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Epidemiology and Treatment of Trichomoniasis

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Abstract

Trichomonas vaginalis is the most common nonviral sexually transmitted infection (STI) in the world. It was once thought to be a nuisance STI, but it is now being recognized as an important source of reproductive morbidity and a facilitator of HIV transmission and acquisition, and thus it is an important public health problem. The prevalence of *T. vaginalis* varies greatly by geography and risk group, but is more common among persons of African descent and appears to increase with age, though this may be a screening phenomenon. Wet mount and culture are simple diagnostics, but have lower sensitivity than nucleic acid amplification techniques presently approved for women only. Single dose (2 g) metronidazole (MTZ) for both the index patient and their sexual partners is the preferred treatment. High rates of retest positivity are found after single-dose treatment which are likely due to clinical resistance rather than re-infection and/or drug resistance.

Keywords

Trichomonas vaginalis; Trichomoniasis; Epidemiology; Treatment

Introduction

Trichomoniasis is a sexually transmitted infection (STI) caused by the parasite *Trichomonas vaginalis* (*T. vaginalis*) which was first discovered in 1836. It was once thought to be a nuisance STI, but it is now being recognized as an important source of reproductive morbidity and a facilitator of both HIV transmission and acquisition. It is, therefore, an important public health problem. While it is not globally a reportable disease, *T. vaginalis* is likely the most common nonviral sexually transmitted infection (STI) in the world. While single-dose metronidazole (MTZ) remains the treatment of choice, many persons retest positive after treatment.

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Compliance with Ethics Guidelines

Conflict of Interest Patricia Kissinger has no disclosures to report.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

Pathogenesis

T. vaginalis is a flagellated parasitic protozoan, typically pyriform but occasionally amoeboid in shape, extracellular to genitourinary track epithelium with a primarily anaerobic lifestyle [1]. The individual organism is 10–20 µm long and 2–14 µm wide. Four flagella project from the anterior portion of the cell and one flagellum extends backwards to the middle of the organism, forming an undulating membrane. An axostyle extends from the posterior aspect of the organism. *T. vaginalis* has a large genome (strain G3, 176,441,227 bp) with ~60,000 protein coding genes organized into six chromosomes [2]. *T. vaginalis* is a highly predatory obligate parasite that phagocytoses bacteria, vaginal epithelial cells, and erythrocytes and is itself ingested by macrophages. *T. vaginalis* uses carbohydrates as its main energy source via fermentative metabolism under aerobic and anaerobic conditions.

T. vaginalis primarily infects the squamous epithelium of the genital tract. Incubation time is generally between 4 and 28 days [3]. *T. vaginalis* resides in the female lower genital tract and the male urethra and prostate, where it replicates by binary fission. *T. vaginalis* is transmitted among humans, its only known host, primarily by sexual intercourse. Infection may persist for long periods, possibly months or even years, in women but generally persists less than 10 days in males [4]. The parasite does not appear to have a cyst form and does not survive well in the external environment, but can survive outside the human body in a wet environment for more than 3 h [5]. While thought to be rare [3], evidence of nonsexual transmission via fomites and possibly water has been described [6–8]. *T. vaginalis* can be infected with double-stranded RNA (dsRNA) viruses that may have important implications for trichomonal virulence and disease pathogenesis.

Clinical Features

The majority of women (85 %) [9] and men (77 %) [10] with *T. vaginalis* are asymptomatic. One third of asymptomatic women become symptomatic within 6 months [3]. Symptomatic men usually have urethral discharge and dysuria. Among women, common sites of infection include the vagina, urethra, and endocervix. Symptoms among women include vaginal discharge (which is often diffuse, malodorous, and yellow-green), dysuria, itching, vulvar irritation, and abdominal pain. The normal vaginal pH is 4.5, but with *T. vaginalis* infection, this increases markedly, often to >5 [3]. *Colpitis macularis* or strawberry cervix is seen in about 5 % of women, though with colposcopy, this rises to nearly 50 % [11]. Other complications include infection of the adnexa, endometrium, and Skene's and Bartholin's glands. In men, it can cause epididymitis, prostatitis, and decreased sperm cell motility [12].

