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Refractory Trichomoniasis in HIV-positive and HIV-negative Subjects

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Abstract *Trichomonas vaginalis*, a common pathogen, remains widely unknown to the public. Its clinical consequences include upper genital tract infection, increased risk of preterm delivery, and increased risk of HIV transmission. Diagnostic tests, especially in men, have historically had low sensitivity, but the recent development of rapid, reliable point-of-care testing is a step toward improved detection. Reliable treatments for trichomoniasis are limited to the nitroimidazoles, and options for cases with either hypersensitivity or resistance remain limited. In select resistant cases, alternatives, most notably paromomycin, may play a role. A complex interaction exists between *T. vaginalis* and HIV, whereby women with trichomoniasis are at increased risk for HIV and vice versa. It is hoped that diagnosis and treatment of trichomoniasis in women at high risk for HIV may help to lower the incidence of both infections.

Keywords *Trichomonas vaginalis* · Vaginitis · Metronidazole resistance · Tinidazole · Paromomycin · HIV

Introduction

Trichomonas vaginalis is one of the most common sexually transmitted pathogens worldwide, and the most common non-viral sexually transmitted pathogen in the United States. An estimated 7 million cases occur in the U.S. annually, more than *Chlamydia trachomatis* and *Neisseria gonorrheae* combined [1•, 2]. Although sobering, this statistic is thought to be a gross underestimation, due to low rates of patient and partner screening, high rates of asymptomatic carriage, and low sensitivity of commonly used diagnostic tests [3]. Further, despite its prevalence and potentially life-altering sequelae, *T. vaginalis* continues to be a relatively unknown pathogen to the public and remains a non-reportable sexually transmitted infection [4].

Presentation

In women, the symptoms of trichomoniasis vary from an asymptomatic carrier state to fulminant vaginitis and cervicitis. Although up to 50% of *T. vaginalis* infections in women are asymptomatic, as many as one third will become symptomatic within 6 months [1•, 5]. The symptoms of *T. vaginalis* infection include vaginal discharge (clear to yellow-green and frothy), dyspareunia, vulvovaginal soreness and itching, and pain on urination. Symptoms often first appear during menstruation [5]. Physical findings may include vulvovaginal erythema, discharge, and occasionally punctate hemorrhages of the vaginal mucosa and cervix, termed colpitis macularis (strawberry cervix) [6].

Asymptomatic carriage of *T. vaginalis* in men is thought to be common, with rates varying from 14% to 77% of infected individuals [7]. This may be due to a long incubation period (1 day to 3 months) between infection and development of symptoms, combined with high rates of spontaneous resolution of symptoms in this population. Common symptoms in men include urethral discharge, pruritus, dysuria, increased urinary frequency, and lower abdominal pain [7, 8].

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T. vaginalis is a potential cause of fairly common syndromes, including urethritis in men and women, and cervicitis in women. Thus, when evaluating patients with symptoms or findings consistent with these conditions, conducting appropriate diagnostic tests for trichomoniasis is essential to an accurate diagnosis.

Diagnosis

Commonly, most clinicians assume that trichomoniasis can be accurately diagnosed with history, pelvic examination and in-office wet mount examination. However, clinical features alone are not sensitive or specific enough to diagnose *T. vaginalis*. Infected women may complain of vaginal discharge (59% of infected women), foul odor (36%), and vaginal itching (33%); findings may include an increased vaginal pH (82%), and white or clear vaginal discharge (53%) [8]. Thus, vaginal discharge and increased vaginal pH should raise suspicion for trichomoniasis, and prompt wet mount examination should follow.

On wet mount, the classic finding is one of motile flagellated trichomonads. Other microscopic findings include increased numbers of polymorphonuclear leukocytes [6]. Although considered the standard by many practicing providers, wet mount shows relatively poor sensitivity, even in experienced hands [9]. The utility of wet mount as a diagnostic tool may be further stymied by low rates of use for this simple test [8]. The current gold standard of *T. vaginalis* diagnosis is culture [10••]. Culture should be obtained when *T. vaginalis* is highly suspected by history, physical findings or wet mount, but trichomonads are not seen. Unfortunately, *T. vaginalis* culture utility is limited by the extended period of time needed for diagnosis (usually 24 to 120 h for final results), as well as the need to maintain culture medium in provider offices [2].

