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ARTICLE

Molecular Mechanisms of Immune Evasion and Host Manipulation by Trichomonas vaginalis: A Narrative Review

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ABSTRACT

Background: Trichomoniasis, caused by the flagellated protozoan Trichomonas vaginalis, is the most common curable non-viral sexually transmitted infection worldwide. Most infections produce no symptoms, yet they are linked to adverse pregnancy outcomes, a higher risk of acquiring human immunodeficiency virus and an association with cervical neoplasia.

Objective: To review how *T. vaginalis* interacts with, and may evade, innate and adaptive immune defenses, and to grade the strength of the evidence behind each proposed mechanism.

Methods: Narrative review of the literature indexed in PubMed. Studies were classified by experimental model (human, murine or parasite-only systems) and by the level of mechanistic support.

Results: The best-supported mechanisms are acquisition of a host membrane regulator of complement, which reduces complement-mediated lysis *in vitro*; induction of neutrophil extracellular traps by parasite surface glycoconjugates; contact-dependent killing of the parasite by neutrophils through trogocytosis; and activation of inflammatory signaling in macrophages and epithelial cells by the parasite and its extracellular vesicles. The roles of parasite cysteine proteases, surface antigenic variation, *Mycoplasma hominis* and *Trichomonas vaginalis* virus are biologically plausible but less firmly established. Much of the mechanistic evidence comes from *in vitro* and murine systems, and several proposed pathways, including epigenetic reprogramming of host cells, remain untested.

Conclusions: Persistence of *T. vaginalis* is best understood as a network of overlapping, partly redundant interactions, not a single evasion program. Priorities are validation in primary human mucosal models, strain-resolved studies, and tests of whether these mechanisms explain treatment failure and clinical sequelae.

Introduction

1.1. Epidemiology and Clinical Burden

Research on sexually transmitted infections has long concentrated on bacteria and viruses, and the protozoa have fared less well. Yet *Trichomonas vaginalis* is the most common curable non-viral sexually transmitted pathogen. The World Health Organization estimated about 156 million new cases among people aged 15–49 years in 2016, with a prevalence of 5.3% in women and 0.6% in men [1,2]. Local figures swing widely with geography and risk profile. A PCR-based national survey in the United States found 3.1% of women aged 14–49 years infected, with a roughly ten-fold higher prevalence in non-Hispanic Black women than in White or Mexican American women [3]; antenatal and family-planning clinics in resource-limited settings have reported between 3.2% and 52% [4]. Prevalence is also high among

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women at elevated risk of sexually transmitted infection [5]. Because trichomoniasis is not a notifiable disease and older estimates rested on microscopy, the true burden is probably higher [4].

Most infections go unnoticed. About 85% of infected women and 77% of infected men have no symptoms [4], although roughly a third of asymptomatic women develop symptoms within six months [4]. Untreated, the infection can persist for months or even years in women, whereas in men it usually lasts under ten days [4]. When symptoms do appear they include vaginal discharge, itching and dysuria in women, and urethritis, prostatitis or epididymitis in men [4].

The consequences reach well beyond vaginitis and urethritis. In pregnancy, trichomoniasis is associated with preterm delivery (pooled odds ratio 1.27), prelabour rupture of membranes and low birth weight [6]. In studies from sub-Saharan Africa the infection raised the hazard of HIV acquisition about 1.5-fold [7]. Meta-analyses of observational studies also link it to cervical neoplasia (pooled odds ratio 2.15, 95% CI 1.61–2.87) [8] and to cervical cancer (odds ratio 5.23) [9], but causality is unproven. For prostate cancer the pooled estimate is smaller (odds ratio 1.17, 95% CI 1.01–1.36), and its authors cautioned against over-interpreting it [10]. With claims of such unequal strength in circulation, a review of the molecular literature has to separate established mechanisms from working hypotheses.