Sequelae of *T. vaginalis*

Reproductive Outcomes

Studies show an association between *T. vaginalis* and vaginitis, cervicitis, urethritis, bacterial vaginosis, candidiasis, herpes simplex virus type-1 and type-2, chlamydia, gonorrhea, and syphilis [13]. *T. vaginalis* has also been associated with poor birth outcomes such as low birth weight, preterm delivery, pelvic inflammatory disease, and premature rupture of membranes [14]. One study showed an association between maternal *T. vaginalis* infection and intellectual disability in children [15]. Although rare, *T. vaginalis* infection can

be transmitted perinatally [16] and cause vaginal and respiratory infections in neonates [17, 18].

HIV Acquisition and Transmission

One of the most compelling reasons to study and control *T. vaginalis* is that it may amplify the risk of HIV acquisition and acquisition [19•]. This greater susceptibility is biologically plausible for three reasons: (1) the inflammatory response to *T. vaginalis* infection results in the appearance of HIV target cells [20]; (2) *T. vaginalis* infection can cause punctate mucosal hemorrhages resulting in a compromised mechanical barrier to HIV [21]; and (3) *T. vaginalis* infection may change the normal vaginal microbiota and therefore increase susceptibility to bacterial vaginosis [22], which would increase the risk of HIV acquisition [23]. These consequences combine to enlarge the portal of entry for HIV in *T. vaginalis*-infected women. A study by Sorvillo et al. estimates that in a community with a *T. vaginalis* prevalence of 25 %, as much as 20 % of HIV could be attributed to *T. vaginalis* infection [24]. Chesson et al. estimated that 6.2 % of all HIV infections among US women may be attributable to *T. vaginalis* infection [25]. Control of *T. vaginalis*, therefore, may provide a cost-effective strategy for reducing HIV transmission especially in settings where *T. vaginalis* is common [26, 27] or among subgroups who are at higher risk for *T. vaginalis* such as African-Americans [28]. In the absence of a national screening program to detect primary infections, reducing repeat *T. vaginalis* infections can be a targeted approach for reducing *T. vaginalis* transmission and *T. vaginalis*-related morbidity. Fortunately, treatment for *T. vaginalis* has demonstrated reductions in HIV genital shedding in several studies. HIV + men with urethritis in Malawi, with *T. vaginalis* diagnosed by nucleic acid amplification techniques (NAAT), experienced a decrease in seminal HIV after MTZ treatment [29]. HIV vaginal shedding was decreased after treatment in one cohort of women, diagnosed by microscopy and culture in Kenya [30], and another, diagnosed by culture, in LA, USA [31]. These data underscore the potential benefit of screening and treatment among HIV-positive persons.

HSV-2

T. vaginalis appears to have a similar bi-directional association with herpes simplex virus II (HSV-2) as it does with HIV-1. Concomitant infection with *T. vaginalis* and previous episodes of genital herpes are associated with HSV-2 shedding. *T. vaginalis* was detected in 4.2 % of women shedding HSV-2 in genital fluids versus 1.7 % of women without detectable HSV-2 ($P=0.001$) [32]. Among women attending STD clinics in the USA in a longitudinal study, *T. vaginalis* infection was associated with a 3.7 increased incidence of HSV-2 [33]. *T. vaginalis* was also associated with a greater likelihood of HSV-2 shedding among women attending colposcopy clinics in Italy [32].

Neoplasia

Evidence that *T. vaginalis* is associated with cervical neoplasia is mounting. A meta-analysis found that *T. vaginalis* was associated with a 1.9-fold risk of cervical neoplasia [34]. A study of Finnish women in a cervical cancer mass screening registry found that women with *T. vaginalis* had elevated risk for HPV [35]. Dutch women undergoing testing for cervical

neoplasia had *T. vaginalis* detected in 3.2 % of smears with cytology indications and women with *T. vaginalis* were two times more likely to have high-grade squamous intraepithelial lesions (HSIL) [36]. Among women in Belgium undergoing cervical cancer screening, those with *T. vaginalis* diagnosed by NAAT were 1.9 times more likely to have HPV [37]. In a population-based sample of women in China (Beijing), women with *T. vaginalis* were 1.4 times more likely to have HPV and 1.7 times more likely to have cervical invasive neoplasia (CIN) I or II [38].

