SUPPLEMENT ARTICLE

Trichomonas vaginalis Genital Infections: Progress and Challenges

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***Trichomonas vaginalis* (TV) infection is the most prevalent curable sexually transmitted infection in the United States and worldwide. Most TV infections are asymptomatic, and the accurate diagnosis of this infection has been limited by lack of sufficiently sensitive and specific diagnostic tests, particularly for men. To provide updates for the 2010 Centers for Disease Control and Prevention's Sexually Transmitted Diseases Treatment Guidelines, a PubMed search was conducted of all TV literature published from 9 January 2004 through 24 September 2008. Approximately 175 pertinent abstracts and articles were reviewed and discussed with national experts. This article describes advances in TV diagnostics which have led to an improved understanding of the epidemiology of this pathogen, as well as potential biologic and epidemiological interactions between TV and human immunodeficiency virus (HIV). New data on treatment outcomes, metronidazole-resistant TV, management of nitroimidazole-allergic patients, frequency of recurrent TV infection following treatment, and screening considerations for TV in certain populations are also presented.**

Trichomonas vaginalis (TV) infection is the most prevalent curable sexually transmitted infection (STI) in the United States and in the world [1]. In the United States, a recent population-based study demonstrated an overall prevalence of 3.1% (95% confidence interval [CI], 2.3%–4.3%) among women aged 14–49 years, with rates as high as 13.3% (95% CI, 10.0%–17.7%) among black women in the general population. Almost 20% of black women aged 40–49 years were infected in this study and symptoms did not predict TV infection [2]. Another recent study found a TV prevalence of 6.2% (95% CI, 4.4%–8.1%) among Baltimore residents aged 15–35 years (Susan Rogers, Research Triangle Institute, personal communication, February 2009). TV prevalence was 5-fold higher among women than among men (10.1% vs 2.0%, respectively; prevalence ratio, 5.1%; 95% CI, 2.0%–13.0%), and 1 in 7 black women were found to be infected (estimated prevalence, 14.2%; 95% CI, 10.3%–19.3%). Among women and men attending US sexually transmitted disease (STD) clinics, TV prevalence is generally higher, with a range of 13%–34% [3] for women and 3%–17% for men [4–8]. Trichomoniasis is also frequently diagnosed among women infected with human immunodeficiency virus (HIV), with reported prevalences of 6.1%–52.6% [9–17]. This article outlines new developments since the 2006 Centers for Disease Control and Prevention (CDC) STD Treatment Guidelines, including advances in TV diagnostics, new data on treatment outcomes, metronidazole-resistant TV, management of nitroimidazole-allergic

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patients, frequency of recurrent TV infection following treatment, TV infection in HIV-infected women, potential biological interactions between TV and HIV, and screening considerations for TV in certain populations.

METHODS

A PubMed (US National Library of Medicine and the National Institutes of Health) search was conducted of all literature published from 9 January 2004 through 24 September 2008 using the search terms ''trichomonas'' (520 articles), ''*Trichomonas vaginalis*'' (398 articles), ''trichomoniasis'' (485 articles), and ''trich'' (21 articles), without limitations except human studies. In addition, the National Center for Biotechnology Information sent notifications of all publications with the keyword ''trichomoniasis,'' subsequent to the dates of the literature review. Abstracts in hard copy and online were reviewed from relevant conferences using the search terms above. All abstracts were reviewed and pertinent articles were read, ~175 documents in total. After each article was read, a determination was made as to whether it provided data relevant to the CDC STD Treatment Guidelines. Pertinent articles were summarized and entered into a table of evidence that was used to inform the key questions addressed in the guidelines document. In addition, 6 subject matter experts were contacted to add their expertise to the literature review.

RESULTS

Improved *Trichomonas vaginalis* Diagnostics

Greater knowledge about TV epidemiology reflects improved TV diagnostics, although new detection methods have yet to be incorporated into most clinical settings. To date, the most common clinical method for TV diagnosis in women remains microscopic evaluation of vaginal wet preparations due to its low cost and simplicity. Unfortunately, the sensitivity of wet preparation for TV diagnosis is poor at 60%–70% and can decrease to 20% if microscopic evaluation is delayed by as few as 10 minutes [18]; such delays are not uncommon in busy clinical settings. Therefore, to maximize the performance of the wet preparation for TV diagnosis, slides of vaginal fluid must be examined immediately following specimen collection.

Culture, using a variety of liquid and semisolid media, remains the gold standard for diagnosis of trichomoniasis and is available in pouches containing modified Diamond medium [19–22]. In women, vaginal secretions should be cultured for TV, as urine culture is less sensitive [23, 24]. Self-collected vaginal swabs are as sensitive as clinician-obtained specimens for TV culture [25]. Once inoculated, cultures are incubated and examined daily for 3–5 days by use of microscopy. If the wet mount is negative, then a combined approach of microscopy followed by culture can be useful [25, 26]. Papanicolaou tests can also detect TV in women, but their sensitivity for TV diagnosis is poor. TV detected by Papanicolaou test should be treated; confirmatory testing is unnecessary [27].

