adherence in men was reported in only 2 trials; all 6 trials had limited power. None assessed whether antibiotic treatment affected the penile microbiota.

Conclusions: While the RCT is the gold standard for assessing efficacy, biased results can mislead decision making. By current standards, it is unlikely that the results of any of these trials would be considered conclusive. Specific recommendations are made to examine whether BV-associated bacteria may be sexually transferred.

Key words: Bacterial vaginosis, randomized controlled trial, systematic review, male partner, sex partner, treatment, recurrence

Brief Summary: Systematic review of 6 RCTs of male treatment to reduce BV recurrence identified significant flaws in each trial. By current standards, it is unlikely that these 6 trial results would be considered conclusive.

Background

Bacterial vaginosis (BV), a polymicrobial pathogenic shift in the vaginal flora, is the most prevalent cause of vaginitis worldwide, affecting 10-30% of women in the general population, and 40-50% of women who are sex workers, HIV-positive, or attending sexually transmitted infection (STI) clinics [1-2]. BV increases the risk of preterm birth by up to 45% [3], and is associated with a doubling in risk of pelvic inflammatory disease [4-5]. The risk of HIV seroconversion is up to 2.5 times greater for women with BV [6-7], and BV increases the risk of HIV transmission through increased genital viral expression [8-9]. Further, BV puts women at increased risk of acquiring other STIs, such as gonorrhea and chlamydia [10-11]. Recurrence after treatment with a recommended antibiotic regimen is common: 15-30% within 3 months [12-17], and 60-80% by 12 months [18].

BV is not considered an STI [19]. However, sexual exposure increases BV risk. A meta-analysis of 28 studies located worldwide estimated a 20% protective effect of condom use on BV, and a 60% increased risk of BV for women with new or multiple male sex partners [1]. The overlapping risks for BV and STIs provide epidemiologic support for sexual transmissibility of BV-associated bacteria [20]. Case control studies have demonstrated concordance of urethral and vaginal recovery of *Gardnerella vaginalis* among couples where the woman has BV [21-22]. Broad survey of the penile bacterial microbiota through pyrosequencing of the 16s rRNA gene has identified a substantial prevalence and abundance of common BV-associated bacteria in uncircumcised men [23-24]. Results from the randomized controlled trial (RCT) of male circumcision in Rakai, Uganda, found a 60% reduction in severe BV and 40% reduction in any BV in female partners of circumcised vs. uncircumcised men at one year follow-up [25]. These data suggest the penile environment may serve as a reservoir for BV-associated bacteria. If

antibiotic treatment in men can reduce carriage of BV-associated bacteria, this may lead to reduced BV recurrence and long term reduction in prevalence and associated morbidity.

Five of 6 RCTs did not report a statistically significant beneficial effect of male partner treatment with antibiotics on reducing BV recurrence [12-17]. These trials form the basis for current Centers for Disease Control and Prevention and World Health Organization recommendations: treatment of the male partner is not recommended as part of BV treatment [19, 26]. In light of epidemiologic evidence across different populations and over time, and recent findings from results of genital microbiota analyses, these 6 RCTs of male sexual partner treatment for improved BV outcomes were reviewed to assess the validity of their results.

Methods

Search Methodology

PubMed was searched using the keywords “sexual partner(s)” or “sexual contact(s)” and “vaginitis” or “vaginosis” or “vaginalis” (no field restriction), limited to “randomized controlled trial”. Among 33 (32 English language) articles returned by the search, six trials of treatment of sexual partners [12-17] were identified. Expanding the search to include Clinical Trial, Clinical Trial Phase I, Clinical Trial Phase II, Clinical Trial Phase III, and Clinical Trial Phase IV returned 59 articles (57 English language) and did not result in identification of any additional trials of treatment of sexual partners related to Bacterial vaginosis in women. Review of references of the 6 trials did not yield additional trials.

Review Methodology and Data Extraction

Five of the trials were published 1985-1993 [12-17], prior to the first Consolidated Standards of Reporting Trials (CONSORT) Statement in 1996 [27]. Reporting of the trial by Colli et al. in 1997 [17] did not follow the CONSORT statement. A participant flow diagram was generated for each trial (Figures 1-6). Trials are summarized according to CONSORT guidelines for items to be included when reporting a randomized trial in a journal abstract [27]. Each article was reviewed to complete the 25-item CONSORT checklist to assess potential risk of bias in individual studies. Potential sources of bias in design and reporting are summarized in the text and detailed for each trial in Table 2, adapted from the CONSORT checklist. Study investigators were not contacted to verify data or obtain additional information. Flow diagrams and checklists were completed by a single reviewer (SDM).