More recently, other tests have been devised to attempt quick, reliable diagnosis; Table 1 summarizes the performance characteristics of these tests to detect *T. vaginalis*. Affirm VPIII (BD Diagnostic Systems, Sparks, MD) is a direct specimen nucleic acid probe test, which has been found to have improved sensitivity over wet mount and culture, and is available as a send-out test, or can be run in less than 1 h in offices that have the capability [2]. The most recently FDA-approved diagnostic test is APTIMA *Trichomonas* (Gen-Probe Inc, San Diego, CA), a nucleic acid amplification test (NAAT), which uses the same technology as *C. trachomatis* and *N. gonorrheae* NAATs. In detecting *T. vaginalis*, Nye found APTIMA to be highly sensitive, while offering the possibility of a single collection for diagnosis of three common sexually transmitted infections [10••].

For providers seeking a point-of-care test which is superior to microscopy, the OSOM *Trichomonas* Rapid Test (Genzyme Diagnostics, Cambridge, MA) is an immunochromatographic capillary flow (dipstick) assay, which can be read 10 min after placement in a buffered sample. This test has been found to be highly sensitive in patient populations with both high and low prevalence of *T. vaginalis* [2, 12•]. Huppert suggests that this method may be especially useful for diagnosing symptomatic women over age 30 [2]. One possible stumbling block to the widespread use of OSOM is economic, as not all insurance payers will fund this diagnostic option.

In men, diagnosis of trichomoniasis is limited by a lack of FDA-approved point-of-care tests [11]. Although urine and urethral swab culture have been considered the gold standard for diagnosis in men, they have relatively low sensitivity. Urine and urethral APTIMA NAAT swabs seem

Table 1 Characteristics of common diagnostic tests for *T. vaginalis*

Diagnostic test	Technique	Time to result	Specimen	Sensitivity	Specificity
Wet Mount [2, 10••, 12•, 43, 44]	Vaginal swab with saline microscopy	Minutes; In office	Vaginal swab	35%–82%	99.6% – 100%
Culture [2, 12•, 45]	Media: Diamond's, Trichosel, InPouch TV	24 – 120 h; Send out	Vaginal swab, urethral swab, urine, semen	F: 75%–87% M: 28.6%–48%	100%
APTIMA Trichomonas (Gen-Probe Inc, San Diego, CA) [10••, 45]	Nucleic acid amplification test, uses transcription-mediated amplification to detect species-specific 16S rRNA	Hours; Send out	Vaginal swab (F)	96.6%– 98.4%	98% – 100%
			Urine (F)	87.5%	100%
			Urethral swab (M)	95.2%	96.5%
			Urine (M)	73.8%	98.4%
Affirm VPIII (BD Diagnostic Systems, Sparks, MD) [43, 44]	Direct specimen nucleic acid probe assay	45 min; Send out or in equipped office	Vaginal swab	83%– 90.5%	99.8%– 100%
OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, MA) [2, 12•]	Immunochromatographic capillary flow (dipstick) assay with murine monoclonal antibody	10 min; In office	Vaginal swab	82%– 94.7%	98.8%– 100%

to be superior to all forms of culture, and the most sensitive test may be a urethral swab APTIMA test [10••].

Treatment of Uncomplicated Infection

Nitroimidazoles, primarily metronidazole, are the mainstay of treatment for *T. vaginalis* infection. These compounds have a 5-nitro group, which is reduced into a nitro radical within the parasite. Nitroimidazoles have a wide range of side effects, some of which are fairly benign, such as nausea, vomiting, headache, insomnia, dizziness, drowsiness, and metallic taste. Others are more serious, and include eosinophilia, leukopenia, palpitations, confusion, and peripheral neuropathy [5].