Newer Food and Drug Administration (FDA)–cleared point-of-care tests for trichomoniasis in women include the OSOM Trichomonas rapid antigen test (Genzyme Diagnostics), an antigen-detection test that uses immunochromatographic capillary flow dipstick technology, and the Affirm VP III (Becton Dickenson), a nucleic acid probe-hybridization test that evaluates TV, *Gardnerella vaginalis,* and *Candida albicans*. These tests are performed on vaginal secretions and provide superior sensitivity (>83%) and specificity (>97%) over wet mount examination for trichomoniasis [28–30]. The OSOM Trichomonas rapid antigen test results are available in ~10 minutes, and the Affirm VP III results are available within 45 minutes. Although both of these tests are more sensitive than vaginal wet preparations, false positives may occur, especially in populations with low TV prevalence in which the positive predictive value of the test is low. The Affirm VP III and OSOM Trichomonas rapid antigen tests offer the potential to improve TV diagnosis, especially in settings where a microscope is not immediately available or in settings where point-of-care testing offers substantial benefit for improved treatment.

In men, wet preparation lacks sensitivity, and neither the OSOM test nor the Affirm VP III test is available for use with male urethral specimens. Culture may be performed using a urine sample, a urethral swab sample, or a semen sample. In men, multiple specimens can be used to inoculate a single culture to improve yield. However, even under optimal conditions, culture is not a sensitive diagnostic method in men.

Highly sensitive nucleic acid amplification TV testing is now commercially available. APTIMA TV analyte-specific reagents (ASRs; manufactured by Gen-Probe) detect TV RNA by transcription-mediated amplification using the same instrumentation platforms available for the FDA-cleared APTIMA Combo2 assay for gonorrhea and chlamydial infection. FDA clearance for TV testing of endocervical swabs, vaginal swabs, urine samples, and specimens collected in PreservCyt solution from both asymptomatic and symptomatic women was granted in April 2011. Although Gen-Probe TV ASRs can be used to test urethral swabs and urine samples from men, FDA clearance has not been received for male specimen types. Therefore, the sale, distribution, and use of ASRs for male specimens are covered under 21 C.F.R. PART 809.30 pertaining to in vitro diagnostic products for human use. Published validation studies from individual laboratories report TV ASR sensitivities of 74%–98% and specificities of 87%–98%, depending on the specimen evaluated and the reference standard used [31–33] (Table 1). In addition, although TV is often considered by clinicians to be strictly a vaginal pathogen, TV can be detected from

Table 1. Selected Studies Demonstrating Performance Characteristics of Transcription-Mediated Amplification and Polymerase Chain Reaction for Detection of *Trichomonas vaginalis* Genital Tract Infection

Citation , study population, specimen site, diagnostic test, details	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Van Der Pol 2006[a]		
STD clinic		
Vaginal (N = 174)		
WP	61.5 (46.2–76.8)	100
PCR		
TVA	48.7 (33.0–64.4)	100 (100)
TVK	79.5 (66.8–92.2)	97.8 (95.3–100.0)
Male urine (N = 503)		
CX	56.0 (36.5–75.5)	100
PCR		
TVK	96.0 (88.3–100.0)	99.2 (98.4–100.0)
β -Tubulin	92.0 (81.4–100.0)	99.4 (98.7–100.0)
Hardick[b,c] 2006		
STD clinic		
Vaginal (N = 321)		
TMA	98.2	98.1
Male urine (N = 290)		
TMA	100	100
Huppert 2007[d]		
Teen health center and emergency department		
Vaginal (N = 330)		
WP	64.6 (49.5–77.8)	NA
CX	95.8 (85.7–99.5)	NA
Rapid antigen[e]	89.6 (77.3–96.5)	97.5 (95.0–99.0)
TMA	97.9 (88.9–100.0)	95.3 (92.3–97.5)
Nye 2009[f]		
STD clinic		
Vaginal, endocervical, female urine (N = 296)		
WP	54.6 (43.6–65.1)	100 (97.7–100)
CX	75.0 (64.4–83.4)	100 (97.7–100)
PCR vaginal	83.0 (73.1–89.8)	100 (97.7–100)
PCR endocervical	80.9 (70.6–88.0)	100 (97.7–100)
PCR urine	76.1 (65.6–84.3)	100 (97.7–100)
TMA vaginal	96.6 (89.7–99.1)	100 (97.7–100)
TMA endocervical	89.8 (81.0–94.9)	100 (97.7–100)
TMA urine	87.5 (78.3–93.3)	100 (97.7–100)
Urethral, male urine (N = 298)		
CX	28.6 (16.2–44.8)	100 (98.2–100)
PCR urethral	54.8 (38.8–69.8)	100 (98.2–100)
PCR urine	47.6 (32.3–63.4)	100 (98.2–100)
TMA urethral	95.2 (82.6–99.2)	96.5 (93.2–98.3)
TMA urine	73.8 (57.7–85.6)	98.4 (95.8–99.5)

APTIMA TV analyte-specific reagents are manufactured by Gen-Probe. Polymerase chain reaction (PCR) assays are commercially available and manufactured by Roche Diagnostic and modified to detect *T. vaginalis*.