Statistical Analyses

One trial partially reported results in terms of absolute or relative effect sizes with precision estimates. For this review, when denominator and numerator data were available, absolute differences and risk ratios (RRs) with binomially obtained 95% confidence intervals (CIs) were estimated using immediate commands in Stata/SE v11.2.

Sample Size

Five trials did not report sample size calculations. For all six trials, post-hoc power analyses were conducted (Two Independent Proportions Power Analysis, Power and Sample Size [PASS] v11 [28]) to determine the probability of rejecting the null hypothesis: (1) for observed relative effect sizes $\geq$10%, and (2) if the observed effect size were <10%, for the smallest relative effect size detectable with $\geq$80% power based.

Results

Table 1 summarizes trial setting, interventions, and primary results of each trial. CONSORT flow diagrams are incomplete with regards to randomization (Swedberg et al. [12], Figure 1) and follow-up (Vejtorp et al. [13], Figure 2) due to insufficient reporting. None of the trials reported recruitment methods or participation rates. Three of the trials explicitly stated that women had to be symptomatic to be eligible. None of the trials reported eligibility criteria for male partners or nature or duration of the relationship. Male circumcision status was reported only in the trial by Moi et al. [15], stating that "few" men were circumcised. *Gardnerella vaginalis* cultures were obtained from women in three trials [13, 15-16] and from a select subset of men in the trial by Moi et al. [15]. In all trials where clinical diagnosis of BV is an outcome, Amsel's criteria [29] are used, except in the trial by Swedberg et al. [12].

Potential sources of bias in each trial are detailed in Table 2. None of the trials reported the mechanism of allocation concealment, how randomization was implemented, or methods for maintaining blinding of researchers. Female participants' baseline demographics [12-13, 15] and clinical characteristics [12, 17] are not reported. Male participants' baseline demographic and clinical characteristics are not reported in three trials [12-13, 15]. Only the trial by Vutyanavich et al. [16] reported adherence in women, and adherence in men was reported only in the trials by Vutyanavich et al. [16] and Colli et al. [17].

Results of Trials

1. Swedberg J, et al. Comparison of single-dose vs. one-week course of metronidazole for symptomatic Bacterial Vaginosis. *JAMA* 1985;254:1046-49.

Women were recruited from a single family practice clinic in the United States for this parallel arm randomized trial. Allocation of women to single dose vs. 7-day treatment was 1:1. Half of the women in each treatment group were randomly selected for partner treatment with the same metronidazole regimen that the woman received. Women, male sex partners, and study clinicians were not blinded to treatment status. Cure was defined as the absence of *Gardnerella vaginalis* on culture plus markedly improved or eliminated symptoms at 21 days. Of 102 women entered into the study, 98 met inclusion criteria, and randomization status is reported for 82. Analysis of the primary outcome is presented for 64 women: single dose metronidazole (n=21); single dose metronidazole plus partner treatment with single dose metronidazole (n=13); 7-day regimen (n=18); 7-day regimen plus partner treatment with 7-day regimen (n=12). The cure rate in women whose sexual contacts were treated vs. not treated was 68% (17/25) vs. 64% (25/39) [RR = 1.06; 95% CI: 0.74 – 1.52]. The authors conclude that treatment of sexual contacts did not significantly improve cure rates. With the observed sample size of 25 intervention subjects and 39 control subjects, $\geq$80% power is achieved for effect sizes $\geq$80% assuming a 35% BV recurrence rate in controls.

2. Vejtorp M, et al. Bacterial vaginosis: a double-blind randomized trial of the effect of treatment of the sexual partner. *British Journal of Obstetrics & Gynaecology* 1988;95:920-6.

