SUPPLEMENT ARTICLE

A Review of Evidence-Based Care of Symptomatic Trichomoniasis and Asymptomatic *Trichomonas vaginalis* Infections

Elissa Meites,[1] Charlotte A. Gaydos,[2] Marcia M. Hobbs,[3] Patricia Kissinger,[4] Paul Nyirjesy,[5] Jane R. Schwebke,[6] W. Evan Secor,[7] Jack D. Sobel,[8] and Kimberly A. Workowski[1,9]

[1]Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [3]Departments of Medicine and Microbiology and Immunology, University of North Carolina School of Medicine, Chapel Hill; [4]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana; [5]Department of Obstetrics and Gynecology, Drexel University College of Medicine, Philadelphia, Pennsylvania; [6]Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham School of Medicine; [7]Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia; [8]Division of Infectious Diseases, Wayne State University School of Medicine, Detroit, Michigan; and [9]Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

***Trichomonas vaginalis* is the most prevalent nonviral sexually transmitted infection, affecting an estimated 3.7 million women and men in the United States. Health disparities are prominent in the epidemiology of this infection, which affects 11% of women aged ≥40 years and a disproportionately high percentage of black women. Particularly high prevalences have been identified among sexually transmitted disease (STD) clinic patients and incarcerated individuals. This article reviews and updates scientific evidence in key topic areas used for the development of the 2015 STD Treatment Guidelines published by the Centers for Disease Control and Prevention. Current evidence is presented regarding conditions associated with *Trichomonas vaginalis* infection, including human immunodeficiency virus (HIV) and pregnancy complications such as preterm birth. Nucleic acid amplification tests and point-of-care tests are newly available diagnostic methods that can be conducted on a variety of specimens, potentially allowing highly sensitive testing and screening of both women and men at risk for infection. Usually, trichomoniasis can be cured with single-dose therapy of an appropriate nitroimidazole antibiotic, but women who are also infected with HIV should receive therapy for 7 days. Antimicrobial resistance is an emerging concern.**

Keywords. *Trichomonas vaginalis*; *Trichomonas* infections; *Trichomonas vaginitis*; antitrichomonal agents; sexually transmitted diseases.

Trichomonas vaginalis is a highly prevalent parasitic infection that causes the sexually transmitted disease (STD) trichomoniasis. Since 2008, when scientific evidence was systematically reviewed for the development of the 2010 STD Treatment Guidelines [1], additional data have been published regarding epidemiology, clinical manifestations, treatment, partner management, antimicrobial resistance, associated conditions (eg, human immunodeficiency virus [HIV], pregnancy complications, and others), diagnostic methods, screening, reporting, and prevention of *T. vaginalis* infections and trichomoniasis. This article reviews current evidence in each of these key topic areas used for the development of the 2015 STD Treatment Guidelines published by the Centers for Disease Control and Prevention (CDC).

METHODS

A PubMed (US National Library of Medicine and the National Institutes of Health) search was conducted

Correspondence: Elissa Meites, MD, MPH, Division of STD Prevention, National Center for Viral Hepatitis, HIV/AIDS, STD and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS E-02, Atlanta, GA 30333 (emeites@cdc.gov).

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of all literature published between 25 September 2008 and 28 January 2013 using the search terms "Trichomonas" (508 articles), "Trichomonas vaginalis" (373 articles), "trichomoniasis" (472 articles), and "trich" (2 articles). The search was confined to human studies, without other limitations. In addition, the National Center for Biotechnology Information sent notifications of all publications with the key words "Trichomonas vaginalis" or "trichomoniasis" subsequent to the dates of the literature review. Abstracts were reviewed from relevant conferences (eg, STD Prevention Conference; Infectious Diseases Society of America; International Society for Sexually Transmitted Diseases Research; American Society for Microbiology; Interscience Conference on Antimicrobial Agents and Chemotherapy; Infectious Diseases Society for Obstetrics and Gynecology) using the dates and search terms above.

Each abstract was reviewed, along with the full text of each pertinent article, to determine whether it contained data relevant to the 2015 CDC STD Treatment Guidelines. A total of 197 pertinent abstracts/articles were summarized and entered into tables of evidence. In addition, 9 subject matter experts were contacted to add their expertise to the guidelines. Tables of evidence were used to inform the responses to key questions regarding clinical management of trichomoniasis and *T. vaginalis* infections. Additional unpublished data of which the experts were aware were added to the tables, with permission of the researchers. Findings were summarized, including published relative risks (RRs), odds ratios (ORs), hazard ratios (HRs), and 95% confidence intervals (CIs).

RESULTS

Epidemiology and Clinical Manifestations

Trichomonas vaginalis is the most prevalent nonviral sexually transmitted infection (STI) in the United States, causing an estimated 3.7 million prevalent infections (including 2.3 million among women and 1.4 million among men), and 1.1 million incident infections annually (including 680 000 among women and 415 000 among men) [2]. These estimates are based on nationally representative samples of the civilian noninstitutionalized population in the 2001–2004 National Health and Nutrition Examination Survey (NHANES), which projected that 3.1% of US women of reproductive age are infected [3]. *Trichomonas vaginalis* parasites preferentially infect the urethra in men and women, and vaginal and vulvar sites in women.