1.2. Parasite Biology and Life Cycle

T. vaginalis is a flagellated, extracellular protozoan that lives in the squamous epithelium of the lower genital tract in women and in the urethra and prostate in men, multiplying by binary fission [4]. Humans are its only known host. Transmission is overwhelmingly sexual, and the incubation period is usually 4–28 days [4]. The parasite does not survive long outside the body, although it can persist in a wet environment for more than three hours [4]. Unlike many persistent protozoa it has no classical environmentally resistant cyst; the infective, symptom-causing stage is the motile pyriform trophozoite, which turns amoeboid on contact with epithelium [11]. Round pseudocysts with internalized flagella appear under stress and have been linked to persistence, though their role in human infection still needs firm evidence [12]. Cyst-like structures have likewise been described in axenic culture and in vaginal swabs from symptomatic patients [13]. Energy metabolism relies on hydrogenosomes, anaerobic organelles that replace mitochondria [14].

1.3. Aim and Scope of the Review

This narrative review has four aims. The first is to summarize how the innate and adaptive arms of the immune system respond to *T. vaginalis* (Sections 4 and 5). The second is to examine the parasite-associated mechanisms proposed to limit those responses: acquisition of host complement regulators, protease activity, neutrophil responses, macrophage signaling and antigenic variation. The third is to assess how extracellular vesicles, *Mycoplasma hominis* and *Trichomonas vaginalis* virus (TVV) shape the host–parasite interface (Sections 6 and 7). The fourth is to grade each mechanism by the model in which it was shown (human cells, murine cells or parasite-only systems) and by the level of mechanistic support, so that readers can see which findings are secure and which remain hypotheses (Table 1). The review closes with the implications for diagnosis, treatment and vaccine design, and with the limitations of the current evidence base (Section 9).

Drug-resistance mechanisms, parasite metabolism and host-cell cytotoxicity are outside the scope unless they bear directly on immune interactions.

2. Literature Search and Selection

This is a narrative review and not a systematic review. PubMed was searched without date limits (most recent search: October 2026) using combinations of *Trichomonas vaginalis*

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with terms for complement, CD59, cysteine protease, neutrophil, neutrophil extracellular trap, trogocytosis, macrophage, Toll-like receptor, T cell, antibody, extracellular vesicle, *Mycoplasma hominis* and double-stranded RNA virus. Reference lists of recent reviews were screened for additional sources. English-language studies of host–parasite interaction were eligible. Primary experimental studies, systematic reviews and meta-analyses were given priority, together with recent reviews (2018–2026) for context. Only peer-reviewed sources were used, with the exception of one World Health Organization fact sheet. No formal risk-of-bias assessment was undertaken. Instead, each mechanism was classified according to the experimental model and the type of evidence (Table 1).

3. Parasite Biology and Morphological Plasticity

The shape of *T. vaginalis* changes markedly once it meets a host. In suspension, trophozoites are usually pyriform, carrying four anterior flagella and a recurrent flagellum that runs along an undulating membrane. Contact with epithelium flattens the cell into an amoeboid form. This widens the area of parasite–host contact and accompanies stronger adherence [11].

Adherence cannot be traced to one receptor–ligand pair. AP65, AP51, AP33 and AP23 were among the first parasite proteins associated with cytoadherence, and later studies added strain-dependent surface proteomes and other host-interacting proteins [11]. A legumain-like cysteine proteinase, TvLEGU-1, has also been implicated in cytoadherence [15].

Some surface metabolic enzymes also have a second job: such “moonlighting” proteins can bind extracellular-matrix components or plasminogen [16]. Because surface composition shifts with strain, growth conditions and host-cell contact, a single invariant molecular signature of adhesion is hard to define [11,16].

4. Innate Immunity in Trichomoniasis

4.1. The Innate Response to *T. vaginalis*: An Overview

The first contact is with the vaginal or urethral epithelium, which answers adherent parasites and their secreted products with cytokines and chemokines. Neutrophils are the predominant inflammatory cells in the vaginal discharge of infected women, and the chemoattractants leukotriene B4 and interleukin-8 (IL-8) are found in that discharge; live trophozoites also stimulate neutrophils themselves to produce IL-8 through nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways [17]. Neutrophils and macrophages are generally regarded as the main cellular effectors, and IL-8, IL-6 and tumor necrosis factor-α (TNF-α) are the cytokines most often reported [18].