Women were recruited from a general or gynecological practice in Denmark for this multicenter, parallel arm, double blind, randomized trial. Women were treated with oral metronidazole given as two, 2-gram doses (day 1 and day 3), and partners were randomly allocated 1:1 to the same regimen (intervention) or placebo (control), in blocks of 4. 126 women and their male partners were randomized. The outcomes were assessed at 5 weeks post-treatment. Diagnosis of BV by

Amsel's criteria [29] for the intervention arm vs. the control arm was 25% (13/53) vs. 29% (15/52) [RR = 0.85; 95% CI: 0.45 – 1.61]. Detection of *G. vaginalis* in the intervention arm vs. the control arm was 26% (14/54) vs. 40% (21/52) [RR = 0.64; 95% CI: 0.37 – 1.12]. Symptom improvement or cure in the intervention arm vs. the control arm was 76% (41/54) vs. 74% (39/53) [RR = 1.03; 95% CI: 0.83 – 1.29]. The authors conclude that treatment of the male partner did not affect symptoms, clinical signs, and isolation of *G. vaginalis* in women at 5 weeks after BV treatment. With the observed sample size, there was 38% power to reject the null hypothesis for the observed difference in recovery of *G. vaginalis* between intervention and control women (26% vs. 40%); $\geq$80% power is achieved for effect sizes $\geq$60% assuming a 40% BV recurrence rate in controls.

3. Mengel B, et al. The effectiveness of single-dose metronidazole therapy for patients and their partners with Bacterial vaginosis. *The Journal of Family Practice* 1989(28);2:163-171.

Women were recruited from primary care practice sites in the United States for this multicenter, multiple parallel arm, randomized trial. 138 women and their male partners were randomly allocated 1:1:1:1 in blocks (4, 8, or 12) to 4 treatment groups: (a) 7-day therapy with partner treatment (n=33); (b) 7-day therapy with partner placebo (n=34); (c) single dose therapy with partner treatment (n=34); (d) single dose therapy with partner placebo (n=37). The outcomes were BV by Gram-stained smear, clinically diagnosed BV, and symptoms at 2, 5, and 8 weeks after initial treatment. No absolute or relative effect sizes or denominators are reported; results are presented graphically and differences between groups appear to be in the range of 10-20%. Symptoms are reported to be statistically significantly less frequent at 8 weeks among women whose partners were treated. Clinical cure did not differ by treatment group. BV by Gram-

stained smear is reported to be statistically significantly lower in partner treatment groups at 2 weeks, and not thereafter. The authors conclude that treatment of the male partner improves BV cure rates. With 67 treated partners and 71 untreated partners, there would be 81% power to detect a 23% difference between groups assuming a 25% BV recurrence rate among control women.

4. Moi H, et al. Should male consorts of women with bacterial vaginosis be treated? *Genitourin Med* 1989;65:263-268.

This multicenter, parallel arm, randomized trial recruited women from hospital-based or private gynecological practices in Finland, Denmark, and Norway, and from outpatient clinics for gynecology and STIs in Sweden. Women were treated with oral metronidazole given as two, 2-gram doses (day 1 and day 3), and were randomly allocated 1:1 to partner treatment with same regimen (intervention) or identical placebo (control). 241 women and their male partners were randomized, 123 to intervention and 118 to control. The outcome was relapse of clinically diagnosed BV, measured at weeks 1, 4, and 12 after treatment. Relapse for the intervention arm vs. the control arm at 12 weeks was 21% (20/95) vs. 16% (15/95) [RR = 1.33; 95% CI: 0.73 to 2.44]. The authors conclude that treatment of the male partner did not increase BV cure rate. With the observed sample size, there was 14% power to reject the null hypothesis for the observed difference in relapse between intervention and control women (21% vs. 16%); $\geq$80% power is achieved for effect size $\geq$67.5% assuming 20% rate of outcome in controls.

5. Vutyanavich T, et al. A randomized double blind trial of tinidazole treatment of the sexual partners of females with bacterial vaginosis. *Obstetrics & Gynecology* 1993;82:550-554.

Women were recruited from a gynecologic outpatient clinic in Thailand for this single center, parallel arm, double blind, randomized trial. Women were treated with a single 2-gram dose of oral tinidazole, and were randomly allocated 1:1 to intervention (partner treatment with the same regimen) or control (partner placebo). The primary outcome was clinical cure at 4 weeks. 250 women and their male partners were randomized, 125 to intervention and 125 to control. Clinically cured BV for the intervention vs. control arm was 71.6% (83/116) vs. 63.2% (74/117) [RR = 1.13; 95% CI: 0.95 - 1.35]. The authors conclude that routine treatment of male partners for women with BV is not recommended. With the observed sample size, there was 27% power to reject the null hypothesis for the observed difference in clinically cured BV between intervention and control women (72% vs. 63%); $\geq$80% power is achieved for effect sizes $\geq$26% assuming a 63% BV cure rate in controls.