Health disparities are prominent in the epidemiology of this infection, including disparities by age and by race/ethnicity. In a nationally representative sample of 12 449 adolescents in school grades 7–12, the prevalence among US adolescents was estimated to be 2.8% among females and 1.7% among males [4]. A study of US female adolescents aged 12–18 years found that *T. vaginalis* incidence was 1.3 per 100 person-months among 257 HIV-infected adolescents, and 0.6 per 100 person-months among 142 HIV-uninfected adolescents ($P = .002$) [5]. Other studies have found that the prevalence of *T. vaginalis* infection can increase with age, peaking at >11% among women aged ≥40 years [3, 6]. In NHANES, the prevalence of infection among non-Hispanic black women was 13.3%, significantly higher than the 1.8% prevalence among Mexican-American women or the 1.3% prevalence among non-Hispanic white women [3].

Particularly high prevalences have been detected among incarcerated individuals, at 9%–32% among incarcerated women [6–10] and 2%–9% among incarcerated men [7, 11–13], using a variety of specimens and diagnostic testing methods. One study among pregnant incarcerated women found an extremely high prevalence of 47% [11]. Prevalence of infection also has been found to be high among STD clinic patients, at 26% of symptomatic women tested [14]. Among women using drugs (including recent heroin, crack or other cocaine, or daily marijuana), prevalence ranges from 13% to 38% [15–17].

Few studies have evaluated rectal or oral infection. One study of 497 men and women reporting receptive anal intercourse detected a rectal prevalence of 5.2% (26/497) by nucleic acid amplification test (NAAT) at clinical sites in Pittsburgh [18]. A study of remnant rectal specimens from 500 men who have sex with men (MSM) attending a San Francisco STD clinic found a prevalence of 0.6% (3/500) by NAAT [19]. A cohort study of 365 HIV-infected MSM in primary care in 4 cities reported zero prevalent and zero incident *T. vaginalis* infections at 6 months, using in-house polymerase chain reaction (PCR) on centrifuged urine [20]. No population-based studies have investigated trichomoniasis in oropharyngeal sites, although *T. vaginalis* has been reported as a cause of purulent sinusitis in at least 1 critically ill patient [21]. It is unclear whether the rectum or the oral cavity can be a reservoir for *T. vaginalis* parasites, or whether this occasional finding might reflect recent deposition of organism during receptive anal or oral sex.

Two studies have evaluated the urethral prevalence of *T. vaginalis* infection among MSM; in both studies, the prevalence detected by an in-house PCR test on urine specimens was negligible [20, 22].

Treatment

Medications approved by the US Food and Drug Administration (FDA) for treatment of trichomoniasis include metronidazole (since 1963) and tinidazole (since 2004). Standard therapy consists of either metronidazole or tinidazole in a single 2-g dose taken orally, or, if necessary, intravenously. The CDC also recommends an alternative regimen of metronidazole 500 mg orally twice a day for 7 days. Tinidazole has a half-life of approximately 12.5 hours, compared with a half-life of 7.3 hours for metronidazole [23]. Furthermore, serum and genitourinary

tract drug levels of tinidazole have been reported to be 1.4–2 times higher than those of metronidazole [24, 25]. In randomized controlled trials, demonstrated efficacy of tinidazole was equal or superior to that of metronidazole, with parasitologic cure rates of 86%–100% [26–30]. However, tinidazole is approximately 10 times more expensive, with an approximate retail price of $44.66 per 2-g dose, compared with $3.47 per 2-g dose of metronidazole.

Both metronidazole and tinidazole are 5-nitroimidazoles, which is currently the only class of antimicrobial medications approved for effective treatment of trichomoniasis and *T. vaginalis* infections. Other nitroimidazoles, such as secnidazole and ornidazole, have been used as antiparasitic agents in other countries but have not been approved for use within the United States. An additional nitroimidazole called fexinidazole was evaluated favorably for toxicity and is under study in humans as a potential novel antiparasitic agent [31, 32]. A small randomized trial involving 60 women with symptomatic trichomoniasis in Brazil showed that a single 24-mg oral dose of peppermint herbal medication, *Mentha crispa*, performed similarly to a nitroimidazole in achieving a microbiologic and symptomatic cure according to wet mounts of vaginal fluid, as 97% of women in the nitroimidazole group were cured, compared with 90% of women in the *Mentha crispa* group ($P = .6$) [33].

Persistent or recurrent infection due to antimicrobial-resistant *T. vaginalis* or other causes should be distinguished from the possibility of reinfection from an untreated or insufficiently treated sex partner. The CDC's Division of STD Prevention and Division of Parasitic Diseases and Malaria have accumulated experience with testing and treatment of nitroimidazole-resistant *T. vaginalis* and can offer susceptibility testing and management recommendations upon request [34]. This issue is discussed in more detail below.