Metronidazole is usually given as a one-time oral 2 g dose, but can also be dosed at 500 mg twice a day for 7 days. These doses have been found to result in a parasitological cure in 85% to 95% of patients [5, 13]. In general, one-time dosing is preferred in patients in whom non-compliance is a possible source of persistent infection. Furthermore, it offers convenience, the possibility of in-office dosing, and the lowest amount of drug [5]. However, this strategy also results in more frequent and more severe side effects than the more prolonged, lower daily doses of metronidazole [13]. For this reason, treatment should be tailored to the patient's history and their reaction to the prescribed medication. Topical metronidazole remains ineffective, with a cure rate of, at most, 50% of cases [13].

Tinidazole, given as a single 2 g oral dose, is another nitroimidazole medication that has been used in the treatment of trichomoniasis. This compound has a longer half-life than metronidazole, and is eliminated at a slower rate [13]. Further, it has superior tissue distribution, and studies have found that it can be found at higher levels in vaginal secretions than metronidazole [5]. Thus, tinidazole is a good alternative to metronidazole, but because they have similar structures and modes of action, cross-resistance and cross-hypersensitivity are concerns [13].

Although there is no clear consensus on when or if to perform a test of cure, current CDC guidelines state that rescreening 3 months after treatment can be "considered" in women, in part because of relatively high reinfection rates. They also note the absence of data with regard to follow-up of treated men [11].

Partner Treatment

The treatment of the male partners of women diagnosed with trichomoniasis has been the object of some controversy over the years. Older investigations have estimated the prevalence of infected male partners to be quite low. One study, using culture and wet mount, found less than 45% of male partners to be infected; another, using culture alone, found only 22% to be infected [8].

A more recent study, however, has found partner infection rates to be between 70% and 80% [8]. In this study, high rates of concordance were associated with shorter time to enrollment of male partners. In fact, if the male partner was enrolled less than 2 days after the infected woman was diagnosed, the pair was twice as likely to be concordant than if the male partner was enrolled more than 7 days after diagnosis. Further, male diagnosis differed greatly based on the diagnostic method and sample. With the combination of urine and urethral culture and urine PCR, the concordance was 71.7%; with the addition of semen culture and PCR, this number increased to 81.1%. Low rates of partner concordance were seen if urine culture alone was performed on men (15.6%) [8]. Thus, time to testing and testing modality appear to be important factors in identifying male partner infection. These data also indicate that it is difficult to be completely certain that a male partner is not infected unless multiple testing sites and techniques are selected.

High rates of partner infection, combined with female recurrence rates estimated at 17% at 3 months, make male partner identification and treatment important aspects of *T. vaginalis* therapy [14]. However, as we know from studies of *C. trachomatis, N. gonorrheae, T. vaginalis* and urethritis, only 29% to 59% of male partners actually seek care [15].

Partner treatment, in general, is complicated by several factors. First, women must identify all possibly infected partners and then must notify them that they may be infected. Second, partners must seek appropriate care in a timely manner. Third, the patient must not engage in sexual activity with this partner between notification and treatment. To circumvent some of these steps, Kissinger investigated the utility of patient-delivered partner treatment (PDPT) for *T. vaginalis*, compared with conventional partner notification counseling and counseling via a booklet. Surprisingly, PDPT was not associated with significantly more partners being treated (77% with PDPT versus 71% with conventional notification) or lower recurrence rates of *T. vaginalis* (9.4% versus 6.3% within 2 months). This was thought to be due to high compliance with partner notification in the conventional group, as well as the relatively older age of the infected population (mean age 25.8 years), which may have been associated with a more mature sense of responsibility in partner notification [15]. Counseling patients about the importance of partner notification is likely as effective as patient-delivered partner treatment, and the method by which partners are treated should therefore be individualized to the patient population. Further, even if a male partner of an infected woman tests negative for *T. vaginalis*, we feel that he should still receive treatment.