Abbreviations: CI, confidence interval; CX, *T. vaginalis* culture; NA, not available; STD, sexually transmitted disease; TMA, transcription-mediated amplification; WP, wet preparation.

[a] Infection is defined by positive wet mount or a sample positive by both PCR assays for women and by positive culture or a urine sample positive by both PCR assays for men.

[b] Infection is defined by 2 positive amplified results from RMA BTUB FRET PCR or alternative PCR using primer set TVK3 and TVK4 or wet preparation result.

[c] Resolved sensitivity and specificity presented; no 95% CI presented.

[d] Performance characteristics utilizing the traditional reference standard are presented where infection is defined by the presence of a positive wet mount or culture result.

[e] OSOM Trichomonas rapid antigen test.

[f] Data from molecular resolved algorithm presented where infection was defined as any positive test result: culture, wet preparation, PCR, or TMA confirmed by an alternative TMA research-use only assay.

endocervical specimens with nucleic acid amplification tests (NAATs) at comparable frequencies to those of vaginal specimens. Therefore, testing for *Chlamydia trachomatis, Neisseria gonorrhoeae,* and TV from the same specimen may provide comparable sensitivity and specificity to those of individually collected specimens while simplifying specimen collection in those patients for whom testing is indicated [34, 35]. In addition, a commercially available, FDA-cleared polymerase chain reaction (PCR) assay for detection of gonorrhea and chlamydial infection (Amplicor, manufactured by Roche Diagnostic) has been modified to detect TV DNA in vaginal or endocervical swabs and in urine samples from women and men with sensitivities of 88%–97% and specificities of 98%–99%, depending on the specimen and reference standard [36]. Other PCR detection assays may be available from laboratories that have developed and validated these tests, but none is FDA-cleared or commercially available.

Therefore, APTIMA GenProbe Combo TV ASRs are now available as an FDA-cleared test for several types of specimens in women, but it has only been studied (not FDA-cleared) for urine samples and urethral swabs in males. Other NAAT-based TV tests are being evaluated; peer-reviewed studies demonstrate that these tests provide optimal sensitivity and acceptable specificity for diagnosis in varied specimens from both men and women (Table 1). Laboratories that currently use the Gen-Probe APTIMA Combo2 test for *N. gonorrhoeae* and *C. trachomatis* can add the TV ASRs to their testing menus if these tests are clinically applicable. Laboratories that use the Roche Amplicor assay can add the modified TV PCR assay as needed.

Treatment of *Trichomonas vaginalis* Infection

Tinidazole, a 5-nitroimidazole, was introduced for treatment of TV infections in 1969 and has been available outside the United States for several decades. The FDA approved tinidazole for trichomoniasis in 2004. Tinidazole is available under the trade name of Tindamax in 250-milligram and 500-milligram form. Tinidazole has a half-life of approximately 12.5 hours compared with 7.3 hours for metronidazole [37]. Serum and genitourinary tract tinidazole levels have been reported to be 1.4–2-fold higher than metronidazole levels [38, 39].

Randomized controlled trials comparing a 2-g single oral dose of tinidazole to a 2-gram single oral dose of metronidazole or short-course metronidazole have demonstrated tinidazole parasitologic cure rates of 86–100% in women [40–46]. In these trials, tinidazole efficacy equaled or proved superior to that of metronidazole. A Cochrane database meta-analysis of 8 randomized trials, all but one comparing short-course therapy for TV using tinidazole and metronidazole, included one trial published in Norwegian and one trial that compared ornidazole with metronidazole [47]. The latter trial was not included in the comparisons of parasitological cure, clinical cure, or adverse effects. Metronidazole users had a significantly higher parasitological failure rate (10.9% [32 of 293 individuals] vs 3.3% [10 of 302 individuals]; $P = .00055$), a higher clinical failure rate (14.8% [31 of 210 individuals] vs 3.7% [8 of 216 individuals]; $P = .00034$), and more frequently reported adverse effects (47.3% [107 of 226 individuals] vs 28.9% [67 of 232] individuals; $P = .00001$) compared with individuals receiving tinidazole [47]. The largest study of tinidazole treatment (2-gram single oral dose) was a multicenter open-label trial that documented parasitologic cure in 818 (95%) of 859 women by wet preparation. Therefore, a 2-gram single oral dose of tinidazole appears to be as effective as or superior to a 2-gram single oral dose of metronidazole, and both of these drugs are recommended for the treatment of TV infection.