Following treatment failure, persistent or recurrent trichomoniasis has been treated successfully with longer courses or additional doses of the same medications used in standard therapy (eg, tinidazole 1 g twice daily for 2 weeks, plus tinidazole vaginal tablets 500 mg twice daily for 1 week) [35, 36]. In vitro data support the likelihood of efficacy with tinidazole following metronidazole treatment failure; although tinidazole is not more active than metronidazole against susceptible organisms, it is predictably more active against isolates demonstrating mild, moderate, or severe resistance [37]. Since there are currently no definitive data to guide treatment for partners of individuals with persistent or recurrent trichomoniasis, where reinfection or nonadherence are unlikely, it is suggested that partners should undergo evaluation and receive the same regimen as the patient.

Occasional individuals have serious adverse reactions to 5-nitroimidazoles. In a series of 127 *T. vaginalis*–infected women whose clinicians all consulted the CDC for suspected metronidazole hypersensitivity, reactions reported by the clinician included urticaria (48%), pruritus (16%), erythema (9%), facial edema (9%), gastrointestinal (7%), anaphylaxis (2%), and other (10%) [38]. Anecdotal experience indicates that urticarial adverse reactions do not always recur if therapy is repeated [39]. Of 15 women who received desensitization to metronidazole using a published oral or intravenous metronidazole desensitization regimen, all had eradication of their infection; 1 woman who received the oral regimen experienced a pruritic rash on the final day (resolved with steroids) and 1 woman who received the intravenous regimen experienced mild urticaria and pruritus 45 minutes following the final 2-g dose (managed with antihistamines) [38]. It is not known why some individuals have adverse reactions upon reexposure while others do not.

Alternative treatment options are limited as no other FDA-approved therapies are available. Combination regimens have not been systematically evaluated. The most anecdotal experience has been with intravaginal paromomycin in combination with high-dose tinidazole. Case series and reports have reported successful treatment with agents including intravaginal paromomycin [35, 40–42], intravaginal boric acid [43, 44], nitazoxanide [45], and intravaginal metronidazole/miconazole [46]. Toxicities are not high with any of these regimens, although painful vulvar ulcers can be an uncommon self-limited side effect of paromomycin. Other attempted treatments that have been reported with a <50% success rate include intravaginal betadine (povidone-iodine), clotrimazole, acetic acid, furazolidone, gentian violet, nonoxynol-9, and potassium permanganate. To date, no topical microbicide has shown an effect on trichomoniasis [47].

Partner Management

Infection is readily passed between sex partners during penile-vaginal sex, although partners may be unaware of their infection; a prospective multicenter study found that 72% of male sex partners of women with trichomoniasis were also infected with *T. vaginalis*, and 77% of these men were asymptomatic [48]. Treatment of all sexual partners can prevent recurrences in the index cases, reduce transmission, and prevent new cases in the community.

Several randomized trials have evaluated patient-delivered partner treatment (PDPT) for trichomoniasis. One trial evaluated partner notification strategies among 458 infected women and found that PDPT did not result in more partners taking the medicine nor lower repeat infection rates than standard notification, but PDPT was less costly and subjects were more likely to see their partners take the medication ($P < .001$) [49]. Patient counseling beyond standard of care in this trial may have dampened the effect. A more recent trial found that of 484 women tested, most infected women (80%) randomized to PDPT delivered the medicine, with no reported increase in serious adverse

events; furthermore, compared with partner referral and disease intervention specialist notification groups combined, the PDPT group had a lower repeat infection rate at 1 month (5.8% vs 15% and 5.8% vs 12.5%, respectively) [50]. Also, 2 randomized trials of 463 women diagnosed with trichomoniasis and 977 men diagnosed with urethritis found that self-reported disclosure of *T. vaginalis* infection status to partners was more likely to occur among those randomized to PDPT [51].

Antimicrobial Resistance

In vitro resistance to metronidazole was observed shortly after this medication was first used to treat trichomoniasis, yet correlation with clinical outcomes is unclear, and other factors may play a role. In a study of 175 *T. vaginalis* isolates from women with persistent infections whose clinicians consulted the CDC for susceptibility testing after standard therapy failed at least twice, 115 (66%) demonstrated some level of metronidazole resistance: 56 (32%) were highly resistant, 24 (14%) isolates were moderately resistant, and 35 (20%) isolates were minimally resistant. For all isolates resistant to metronidazole, in vitro resistance to tinidazole was similar or lower [34].

Although antimicrobial-resistant *T. vaginalis* is not systematically assessed or reported at a national level, several studies have evaluated prevalence of metronidazole- or tinidazole-resistant *T. vaginalis*. A study of 178 isolates from STD clinic patients in Alabama found that 17 (9.6%) demonstrated metronidazole resistance and 1 (1.1%) demonstrated resistance to tinidazole [52]. Among adolescents, one study of 78 isolates from HIV-uninfected sexually active teens visiting an inner-city public primary care clinic found that 4 (5%) demonstrated metronidazole resistance and none demonstrated tinidazole resistance [53]. A prospective cohort of specimens from 538 women diagnosed with trichomoniasis at STD clinics in 6 cities found that 4.3% exhibited low-level metronidazole resistance in vitro and no isolates demonstrated tinidazole resistance [54]. Nationally, this prevalence corresponds to an estimated 159 000 people in the United States who might require treatment with an alternative to nitroimidazoles [55].