These defenses are not simply ineffective. Human neutrophils kill *T. vaginalis* rapidly *in vitro* in a contact-dependent manner, taking small “bites” of the parasite (trogocytosis) before it dies; the process needs neutrophil serine proteases and serum factors and does not depend on NETs [19]. Complement receptor 3 (CR3) is required for maximal killing [20], and the killing mechanisms differ between parasite strains [21].

4.2. Acquisition of Host Complement Regulators

Complement is present at mucosal surfaces and can injure extracellular pathogens by opsonization, inflammatory signaling and assembly of the membrane attack complex (MAC). Several ways in which *T. vaginalis* might blunt this attack have been reported. The best characterized is acquisition of host CD59, a glycosylphosphatidylinositol-anchored regulator, onto the parasite surface [22]. CD59 blocks the final steps of MAC assembly [23], so its retention on trophozoites offers a credible route to greater resistance to MAC-mediated lysis.

The evidence deserves a careful reading. Parasites grown in serum-based medium carried no detectable CD59. Surface CD59 appeared only after the parasites had been recovered from the

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ascites of infected mice or co-cultured with murine erythrocytes, and CD59-bearing parasites were then killed less efficiently by human serum than parasites without it [22]. The acquired regulator was therefore of murine origin, and acquisition from human cells during genital infection has not been demonstrated. How host membrane proteins reach the parasite is unresolved.

4.3. Proteases, Complement and Opsonization

Proteolysis may add another layer of protection. *T. vaginalis* expresses and secretes numerous cysteine proteases, and several bear on adhesion, cytotoxicity and contact with host immune components [11,15,24]. Complement proteins, including C3-derived fragments, are reasonable substrates. Direct evidence for cleavage of C3 by a defined parasite protease is, however, lacking in the studies reviewed here. Which proteases act on complement, and how much that matters *in vivo*, has not been settled. Complement resistance looks more like a composite phenotype than the result of a single cleavage event.

C3b sits at the center of complement amplification and opsonization, and the way it is processed alters recognition by complement receptors; purified C3b, for example, triggers phagocytosis and activation of human neutrophils through complement receptor 1 [25]. Any parasite mechanism that reduced C3b deposition on the surface, or hastened its breakdown, would weaken phagocytic clearance. Complement is not only a threat to the parasite, though. The requirement for CR3 in neutrophil trogocytosis [20] means that opsonization also assists killing, so interference with complement could cut both ways. The responsible enzymes, their substrates under physiological conditions and their role during human infection remain to be identified.

4.4. Neutrophils: Extracellular Traps and Trogocytosis

Besides phagocytosis and degranulation, activated neutrophils can release neutrophil extracellular traps (NETs), meshes of extracellular DNA decorated with histones and granule proteins that entangle and damage microorganisms [26]. The best-described route, suicidal NETosis, begins when a stimulus activates the neutrophil and assembles NADPH oxidase, generating reactive oxygen species. Neutrophil elastase and myeloperoxidase then leave the granules and enter the nucleus, where, together with peptidylarginine deiminase 4 (PAD4)-mediated citrullination of histones, they drive chromatin decondensation. The nuclear envelope and plasma membrane finally rupture and the chromatin is expelled [27]. NADPH-oxidase-independent and vital forms of NET release have also been described [27], and it is not yet known which of these routes the parasite engages.

In experimental systems *T. vaginalis* and its surface glycoconjugates, lipophosphoglycan and lipoglycan, trigger NET formation in human neutrophils. After co-culture, parasite integrity fell to about a third of control values, and later growth was similarly reduced [28]. Blocking Toll-like receptor 4 (TLR-4) with an antibody, or digesting NET DNA with DNase I or micrococcal nuclease, allowed more parasite growth [28].

These observations make NETs a relevant part of the neutrophil response, but they do not show that the parasite makes a DNase that dismantles them. Nor are NETs the only route: in a separate study, human neutrophils killed *T. vaginalis* independently of NETs by trogocytosis [19], and the dominant killing mechanism varies between strains [21]. Whether the parasite has countermeasures against either mechanism is an open question, and answering it will take biochemical and genetic evidence.