There are few published data available on the efficacy of metronidazole or tinidazole in men. In one study, all of 39 TV-infected men were cured after treatment with a 1-gram single oral dose of tinidazole [48]. Wallin and colleagues reported on 11 men treated with a 1.6-gram or 2-gram single oral dose of tinidazole, including 10 men who were cured on follow-up evaluation [49]. Massa and colleagues reported an 83% cure rate for 2-gram single oral dose tinidazole therapy in a cohort of 30 men [50]. Despite the paucity of data derived from clinical trials, both metronidazole and tinidazole are recommended treatment regimens in men.

The initial treatment regimen for nongonococcal urethritis (NGU) in men does not currently include a nitroimidazole for TV infection. A recent randomized controlled trial for treatment of NGU in men has found that the addition of tinidazole to the treatment regimen does not result in higher cure rates but does effectively eradicate trichomonas [51]. Prior studies have shown that urethritis on Gram stain does not appear to be associated with PCR-diagnosed TV infection in men [6, 52]. Data from a trial conducted in Malawi found that adding metronidazole to an empiric antibiotic regimen for urethritis did not improve symptom resolution among men with TV infection who returned for follow-up, although TV infection was cleared in these men [53]. These data suggest that a nitroimidazole should not be added to recommended first-line empirical NGU therapies but should be considered as part of second-line therapy if symptoms or signs of urethritis persist after initial treatment.

Treatment of Metronidazole-resistant *Trichomonas vaginalis* Infection

Clinical failures with metronidazole have been reported since 1962. Current recommendations are to treat women in whom initial therapy fails with either single-dose tinidazole therapy or 500 milligrams of metronidazole twice a day for 7 days. There is minimal new data on the most appropriate management of women in whom initial therapy with metronidazole fails. Saurina and colleagues found low-level metronidazole resistance in 3 (2.5%) of 118 TV isolates after treatment failure with single-dose metronidazole. Treatment with 500 milligrams of

metronidazole twice a day for 7 days resulted in cure in 2 of 3 women [54]. Schmid and colleages found low-level metronidazole resistance in 2.4% of 82 isolates [55]. Follow-up was available in only 1 of the 2 cases identified, and that patient was cured after a single 2-gram dose of metronidazole.

In vitro data support the likelihood that tinidazole will be effective following unsuccessful metronidazole therapy [56]. An evaluation of 104 clinical TV isolates from patients in whom metronidazole treatment failed found that the mean aerobic minimum lethal concentration (MLC) for tinidazole was ~1014.9 μM compared with 2618 μM for metronidazole. Sixty percent of isolates had a lower MLC to tinidazole than to metronidazole. In addition, serum and genitourinary tract drug levels of tinidazole are 1.5–2-fold higher than those of metronidazole in men receiving 500 milligrams three times a day (TID) a day of each medication [39]. Similarly, serum and genitourinary tract drug levels of tinidazole are 1.4–1.8-fold higher than of those of metronidazole in women receiving 400 milligrams of metronidazole TID or 500 milligrams of tinidazole twice a day [38]. Tinidazole as a 2-gram single oral dose proved effective in a limited number of cases with documented TV treatment failure after divided-dose metronidazole therapy of unspecified length (2 of 2 individuals cured) and standard 7-day metronidazole therapy (13 of 14 individuals cured) [40, 44].

Although the incidence of high-level metronidazole resistance appears to be low, several case series published since 2000 document cases of metronidazole treatment failure, with the largest series including 24 cases [57]. Several of these reports documented response to oral and/or intravaginal tinidazole with dosing regimens ranging from 2 grams of tinidazole orally once a day for 2 days [58] to 1 gram of tinidazole orally TID with 500 milligrams intravaginally TID for 14 days [57, 58]. In patients with clinical failure following metronidazole and tinidazole at a total daily dose of 2 grams orally plus a total dose of 1 g intravaginally or at a total dose of 3 grams orally plus a total dose of 1.5 grams intravaginally resulted in parasitologic cure for 30 of 34 patients reported (Presutti laboratories compassionate availability program).

For women who have persistent trichomoniasis following a 2-gram single dose of metronidazole, in whom treatment failure is suspected and reinfection has been excluded, the current recommendation is to treat with 500 milligrams of metronidazole orally twice daily for 7 days. For patients failing this regimen, clinicians should consider treatment with tinidazole or metronidazole at 2 grams orally for 5 days. If these therapies are not effective, further management should be discussed with a specialist. The consultation should ideally include determination of the susceptibility of TV to metronidazole and tinidazole. Paromomycin, povidone-iodine, furazolidone, and nonxynol-9 are topically applied agents that have anecdotal reports of success although toxicity is high; a 40%–58% success rate can be expected with these topical agents [57, 59, 60].

Although there are no data to guide treatment of the male partners of women with treatment failure, the male partner should be evaluated and treated with 500 milligrams of metronidazole orally twice a day for 7 days or 2 grams of tinidazole orally in a single dose. Single-dose metronidazole therapy should be avoided in the male partners of women with TV treatment failure.