Treatment in Pregnancy

T. vaginalis infection has been associated with a number of adverse effects during pregnancy. The Vaginal Infections and Prematurity Study found that women colonized with *T. vaginalis* had a 30% increased risk of delivering a low birth weight or preterm infant, a 40% increased risk of delivering an infant who is both preterm and of low birth weight, and twice the risk of stillbirth or neonatal death [16]. These consequences are thought to be due to a state of neutrophil activation in *T. vaginalis* infection [17, 18].

Infection with *T. vaginalis* at the time of delivery can also lead to neonatal trichomoniasis, with symptoms similar to adult infection, such as vaginal discharge, which wane as the infant's estrogen levels drop after birth [5]. A more striking and serious neonatal consequence is described in a case study by Carter, in which an infant presenting with ventilator-dependent respiratory distress was found to have *T. vaginalis* infecting her respiratory tract [19]. Infants with severe presentations such as this, or with neonatal trichomoniasis lasting more than 6 weeks, can be treated with metronidazole in a single 50 mg/kg dose [5].

Studies in the past have suggested that treatment of pregnant women with trichomoniasis does not change the risk of adverse outcomes [20]. Nevertheless, for public health reasons, treatment is recommended for all symptomatic pregnant women. Women can be treated with a single 2 g dose of metronidazole at any stage of pregnancy [11]. Metronidazole is known to the cross the placenta, and has been shown to be carcinogenic in mice. However, no association with birth defects has been described. It is considered a Pregnancy Class B medication [5]. The safety of tinidazole during pregnancy has not been well evaluated [11].

Treatment of asymptomatic women, however, is more controversial. In 2001, Klebanoff [21] determined that treatment of pregnant women with asymptomatic *T. vaginalis* infection did not prevent preterm delivery and may increase the risk of preterm delivery. However, the finding that 26% of the placebo group received metronidazole outside of protocol, primarily for symptomatic trichomoniasis, prevents definitive conclusions about the risk of treatment [21]. The CDC continues to recommend appropriate treatment of any pregnant woman found to be infected with *T. vaginalis*. Clinicians can choose to delay treatment until after 37 weeks gestation, but should counsel their patients about condom use and the continued risk of sexual transmission [11].

Metronidazole-Resistant *T. Vaginalis*

Over the years, there have been many reports of refractory *T. vaginalis* infections and metronidazole-resistant *T. vaginalis* isolates, and anecdotal evidence suggests that resistance may be increasing. In *T. vaginalis*, metronidazole resistance occurs via two mechanisms: aerobic and anaerobic. The most clinically relevant is the aerobic pathway, in which ferredoxin and oxygen scavenging pathways are downregulated. This can develop in vivo at therapeutic levels of metronidazole, and is therefore clinically concerning. The other (anaerobic) pathway involves downregulation of pyruvate ferridoxin oxidoreductase (PFOR), and has been found to occur at increasing, sublethal levels of metronidazole over a 12–21 month period [5, 22]. These enzymatic pathways are involved in activation of metronidazole to its toxic radical state; thus, downregulation prevents metronidazole from becoming effective [23].

The prevalence of resistance seems to vary widely, with several studies estimating it to be between 1.7% and 10.1% [24••]. A recent study of adolescent women found that in a population with a 14.4% prevalence of *T. vaginalis*, only 2.7% of these had in vitro resistance to metronidazole [24••]. Conversely, another study found the prevalence of metronidazole-resistant *T. vaginalis* in a population of women attending an STD clinic was 9.6%, with 1 isolate out of 178 also displaying resistance to tinidazole. However, clinical outcomes did not correlate with in vitro results. In fact, only two patients with highly resistant strains of *T. vaginalis* (MLC, 100mcg/mL) failed initial treatment. Further, although increasing metronidazole resistance correlated with increasing tinidazole resistance, MLCs for tinidazole were consistently lower [23].

Thus, treatment failure and metronidazole in vitro resistance should not be considered synonymous conditions. On the contrary, it appears that many metronidazole-resistant strains can still be controlled with standard dosing. One study found that 80% of refractory *T. vaginalis* infections responded to increased dose or duration of metronidazole [25]. In the case of treatment refractory trichomoniasis, the clinician should first question the patient about treatment compliance and the possibility of reinfection by an untreated partner [5]. If reinfection is likely, a repeated course of metronidazole with counseling about condom use is warranted.

