

## Review article

# Past, present and future of *Trichomonas vaginalis*: a review study

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**ABSTRACT.** *Trichomonas vaginalis* (TV) is the most common non-viral sexually transmitted infection (STI) microaerophilic protist parasite, which is the causative agent of trichomonosis. Globally, the estimated annual incidence is more than 270 million cases. It is correlated for several health problems including pelvic inflammatory disease (PID), pregnancy miscarriages, cervical carcinoma, prostatitis, prostatic adenocarcinomas, infertility, and the acquisition of human immunodeficiency virus (HIV). Most individuals infected with TV are asymptomatic. Metronidazole (MTZ) has been the treatment of choice for women. Currently, there is no effective vaccine against this pathogen despite efforts at vaccine development. Different socio-economic, demographic, behavioral, and biological factors are associated with the disease. Apart from its role as a pathogenic agent of diseases, it is also a fascinating organism with a surprisingly large genome for a parasite, *i.e.* larger than 160 Mb, and physiology adapted to its microaerophilic lifestyle. Particularly, the hydrogenosome, a mitochondria-derived organelle that releases hydrogen, attracted much interest in the last decades and rendered TV a model organism for eukaryotic evolution. According to the high prevalence and health consequences associated with TV, there is a requirement for improved screening programs in Iraq. The early diagnosis of asymptomatic diseases and effective treatment regimens are mandatory. Despite being highly prevalent of trichomonosis in the world, there is no review research published that solely focuses on *T. vaginalis* infections in Iraq.

**Keywords:** *Trichomonas vaginalis*, trichomonosis, sexually transmitted infection, metronidazole, parasitology

## Introduction

Globally, *Trichomonas vaginalis* (TV) is the most frequent, non-viral sexually transmitted infection (STI), which colonizes the epithelium layer of the human urogenital tract system including the cervix, vagina, prostate, and urethra [1]. Different symptoms and signs of TV, including vaginal discharge (VD) plus dysuria in females, and urethral discharge (UD) plus dysuria in males [2–4]. Asymptomatic disease, however, is present in many patients [3]. Dis-management or chronic TV lead to infertility and adverse pregnancy outcomes [5–7]. In a male, TV is cause non-gonococcal urethritis (NGU), prostatitis, and epididymitis [4]. Also, it has been linked to a rising risk of HIV, and carcinoma of the cervix in women or prostate in men [8].

In 2008, the World Health Organization (WHO) concluded that trichomonosis is the most common non-viral sexually transmitted disease (STD)

worldwide, infecting more than 276 million annually. Both genders are infected with different frequencies, but in males, symptoms are mild, whereas in females the infection is considered a major health problem [9]. Chronic TV in women persists for many years, and the manifestations are pruritus, itching, and odorous VD. In addition, it is cause abortions and contagion with HIV infection [10]. Factually, the connection between TV and HIV is an alarming epidemic issue in many countries [10]. Most infected patients can be successfully cured with metronidazole or tinidazole [11]. Recently, the discovery of the hydrogenosome (a mitochondrion-like organelle that generates hydrogen) of TV led to an increment of interest from geneticists, biochemists, and evolutionary biologists in this parasite [12]. Ethnicity, (*i.e.* African Americans more than about ten times higher than white women to be infected), increased age, incarceration, abuse of intravenous drugs,

commercial sex work, and bacteria vaginosis infection are the risk factors [13–16]. In total, TV is more frequent than *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and syphilis combined. Generally, TV prevalence has been estimated at more than 10% for females and more than 1% for males by classical microscopy examination [17].

This research review aims to determine an update on recent advances in TV epidemiology, pathogenesis, biology, diagnosis, and management.

## Epidemiology

In 2016, the WHO recorded more than 156 million individuals of TV globally [1]. The prevalence of TV was noted to be high among African American women and men than the white race, (6.8% vs. 0.4%) [18]. This sounded racial disparity is likely multifactorial, including differences in sexual networks, individual-level sexual risk behaviors, larger numbers of sexual partners, and structural disparities or inadequate entrance to healthcare resources [19–21].

Recently, National Health and Nutrition Examination Survey (NHANES) study, TV was documented to be significantly related to older age, lower educational level, lower socioeconomic status, and having more than one sexual partner [18]. Compared to other developed countries such as the UK, Germany, and Italy, TV prevalence in the US is higher, due to the lack of public health consideration [22].

The HIV-infected women are the only population for whom routine TV screening is currently done [23]. Recently, many studies reported high TV prevalence ranging between 17.4% to 20% [24–27] and frequent infection rates are up to 22.7% over a median of two years among HIV-infected women [24]. The same to non-HIV-infected men, TV is less common in HIV-infected men [25].