Patients Allergic to 5-Nitroimidazoles

Few individuals have serious adverse reactions, including anaphylaxis, to 5-nitroimidazoles. Urticarial adverse reactions do not always recur if therapy is repeated [61]. More severe, anaphylactic-type reactions occur, but it is not known whether urticarial reactions predict subsequent anaphylaxis. Recently, Helms et al [59] reported data collected from clinicians who consulted the CDC on 59 patients with suspected hypersensitivity to metronidazole. The most common reactions were urticaria (47%) and facial edema (11%), based on patient history. Only 41 (69%) of 59 patients were treated following consultation, including 26 patients treated with alternative regimens and 15 women who underwent metronidazole desensitization that utilized either the oral (8 women) or the intravenous (7 women) published desensitization regimen [59]. All patients who underwent desensitization and were treated with metronidazole had their infections eradicated. One woman who received the oral desensitization regimen experienced a pruritic rash on the final day that resolved with steroids, and 1 women who received the intravenous desensitization regimen experienced mild urticaria and pruritis 45 minutes after the final 2-gram dose that was managed with diphenhydramine. Alternative treatment regimens were used for 17 study subjects with a cure rate of only 29.4% (5 of 17 subjects).

These observations suggest that severe reactions do not always occur with subsequent metronidazole doses. However, there is no proven way to determine who will react to re-exposure. It appears that the best approach is to avoid nitroimidazoles in patients with a history of prior allergic reactions, and that potential alternative therapies have low success rates for trichomoniasis. For patients with adverse reactions to metronidazole or tinidazole who require 5-nitroimidazole therapy, consultation with an allergist or immunologist and, likely, desensitization are recommended.

Trichomonas vaginalis Infection in HIV-infected Women

Despite the high prevalence of trichomoniasis demonstrated in HIV-infected women (6.1%–33% tested using wet preparation and/or culture and up to 52.6% tested with nucleic acid amplification) [10, 11, 13–15, 17], there are few data available to guide TV infection management in this population. Kissinger et al [62] found that TV infections were detected in 18.3% of HIV-positive women at 1 month after treatment. There was no difference in the proportion of cases determined to be due to treatment failure between HIV-infected women (10%) and

HIV-negative women (7.3%; $P = .44$). Moodley et al [14] also found that HIV status did not influence TV infection cure rates among symptomatic women treated with 2 grams of metronidazole. Moodley et al [63] reported a significant 1.9-fold increased risk of pelvic inflammatory disease in TV-positive HIV-infected women in a cross-sectional study. The association remained statistically significant regardless of whether trichomoniasis occurred as a single infection (relative risk, 3.4; 95% CI, 1.1–11.1) or in combination with *N. gonorrhoeae, C. trachomatis,* or bacterial vaginosis (relative risk, 2.1 95%, CI 1.2–3.6); however, there was no information on treatment outcomes from this study.

The standard treatment recommendations for trichomoniasis have been based on studies that were conducted in HIV-negative persons. However, a recent randomized clinical trial demonstrated that a 2-gram single oral dose of metronidazole was not as effective as 500 milligrams of metronidazole twice daily for 7 days for trichomoniasis among HIV-infected women [64]. Women in the 7-day arm had lower repeat TV infection rates at test of cure (6–12 days after treatment completion; 8.5% [11 of 130 women] vs 16.8% [21 of 125 women]) and at 3 months (11% [8 of 73 women] vs 24.1% [19 of 79 women]). Therefore, a multidose treatment regimen for TV infection may be considered in HIV-infected women.

Potential *Trichomonas vaginalis*-HIV Interactions

The plausible biological synergy between TV and HIV has been investigated in several studies (Table 2). Price et al [65] demonstrated increased seminal HIV RNA levels in HIV-positive men with TV urethral infections in Malawi. Mostad et al [15] found no significant increases in HIV-infected cells from cervical and vaginal secretions. In 2001, Wang and colleagues noted a 4.2× decrease in mean HIV RNA genital shedding (log 3.67 to log 3.05; $P < .001$) among HIV-infected women after treatment of TV infection [66]. Kissinger et al [67] showed that TV treatment reduced vaginal HIV shedding over a 1–3-month period and that HIV-infected women with TV infection had higher prevalence of HIV RNA in vaginal secretions than did those without TV infection. Multiple reports support the epidemiological association between HIV and trichomoniasis. In a prospective cohort study, Laga and colleagues found that TV infection was associated with a 1.7-fold increased risk of HIV acquisition [68]. This finding was supported in another cohort study in which McClelland et al [12] demonstrated that TV infection was associated with a significant 1.5-fold increased risk of HIV infection. A nested case-control study of women by Van der Pol et al [69] also found an association between TV infection and incident HIV infection in multivariate analysis using wet mount (adjusted odds ratio, 5.10) and PCR (adjusted odds ratio 2.74) for TV detection.

Periodic screening of those at high risk of TV infection and prompt treatment of TV infection is recommended for HIV-positive women [70] on the basis of the high prevalence of TV infection, the benefit of TV treatment in reducing vaginal HIV shedding, and the potential to decrease upper genital tract infections. Clinicians should consider screening for TV by wet mount, culture, or a NAAT-based test for HIV-infected women at the initial clinic visit, at least annually for sexually active individuals, and more often (ie, at 3–6-month intervals) for asymptomatic persons at higher risk as suggested by current guidelines [70]. If TV infection is identified in HIV-positive women, then a multidose treatment regimen should be considered.