Evidence that *T. vaginalis* influences prostate cancer among men is inconclusive. Yap et al. found an independent association between *T. vaginalis* and cervical cancer [39]. Sutcliffe et al. found an association between *T. vaginalis* and prostate cancer in one study [40] but not in a subsequent study [41].

Diagnosis

The criteria for treatment differ by gender since not all Federal Drug Administration (FDA)-approved tests for women have been tested with men. Traditional wet mount is cheap, fast, and widely available; however, it is insensitive (i.e., 58 %) [42]. While culture has better sensitivity than wet mount, in women, it is more expensive and time-consuming, and demonstrates poor sensitivity in men. Two studies, one of HIV– and one of HIV+ women found that after diagnosis by culture and treatment with 2 g MTZ, *T. vaginalis* infection was non-detectable for months and then reappeared in the absence of reported sexual exposure [43, 44], underscoring the need for more sensitive testing than culture.

Nucleic acid probe techniques are moderately priced and fast, but require instrumentation. An FDA-cleared PCR assay for detection of gonorrhea and chlamydial infection (Amplicor, manufactured by Roche Diagnostic Corp.) has been modified for *T. vaginalis* detection in vaginal or endocervical swabs and in urine from women and men with sensitivity ranging from 88 to 97 % and specificity from 98 to 99 % using wet mount or two positive DNA tests as the gold standard [45]. APTIMA *T. vaginalis* Analyte Specific Reagents (ASR; manufactured by Gen-Probe, Inc.) also can detect *T. vaginalis* RNA by transcription-mediated amplification using the same instrumentation platforms available for the FDA-cleared APTIMA Combo2 assay for diagnosis of gonorrhea and chlamydial infection; published validation studies of *T. vaginalis* ASR found sensitivity ranging from 74 to 98 % and specificity of 87–98 % [46]. There are two point-of-care tests that have been approved by the US FDA for diagnosis of *T. vaginalis* among women: OSOM Trichomonas Rapid Test (Genzyme Diagnostics; Cambridge, MA), an immunochromatographic capillary flow dipstick technology [47] and Affirm VP III (Becton, Dickinson & Co.; Franklin Lakes, NJ), a nucleic acid probe test that evaluates for *T. vaginalis*, *Gardnerella vaginalis*, and *Candida albicans* [48]. Both tests are performed on vaginal secretions and have a sensitivity of more than 83 % and a specificity of more than 97 %. Results of the OSOM test are available in about 10 min, while results of the Affirm VP III test are available within 45 min.

It has been generally thought that only vaginal specimens should be collected for *T. vaginalis* testing. There is, however, some evidence that endocervical specimens are suitable. Endocervical specimens have been found to be 88 % sensitive and 99 % specific for *T.*

vaginalis by PCR compared to 90 and 99 % for vaginal swab [45]. Huppert showed that endocervical specimens were 100 % sensitive and 98 % specific by TMA compared to 100 % sensitivity and specificity for vaginal specimen using latent class analysis [49].

Detection of Repeat *T. vaginalis* Infection

PCR testing too soon after treatment can result in detection of remnant trichomonad DNA, thus producing false positives. By 2–3 weeks post treatment, however, most remnant DNA has cleared [50].

Epidemiology

T. vaginalis is likely the most common nonviral sexually transmitted infection (STI) in the world. While not a reportable disease, the World Health Organization estimated that there were 248 million cases in 2005 and nearly 90 % of these infections occurred among people living in resource-limited settings [51]. Compared to a global prevalence of 101 million cases of *Chlamydia trachomatis*, 88 million cases of *Neisseria gonorrhoeae*, and 11 million of syphilis, *T. vaginalis* constitutes over half of the curable STIs worldwide. These estimates are in need of updating using more sensitive nucleic acid amplification techniques (NAAT) with prevalence rates from more population-based studies as inputs.