4.5. Macrophage and Epithelial Signaling

Macrophages sense *T. vaginalis* through pattern-recognition receptors. In murine macrophages the parasite induces interleukin-6 (IL-6), TNF-α and interferon-γ (IFN-γ) through p38, extracellular signal-regulated kinase (ERK) and NF-κB p65 signaling, with Toll-like receptor 2 (TLR2) contributing in part, as shown by reduced responses in TLR2-deficient cells [29]. These results support receptor-dependent activation, although the response changes with

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the parasite preparation, the host-cell model and the experimental conditions. They come from mouse cells, and their transfer to human macrophages remains to be shown.

Lipoglycan and related surface glycoconjugates are good candidates for starting this signaling. A defined sequence in which TLR2/TLR1 engagement activates phosphoinositide 3-kinase (PI3K)–Akt, stabilizes IκB and thereby suppresses NF-κB is, however, not established in the literature reviewed here; the data that do exist show NF-κB activation after exposure to the parasite [29].

Polarization is also more complicated than a binary switch from M1 to M2. PI3K–Akt signaling and arginine metabolism regulate macrophage phenotype in many infections [30], but direct evidence tying a defined *T. vaginalis* ligand to an arginase-1-dependent M2 program is scarce.

5. Adaptive Immunity in Trichomoniasis

5.1. Antibody and T-cell Responses

Antibodies against the parasite are readily detected in serum and vaginal washes during infection, yet they do not reliably prevent reinfection [18,31]. Reinfection is common, so naturally acquired immunity is often incomplete. That observation alone, however, does not point to a parasite mechanism that disables adaptive responses. Antigenic heterogeneity, protease activity, local cytokine conditions and the short life of some mucosal responses may each limit durable protection [31].

T cells are the less well characterized arm. $CD4^+$ T-helper cells orchestrate much of the response. Th1 cells, through interferon-γ, activate macrophages; Th17 cells, through IL-17, recruit neutrophils and support epithelial defense; and regulatory T cells and the cytokines IL-10 and transforming growth factor-β (TGF-β) restrain inflammation and may allow the parasite to persist [31]. Evidence for each subset comes mainly from small human studies and murine models, and the quantitative importance of any one subset in human infection has not been defined [31]. The balance between these responses probably depends on the stage of infection, the parasite strain, the microbiota and coinfections [31].

5.2. Parasite Mechanisms That May Limit Adaptive Immunity

Antigen-presenting cells, dendritic cells among them, respond to parasite-derived molecules and in turn shape T-cell responses. Cysteine proteases could plausibly alter antigen processing or surface immune molecules. Direct cleavage of major histocompatibility complex (MHC) class II, or a uniform tolerogenic dendritic-cell phenotype, would need mechanism-specific evidence before being accepted. The firmer conclusion from current data is narrower: *T. vaginalis* can modify the activation and cytokine output of antigen-presenting cells, with downstream consequences for T cells [24,31].

Parasite proteases may also act on antibodies themselves. Lysates of *T. vaginalis* degraded the heavy chains of human IgG and of secretory IgA, and cysteine proteinase inhibitors abolished the degradation [32]. The experiments used parasite lysates, so how far they reflect events at the mucosal surface is uncertain.

A second candidate is variation in surface immunogens. Isolates differ in expression of the 267-kDa surface glycoprotein later named P270: populations within one isolate can be positive or negative on flow cytometry, and the pattern correlates with virulence-associated traits [33]. In isolates that carry the double-stranded RNA virus, the P270 immunogen varies between surface and cytoplasmic expression, and only virus-infected trichomonads display it on the surface [34]. Whether this amounts to a systematic antigenic-variation program, as in trypanosomes, remains unknown, so “phenotypic surface variation” is the safer term.

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6. Extracellular Vesicles and Modulation of Host-Cell Responses

Extracellular vesicles (EVs) have become important mediators of communication between *T. vaginalis* and host cells. Parasite EVs carry proteins and other macromolecules, host cells take them up, and the vesicles modulate host–parasite interactions [35]. They also act between parasites: EVs from a more adherent strain were internalized more efficiently by a less adherent strain, increased its aggregation and adherence to host cells, and transferred an adherence factor, a cadherin-like protein, directly to the recipient parasite's surface [36]. That finding bears on mixed-strain infections, which make up roughly 11% of the total [36].