Rationale for *Trichomonas vaginalis* Screening in At-Risk Populations

Because of the high prevalence of trichomoniasis in clinical and nonclinical settings, testing for TV should be performed for women seeking care for vaginal discharge. However, although no study has adequately assessed screening for TV among asymptomatic patients at STD clinics, including the optimal frequency or cost-benefit of screening, epidemiological data do suggest that TV infection is highly prevalent (3.1% among women aged 14–49 years, with a rate as high as 13.3% among black women in one national population-based study [2]) and frequently asymptomatic (Susan Rogers, Research Triangle Institute, personal communication, February 2009). For instance, Rogers and colleagues found that 76% of the respondents diagnosed with TV infection in their probability-based sample of Baltimore adolescents and young adults denied discharge and/or dysuria within the past 3 months (Susan Rogers, Research Triangle Institute, personal communication, February 2009), and the larger population-based study performed by Sutton and colleagues found no significant differences in reported symptoms between women with and those without TV infection [2]. In addition, several studies have demonstrated that women with other STIs, including gonorrhea and chlamydial infection, have increased risk of TV coinfections and share common risk factors [2, 71]. Additionally, studies have found an association between TV infection and complications including preterm birth [72] and pelvic inflammatory disease [63], and, as documented above, there are potential interactions between TV and HIV infection [12, 65–69]. As such, screening for TV may be considered in those women at high risk of infection (women with new or multiple partners, history of STD, exchange of sex for payment, or injection drug use), although further research to address the optimal frequency and the cost-benefit of screening is certainly warranted.

Trichomonas vaginalis Persistence and Recurrence Following Treatment

Kissinger et al [62] provided data from HIV-positive and HIV-negative women suggesting that evaluation of organism eradication for TV infection warrants consideration. Among

Table 2. Selected Studies Examining Interaction Between *Trichomonas vaginalis* Infection and Human HIV Infection in Women

Study type citation	Study design	Study population type and setting	Exposure and/or intervention	Outcome measures	Reported findings
Impact of TV infection on HIV shedding in the genital tract					
Mostad 1997	Cross-sectional study (N = 318)	HIV-positive women at STD clinic in Mombasa, Kenya	Interview, blood sample, testing for BV (Gram stain), CA, NG, CT, TV; vaginal and endocervical swabs for HIV-1 DNA PCR of *gag* gene	HIV-1 shedding from vagina and cervix	Mean age, 28 years; 70% were CSWs, 9% had TV infection, 56% had BV, 13% had active syphilis, 8% had NG infection, and 4% had CT infection; mean CD4 cell count, 451 cells/μL; 51% of women had endocervical HIV shedding; endocervical shedding more likely with contraceptive use, lower CD4 cell count, or NG infection; vaginal shedding seen in 14% of women and more likely with lower CD4 cell count and candidal infection; TV not associated with vaginal shedding
Wang 2001	Longitudinal cohort (N = 203) with 242 vaginitis episodes	Excluded women with evidence of cervicitis or GUD	Inclusion of women with BV at initial or follow-up visit in women with CA or TV treatment; measurement of qualitative HIV DNA and quantitative vaginal HIV RNA levels	Effect of treatment of vaginitis on HIV DNA and RNA levels	27% of women had CD4 cell count of <200 cells/μL; TV analyzed in 67 women (6 missing swabs and 6 invalid RNA results); 4.2× decrease in mean HIV RNA level (decrease from log 3.67 copies/mL to 3.05 copies/mL; $P < .001$) but no significant change in HIV DNA level with treatment; adjusting for BV or sperm did not significantly alter results

Table 2 continued.