With no surveillance programs in place, and the widespread use of wet mount as a diagnostic tool, the epidemiology of *T. vaginalis* is not completely known. It is known, however, to vary greatly by population and geography. Among high-risk women, rates range from 5 % among female sex workers (FSW) in Pakistan [52], to 53 % among incarcerated women in the USA (IN) [53]. Among high-risk men, rates range from 2 % among jail inmates in the USA (CA) [54] to 73 % among male partners of women with *T. vaginalis* (Southeast USA) [55]. A systematic review of STIs in Papua New Guinea found the pooled prevalence of *T. vaginalis* to be 39.3 % using various diagnostic tests [56]. Sentinel surveillance in five Central American cities found a prevalence of 11.0 % among FSW [57]. In a survey of STD clinics in the USA, the rate was 26.2 % among symptomatic, 6.5 % among asymptomatic, and 29 % in HIV+ women [58].

In the USA, two population-based studies that used PCR testing found rates of 2.3 % among adolescents [59] to 3.1 % among women 14–49 [9]. Population-based studies in Africa show distinctly higher rates. In Zimbabwe, the rate was 9.5 % among both genders using antibody testing [60], and among men in Tanzania, the rate was 11 % among men using NAAT [61]. Other population-based studies that used NAAT testing among reproductive-aged women in other parts of the world found lower rates (i.e., 1 % in Vietnam [62] and 0.37 % in Flanders, Belgium [37], 2.9 % in Shandong Province in China) [63]. Screening rates among women attending antenatal or family planning clinics are often used as an indicator of the prevalence in the general population. Studies at these sites found prevalence rates from 3.2 to 52 % in resource-limited settings and 7.6–12.6 % in the USA [64]. Thus, rates of *T. vaginalis* vary greatly and are dependent on the risk factor profile of the population.

In general, Africans or persons of African descent have higher rates of *T. vaginalis*, as evidenced by higher rates in Sub-Saharan Africa [60, 61], and among persons of African

descent such as Garifunas [65] and African-Americans in the USA [9, 59]. In the USA, the highest prevalence of *T. vaginalis* infection in US women is seen among African-Americans with rates ranging from 13 to 51 % [66]. African-American women have rates that are ten times higher than White women, constituting a remarkable health disparity [9].

Other risk factors for *T. vaginalis* include increased age, concomitant STIs, incarceration, intravenous drug use and commercial sex work [54], the presence of bacterial vaginosis [67], and smoking cigarettes [68].

In the USA, there are approximately seven million new cases of *T. vaginalis* each year and prevalence rates range from 3 % in a nationally representative sample of women [9], to 14 % in adolescents [69], 13–36 % in pregnant women [70, 71], 11–26 % in women attending STD clinics [72–75], 27 % among an urban, inner-city population [76], 38 % among drug users [77], and up to 47 % in newly incarcerated pregnant women [78]. Despite the high rate of TV in both the general and selected subpopulations, there is no screening program in the USA for TV. And since over 80 % of cases can be asymptomatic [13], most TV infections likely go undetected.

Management and Treatment

Criteria for Treatment

T. vaginalis infection is treated with metronidazole (MTZ) as the treatment of choice [79]. MTZ belongs to the 5-nitroimidazole drug family, and it and related compounds such as tinidazole (TNZ) and secnidazole are reported to have about a 95 % success rate in curing *T. vaginalis* [80]. MTZ is a class B drug, and several meta-analyses have found it to be safe in pregnant women in all stages of pregnancy [81, 82]. TNZ has not been evaluated in pregnant women and remains a class C drug. In lactating women who are administered MTZ, withholding breastfeeding during treatment and for 12–24 h after the last dose will reduce the exposure of the infant to metronidazole. For women treated with TNZ, interruption of breastfeeding is recommended during treatment and for 3 days after the last dose.

Single Versus Multidose MTZ

There have only been a few randomized trials with good follow-up that have compared single-dose MTZ to multidose. In these trials, cure rates for single versus multidose MTZ have been shown to be similar (82–88 versus 92–94 %) [83, 84]. Both studies found that the single dose had higher rates of side effects (notably nausea and vomiting).