EV composition and activity vary with parasite strain and culture conditions [35,36]. Proteomic studies have identified a broad cargo that includes proteins of membrane trafficking, stress responses and host interaction [35].

One target of EVs is supported experimentally: host inflammatory signaling. In human THP-1 macrophages and ectocervical cells, EVs induced secretion of CXCL1, IL-6, IL-8 and macrophage inflammatory protein-1β (MIP-1β). In THP-1 cells the effect ran through TLR3 overexpression and the NF-κB/NLRP3 inflammasome pathway, and in ectocervical cells through PI3K-mediated NF-κB, p38 MAPK and ERK pathways [37]. The epigenetic route is more speculative. To current knowledge, no study has tested whether *T. vaginalis* EVs deposit H3K27me3 at the *IL6* or *IL8* promoters; the general chromatin literature [38] provides a framework, but no evidence for this parasite. Epigenetic regulation remains a hypothesis until direct experiments say otherwise, and it should not be presented as an established evasion pathway.

7. The Microbial Context of Infection

T. vaginalis does not always act alone. Two associations deserve attention: infection of the parasite by TVV, and its frequent partnership with *M. hominis*. Each can change parasite biology and host inflammatory responses, though prevalence and effects differ among isolates [39,40]. Not every infection involves all three organisms.

7.1. Association with *Mycoplasma hominis*

Close association with *T. vaginalis* is typical of *M. hominis*, and the bacterium has been detected inside trophozoites [39]. Reported frequencies are high but variable and rest on small series of isolates: *M. hominis* was found in 81% of 48 Italian isolates [41], in 86% (18 of 21) of South African clinical isolates [42], and five of seven Spanish isolates examined carried mycoplasmas [43]. Parasite fitness, host-cell interactions and the vaginal microbial environment may all be affected [39,44]. Metabolic exchange, including pathways involving arginine, has been proposed to underlie the relationship [39]. Its contribution to disease severity *in vivo* is still being worked out.

Treatment is another reason the association matters. Location inside the parasite can change how much antibacterial agent reaches *M. hominis* [44], and some reports suggest that the symbiosis alters parasite growth and inflammatory responses [39]. Studying the two organisms together in selected settings is warranted. What is not warranted is the assumption that *M. hominis* uniformly raises ATP production in *T. vaginalis* through hydrogenosomal oxidative phosphorylation. Hydrogenosomes are anaerobic organelles that have lost the respiratory chain, and they make ATP only inefficiently, by substrate-level phosphorylation [14].

7.2. TVV, Inflammatory Amplification and HIV-1 Susceptibility

TVV is a double-stranded RNA (dsRNA) virus carried by some *T. vaginalis* isolates, and it can alter parasite phenotype and host responses [40]. Its prevalence varies: 50% of 48 Italian isolates tested positive for at least one TVV species, and 75% of the positive isolates carried more than one [41]; 76% (16 of 21) of South African isolates were positive [42]; and

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five of seven Spanish isolates carried the virus [43]. Associations with metronidazole susceptibility are inconsistent between studies [41,42], and the samples are small.

Disruption of trophozoites, for example during antimicrobial treatment, may make the virus matter more, because released dsRNA can be sensed by host pattern-recognition pathways. Human epithelial cells sense the endosymbiotic virus through Toll-like receptor 3 (TLR3), which activates interferon regulatory factor 3 (IRF3), type I interferon and proinflammatory cascades, and metronidazole treatment amplified these responses in that study [45]. TLR3 is a canonical dsRNA sensor and signals through the adaptor TIR-domain-containing adaptor-inducing interferon-β (TRIF) to activate IRF3 and NF-κB. In *T. vaginalis* infection, TVV-associated signaling therefore offers a plausible way for parasite lysis to intensify mucosal inflammation [37,45]. Inflammation of this kind may weaken epithelial integrity and attract HIV-susceptible immune cells, giving a mechanistic bridge to the epidemiological link between trichomoniasis and HIV acquisition [7,46]. Population-level evidence supports raised susceptibility; it does not allow the whole association to be assigned to a single TLR3–C-C chemokine receptor type 5 (CCR5) pathway. The size of the TVV effect depends on viral and parasite background and cannot be assumed for every infection.