HIV Infection

The incidence of *T. vaginalis* infection is higher among HIV-infected individuals compared with those who are not HIV-infected [5]. Up to 52.6% of HIV-infected women have been found to be coinfected with *T. vaginalis* [17, 56]. Among HIV-infected women, *T. vaginalis* infection is significantly associated with pelvic inflammatory disease (PID) [57], and treatment of *T. vaginalis* infection is associated with significant decreases in genital tract viral load and vaginal HIV viral shedding [58, 59]. Among HIV-infected men, data are scant. Both HIV acquisition and transmission have been studied in relationship to *T. vaginalis* infection.

Trichomonas vaginalis infection is epidemiologically associated with HIV acquisition. A prospective study of 3297 African HIV-serodiscordant couples found that *T. vaginalis* infection is an independent risk factor for HIV acquisition; *T. vaginalis* infection of the female partner was associated with an increased per-act probability of her acquiring HIV during sex (OR, 2.57 [95% CI, 1.42–4.65]) [60]. Another prospective study of 4948 sexually active women in Zimbabwe and South Africa found that *T. vaginalis*–infected women were more likely to test positive for HIV at the following visit (adjusted HR [aHR], 2.05 [95% CI, 1.05–4.02]), and similarly, HIV-infected women were more likely to test positive for *T. vaginalis* at the following visit (aHR, 2.1 [95% CI, 1.35–3.32]) [61]. Multivariate analysis of data from a nested case-control study conducted among 218 women with incident HIV infection and 419 controls in Uganda and Zimbabwe showed a significant association between receiving a diagnosis of *T. vaginalis* infection and subsequently testing positive for HIV infection at the following visit (adjusted OR [aOR], 2.74 [95% CI, 1.25–6.00]) [62]. In a prospective study of 1335 female sex workers in Kenya, *T. vaginalis* infection increased the risk of HIV acquisition in multivariate analysis (aOR, 1.52 [95% CI, 1.04–2.24]) [63]. A mathematical model based on data from HIV-infected patients in North Carolina predicted that 0.062 HIV transmission events will occur per 100 HIV-infected women in the absence of *T. vaginalis* infection, and 0.076 HIV transmission events will occur if *T. vaginalis* is prevalent in 22% of the HIV-infected women; in the latter scenario, more than one-fifth (23%) of HIV transmission events from HIV-infected women are attributable to *T. vaginalis* infection [64].

Trichomonas vaginalis infection also has been associated with a potential for increased transmission of HIV. In a prospective cohort study of 557 HIV-infected women in South Africa, genital tract viral load decreased significantly 1 month after treatment with 2 g of oral metronidazole [58]. A prospective study of 58 *T. vaginalis*–infected women in Louisiana matched with 92 *T. vaginalis*–uninfected controls showed that *T. vaginalis*–infected women who were effectively treated for *T. vaginalis* infection were less likely to shed HIV vaginally at 3 months posttreatment compared with baseline (RR, 0.34 [95% CI, .12–.92]), while there was no change for *T. vaginalis*–uninfected women [59]. A study of 1187 HIV-infected men in Malawi showed that the rate of HIV positivity was not different across *T. vaginalis* infection status, but men with *T. vaginalis* infection demonstrated increased seminal plasma HIV RNA concentrations ($P = .02$) [65]. In a cross-sectional study of 336 HIV-infected men with genital ulcer disease at primary health clinics in South America, 43 (13%) were infected with *T. vaginalis*; these men had higher ulcer viral loads on average than did those without *T. vaginalis* infection, but the difference was not significant (mean difference, 0.62 [95% CI, .07–1.2]) [66].

Few studies have evaluated the management of trichomoniasis among HIV-infected women; factors that may interfere with standard single-dose treatment for trichomoniasis in these women include high rates of asymptomatic bacterial vaginosis (BV) coinfections, use of antiretroviral therapy, changes in vaginal ecology, and impaired immunity [67, 68]. A 2003 cross-sectional study in South Africa found that among 692 symptomatic women receiving syndromic treatment including a single 2-g dose of metronidazole, microbiologic cure rates for *T. vaginalis* did not vary significantly by HIV status [69]. More recently, however, a randomized trial of 270 HIV-infected women receiving care at public HIV clinics in the southern United States randomized participants to receive metronidazole for either a standard single dose (2 g once) or a week-long regimen (500 mg twice daily for 7 days). Women randomized to the week-long regimen were significantly more likely to be cured of *T. vaginalis* at 6–12 days following medication completion (*T. vaginalis* prevalence of 8.5% in week-long regimen arm vs 16.8% in single-dose arm: RR, 0.50 [95% CI, .25–1.00]; $P = .045$) and at 3 months (11.0% in the week-long regimen arm vs 24.1% in the single-dose arm; RR, 0.46 [95% CI, .21–.98]; $P = .03$); the lack of single-dose treatment efficacy was found only among women with asymptomatic BV, and there was no significant difference in partner treatment between the 2 arms [70]. Further analysis of 244 of these women found that participants reported a high adherence to PDPT (75.4% provided PDPT to all partners and 61.7% reported they were sure all of their partners took the medication). Of the 24 repeat infections 6–12 days following treatment, adherence to medication and no sexual exposure were reported in 21 (87.5%), indicating that failure of the standard treatment was the most common probable cause of recurrent infection [71].