Study type citation	Study design	Study population type and setting	Exposure and/or intervention	Outcome measures	Reported findings
Kissinger 2009	Prospective cohort with matched controls on selected confounders (N = 58 TV-positive women successfully treated with at least 1 follow-up; N = 92 TV-negative controls); GEEs used for repeat measures	HIV-positive women attending HIV outpatient program in New Orleans, Louisiana	HIV-positive women ≥18 years old scheduled to undergo gynecological examination with at least 1 follow-up visit enrolled; women who tested positive by wet mount or TV culture performed at enrollment and tested negative on at least 1 follow-up visit matched on ART status and date of enrollment to women testing negative at all time points who returned for at least 1 follow-up visit (ratio, 1:2)	Detectable HIV-1 levels in vaginal fluids (>50 copies/swab); testing performed at 0, 1, and 3 months; accounted for phase of menstrual cycle	Most women were black (81.3%); median age, 37 years; median CD4 cell count, 410 cells/μL (range, 6–1823 cells/μl); median plasma HIV-1 RNA level among those with detectable virus (n = 120), 17,001 copies/mL (range, 51–818,575 copies/mL); median viral load of those shedding vaginally (N = 39), 553 copies/mL (range, 52–89, 300 copies/mL); TV-positive women had higher prevalence of detectable HIV-1 RNA in vaginal secretions at baseline (36.2% vs 19.6%; P = .02) which remained at 1 month (34.6% vs 14.1%; P = .01) and then diminished at 3 months (18.4% vs 12.2%; P = .91); after adjusting for ART (yes or no) and accounting for repeat measures, women successfully treated for TV infection less likely to shed virus at visits 2 and 3, compared with visit 1, but TV-negative women equally likely to be shedding at all visits; no effect of TV treatment on plasma viral load
Impact of TV on HIV acquisition					
McClelland 2007	Prospective study (N = 1335)	Open cohort study of FSWs attending municipal clinic in Mombasa, Kenya	Standardized interview, physical examination, and laboratory testing for HIV and STIs at enrollment and monthly; women with signs or symptoms of STI syndromically managed at visit and asked to return in 1 week for follow-up test results; TV diagnosed by wet preparation; HIV-negative women with at least 1 follow-up visit included in analyses	Tested hypothesis that TV infection increases risk of HIV-1 acquisition in study population	Median age, 26 years; mean duration of prostitution, 1 year; at enrollment, 6% of women were TV-positive, 37% BV-positive, and 5% NG-positive; 806 incident TV infections (23.6 per 100 person-years) and 265 HIV seroconversions (7.7 per 100 person-years); multivariate model with adjusted HR, 1.52 (95% CI, 1.04–2.24; P = .03) for the association of TV infection with HIV seroconversion; model controlled for baseline education level, parity, alcohol use, workplace, vaginal washing practices, other STIs, contraceptive method, age, duration of prostitution, no. of partners per week, condom use, and frequency of sex

Table 2 continued.

Study type citation	Study design	Study population type and setting	Exposure and/or intervention	Outcome measures	Reported findings
Van der Pol 2008	Nested case-control study (N = 218 cases; N = 419 controls)	Women enrolled in longitudinal cohort study of hormonal contraception and HIV acquisition in Uganda and Zimbabwe	Women with incident HIV infection (63 in Uganda; 155 in Zimbabwe) classified as cases; controls matched on study site on age, composite STI variable (CT, NG, or BV), and length of follow-up; for cases, samples analyzed from seroconversion visit and visit preceding seroconversion; for controls, samples analyzed based on follow-up closest to follow-up for visits for cases; composite behavioral risk variable used and primary sex partner risk composite score used; TV status based on microscopy from parent study and PCR analysis of case and control samples	Association between TV infection and incident HIV infection	Median age, 24 years (cases and controls); in multivariable analysis, TV infection associated with incident HIV infection (adjusted OR, 2.74; 95% CI, 1.25–6.00); this risk was higher after analyses limited to lower-risk setting (family planning participants) with adjusted OR of 3.3 (95% CI, 1.36–7.85); relationships even stronger if analyses limited to positive wet preparations only (ie, eliminating those positive only through PCR)
Impact of HIV on TV acquisition and clearance					
Cu-Uvin 2002	Multicenter longitudinal cohort study (N = 871 HIV-positive women; N = 439 HIV-negative women)	Women with HIV and women at high risk of HIV acquisition recruited from April 1993 through January 1995; women with AIDS-defining illness excluded	Every 6 months patients evaluated with interview, examination, and blood, urine, and genital tract specimen collection; TV assessed by wet preparation and TV culture on visits 4–12	Analysis of data from first 12 visits	Majority of patients black; imputed TV infection prevalence among HIV-positive women, 29% vs 23% for HIV-negative women; patients with CD4 cell count of <200 cells/μL less likely to have baseline TV infection ($P = .03$); on multivariate analysis, baseline TV infection associated with IDU, crack cocaine use, ETOH, candidiasis, and BV; black race, recent crack cocaine use, cigarette use, and BV associated with TV infection in time trend; no significant difference in incidence, persistence, or recurrence of TV infection between HIV-positive and HIV-negative women; in HIV-positive women, no difference based on CD4 cell count

Table 2 continued.