8. Synthesis of Molecular Pathogenicity

Figure 1 places the mechanisms discussed in Sections 4 to 6 in one diagram, and Table 1 summarizes each one with its experimental model and level of support.

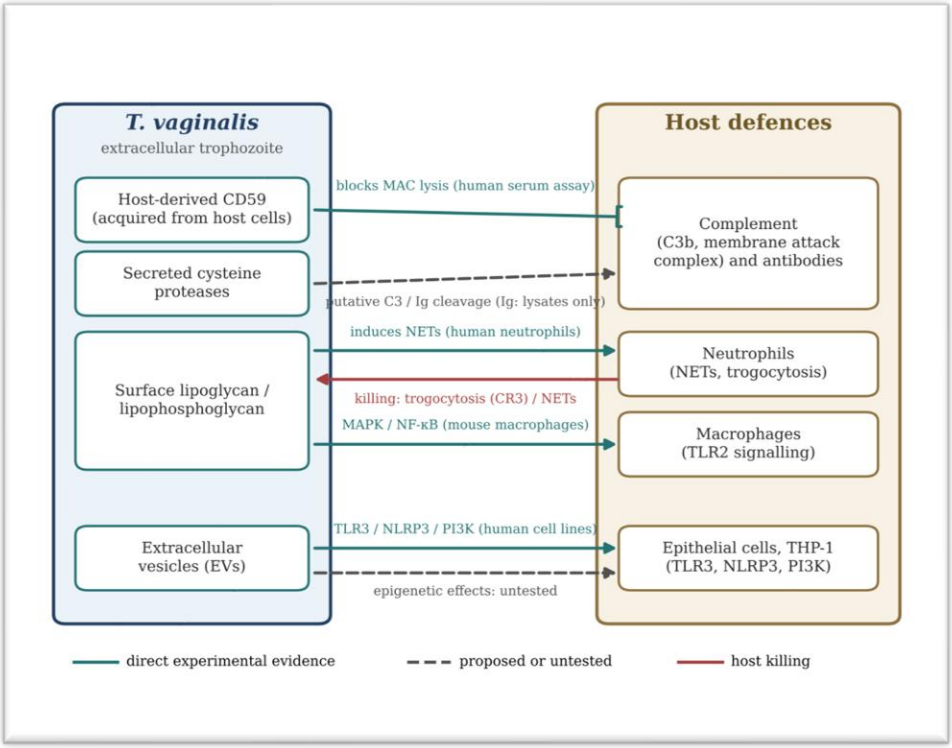


Figure 1. Innate immune interactions with *T. vaginalis* and the strength of the supporting evidence. Solid lines mark interactions supported by direct experiments; dashed lines mark interactions that are proposed or untested. Experimental models: acquisition of CD59 (murine host cells, human-serum killing assay) [22]; NET induction and trogocytic killing (human neutrophils) [19,20,28]; macrophage signaling (mouse macrophages) [29]; EV-induced signaling (human cell lines) [37]. CR3, complement receptor 3; EVs, extracellular vesicles; MAC, membrane attack complex; NETs, neutrophil extracellular traps.

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Table 1. Molecular mechanisms implicated in *T. vaginalis*–host interactions, with experimental model and strength of evidence