Pregnancy

Several studies have investigated the implications of maternal *T. vaginalis* infection during pregnancy; the most established association is with preterm delivery. A prospective cohort study of 13 816 pregnant women in 5 US cities found that *T. vaginalis* infection at midgestation was significantly associated with low birth weight (aOR, 1.3 [95% CI, 1.1–1.5]), preterm delivery (aOR, 1.3 [95% CI, 1.1–1.4]), and preterm delivery of a low-birth-weight infant (aOR, 1.4 [95% CI, 1.1–1.6]) [72]. A large retrospective study of administrative data from 108 346 pregnant women with Medicaid in South Carolina found that women diagnosed with trichomoniasis in the first 7 months of pregnancy were more likely to deliver very preterm (≤33 weeks) infants (HR, 1.22 [95% CI, 1.02–1.46]), and those diagnosed in the first 8 months of pregnancy were more likely to deliver late preterm (33–36 weeks) infants (HR, 1.59 [95% CI, 1.18–2.14]) [73]. Further study is urgently needed to determine whether treatment of trichomoniasis during pregnancy can reduce such complications.

Other analyses of ecological data from pregnant women in the South Carolina Medicaid population, along with linked administrative data from the South Carolina Department of Education and the Department of Disabilities and Special Needs, found associations between maternal trichomoniasis during pregnancy and having a child who was later diagnosed with intellectual disability (HR, 1.28 [95% CI, 1.12–1.46]) or attention-deficit hyperactivity disorder (OR, 1.29 [95% CI, 1.23–1.35]), although biological mechanisms were unclear [74, 75].

Perinatal transmission of trichomoniasis is believed to be rare, as few cases of trichomoniasis have been reported in premature newborns [76, 77]. However, a study of 479 HIV-infected pregnant women in Zimbabwe reported that vaginal infections including *T. vaginalis* were significant predictors of HIV vertical transmission in multivariate analysis (RR, 1.72 [95% CI, 1.03–2.88]) [78].

Metronidazole crosses the placenta and is classified as pregnancy class B by the FDA; although it is positive in the Ames test in vitro, studies in humans and other animals have shown no evidence of fetotoxicity at any stage of pregnancy. In pregnant rats, studies of doses up to 5 times the human dose revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. In pregnant mice, no fetotoxicity was observed when metronidazole was administered orally at 20 mg/kg/day [79]. A large population-based dataset from the Hungarian Congenital Abnormality Registry assessed use of metronidazole during pregnancy for 17 300 women who had offspring with congenital abnormalities and 30 663 women whose offspring did not, and found no association between metronidazole use and congenital abnormalities [80]. Also reassuringly, a retrospective cohort study of 2829 pregnant women delivering at a major teaching hospital in Syracuse, New York, found no association between metronidazole use during any trimester of pregnancy with any adverse outcomes (preterm birth, low birth weight, or congenital anomalies) [81]. However, adequate and well-controlled studies in pregnant women are lacking.

Various cross-sectional and cohort studies have investigated the effects of metronidazole for pregnant women with trichomoniasis. In the largest study to date, a retrospective study of Medicaid billing data and birth certificate records from 144 737 pregnant women delivering in South Carolina, metronidazole treatment was found to be protective against preterm delivery, both among women with another genitourinary infection at some point during pregnancy (HR, 0.69 [95% CI, .50–.95]) and those without (HR, 0.69 [95% CI, .52–.92]) [82]. A Cochrane review of data from 2 trials involving a combined 842 pregnant women concluded that metronidazole, given as a single dose, is effective against trichomoniasis (both trials showed high rates of parasitological cure, around 90%, following treatment), although effect on pregnancy outcome was not clear [83]. A large randomized trial of 2428 pregnant

women randomized to receive both metronidazole and erythromycin (both 250 mg 3 times a day for 7 days) or placebo found that women randomized to receive antibiotics were more likely to have resolution of trichomoniasis compared with women who received placebo, yet no significant differences were detected in birth weights [84]. A double-blinded placebo-controlled trial involving 2098 HIV-infected and 335 HIV-uninfected pregnant women in Zambia, Malawi, and Tanzania found no significant difference in gestational age of the infants of women randomized to receive antibiotics even after stratification by HIV status [85].

Metronidazole is secreted in breast milk. Although there was no evidence of adverse effects in infants in several case series, some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a 2-g dose of metronidazole [86]. Lower doses produce a lower concentration in breast milk and are considered compatible with breastfeeding over longer periods [87, 88].

Tinidazole is currently classified as pregnancy category C, given reproduction studies in animals suggesting some mutagenic potential. There are few data on tinidazole use by pregnant or breastfeeding women. A study of data from the Hungarian Congenital Abnormality Registry demonstrated no higher rate of congenital abnormalities among children born to mothers who had received oral tinidazole during pregnancy (10/22 843 cases vs 16/38 151 controls; OR, 1.0 [95% CI, .7–1.3]) [89].