Globally, TV prevalence in pregnancy varies according to geographic distribution. Seventy-five systematic review studies of STI prevalence in pregnancy reported that TV prevalence ranged from 3.9% to 24.6% in developing countries [28]. In African countries, recent studies figured 20% HIV infected pregnant females have TV infection [27,29].

Furthermore, the prevalence rates of TV differ very strongly in different regions of the world [28]. In the Americas, TV incidence is measured to be as

high as 180/1000 men and women, whereas in South-East and Asia's areas estimated are much lower, with 40 to 50/1000 men and women [30].

Importantly, the main concern among TV infection, moreover, is their predisposing abilities to a predisposition for other diseases or sequelae [10], as it is associated with human papillomavirus infections and cervical hyperplasia and carcinomas [31]. Seriously, TV has evidence for a predisposition for HIV about 2- to 3-fold in carriers [32].

## Epidemiology of TV in Iraq

Nationally, in Iraq, trichomonosis was one of the neglected diseases. In Basrah city, in Southern Iraq, Al-Assadi et al. reported that infection rate (IR) was 5.7–8.5% [33,34]. In addition, the IR in Baghdad was very high and reached to 85.50% [35], and higher than of earlier studies in different provinces of Iraq such as Al-Mosul, 25.86% [36], Baghdad, 22.60% [37], Basrah, 57.85% [38], Diyala, 24.60% [39], Baghdad, 19.10% [40], Al-Najaf, 27.9% [41], Al-Muthana, 26.00% [42].

In Misan, Iraq, Al-Majidii and Al-Saady [33], documented a high IR of TV in major cities of the province. They showed a high overall IR of TV among females of 75.22%, and the highest IR (96.15%) is recorded in Al-Kahla district, and the lowest (60.00%) is in Al-Maymouna district, with a strong significant differences between the IRs of trichomonosis ( $P=0.007$ ). The high IR may be contributed to the low personal hygiene, low level of education, decrement of socio-economic status, or due to asymptomatic infection, or lack of medical staff in the primary health care center, or as a result of faulty management [34].

## Pathogenesis

TV is an anaerobic parasitic flagellated protozoan, with a pyriform to amoeboid shape. It is extracellular to the epithelium of the genitourinary tract [43]. There are 4 flagella projects from the forward part of the organism and extend one flagellum posteriorly to the middle of the cell to form the undulating membrane. The cell is 10–20  $\mu\text{m}$  in length and 2–14  $\mu\text{m}$  in width. The genome of TV is large (strain G3, 176,441,227 bp) with ~60,000 protein-coding genes arranged into 6 chromosomes [44]. It is a highly obligate hijacked parasite that can phagocytose bacteria, epithelial cells of the vagina, and erythrocytes, and they are

Table 1. Summarized of molecular developments in the diagnosis and typing of TV

Name of test	Target	Mode	Sensitivity	Specificity	Timing	Specimens	Individual	References
Aptima® T. vaginalis Assay (Hologic, Bedford, MA)	rRNA	Transcription-mediated amplification (TMA)	88–100%	98–100%	8 hr	Vaginal and endocervical swab specimens, urine specimens, and ThinPrep PreservCyt specimens	Infected women only	[77,80]
BD ProTect T. vaginalis Qx (TVQ) amplified DNA Assay (BD Diagnostics, Baltimore, MD)	–	–	–	–	8 hr	Female urine, endocervical swab specimens, and patient or clinician obtained vaginal specimens	Women	[81]
Xpert® TV Assay (Cepheid, Sunnyvale, CA)	–	–	99.5–100% for female genital specimens and 97.2–99.9% for male urine specimens	99.4–99.9% for female genital	60–90 min	Female urine, endocervical swab, and patient- and clinician-collected vaginal specimens as well as male urine	Women and men	[28,82]
Solana® Trichomonas Assay (Quidel, San Diego, CA)	–	–	98% for vaginal specimens and over 92% for urine	–	40 min	Female vaginal and urine specimens from asymptomatic and symptomatic women	Women	[83]
OSOM Trichomonas Rapid Test (Genzyme Diagnostics; Cambridge, MA)	–	Qualitative antigen- detection immuno- chromatographic assay	83–92%	99%	10–15 min	Vaginal specimens	Women	[107,108]
AmpliVue® Trichomonas Assay (Quidel, San Diego, CA)	–	–	90.7%	98.9%	–	Vaginal specimens from symptomatic and asymptomatic women	Women	[86]

ingested by macrophages in the tissues. It uses carbohydrates as a source of energy through fermentative metabolism under both aerobic and anaerobic conditions. In addition, the incubation period is four to 28 days in general [45].