If true refractory *T. vaginalis* infection exists, CDC guidelines recommend obtaining cultures for resistance testing, and a stepwise approach to treatment. After failing the standard one-time 2 g dose of metronidazole, a more extended regimen of metronidazole 500 mg orally twice daily for 7 days can be attempted. Failing this regimen, clinicians should consider treatment with metronidazole or tinidazole 2 g orally for 5 days [11].

If infection persists, increasing dosage and duration of metronidazole or tinidazole, with or without metronidazole vaginally, can be attempted. Many different regimens have been attempted, with differing efficacies seen. In one case series, most patients were cured with the CDC-recommended metronidazole 2 g orally for 5 days, or eventually with

metronidazole 1 g orally three times daily, combined with intravaginal metonidazole 500 mg daily, for 14 days [26, 27]. In another study, 79% of treatment-refractory patients were cured using metronidazole 3 g orally, combined with intravaginal metronidazole, daily for 14 days [28]. In a more recent case series, however, only 2 of 33 patients were cured with high doses of metronidazole (one with 500 mg qid for 14 days, and one with 1 g orally tid combined with 500 mg vaginally for 14 days), while 92% of patients were cured with a single course of combined high dose oral and vaginal tinidazole [29].

Many other treatments have been attempted, with some exhibiting cure despite failing multiple other treatments. Overall results with these regimens are summarized in Table 2; it should be emphasized that these are all case series with different methods for determining that patients were cured. Of these, the most reported experience is with intravaginal paromomycin. Paromomycin is an aminoglycoside antibiotic, which is active against certain protozoa. In one case series, paromomycin had a 58% cure rate, but was associated with a high frequency of side effects, particularly vulvovestibular excoriation and ulceration [29]. When it is used, patients should be extensively counseled about the possible side effects, and we routinely have patients apply a barrier such as petrolatum to the vestibule to protect the area. Finally, paromomycin in combination with high dose tinidazole has recently been described as a successful option where other treatments have failed [30].

Metronidazole Hypersensitivity

Metronidazole has several adverse effects, including an immediate-type hypersensitivity reaction, characterized by flushing, urticaria, fever, angioedema, or anaphylactic shock. The frequency and severity of these reactions are largely unknown. Unfortunately, in the case of trichomoniasis, there are few alternative treatment options for patients with hypersensitivity. The similar chemical structure of tinidazole makes cross-reaction a concern, and, as noted earlier, other treatments are less effective [31••].

Thus, the treatment of choice for patients with trichomoniasis and nitroimidazole hypersensitivity is nitroimidazole (metronidazole or tinidazole) desensitization. Studies have found that both oral and parenteral desensitization, as per protocol, is 100% effective. In one such study by Helms of 41 women with metronidazole hypersensitivity, 15 (37%) were treated with oral or parenteral metronidazole desensitization. All 15 of these women (100%) were cured [31••]. Two additional case reports have found a 100% cure rate (2 of 2, and 1 of 1 patients cured, respectively) [32, 33]. Several of the remaining women in the Helms study were treated with a variety of alternative treatments, with extremely variable rates of cure. With follow-up on 12/17 patients treated with these regimens, the overall cure rate was 42%, including 3/4 cured with betadine douches, 1/2 with intravaginal clotrimazole, 1/4 with paromomycin, and 0/2 with furazolidone [31••]. Therefore, nitroimidazole desensitization remains the most reliable therapy in this situation. Minor adverse reactions can occur during treatment, but can be easily managed with antihistamines and steroids [31••].

T. Vaginalis and HIV

In women, the consequences of untreated *T. vaginalis* can be devastating. These include adnexitis, endometritis, and salpingitis (collectively PID), which can lead to infertility and increased risk of ectopic pregnancy. In men, untreated *T. vaginalis* infection causes epididymitis, prostatitis, and infertility [34]. Of further concern, active *T. vaginalis* infection is associated with a 1.5 to 2-fold increase in HIV-1 transmission [34]. The basis of this association is thought to be a result of a complex interplay between the two pathogens, and the body's defenses against them.