Other Associated Conditions

Bacterial Vaginosis

Symptomatic trichomoniasis may occur in the context of a disruption of vaginal flora, on a spectrum with fewer lactobacilli than normal yet more than BV [90, 91]. In a randomized trial of intravaginal metronidazole gel involving 107 women with asymptomatic BV presenting to an STD clinic in Alabama, women in the treatment group had a significantly longer time to STD development overall ($P = .02$); however, this difference was driven by a reduction in chlamydia and there was no significant difference in the incidence of trichomoniasis over 12 months, with 16 new *T. vaginalis* infections in the treatment group and 22 new *T. vaginalis* infections in the observation group [92]. Among HIV-infected women, 1 study has examined the effect of BV on the response to *T. vaginalis* treatment. In a randomized trial of 244 HIV-infected women with *T. vaginalis* coinfection receiving metronidazole for either a standard single dose (2 g once) or a week-long regimen (500 mg twice daily for 7 days), the rate of BV was 66.8%, and BV was associated with early failure of the single-dose treatment for *T. vaginalis* infection, although differences did not persist at 3 months [93].

Nongonococcal Urethritis

Trichomonas vaginalis infection in men is often asymptomatic, but in a study of 355 infected men at a Baltimore STD clinic, 47% reported discharge and 22% reported dysuria [94]. Among men with symptoms of urethritis, the reported prevalence of *T. vaginalis* infection ranges from 3% to 17% in US STD clinics, varying by specimen type and assay sensitivity [95–98]. Although these observations suggest a need for testing and treatment among men for this pathogen, especially in STD clinics, urethritis on Gram stain does not appear to be associated with *T. vaginalis* infection as diagnosed by PCR [98, 99]. In a placebo-controlled trial of 411 men in Malawi, adding metronidazole to an antibiotic regimen for empiric treatment of urethritis did not improve symptom resolution [100]. In addition, a randomized controlled trial of heterosexual men with nongonococcal urethritis (NGU) at STD clinics in 4 cities found that addition of a single 2-g dose of tinidazole to the treatment regimen for NGU (doxycycline or azithromycin) effectively eradicated *T. vaginalis* infections but did not result in higher NGU cure rates [96, 97].

Other Sexually Transmitted Infections

In addition to its association with HIV, *T. vaginalis* infection has been linked with various other STIs, although it can be challenging to sort out the influence of confounding factors such as sexual behavior or changing diagnostic test methods. In a nationally representative sample of women participating in NHANES, 6 other STIs (chlamydia, gonorrhea, herpes simplex virus type 1 [HSV-1], herpes simplex virus type 2 [HSV-2], syphilis, and HIV) were all more common among women with a positive test for *T. vaginalis*. However, after adjusting for race/ethnicity, age, and recent sexual partners, only HSV-1 (RR, 1.20 [95% CI, 1.09–1.34]) and HSV-2 (RR, 1.51 [95% CI, 2.32–3.23]) were significantly associated with *T. vaginalis* infection [101].

Endometritis and Pelvic Inflammatory Disease

It has not been clearly established whether *T. vaginalis* infection causes endometritis or PID. Among 696 women at an STD clinic in South Africa, patients with trichomoniasis had a significantly higher risk of PID than did women without trichomoniasis ($P = .03$). However, after stratification by HIV status, the association between *T. vaginalis* infection and PID was significant only among HIV-infected women (RR, 1.9; $P = .002$) [57]. Furthermore, a study of 736 women with risk factors for PID in Pittsburgh found that women with *T. vaginalis* infection at enrollment were more likely to develop acute endometritis (19/82 [23%]; $P = .001$), but not fallopian tube obstruction [102].

Infertility

Trichomoniasis could plausibly interfere with male and female fertility, although few studies have been conducted to investigate this potential connection. Among men, an in vitro study

showed that *T. vaginalis* parasites can adhere to, immobilize, and phagocytose sperm cells [103]. A Turkish study found that among 80 infertile men, 2.5% had a positive *T. vaginalis* test by PCR, but serology was not available [104]. Among women, a study of 321 women with tubal infertility in Seattle found that the RR of tubal infertility was significantly higher among women who self-reported a history of trichomoniasis (adjusted RR, 1.7 [95% CI, 1.1–2.6]) [105].

Prostate Cancer and Prostatitis

Three studies have evaluated the link between trichomoniasis and prostate cancer. The Health Professionals Follow-up Study, a case-control study of 691 men with prostate cancer, showed that 13% of men with prostate cancer and 9% of controls had serologic evidence of *T. vaginalis* infection (aOR, 1.43 [95% CI, 1.00–2.03]) [106]. The Physician's Health Study, a case-control study of 673 men with prostate cancer, linked *T. vaginalis* seropositivity with increased risks of both extraprostatic prostate cancer (OR, 2.17 [95% CI, 1.08–4.37]), and cancer that would ultimately progress to bony metastases or prostate cancer–specific death (OR, 2.69 [95% CI, 1.37–5.28]) [107]. However, among 616 men in the Prostate Cancer Prevention Trial, the odds of prostate cancer were not significantly higher among men with high seropositivity (OR, 0.97 [95% CI, .70–1.34]), nor significantly lower among men with low seropositivity (OR, 0.83 [95% CI, .63–1.09]). Of note, nearly half (47%) of the men with prostate cancer in this study were diagnosed by study investigators by end-of-study biopsy, before these early-stage lesions could produce any symptoms or abnormal screening tests [108].