Initially, TV replicates via binary fission in the squamous epithelium of the genital tract of the female lower genital tract and male urethra and prostate, besides, a human being is the only known host, and it is transmitted among by sexual intercourse [10]. The trophozoite is the only form of this parasite, however, pseudocyst and cyst are rarely described [28].

In several literatures, including proteomoglycol-biological approaches, different key components of the surface of the organism documented involving TV lipoglycan [46], putative membrane proteins as ABC transporters, fibronectin and 11 BspA proteins [47], tetraspanins [48], glyceraldehyde 3-phosphate dehydrogenase [49], enolase [50], succinyl-CoA synthetase [51], and GP63 protease [52], they are responsible for binding to the extracellular matrix of human epithelium, enhancing the immune system, and increment or enhance cell adhesion.

Exosomes have short RNA molecules (25 to 200 nucleotides) and enhance adhesion to vaginal ectocervical cells (VECs) when added to the strains extraneously [48]. The TV cell adhesion is important to promote lysis when taken place, in addition to other factors are metalloproteases [53], cysteine proteases [54], a rhomboid protease (TvROM1) [55], and phospholipase A2 [56].

TV could be infected with double-stranded RNA (dsRNA) viruses which have an important implication for virulence and pathogenesis called *T. vaginalis* viruses (TVV) [57]. TVV infection triggers a far more pronounced proinflammatory reaction than when its absence [58]. The enhancing effect of TVV (which resides in about 50% of all isolates samples) on the proinflammatory response seems to be even more stronger or harmful [59], as TVV is sensed by Toll-like receptor-3 on the vaginal ectocervical cells surface. Especially worrying is the observation that MTZ treatment, accompanied by the release of large amounts of virus particles from necrotic TV, further amplifies this adverse response. In the presence of TVV, symptoms became more exacerbated [60].

## Cell biology

The gene expression in TV has seen studied by several transcriptomic and proteomic studies that address the impaction of growth and culture conditions [61].

Oxidative stress is the main condition in cell biology, which can lead to an upregulation of expression of 218 genes [62], furthermore, glucose starvation also can lead to upregulation of other genes, resulting in a more H<sub>2</sub>O<sub>2</sub>-resistant phenotype [63]. In a study of phosphoproteomic, eighty-two phosphoproteins were detected in TV, with more than 1000 genes for kinases existing in the genome [64,65]. Recently, TV glycobiology has involved four strains, described by N-glycan composition, oligomannose form, phosphoethanolamine, N-acetyllactosamine, xylose, UDPxylose synthase, asparagine-linked N-glycans, and hydrogenosome [66–70].

## Genomics of TV

The genome is extremely large for a protist, it is 175 Mb in size [71], with repetitive sequences in 65%, including representatives of the types Maverick and Tc1/mariner [72], and microRNA [73]. Approximately, 60,000 genes have accumulated in the genome due to the expansion of gene families [46]. Otherwise, the pseudogenes seem to be extraordinarily present in a large amount [74]. In TV, the mRNA possesses a metazoan/plant-like cap structure and enzyme [75].

## Diagnosis

The traditional microscopic examination of a vaginal discharge is the main way for diagnosis of TV, it is cheap and quick, but has low sensitivity, about 44% to 68% compared to culture [76,77]. Whereas the TV culture is the gold standard for diagnosis, with a sensitivity reach to 94% [78], in Diamond's medium, using culturing systems, such as the InPouch® system (BioMed Diagnostics, White City, OR) [28,78,79]. Recently, molecular techniques for the detection of TV have been the preferable diagnostic approaches [24]. These are many tests like APTIMA® *T. vaginalis* Assay (Hologic, Bedford, MA) [80], BD ProbTec *T. vaginalis* Qx (TVQ) Amplified DNA Assay (BD Diagnostics, Baltimore, MD) [81], Xpert® TV Assay (Cepheid, Sunnyvale, CA) [82], Solana®

Trichomonas Assay (Quidel, San Diego, CA) [83], OSOM Trichomonas Rapid Test (Genzyme Diagnostics; Cambridge, MA) [84], Affirm VP III (Becton, Dickinson & Co.; Franklin Lakes, NJ) [85], and AmpliVue® Trichomonas Assay (Quidel, San Diego, CA) [86]. The diagnostic sensitivity and specificity for the molecular assay tests range from 95–100% [83]. The summarized of molecular developments in the diagnosis and typing of TV listed in table 1.