6. Colli R, et al. Treatment of male partners and recurrence of bacterial vaginosis: a randomized trial. *Genitourin Med* 1997;73:267-270.

In this multicenter, parallel arm, randomized trial, women were treated with clindamycin 2% vaginal cream at bedtime for 7 days and partners were randomized 1:1 to receive clindamycin 150mg by mouth 4 times daily for 7 days (intervention, n=69) or placebo (control, n=40). Women were recruited from 14 outpatient clinics in Italy. Recurrence was defined as the presence of clue cells plus at least 2 other Amsel's criteria [29]. Recurrence for intervention arm compared to control arm was 32% (22/69) vs. 30% (21/70) [RR = 1.06; 95% CI: 0.65 - 1.75]. The authors conclude that their findings do not support male treatment for reducing short term BV recurrence. With the observed sample size, $\geq$80% power is achieved only for effect sizes $\geq$63%, assuming a 30% BV recurrence rate among controls.

Discussion

While the RCT is the gold standard for assessing efficacy, biased results from poorly designed and reported trials can mislead decision making [30]. The primary limitations of these 6 trials were insufficient randomization methods, limited power, use of sub-optimal treatment regimens, and unknown adherence levels.

In all 6 trials, the limited details regarding randomization, and overt deficiencies in some studies, prohibit knowledge of whether randomization was successful. Thus the advantages of randomization (elimination of selection bias, facilitation of blinding, adoption of probability theory to explain chance differences between groups [30]) are not ensured.

Three trials found an association in a protective direction between male partner treatment and BV recurrence. While Mengel et al. [14] reported some statistically significant ($p<0.05$) improvements in BV cure and symptom resolution in women with treated partners, no tabular data or effect sizes are reported, making it ineligible for quantitative consideration. In the trial by Vejtorp et al. [13], at 5 weeks there was a 15% reduction in BV diagnosed and a 36% reduction in culture detected *G. vaginalis* for women whose partners were treated compared to those whose were not. The trial by Vutyanavich et al. [16] found a 13% increase in clinical cure of BV at 4 weeks for women whose partners were treated compared to those whose partner received placebo. The trial by Moi et al. [15] found an association in a harmful direction: the risk of relapse of BV at 12 weeks was 33% greater for women whose partners were treated compared to those whose were not. Two trials observed associations close to the null between partner treatment and outcome: an RR of 1.06 for cure in the trial by Swedberg et al. [12], and an RR of 1.06 for recurrence in the trial by Colli et al. [17]. For commonly occurring and recurrent

outcomes such as BV, even modest treatment effects can be of public health significance [30]. None of these 6 trials were powered to detect modest (10-20%) effects – harmful or beneficial – of male treatment on BV outcomes in women; the smallest detectable effect size was 26% in the trial by Vutyanavich et al. [16]. The rate of relapse varied widely among trials – from 16% to 37% - due to different outcome definitions and time at assessment. To be adequately powered to detect modest differences, future studies will need to consider a broad range of recurrence rates. Meta-analysis was not conducted as a potential solution due to significant bias in these studies; pooled analysis can be inappropriate if the methodologic quality of individual trials is inadequate [31].

Five trials employed sub-optimal treatment in women, which would lead to lower cure rates and higher rates of recurrence, attenuating potential effects of male partner treatment. The trial by Swedberg et al. [12] included single dose metronidazole for treating women, a treatment regimen that is no longer recommended. Three trials [13-15] employed a 2-gram dose of metronidazole administered on day 1 and day 3; to the author's knowledge, no randomized trials assessing the efficacy of this treatment regimen have been conducted. The trial by Vutynavich et al. [16] treated women with a single 2-gram dose of tinidazole [19]. Oral tinidazole 2g given once daily for 2 days is an alternative CDC-recommended treatment for BV with similar efficacy to the 7-day course of metronidazole [32]. Compared to metronidazole, tinidazole has similar maximum concentration and penetration in various tissues [33-34], but with superior penetration in male genital tissue [35] and lower side effects profile [34]. These traits, plus higher likelihood of adherence and comparable costs [36], make tinidazole a well-suited regimen to test the effects of male treatment on penile bacterial carriage and BV outcomes in women.