Parasite mediator	Host target	Reported mechanism	Experimental model (human / murine)	Evidence status	References
Host CD59 acquisition	Terminal complement pathway (MAC)	Parasite acquires CD59 on its surface; CD59-bearing parasites are lysed less by human serum	Murine: CD59 acquired in infected mice or from murine erythrocytes; killing tested in human serum	*In vitro*; acquisition from human cells not shown	[22,23]
Cysteine proteases	Immunoglobulins; complement (putative); adhesion	Lysates degrade human IgG and secretory IgA; C3 cleavage inferred but not shown	Human immunoglobulins with parasite lysates (cell-free)	Indirect; enzymes and substrates unresolved	[15,24,32]
Surface glycoconjugates → NET formation	Neutrophils	Lipophosphoglycan/lipoglycan induce NETs; TLR-4 involved; DNase restores growth	Human: neutrophils isolated from blood	*In vitro*; parasite countermeasures not defined	[27,28]
Neutrophil trogocytosis	Neutrophils; CR3; serum factors	Contact-dependent killing by "biting"; NET-independent; strain-dependent	Human: neutrophils and neutrophil-like cells	*In vitro*; relevance *in vivo* untested	[19–21]
Surface glycoconjugates and other parasite factors	Macrophage pattern-recognition pathways	MAPK and NF-κB activation with partial TLR2 involvement; cytokine production	Murine: mouse macrophages (wild-type and TLR2-deficient)	*In vitro*; human macrophages not tested	[29]
Extracellular vesicles	Epithelial cells, macrophages and other parasites	Cargo transfer; TLR3/NLRP3 and PI3K/MAPK signaling; adherence-factor transfer between strains	Human: THP-1 macrophages, ectocervical cells; parasite strains	*In vitro*; epigenetic effects untested	[35–37]
Mycoplasma hominis	Parasite–microbiota interface	Intracellular association; proposed metabolic exchange; altered antibiotic exposure	Clinical parasite isolates (small series)	Observational and *in vitro*	[39,41,44]
TVV dsRNA	Host dsRNA-sensing pathway (TLR3)	TLR3/IRF3, type I interferon and proinflammatory signaling; amplified after metronidazole	Human: epithelial cells *in vitro*	*In vitro*; link to HIV hypothetical	[40,45,46]
Surface antigen variation (P270)	Antibody recognition	Phenotypic switching between surface and cytoplasmic expression; linked to virus-infected isolates	Parasite isolates (flow cytometry, monoclonal antibody)	Descriptive; role *in vivo* unknown	[33,34]

Abbreviations: CR3, complement receptor 3; dsRNA, double-stranded RNA; IRF3, interferon regulatory factor 3; MAC, membrane attack complex; MAPK, mitogen-activated protein kinase; NET, neutrophil extracellular trap; NF-κB, nuclear factor-κB; PI3K, phosphoinositide 3-kinase; TLR, Toll-like receptor; TVV, *Trichomonas vaginalis* virus.

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9. Discussion

9.1. What the Evidence Supports

Current evidence presents *T. vaginalis* persistence as the outcome of several overlapping host–parasite interactions, not of one evasion program. Complement regulation, protease activity, neutrophil responses, antigenic variation, vesicle signaling and microbial partners each contribute, at different stages of infection or in different experimental systems. The mechanisms with the most direct support are those demonstrated in human cells or with human serum: neutrophil trogocytosis and NET formation [19,28], EV-induced signaling in human cell lines [37], and TVV sensing by human epithelial cells [45]. Others rest on murine material, including CD59 acquisition [22] and TLR2-dependent macrophage activation [29] (Table 1).

A feature that deserves more attention is the strain dependence of almost every phenotype. Clinical isolates differ in adherence, cytolysis and susceptibility to neutrophil killing [21,36], and infections range from asymptomatic to intensely inflammatory depending on host and parasite strain [35]. A mechanism demonstrated in one reference strain may therefore not generalize.

9.2. Clinical Implications

Several findings in this review connect to practice, although none yet justifies a change in management. First, because 85% of infected women and 77% of infected men have no symptoms [4], diagnosis depends on testing. Nucleic acid amplification tests are the most sensitive option and can be run on urine and genital swabs in both sexes [47]. The immunological picture explains why silent infection matters: low-grade mucosal inflammation, even without symptoms, is the plausible link to HIV acquisition and to adverse pregnancy outcomes [6,7].

Second, treatment rests on the 5-nitroimidazoles. Metronidazole 500 mg twice daily for seven days cleared infection better than a single 2 g dose in women (positive at test of cure in 11% versus 19%; relative risk 0.55) [48], and current guidance recommends the seven-day regimen for women, retesting at three months and treatment of partners [47]. *In vitro* resistance remains low, at 4.3% in the guideline review [47], so many repeat positives are attributed to reinfection or clinical treatment failure rather than resistance [4]. Host and parasite factors discussed here, strain-dependent neutrophil killing, the microbiota and endosymbionts, are candidate explanations for treatment failure and deserve study.