### Life cycle

*Trichomonas vaginalis* resides in the female lower genital tract and the male urethra and prostate, where it replicates by binary fission. The parasite does not appear to have a cyst form and does not survive well in the external environment. TV is transmitted among humans, its only known host, primarily by sexual intercourse [87]. TV trophozoite (diagnostic stage) in vaginal and prostatic secretions and urine, multiplies by longitudinal binary fission. During sexual intercourse, trophozoite in vagina or orifice of urethra became infective stages [87].

### Management

The medical management of trichomonosis continues accordingly to Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) for sexually transmitted disease guidelines [23], first-line treatment is a single 2-gram dose of oral metronidazole (MTZ) or tinidazole (TIN) or oral MTZ 500 mg twice/day (BID) for 7 days. The CDC recommends only 7-day MTZ for HIV-infected women [88]. TIN has better absorption and fewer GIT side effects than MTZ [89] but is ten times more expensive [3]. When treatment fails, two additional treatment options are chosen. The first is high-dose oral TIN plus intravaginal TIN [90]. The second is high-dose oral TIN plus intravaginal paromomycin for 14 days [91].

The concurrent treatment of all sexual partners is critical for symptomatic relief, microbiologic cure, and prevention of transmission and reinfection according to CDC sexually transmitted disease treatment guidelines [23]. The CDC recommends expedited partner therapy (EPT) as an option for STIs in women and heterosexual men as partner therapy [23,92].

In pregnancy, the safe drug in all stages of pregnancy is MTZ [93,94]. In breastfeeding women, the lactation must be held 12–24 hrs from the last dose of MTZ [10]. Repeated infections are the most common pattern due to drugs resistance of infected partners [10].

### Drugs resistance in TV

Repeat TV infections are common, ranging from 5–31% [79,95], which is high. The sources of repeat TV infections beyond treatment are: re-infection from an untreated partner, infection from a new partner, or treatment resistance or failure. In case of treatment resistance, the rescreening is required [10]. Drugs resistance in TV found to be one of the common cause of repeat infection in one study that examined the base of causes [79], however, resistance appear to play only a minor role in treatment failure. The potential reasons of acute repeat TV infections are drug resistance, non-adherence to treatment, clinical treatment failure, or re-infection from an untreated partner. Mostly non-HIV infected women are reported rates of MTZ resistance range from 2.2–9.6% [95,96] and usually they resolved with repeat MTZ course at the similar or higher dosage [97]. The molecular mechanism(s) of clinical resistance of drugs against TV are poorly understood [10]. As a result, persistent or recurrent infection due to drugs resistant TV should be distinguished from reinfection from an untreated partner or insufficiently treated partner. If drug resistance is approved, the isolate samples can be sent to the CDC for drug resistance testing ([https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-1023 9](https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-1023%209)) [28]. If the regimen of high-dose oral MTZ fails within 7-days, two additional drugs are available. The first is high-dose oral tinidazole (TIN) 2–3 g/day (in divided doses) plus intra-vaginal TIN 500 mg twice/day for two weeks [82]. The second is high-dose oral TIN (1 gram) three times/day plus intra-vaginal paromomycin (4 g) of 6.25% intra-vaginal paromomycin cream nightly, for two weeks [91,98].

### TV and carcinogenesis

Recently, TV was found to be highly associated with human papilloma virus (HPV) infections and cervical cytological abnormalities such as cervical neoplasia, metaplasia and carcinoma in situ [99]. Evidence revealed that TV is associated with HPV

acquisition, thus there may be an indirect link between both TV and cervical neoplasia. A meta-analysis by Zhang and Begg [100] found that TV was associated with a 1.9 fold risk of cervical neoplasia. Several studies in developed countries as Finnish, Dutch, Belgian and Chinese documented elevated odds ratios (1.4–2.0) of cervical neoplasia among women who have TV or vice versa [101–105]. Sutcliffe and colleagues found an association between TV and prostate cancer in one study but not in a subsequent study, and they concluded an association between prostatic adenocarcinoma, neoplasia, metaplasia and TV proctitis [106,107].

In conclusion, this TV parasite is an important source of morbidity and may play a role in the transmission of other pathogens. Globally, it is the most common non-viral STI with an asymptomatic pattern. We suggest further studies on TV in men. According to the high prevalence and health consequences associated with TV, there is a requirement for improved screening programs in Iraq. The early diagnosis of asymptomatic diseases and effective treatment regimens are mandatory. There is no review research published that solely focuses on *Trichomonas vaginalis* infections in Iraq, as a result, this is first time review of TV in our country.

### Ethics approval

This study was approved by University of Misan, Faculty of Medicine Committee Board (ID No. 1002/ Feb 2021).

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