Tinidazole Versus Metronidazole

Tinidazole (TNZ)–MTZ and TNZ are from the same class of drugs (i.e., nitroimidazoles) and single-dose therapy with either is considered first line therapy by Centers for Disease Control and Prevention (CDC). A meta-analysis of treatment for *T. vaginalis* found that MTZ had significantly higher rates of treatment failure, clinical failure, and side effects compared to TNZ, though the only blinded study included in this analysis did not show any advantages for TNZ. This drug has not shown superiority over MTZ for the treatment of

bacterial vaginosis [85]. Generic TNZ is three times more costly than MTZ. Thus, worldwide practitioners will likely continue to use MTZ for *T. vaginalis* infections.

The Centers for Disease Control and Prevention (CDC) guidelines for treatment of *T. vaginalis* include MTZ or TNZ 2 g single dose as the recommended regimens, and MTZ 500 mg BID 7-day dose as the alternative treatment regimen [86•]. Treatment with 2 g MTZ is recommended by CDC at any time during pregnancy [86•]. Abstinence from alcohol use should continue for 24 h after completion of MTZ or 72 h after completion of TNZ. If a patient fails single-dose MTZ therapy, he or she can be given single-dose TNZ or 7-day dosing of MTZ. If this fails, 2 g MTZ or TNZ daily for 5 days can be administered. If this fails and there is no history of sexual re-exposure, a consultation for medication resistance testing should be done. Consultation and *T. vaginalis* susceptibility testing is available from CDC (telephone: 404-718-4141; website: <http://www.cdc.gov/std>).

HIV-Infected Women

An RCT among HIV-infected women with *T. vaginalis* found multidose MTZ to be superior to single-dose treatment [87]. Further analysis revealed that the superiority is only in the presence of bacterial vaginosis (BV) [88]. Studies have also found that antiretroviral therapy may interfere with the efficacy of MTZ among HIV-infected women [89, 90].

Repeated Infections

Repeat infections are common, ranging from 5 to 31 % [69, 91–93, 94•], and share similar sequelae to primary infections. While it is clear that the *T. vaginalis* repeat infection rate is unacceptably high, the source of these repeat infections is less clear. Possible sources are drug resistance, host resistance, or sexual exposure (either by an untreated original partner or a newly acquired sex partner). One study that examined the origins of repeat infection found treatment failure to be the most common cause [91]. Potential causes of early repeat *T. vaginalis* infections include drug resistance, nonadherence to treatment, host factors, or re-infection from an untreated partner. Single-dose therapy has removed adherence as an issue and in vitro resistance testing has consistently demonstrated low rates of non-susceptibility. Reported rates of MTZ resistance among mostly non-HIV-infected women range from 2.2 to 9.6 % [69, 95–97] and were usually resolved with repeat MTZ treatment at the same or higher dosage [97]. The most likely sources of repeat infections, therefore, are clinical treatment failure or re-infection from an untreated partner.

In one study of HIV+ and HIV– women, a large proportion of the repeat infections were attributed to treatment failure (i.e., no sexual exposure and no drug resistance) [91]. Therefore, resistance appears to play only a minor role in explaining probable treatment failure. In *T. vaginalis*-infected women who were given single-dose MTZ and provided with medication to deliver to their sex partner(s), repeat infections rates were high (8 %) and nearly all (92 %) were attributed to clinical treatment failure [91]. The molecular mechanism(s) of failure to eradicate the primary infection are poorly understood.

Repeat *T. vaginalis* infections among HIV+ women are substantially higher with rates between 18.3 and 36.9 % [91, 98, 99], and since these studies used culture, the true rate may be even higher. One study of HIV+ and HIV– women found that repeat infections with *T.*

vaginalis among HIV-negative women was 8 %, but among HIV+ women it as 18.3 %. While the differences in cure rates between HIV+ and HIV– women is not completely understood, there is some indication that bacterial vaginosis may play a factor [44].