Study type citation	Study design	Study population type and setting	Exposure and/or intervention	Outcome measures	Reported findings
Magnus 2003	Retrospective cohort study (N = 1578)	HIV outpatient program database, Louisiana, 1990–2000; HIV-positive women aged >13 years with at least 1 year data available	Screened every 6 months by wet preparation and CT antigen test or ELISA for GC symptoms or urine syphilis test and examination for HPV; TV infection treated with metronidazole (2 g or 500 mg twice a day for 7 days); partners referred for treatment	TV infection and risk factors in HIV-positive women	13.1% of women were TV-positive, 5.3% CT-positive, and 4.9% NG-positive; 30% of 1578 women had TV infection at least 1 time; 37% had at least 1 subsequent positive test; women <22 years old, black, with other STD, and substance users had significantly higher incidences of initial TV infection; subsequent positive TV test significantly higher in women with any other STD; immune status, ART use, and PI use not associated with TV infection
Moodley 2003	Cross-sectional study (N = 692)	Women presenting to primary health clinic in Kwa Zulu-Natal with GU symptoms	Interview and examination; TV infection diagnosis by culture; syndromic symptoms treated with cipro (250 mg orally once), metronidazole (2 g once), and doxy (200 mg a day for 7 days); return to clinic 8−10 days later for repeat examination	Clinical (resolution of signs and symptoms) and microbiologic cure	Mean age, 24 years; vaginal discharge present in 91% of participants; 75% positive for any STD; 29% had TV infection (33% of HIV-positive women and 25% of HIV-negative women; $P = .02$); 80% of women returned for follow-up and 70% allowed another examination; 65% of women had TV infection clinically cured and 88% microbiologically cured; no difference in cure rate by HIV status (90% HIV-positive and 82% HIV-negative women cured; $P = .3$)

Abbreviations: ART, antiretroviral therapy; BV, bacterial vaginosis; CA, *Candida albicans;* CI, confidence interval; CSW, commercial sex worker; CT, *Chlamydia trachomatis;* ELISA, enzyme-linked immunosorbent assay; FSW, female sex worker; GEE, generalized estimating equation; GU, genitourinary; GUD, genital ulcer disease; HIV, human immunodeficiency virus; HPV, human papillomavirus; HR, hazard ratio; IDU, injection drug use; NG, *Neisseria gonorrhoeae;* OR, odds ratio; PCR, polymerase chain reaction; PI, protease inhibitor; STD, sexually transmitted disease; STI, sexually transmitted infection; TV, *Trichomonas vaginalis*.

60 HIV-positive women with trichomoniasis, 11 (18.3%) were positive by TV culture 1 month after treatment with 2-gram single-dose metronidazole therapy, including 6 (10.0%) who were considered to have probable treatment failure. Among 301 HIV-negative women with trichomoniasis who were recruited from family planning clinics, 24 (8.0%) were positive at 1 month after treatment, including 22 (7.3%) who were considered to have probable treatment failure. There was no significant difference in drug resistance between isolates from HIV-positive women and those from HIV-negative women (3.3%), and the majority of individuals responded to higher doses of metronidazole (ie, 500 milligrams twice daily for 7–10 days). Similarly, in a study involving in vitro susceptibility testing of TV isolates, Schwebke and colleagues found that in vitro resistance was poorly correlated with clinical response to treatment, a finding that potentially implicates poor metronidazole efficacy in several of the treatment failures documented in this study [73].

The argument for retesting young women diagnosed with trichomoniasis after treatment can be based on the observation of high recurrence rates. Peterman et al [71] studied 119 sexually active women 15–39 years of age with TV infections recruited from 3 public STD clinics. In this population, 16.5% were culture-positive after 3 months, 18.5% were culture-positive after 6 months, and 12.5% were culture-positive after 9 months. A new TV infection was more likely for women with initial diagnoses of TV infection (16.5%) or gonococcal infection (14.8%). Because all infections were initially treated with standard single-dose therapy, we suggest that some TV infections may have been treatment failures or reflect lack of partner treatment. Observations such as those above highlight the need for additional research on the prevalence and significance of persistent infection.

As discussed above, high rates of persistent and/or recurrent trichomoniasis, although often difficult to sort out from reinfection, raise concerns about treatment failure. Regardless of the sex of the study participant, the choice of diagnostic test used to document parasite eradication in treatment studies is particularly pertinent in terms of determination of treatment efficacy. As mentioned above, wet preparation, the primary methodology available for the majority of trichomonas treatment study protocols performed in the past, is less sensitive than culture and dramatically less sensitive than newer nucleic acid amplification tests. In fact, it is possible that utilization of wet preparation for test of cure may have led to erroneously high TV eradication rates due to false negative results in the earlier treatment studies, an issue that raises concerns about the true treatment efficacy of metronidazole. Future treatment studies designed to address this issue should use newer, more sensitive diagnostic tests in order to document organism eradication. Whether the high TV recurrence rates are due to reinfection or treatment failure, they argue that rescreening individuals with documented TV infection following therapy may be considered.

CONCLUSION

Trichomoniasis is an extremely common, often asymptomatic, STI that has been associated with potentially serious sequelae. Advances in TV diagnosis have led to a greater appreciation of the burden of trichomoniasis in the general population and the biological and epidemiological interactions between TV and HIV. Effective alternatives to the 5-nitroimidazole drugs are needed for patients with drug allergy and nitroimidazole-resistant TV infections. Optimal treatment regimens in men and women require additional evaluation using newer diagnostic tests to define therapeutic endpoints. Clinicians may consider screening in those at high risk of infection. Emerging data demonstrating the high prevalence of TV infection in the general population and interactions between TV and HIV suggest that additional research efforts should be directed at determining the possible benefits of enhanced screening (optimal population and intervals) for this important pathogen.

Notes

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