Third, the endosymbiont findings raise testable questions. If TVV-infected parasites release dsRNA when killed, metronidazole could transiently amplify mucosal inflammation, as shown in epithelial-cell experiments [45]. Whether this happens in patients, and whether it matters for pregnancy or HIV outcomes, is unknown. Likewise, intracellular *M. hominis* is shielded from some antibacterial agents [44]. These are hypotheses for clinical studies, not grounds for routine testing of isolates.

9.3. Therapeutic and Vaccine Perspectives

Nitroimidazoles remain the mainstay of treatment, but treatment failure and resistance create a need for additional targets. Candidates should be essential, conserved across clinical isolates and distinct from host proteins. EV biogenesis and uptake [36], parasite proteases [15] and conserved adhesion-associated proteins deserve investigation; therapeutic claims, though, should wait for target validation.

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Vaccine development faces comparable limits. Antibody recognition may be eroded by surface variability, and some adhesion-associated proteins double as metabolic enzymes or are expressed differently between strains [11]. Conserved surface-exposed or secreted antigens remain attractive, especially if they can elicit mucosal immunity; a transient receptor potential-like channel, cysteine peptidases and α-actinin are among the candidates proposed [18]. AP65 and lipoglycan, however, cannot be called validated vaccine targets merely because of their proposed roles in adhesion or immune signaling. Ranking candidates will take comparative genomics, structural analysis and testing across diverse clinical isolates.

9.4. Limitations

The conclusions of this review should be read with several limitations in mind. It is a narrative review based mainly on PubMed, restricted to English, with no formal quality scoring; studies were selected by the author and selection bias cannot be excluded. The field is also small and dominated by a limited number of research groups and reference strains, so findings may be correlated rather than independent. Much of the mechanistic evidence comes from *in vitro* and murine experiments, which do not reproduce the vaginal microbiota, hormonal environment or mucus layer. Several of the quantitative epidemiological associations come from observational meta-analyses with high heterogeneity and cannot establish causation [8–10]. Prevalence figures for *M. hominis* and TVV come from small isolate collections in three countries [41–43]. Finally, the literature is moving quickly, and some of the 2024–2025 studies cited here have not yet been replicated.

9.5. Future Directions

Future work should treat parasite genotype, TVV status, *M. hominis* carriage, vaginal microbiota and host immune phenotype as interacting variables, not independent ones. Single-cell and spatial methods, longitudinal sampling and primary human mucosal models may help reconcile findings that seem to contradict one another between cell lines and animal systems. Only then can robust mechanisms be told apart from appealing but unverified ones and translated into interventions of clinical use.

10. Conclusions

T. vaginalis survives in the human urogenital tract through a web of partly redundant interactions. The best-supported themes are acquisition of host complement regulators, neutrophil responses (NETs and trogocytosis), vesicle-mediated signaling and microbial partnerships; the least supported are specific protease substrates, macrophage polarization and epigenetic effects. For clinical practice the findings reinforce three points: infection is mostly silent and must be sought by testing, seven-day metronidazole is the more effective regimen in women, and repeat positivity should prompt consideration of reinfection, partner treatment and host–parasite factors before resistance. Closing the remaining gaps in primary human systems is the most direct route to targets worth pursuing and to a better understanding of treatment failure.

Abbreviations

CCR5, C-C chemokine receptor type 5; CR3, complement receptor 3; dsRNA, double-stranded RNA; ERK, extracellular signal-regulated kinase; EV, extracellular vesicle; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; IRF3, interferon regulatory factor 3; MAC, membrane attack complex; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; NET, neutrophil extracellular trap; NF-κB, nuclear factor-

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κB; PAD4, peptidylarginine deiminase 4; PI3K, phosphoinositide 3-kinase; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; TRIF, TIR-domain-containing adaptor-inducing interferon-β; TVV, *Trichomonas vaginalis* virus.

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The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethical Approval

Not applicable. This article reviews published literature and involved no new studies of humans or animals.

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Sinan Khalid Abood: Conceptualization, Literature search and analysis, Writing – original draft, Writing – review and editing.

Declaration of Artificial Intelligence (AI) Use

The author used an AI language assistant to improve grammar, sentence structure and readability, and to help reorganize the text in response to the reviewers' comments. All suggested changes were reviewed and edited by the author, who takes full responsibility for the accuracy and integrity of the final manuscript.

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