One randomized trial of 61 men in Croatia with prostatitis thought to be caused by trichomoniasis reported a higher percentage of both clinical cure (96.7% vs 67.7%; $P = .006$) and *T. vaginalis* eradication (93.3% vs 71.0%; $P = .043$) among men who received a treatment course of 1.5 g oral metronidazole daily for 14 days vs 7 days [109].

Diagnostic Methods

Highly sensitive NAATs are now available for detection of *T. vaginalis*. Among women, such assays may detect a prevalence 3- to 5-fold higher than wet mount [110, 111]. Clinical diagnosis may be less sensitive than molecular tests, with a sensitivity of 84.6% and a specificity of 99.6% compared with molecular testing [112]. The APTIMA Trichomonas vaginalis assay (Hologic Gen-Probe, San Diego, California) was FDA-cleared in 2011 for detection of *T. vaginalis* from endocervical or vaginal swabs or urine from symptomatic or asymptomatic women [113]. This assay detects *T. vaginalis* RNA by transcription-mediated amplification with a clinical sensitivity of 95.2%–100% and specificity of 95.3%–100.0% [113–115]. Among women, vaginal swabs and urine have a high degree of concordance [110]. As analyte-specific reagents, this assay can be used with urethral swabs or urine from men. Sale, distribution, and use of analyte-specific reagents are covered under the Code of Federal Regulations, Title 21, Part 809.30 pertaining to in vitro diagnostic products for human use. In men, the sensitivity of penile-meatal swabs may be higher than that of urine (80.4% and 39.3%, respectively, in a study of 634 men) [116]. The Cobas Amplicor CT/NG PCR assay (Roche, Indianapolis, Indiana) is a commercially available, FDA-cleared assay for detection of chlamydia and gonorrhea infections that can be modified for *T. vaginalis* detection in vaginal or endocervical swabs or urine. The assay may perform with sensitivities from 88% to 97% and specificities from 98% to 99%, depending on the specimen and reference standard [117]. The BD Probe Tec TV Q^x Amplified DNA Assay (Becton Dickinson, Franklin Lakes, New Jersey) was FDA-cleared in late 2013 for detection of *T. vaginalis* from endocervical, vaginal, or urine specimens in women [118]. Self-obtained vaginal samples may be an option [119]. Although it may be feasible to perform a *T. vaginalis* NAAT on the same specimen used for a chlamydia/gonorrhea screening test in a young adult, the epidemiology of *T. vaginalis* infection is distinct and should not be overlooked in older adults.

FDA-cleared same-day rapid tests for trichomoniasis in women that may be performed at the point of care include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, Massachusetts), an antigen-detection test using immunochromatographic capillary flow dipstick technology that is Clinical Laboratory Improvement Amendments (CLIA)–waived, and the Affirm VP III (Becton Dickinson, Sparks, Maryland), a nucleic acid probe-hybridization test that evaluates for *T. vaginalis*, *Gardnerella vaginalis*, and *Candida albicans* in vaginal secretions. The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, with a sensitivity of 82%–95% and specificity of 97%–100% [114, 120]. Self-testing may be an option; a study of 209 young women aged 14–22 years found that >99% could correctly perform and interpret her own self-test using the OSOM assay, with a high correlation with clinician interpretation (96% agreement, $\kappa = 0.87$) [121]. The results of the Affirm VP III are available within 45 minutes, with a sensitivity of 63% and specificity of 99.9%; sensitivity may be higher among women who are symptomatic [115, 122]. Neither the OSOM nor the Affirm VP III test is approved for use with specimens from men.

Before molecular methods became available, culture was considered the gold standard method for diagnosing *T. vaginalis* infection. Culture has a sensitivity of 75%–96% and a specificity of up to 100% [114, 123]. In women, vaginal secretions are the preferred specimen type for culture, as urine culture is less sensitive. In men, culture requires a urethral swab, urine, and/or semen.

The most common method for diagnosing trichomoniasis may be microscopic evaluation of genital secretions ("wet mount"), due to convenience and relatively low cost. Unfortunately, the sensitivity of wet mount for *T. vaginalis* diagnosis is poor (51%–65%) in vaginal specimens [114, 123]. Furthermore, sensitivity declines as evaluation is delayed, decreasing by up to 20% within 1 hour after collection, although storage in saline may prolong specimen viability [124]. In male urine, wet mount is even less sensitive [125]. A molecular test–resolved algorithm, in which patients with an initial negative wet mount then receive a molecular test, had an overall sensitivity of 87.5%–96.6% and a specificity of 97.7%–100% among 296 female subjects [123].