Although *T. vaginalis* is not an opportunistic pathogen, repeated and persistent infections with *T. vaginalis* are more common in HIV-positive women than HIV-negative women [35]. This observation may be due to several factors. HIV-positive women are more likely to be asymptomatic at baseline, which may lead to unintentional passage to male partners, and subsequent reinfection. Further, after being diagnosed with trichomoniasis, HIV-positive women are significantly more likely to engage in unprotected sex with an untreated baseline partner, or a new partner, during or following treatment. Thus, it is difficult to determine whether persistence of *T. vaginalis* infection in this population is due to reinfection or treatment failure [36•].

T. vaginalis infection in HIV-positive women is thought to increase the likelihood of HIV-1 transmission to a male partner. Women with trichomoniasis have been found to have increased vaginal shedding of HIV-1 RNA. In one study, HIV-1 RNA was found in vaginal secretions of 36.2% of *T. vaginalis*-infected patients, compared with 19.6% of non-infected patients, and these increased levels persisted for 1 month after treatment with metronidazole. Vaginal HIV-1 RNA levels were significantly reduced 3 months after successful metronidazole therapy, and with HAART therapy [37••]. Thus, treatment of trichomoniasis may decrease HIV transmission risk by way of decreasing HIV-1 shedding.

In addition to HIV transmission from female to male partners, trichomoniasis in women is believed to increase the likelihood of HIV acquisition from a male partner. The intact epithelial lining of the vagina represents a protective barrier against HIV-1 acquisition [38]. Guenther found that *T. vaginalis* causes disruption of this barrier in a time and

Table 2 Reported efficacy of alternative treatments for refractory *T. vaginalis*

Treatment	Formulation	# Treated	# (%) Cured	Adverse effects
Tinidazole [25, 29, 46]	500 mg PO BID+500 mg PV BID × 14 d, OR 1 g PO TID+500 mg PV TID × 14 d	24	22 (92%)	GI intolerance (mild)
	400 mg PO TID × 10 d	2	2 (100%)	
	500 mg PO TID × 10 d (and ×7d)	3	3 (100%)	Metallic taste, mild nausea
	2 g PO stat dose	1	1 (100%)	
Paromomycin [29, 47–50]	250 mg applicator PV daily × 14 d	13	8 (62%)	Vaginal ulceration
	250 mg tablet (Gabboral®) PV BID × 14 d (stopped after 10 d)	1	1 (100%)	Vaginal pain & ulcers
	250 mg suspension in unguentum base, PV daily × 7 d (stopped after 2 d)	1	1 (100%)	Vaginal ulceration, resolved with saline soaks
	250 mg applicator PV daily × 7 d (stopped after 5 d)	1	1 (100%)	
Paromomycin/Tinidazole [29, 30]	Paromomycin 5% cream – 5 g PV daily+Tinidazole 1 g PO TID × 14 d	3	3 (100%)	Mild irritation
Clotrimazole [51]	2 – 100 mg tablets PV QHS × 7 d	45	5 (11%)	None
Acetarsol Pessary [25, 52–55]	250 mg acetarsol pessary PV BID × 7 – 14 d	5	3 (60%)	
	500 mg acetarsol pessary PV daily × 7 d	2	1 (50%)	Vaginal irritation
	500 mg acetarsol pessary PV daily × 10 d	3	2 (67%)	None
	500 mg acetarsol pessary PV daily × 14 d	1	1 (100%)	None
Povidine – Iodine [25, 56]	Povidine-iodine gel – 5 g applicator QHS+povidine-iodine douche (2 tbs povidine-iodine in 1 qt water) × 4 wk	19	17 (89%)	Vaginal burning, rash (1)
	Povidine-iodine pessary daily x7d	1	1 (100%)	
	Povidine-iodine pessary daily+Metronidazole ×7d	2	2 (100%)	
Nonoxynol-9 [25, 57, 58]	Contraceptive suppository – 100 mg nonoxynol-9 (incidental)	1	1 (100%)	
	Nonoxynol 150 mg suppository PV daily × 3 d	23	4 (17.5%)	None
	Nonoxynol suppository PV daily × 2 d	1	1 (100%)	
Zinc Sulfate [59]	Zinc sulfate 1% solution douche PV, followed by Metronidazole 500 mg suppository PV daily × 10 d	4	4 (100%)	Mild vaginal irritation
Furazolidone [60]	Topical furazolidone PV	1	1 (100%)	
Trichofuran [61]	Trichofuran powder 5 g insufflation PV QHS+vinegar douche PV QAM × 10 d	48	44 (92%)	
Combination [62]	Tinidazole 2 g PO BID+Ampicillin 500 mg PO TID+Clotrimazole pessary 500 mg PV QHS × 7 – 14 d	8	6 (75%)	
	Tinidazole 2 g PO BID+Ampicillin 500 mg PO TID × 7-14 d	3	3 (100%)	
Vaginal/Bladder Irrigation [63]	Metronidazole 500 mg PO TID+Metronidazole 1 g PV TID × 21 d	1	1 (100%)	
	Vaginal irrigation – 5% acetic acid			
	Bladder irrigation – Silver nitrate 1:100			
AVC Tablets [51]	AVC (1.05 g sulfanilamide, allantoin, aminacrine hydrochloride) PV QHS × 7 d	43	8 (18.6%)	Vulvovaginal discomfort