Partner Treatment of *T. vaginalis*

Sex partners of patients with *T. vaginalis* should be treated. Commonly, patients are told by their providers to tell their partners to seek testing and treatment. Providers may consider treating partners of positive patients presumptively. A third option is called expedited partner therapy (EPT). EPT is the clinical practice of treating the sex partners of patients diagnosed with an STI by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner. EPT was developed because traditional approaches to partner treatment for common treatable STIs (i.e., partner notification by a provider or partner referral) have not worked well. The rationale for EPT is that most repeat infections are caused by untreated original partner(s) and that most partners will not come to clinic in a timely manner for treatment, so expediting the treatment via the index person will reduce the likelihood of reinfection to the index person.

One RCT demonstrated that partner treatment resulted in a >4-fold reduction in repeat infections among *T. vaginalis*+ index women [100]. The efficacy of patient delivered partner treatment (PDPT), a form of EPT, for reducing repeat *T. vaginalis* infections among women was examined in two separate RCTs. In a study in New Orleans [92] among women attending a family-planning clinic ($n=463$), PDPT was not found to be superior to partner referral for reducing repeat *T. vaginalis* infections at 1-month test-of-cure visit. The study did find PDPT to be more cost-effective than PR. A few years later, Schwebke et al. [101] conducted a similar study among women attending a public health clinic in Birmingham ($n=484$) and found infection rates among women receiving PDPT to be lower than those in the PR arm, though the *P* value was borderline. Both studies suffered from low power as they both had a third arm making sample size requirements very high. The New Orleans study had a booklet referral arm, and the Birmingham study had a disease intervention specialist arm. Also, in New Orleans, participants in both arms of the study received greater than standard of care counseling. This may have accounted for high rate of partner treatment in PR compared to PDPT (70.4 versus 76.5 %) compared to Birmingham (25.1 versus 79.9 %).

Altered Microbiota, Bacterial Vaginosis, and *T. vaginalis*

One possible factor in the treatment failure of *T. vaginalis* is vaginal microbiota disturbances. Bacterial vaginosis (BV) is a common vaginal condition in women of childbearing age. The prevalence of BV in the USA ranges from 29 % in a nationally representative sample (where the prevalence was 3.1 times greater for African-American women compared to Whites), 44 % in a group of women at high-risk for HIV [102], and as high as 56 % among injection drug users [103]. Like *T. vaginalis*, BV can also increase a woman's susceptibility to HIV infection [23, 104, 105]. Several studies have shown a strong association between *T. vaginalis* and BV [71, 106–108], meaning that the two frequently occur as co-infections among women. While these two vaginal infections have similar symptomatology and are treated with similar medication, the dosing is not the same.

In a screening study of HIV-positive women, the prevalence of *T. vaginalis* was higher among women who had altered vaginal bacteria and the majority (61.0 %) of HIV+/ *T. vaginalis*+ women also had BV [109]. This high rate of BV that accompanies *T. vaginalis* infection among HIV+ women has implications for treatment decisions since multidose MTZ is recommended for BV. Martin et al. found that *T. vaginalis* prevalence was highest in the women with intermediate Nugent scores confirming the observations of Hillier et al. [110] and Gatski [109]. A heat map analysis of pyrosequencing data showed that the vaginal microbiota of 18/30 *T. vaginalis*+ women had a similar unique profile characterized by high abundance of *Mycoplasma* spp. or *Ureaplasma* spp. and relatively low abundance of *Lactobacillus* spp. and *Gardnerella* spp. [111], suggesting that *T. vaginalis* directly influences or is influenced by the microbial environment and confirming the potential importance of interactions between *T. vaginalis* and vaginal microbiota.

Conclusion

T. vaginalis is now gaining greater recognition as an important source of reproductive morbidity and, possibly more urgently because of the potential for it to amplify the acquisition and transmission of HIV and possibly HSV-2. While it is not a reportable disease and screening programs generally do not exist, it has been estimated to be the most common nonviral STI globally. Scientists are focusing on better diagnostic and treatment for both index persons and their partners. More focus is also being placed on diagnosis and treatment of *T. vaginalis* among men. Cost studies are needed to determine the benefit of screening women for *T. vaginalis*.

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