Adherence to BV treatment in women was not reported in any of the trials, but may be inferred as complete in the trial by Vutyanavich et al. [16], due to use of directly observed single dose therapy. Adherence to treatment in men was reported in the trials by Vutyanavich et al. [16] and Colli et al. [17]. In the trial by Vutyanavich et al. [16], 4 men in the tinidazole group and 2 men in the placebo group were reported by their female partners as refusing medication. In the study by Colli et al. [17], non-adherence was 19% (27 men of 139 randomized), and did not differ by treatment arm. While not reported in the other trials and not addressed in analyses, non-adherence in women or male partners may have led to attenuation of a potential effect of treatment in men on BV recurrence in female partners. Further, it is unknown whether any of the treatment regimens significantly reduced BV-associated bacteria from the penile microbiota, as microbiologic studies of the penile microbiota before and after treatment were not conducted.

This review is limited by incomplete reporting of methods and data in individual trials. Incomplete reporting should be considered separately from methodologic flaws; a trial that is well-designed and well-conducted may be poorly reported. However, several evaluations of RCTs find that inadequate and unclear reporting are associated with inaccurate estimation of efficacy, independent of study design [37-38], that the design and quality of trials are correlated with the quality of reporting [39], and that contact with original authors leads to minimal improvements in reporting [40].

Conclusions

The trials that assessed the effect of male treatment on BV recurrence in women did not find a beneficial effect, but were significantly flawed. Epidemiologic and microbiologic evidence indicating that BV-associated bacteria may be transferrable between male and female sex

partners continues to mount. Disregarding this disconnect based on the results of the trials may be a failed opportunity to expand our understanding of BV transmission dynamics. In a recent review of current knowledge of BV, Marrazzo summarizes potential risks for BV: sexual partners, specific sexual practices, and the vaginal microbiota [41]. While it would be convenient to identify a sole mechanism of pathogenesis and a single causative bacterium, BV is multi-factorial, with direct effects from the individual- and couple-level genital microbiota as well as mediation by individual- and couple-level behavior. To carefully examine whether BV-associated bacteria are transferred between sex partners, the next steps are to apply methods such as pyrosequencing to study the temporal correlation between the penile and vaginal microbiota; assess factors affecting the couples-level genital microbial environments; and determine whether efficacious BV treatment, such as tinidazole, reduces BV-associated bacteria in the penile microbiota. By current standards, it is unlikely that any of the 6 trials would be considered conclusive. To generate an accurate evidence base for treatment recommendations, well-conducted RCTs are needed to determine whether antibiotic treatment in men can reduce BV and associated sequelae in female sex partners.

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Table 1. Summary of Six Trials of Male Sex Partner Treatment for Bacterial vaginosis in Women.

First Author, Year [ref]	Location	Number of Women randomized to partner treatment vs. control^	Number of women in primary analyses*	Treatment regimen Women	Treatment regimen Men	Primary outcome(s) and result for intervention (partner treatment) vs. control (no partner treatment)
Swedberg, 1985 [12]	United States	Not reported	25 vs. 39	Metronidazole 2g single dose, Metronidazole 500 mg twice daily for 7 days	Metronidazole 2g single dose, Metronidazole 500 mg twice daily for 7 days	Cure (culture negative for *G. vaginalis* plus improved symptoms) at 21 days: 68% (17/25) vs. 64% (25/39) [RR=1.06; 95% CI: 0.74 to 1.52]
Vejtorp, 1988 [13]	Denmark	63 vs. 63	54 vs. 52	Metronidazole 2g dose on Day 1 and Day 3	Metronidazole 2g dose on Day 1 and Day 3, vs. Placebo	Clinically diagnosed BV at 5 weeks: 25% (13/53) vs. 29% (15/52) [RR=0.85; 95% CI: 0.45 to 1.61] *G. vaginalis* at 5 weeks: 26% (14/54) vs. 40% (21/52) [RR=0.64; 95% CI: 0.37 to 1.12] Symptom improvement or cure at 5 weeks: 76% (41/54) vs. 74 (39/53) [RR = 1.03; 95% CI: 0.83 – 1.29]
Mengel, 1989 [14]	United States	33 vs. 34 vs. 34 vs. 37	98 (not reported by arm)	Metronidazole 2g single dose, Metronidazole 500 mg twice daily for 7 days	Metronidazole 2g single dose, vs. Placebo	No point estimates are reported.
Moi, 1989 [15]	Denmark, Finland, Norway, Sweden	123 vs. 118	95 vs. 95	Metronidazole 2g dose on Day 1 and Day 3	Metronidazole 2g dose on Day 1 and Day 3, vs. Placebo	Relapse of clinically diagnosed BV at 12 weeks: 21.1% (20/95) vs. 15.8% (15/95) [RR=1.33; 95% CI: 0.73 to 2.44]
Vutyanavich, 1993 [16]	Thailand	125 vs. 125	117 vs. 116	Tinidazole 2g single dose	Tinidazole 2g single dose, vs. Placebo	Clinical cure of BV at 4 weeks: 71.6% (83/116) vs. 63.2% (74/117) [RR=1.13; 95% CI: 0.95 to 1.35]
Colli, 1997 [17]	Italy	69 vs. 70	69 vs. 70	Clindamycin 2% vaginal cream at bedtime for 7 days	Clindamycin 150mg orally four times daily for 7 days, vs. Placebo	Clinically diagnosed BV recurrence at 12 weeks: 31.9% (22/69) vs. 30.0% (21/70) [RR=1.06; 95% CI: 0.65 to 1.75]