dose-dependent manner, and co-incubation of *T. vaginalis* and HIV-1 results in a 4-fold to 4.6-fold increase in the passage of the HIV virus across the epithelial membrane. *T. vaginalis* strains causing asymptomatic infection, however, induced less epithelial integrity disruption. Thus, patients with symptomatic infection may have a higher likelihood of HIV-1 acquisition [39]. Furthermore, the inflammatory reaction to *T. vaginalis* infection may play a role in the increased risk of HIV-1 acquisition. Co-incubation of *T. vaginalis* and HIV-infected peripheral blood lymphocytes leads to increased HIV-1 replication. This is thought to be due to an innate immune response via the TLR-4 receptor, and release of TNF-alpha in response to infection [39].

Finally, *T. vaginalis* and HIV-1 have also been found to have direct interactions in vitro. When incubated with *T. vaginalis*, HIV-1 particles are incorporated into *T. vaginalis*

trophozoites via non-specific endocytosis, and can be carried for up to 2 days. Within these vacuoles, naked HIV particles are able to escape degradation, while HIV-1-infected lymphocytes are ingested and digested. There is no evidence of replication or release of HIV from trichomonads [40].

Because this interaction between *T. vaginalis* and HIV infection exists, it is believed that a certain number of HIV infections can be attributed to preexisting *T. vaginalis* infection. This number is dependent on the prevalence of *T. vaginalis* in the population, which varies substantially [41]. However, populations at high risk for HIV are also at high risk for *T. vaginalis* infection, and in these populations, efforts to identify and treat persons with *T. vaginalis* infections are recommended [11].

Current CDC guidelines recommend that HIV-positive women be screened for trichomoniasis at entry into care, followed by rescreening at least annually, as treatment of this condition can decrease both vaginal HIV shedding and the likelihood of upper genital tract infections [11, 37••]. If trichomoniasis is diagnosed, treatment should be followed by rescreening after 3 months, as recurrent and persistent infections are very common in this patient population [11, 36•]. Because recent evidence suggests that metronidazole 500 mg orally twice daily for 7 days is more effective than a one-time 2 g dose in HIV-positive women [42••], the longer regimen is recommended as first-line treatment [11].

Conclusions

Trichomonasis remains an underappreciated pathogen in both women and men. New approaches to diagnosis can improve detection but remain underutilized. Nitrimidazoles remain the mainstay of therapy, with descriptions of alternative drugs limited to case reports or case series.

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- • Of importance
- •• Of major importance

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