Screening

Data presented earlier suggest that *T. vaginalis* infection is (1) common, (2) frequently asymptomatic, (3) easily communicable to sex partners, and (4) associated with significantly increased risks of HIV acquisition and transmission, pregnancy complications, PID among HIV-infected women, and other conditions. Particularly high prevalences have been observed among incarcerated individuals, HIV-infected individuals, and STD clinic patients. Among asymptomatic women screened for *T. vaginalis* infection by wet mount at STD clinics in 6 areas, the prevalence of infection was 6.5% [14]. Although treatment with nitroimidazoles has been shown to be relatively cheap, safe, simple, accessible, and effective at reducing *T. vaginalis* infections and symptoms of trichomoniasis, evidence is generally lacking that curing *T. vaginalis* infections also reduces the risk of associated conditions. No studies have adequately assessed the cost-effectiveness or the optimal frequency of screening asymptomatic persons for *T. vaginalis* infection. Decisions about screening may be informed by local, regional, or national epidemiology.

Screening and prompt treatment for trichomoniasis are recommended at least annually for all HIV-infected women, based on the high prevalence of *T. vaginalis* infection, the increased risk of PID associated with this infection, and the ability of treatment to reduce genital tract viral load and vaginal HIV shedding. This includes HIV-infected women who are pregnant, as *T. vaginalis* infection is a risk factor for vertical transmission of HIV [78]. For other pregnant women, screening may be considered at the discretion of the treating clinician, as the benefit of routine screening for pregnant women has not been established.

Among previously treated individuals, several studies have examined the timing of rescreening or test of cure for *T. vaginalis* infection. A study of 268 adolescent women in Indiana found that 85% of infections were undetectable by PCR within 2 weeks following treatment [126]. A follow-up study of 42 infected women found that the mean time to first negative PCR result was 1.4 ± 0.1 weeks [127]. A study of 1236 reproductive-age women periodically tested for *T. vaginalis* infection by culture and treated with standard therapy at STD clinics found that 119 (10%) were positive at baseline, 16.5% were positive at 3 months, 18.5% were positive at 6 months, 12.5% were positive at 9 months, and 6.9% were positive at 12 months. Among the women who were infected at baseline, 16.5% had another positive *T. vaginalis* culture during the study, indicating potential treatment failure vs reinfection from an untreated sex partner [128]. Further analysis of these data indicated that of the 21 new infections, 13 occurred in women who had been treated previously for *T. vaginalis* infections, and 11 of these 13 (85%) had an intervening negative test result before having another positive result when no sexual exposure was reported [129]. Probable persistent, undetected *T. vaginalis* infections have also been observed among HIV-infected women retested 3 and 6 months after initial evaluation [130].

Reporting and Costs

Neither trichomoniasis nor *T. vaginalis* infection is a nationally notifiable condition, and no US states require reporting of these conditions. Indices of public health importance warranting surveillance may include frequency, severity of illness, disparities, costs, preventability of serious adverse events, communicability, and public interest; according to a recent CDC editorial, *T. vaginalis* infection clearly meets only 3 of these 7 criteria (frequency, disparities, and communicability), with insufficient available data or arguable conclusions regarding other criteria [131]. Due to a paucity of public interest, trichomoniasis has been called a "neglected" STD [55, 132].

Assuming no sequelae of any *T. vaginalis* infection, and assuming that many asymptomatic cases are never detected, the estimated direct medical costs per year of treating incident cases of trichomoniasis in the United States total $24 million annually [133]. However, a mathematical model estimated that, annually, 746 new HIV cases occurring among US women are attributable to *T. vaginalis* infection; the lifetime medical costs of these 746 infections are estimated to be $167 million [134].

Prevention

Trichomoniasis is an STD that can be avoided by abstaining from sex. Among sexually active individuals, the most effective way to prevent trichomoniasis is by using condoms consistently and correctly during vaginal-penile sexual encounters [135]. Periodic presumptive treatment for high-risk individuals such as sex workers can effectively reduce trichomoniasis [136, 137]. Male circumcision might reduce the risk of infection in both circumcised men (aOR, 0.41; $P = .030$) [138] and their female sex partners (adjusted RR, 0.52 [95% CI, .05–.98]) [139]. It remains to be seen whether treatment and prevention of trichomoniasis

and *T. vaginalis* infections can also prevent associated conditions such as HIV infections and complications of pregnancy. Data are lacking on effective intervention strategies to reduce associated health disparities.

CONCLUSIONS

Trichomonas vaginalis infection is highly prevalent, often asymptomatic, and easily communicable between sex partners. Infection is associated with significantly increased risks of HIV acquisition and transmission, pregnancy complications including preterm delivery, PID among HIV-infected women, and other conditions. Highly sensitive NAATs and point-of-care tests can be conducted on a variety of specimens and may expand available diagnostic methods beyond traditional wet mount and culture. Usually, trichomoniasis can be cured with single-dose therapy of an appropriate nitroimidazole antibiotic (eg, metronidazole or tinidazole), but women who are also infected with HIV should receive therapy for 7 days. Antimicrobial resistance is an emerging concern. Screening should be provided at least annually to all HIV-infected women; decisions about screening others may be informed by local, regional, or national epidemiology at the discretion of the clinician. Condoms may prevent infections, but all sex partners must be treated to reduce reinfections. Further study is needed to identify effective intervention strategies to reduce associated racial/ethnic and age-related health disparities.

Notes

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