^ "Control" indicates no BV treatment of the male partner. *The maximum number of women in any primary analysis is reported. RR = Risk Ratio; CI = Confidence Interval; BV = Bacterial vaginosis.

Table 2. Potential Sources of Bias in Study Design and Reporting.

Study / Measure	Swedberg, 1985 [12]	Vejtorp, 1988 [13]	Mengel, 1989 [14]	Moi, 1989 [15]	Vutyanavich, 1993 [16]	Colli, 1997 [17]
Reproducible recruitment and screening methods	No	No	No	No	No	No
Reproducible eligibility criteria: women/men	Yes/No	No/No	Yes/No	Yes/No	Yes/No	Yes/No
Reproducible intervention administration: women/men	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Sample size calculation	No	No	No	No	No	Yes*
Adequate sequence generation: women/men	Yes/No	NR/NR	NR/NR	NR/NR	Unclear^	NR
Allocation concealment mechanism: women/men	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Randomization implementation (enrollment & assignment of subjects)	NR	NR	NR	NR	NR	NR
Blinding of women/men	No/No	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Blinding of care providers/those assessing outcome	Yes	Yes	Yes	Yes	Yes	Unclear+
Methods of maintaining blinding of researchers reported	No	No	No	No	No	No
Intention to treat analysis	Yes	Yes	Yes	Yes	Yes	Yes
Groups balanced at baseline, women: demographics/clinical	NR/NR	NR/Yes	Yes/Yes	NR/Yes	Yes/Yes	Yes/NR
Groups balanced at baseline, men: demographics/clinical	NR/NR	NR/NR	Yes/Yes	NR/NR	Yes#/Yes$	Yes#/Yes$
Number lost to follow-up reported by arm	Yes	Yes	Yes	No	Yes	Yes
Exclusions after randomization reported by arm with reasons	No	Yes	Yes	No	Yes§	Yes
Adherence reported in women/men	No/No	No/No	No/No	No/No	Yes/Yes	No/Yes
Harms of treatment (i.e., side effects) reported in women/men	Yes/No	No/No	Yes/Yes	No/No	Yes/Yes	Yes/Yes

NR = Not Reported. No information is reported to assess the measure.
Yes: Sufficient information was reported, and the measure was appropriately addressed.
No: Sufficient information was reported, and the measure was not appropriately addressed.
Unclear: Insufficient information is reported to fully assess whether the measure was appropriately addressed.

*Sample size goal not achieved; shortfall not explained.
^It is reported that "Patients were randomized into two groups using a table of random numbers".
+The study is reported as double blind, but other than participants, no other blind is specified (e.g., clinicians, data collectors, analysts).
#Age is the only male partner characteristic compared, and does not differ by treatment arm.
$In the study by Vutyanavich et al., men's history of gonorrhea and syphilis infection is compared by arm (with no differences), and in the study by Colli et al., men's history of urethritis is compared by arm (with no difference).
§There were 7 exclusions after randomization reported with reasons in aggregate (not by arm).