

# Resistant Trichomoniasis: Successful Treatment With Combination Therapy

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**Abstract:** Metronidazole-resistant vaginal trichomoniasis remains a major therapeutic challenge. Two women with symptomatic metronidazole-resistant trichomoniasis had multiple unsuccessful courses of therapy with a broad array of medications. Both patients finally responded to combination treatment with intravaginal paromomycin cream and high-dose oral tinidazole.

Vaginal trichomoniasis, caused by the flagellated protozoan *Trichomonas vaginalis*, is a common sexually transmitted infection with an estimated 7.4 million cases in the United States<sup>1</sup> per year. Metronidazole and tinidazole, both nitroimidazoles, are the only currently recommended antibiotics for this infection.<sup>1</sup> Although most patients are cured with standard treatment with single or week-long courses of these antibiotics, organisms resistant to both therapies have been reported.<sup>2,3</sup>

Metronidazole-refractory vaginal trichomoniasis remains a major therapeutic challenge. Clinical resistance is defined as a failure to cure infection after 2 consecutive courses of treatment.<sup>4</sup> It is postulated to occur for various reasons, including lack of absorption of the medication, lack of transport to site, or presence of other bacteria that inactivate the drugs.<sup>4</sup> Options for treatment are extremely limited for these patients.<sup>5</sup> In cases of suspected resistance, providers are urged to obtain a history to exclude reinfection or noncompliance as the reason for treatment failure. The Centers for Disease Control and Prevention (CDC) is available for consultation and can perform susceptibility testing.<sup>1</sup> A number of alternative treatment regimens, none FDA approved, have been reported as options to treat difficult cases. Successful treatment has been reported with high-dose metronidazole or tinidazole given both orally and vaginally,<sup>5</sup> povidone-iodine douches,<sup>6</sup> acetarsol (arsenic) pessary,<sup>7</sup> nonoxynol-9,<sup>8</sup> clotrimazole cream,<sup>9,10</sup> paromomycin cream,<sup>11</sup> furazolidone cream,<sup>12</sup> and zinc sulfate.<sup>13</sup> To date, all case series have focused on single-agent therapies for treating metronidazole-resistant trichomoniasis. We present 2 cases who failed a broad array of therapies who eventually were cured with a combination of oral tinidazole and vaginal paromomycin.

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## PATIENT 1

A 54-year-old woman presented with a 7-year history of unremitting trichomoniasis which caused persistent vaginal burning, irritation, discharge, and dysuria. She denied any sexual contact since this began. Previous treatments included multiple courses of metronidazole and tinidazole, both standard and high dosages, as well as intravaginal treatment. Paromomycin intravaginal cream for 14 days and gentian violet 1% topically were also used without success.

On the day of her initial visit, a discharge was present, and trichomonads were visualized under saline wet mount examination. Her partner's evaluation, which included a urethral culture for trichomonas, was unremarkable. He did report outside sexual contact before the diagnosis and had been treated in the past.

Results of metronidazole and tinidazole sensitivity testing by the CDC concluded that the organism was "moderately resistant" to both. A trial of furazolidone 100 mg in 5 g of 3% nonoxynol-9, for topical vaginal application twice daily for 14 days was recommended. The patient failed this therapy and returned with symptoms. A course of high-dose tinidazole (1 g orally 3 times daily with 500 mg vaginally twice daily for 14 days) was similarly ineffective. Over the next few months, treatment with the following medications was also attempted: povidone-iodine suppositories vaginally for 14 days, nitazoxanide cream 500 mg/5 g vehicle twice daily for 14 days, metronidazole/miconazole/lidocaine pessary for 14 days, and potassium permanganate (1:2500 dilution) vaginal douches for 14 days. All failed, with trichomonads visualized on wet mount after treatment.

A trial of intravaginal paromomycin, 5 g of a 5% cream inserted nightly, along with concomitant oral tinidazole 1 g 3 times daily for 14 days was given. At 1 and 6 weeks after the treatment was completed, the patient returned with no signs or symptoms of infection; urine, saline wet mount, and Diamond's culture were all negative.

## PATIENT 2

A 29-year-old woman was referred for treatment of a 2-year trichomonas infection. At the time of initial diagnosis, her boyfriend was treated and cured with a course of metronidazole. The relationship subsequently ended, and she denied any sexual contact since then. Before referral, in the previous 12 months alone, she had been treated with 6 courses of metronidazole, 3 courses of tinidazole (including a 14-day regimen with 3 g orally and 1 g vaginally per day), and zinc supplements. Results of metronidazole and tinidazole sensitivity testing by the CDC concluded that the organism was "highly resistant" to metronidazole and "moderately resistant" to tinidazole. She had also received a 14-day course of 2% furazolidone cream course twice a day for 14 days, again with no improvement. On initial evaluation, many trichomonads were seen on microscopy.

A course of 5% intravaginal paromomycin, 1 applicator full (5 g) inserted vaginally nightly  $\times$  14 days with concomitant oral tinidazole 1 g 3 times daily for 14 days was completed. Apart from mild irritation, she tolerated the treatment well. At 6 weeks and 3 months after treatment, there was no evidence of infection, and cultures for *T. vaginalis* were negative at each visit.

High-dose tinidazole has emerged as the mainstay of treatment for metronidazole-resistant trichomoniasis. However, as demonstrated with both of these cases, alternatives when these options fail are limited. As it is not absorbed from the GI tract, paromomycin must be used vaginally for trichomoniasis. It has been described as a successful alternative treatment.<sup>11</sup> However, in a larger case series of 13 patients,<sup>5</sup> it only cured 58% of patients and sometimes caused local irritation and ulceration. Because of the risk of local side effects, both of our patients were instructed to apply barrier creams (i.e., petrolatum) liberally to the vestibule to protect the skin from possible irritation and to discontinue the cream immediately if any problems developed. Both patients tolerated the regimen well. None of the patients had any viable option to treat their infection, and the first had tried paromomycin cream alone without success.

As paromomycin and tinidazole have different mechanisms of action and have been clinically useful in treating metronidazole-resistant trichomoniasis, we felt that an attempt at combination therapy was appropriate, particularly because we would not expect antagonistic effects based on their respective mechanisms of action. Tinidazole, a second-generation nitroimidazole, exerts its antiparasitic effect through its reduction to free radicals once it is transported into the organism.<sup>14</sup> As an aminocyclitol antibiotic, the antimicrobial effects of paromomycin are attributed to its effects on ribosomal RNA.<sup>15</sup> Although it is possible that the negative cultures simply failed to detect low levels of persistent trichomonads, the relatively long follow-up before obtaining negative cultures makes this possibility unlikely. Our experience with these 2 cases, as well as an earlier case of a woman who was cured despite failing prior individual courses with both medications,<sup>5</sup> supports the concept that the combination of oral high-dose tinidazole and vaginal paromomycin should be considered when alternative approaches have failed.

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