Trichomonas vaginalis screening and prevention in order to impact the HIV pandemic: Isn't it time we take this infection seriously?

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Abstract

Trichomonas vaginalis (TV) is the second most common sexually transmitted infection (STI) in the world. It is associated with significant morbidity in women: pelvic inflammatory disease (PID), concurrent vaginitis and sexually transmitted infections (STIs), post-operative infection, and pregnancy complications. TV infection has been implicated in HIV acquisition and transmission in men and women. There are multiple mechanisms to explain this association. TV is not routinely screened for in asymptomatic patients; however, infected individuals are most often asymptomatic. Due to the association with the spread of HIV infection, screening should not be limited to symptomatic patients or those seeking treatment for STIs. There are a variety of tests available to detect TV. Treatment of TV has demonstrated lower rates of HIV acquisition in at risk women. In HIV positive men and women, treatment decreases the amount of genital HIV shedding and subsequent infectivity. Initiation of an effective TV screening and treatment program in HIV positive and HIV susceptible populations may limit further transmission of HIV.

Worldwide, more than 33 million people are infected with Human Immunodeficiency Virus (HIV).¹ Seventy-five percent of cases globally are attributable to heterosexual contact.^{2,3} Risky sexual behaviors are associated with sexually transmitted infections (STIs) and patients reporting a history of or presenting with an STI are at increased risk of HIV acquisition.⁴⁻¹⁰ *Trichomonas vaginalis* (TV) is the second most common STI in the world, accounting for 30% of STI cases.^{2,5,6,11-15} *Trichomonas* has been associated with a 1.5 (1.5-3.0) times increased risk of HIV acquisition and implicated as a cause of increased risk of transmission.¹⁵⁻²⁰ Although modest, this increase in risk for both transmission and acquisition of HIV is significant given the large burden of TV infection worldwide.^{3,15} In light of the suspected contribution of TV on the HIV pandemic, active surveillance and treatment of TV may result in a significant reduc-

tion in the spread of HIV.

Trichomonas vaginalis is a single-celled protozoan that causes vaginitis in women and urethritis in men.^{6,11,16} Each year, there are approximately 200 million new cases of TV worldwide and 3-5 million in the United States.^{5,21,22} The majority of patients with TV are asymptomatic. 70-100% of men are asymptomatic versus 30-85% of women.^{12-14,19,23,24} Symptomatic women may present with any combination of vaginal discharge, odor, vulvar irritation and itching, dysuria, abdominal pain, and dyspareunia.^{13,14,25} Symptomatic men present with urethritis and infrequently prostatitis, epididymitis, and penile discharge.¹⁴ TV is associated with significant morbidity in women: pelvic inflammatory disease (PID), post-operative infection, cervical dysplasia, and low birth weight infants.¹³ TV is more prevalent in HIV positive women with similar rates of recurrence.^{21,26,27} Multiple investigations have cited an association between TV and HIV transmission and acquisition.^{3,13,15,16,19,24} There are several plausible biologic mechanisms that support this association.^{15,19}

Proposed mechanisms for increased HIV acquisition in TV infected individuals include: i) prolonged asymptomatic infection may increase the susceptibility to HIV acquisition;^{13,15,25,28,29} ii) TV causes micro-tears in the genital epithelium which may allow entry of HIV into circulation;^{2,5,6,8,13,15,18,26,30} iii) TV leads to an increased recruitment of inflammatory cells that are more susceptible to HIV;^{5,8,9,13,16,18,30-32} and iv) TV inhibits the production of immune cells that are able to bind to and block HIV infection.¹⁵ A high proportion of patients with TV infections are asymptomatic, and infections may persist from 3-12 months.^{13,27,33} TV is more common in older individuals, which may be a reflection of long-standing asymptomatic carriage.^{13,25} In HIV susceptible patients, this may lead to a prolonged period of increased risk of HIV acquisition.^{15,28,29} Trichomonads adhere to and phagocytose epithelial cells causing punctuate hemorrhages in the epithelial layer of the vagina.³⁴ These breaks in the epithelium allow for entry of HIV into host circulation.^{6,15} HIV may also attach to trichomonads and gain access to the basement membrane by *hitching a ride* to areas where are inflammatory cells have been recruited.² TV elicits a robust immune response resulting in the recruitment of HIV-susceptible inflammatory cells.^{2,6,15,16,18,30} In addition, TV degrades secretory leukocyte protease inhibitors, which normally block HIV attachment to cells. This allows for increased attachment of HIV to susceptible immune cells.¹⁵

In regards to increased risk of HIV transmission, HIV positive patients infected with TV have higher rates of HIV genital shedding.^{6,10,11,13,19,21,28,30,32} Maternal to child

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(MTCT) and sexual HIV transmission are directly related to viral genital shedding.^{32,35} Increased genital HIV shedding is associated with increased infectivity.²¹ Factors associated with increased genital shedding include: low host CD4 cell count, high plasma viral load, cervical inflammation, pregnancy, and STI co-infection.^{11,30,32,35} Male and female patients infected with TV demonstrate increased rates of genital HIV shedding.^{15,19,26,28,36} This may result from TV inducing TNF- α , which increases the rate of HIV replication.² Treatment of TV in HIV positive men and women decreases genital shedding, but the response is delayed over a period of up to 3 weeks following therapy, possibly due to the robust inflammatory response associated with TV infection.^{10,11} By decreasing genital HIV shedding, treatment of TV infection in HIV positive patients may result in decreased infectivity through MTCT or heterosexual contact.³²

In order to effectively decrease the risk of HIV acquisition and transmission as a result of TV infections, accurate diagnostic techniques must be employed in order to identify and treat infected individuals. The current standard for diagnosis of TV is culture.¹³ In comparison to PCR, culture is 70-80% sensitive.^{15,25} The viability of the organisms collected for culture has a significant impact on sensitivity. Cultures should be inoculated immediately. If not inoculated within one hour, the viability of TV is

lost and culture becomes ineffective.¹⁵ Cultures in men may be inoculated from urine or a urethral swab whereas a vaginal swab is preferable in females.^{13,14,23,25,28,36,37} The disadvantages of culture are required incubation at 37°C, availability of a microscope, trained personnel to interpret the culture, and results may take up to 5 days.¹⁴ These limitations are more pronounced in low resource settings. Microscopy, which is limited by low sensitivity in both sexes (60–80%), is most often used in the United States and worldwide for diagnosis of TV.^{13,15,19,23} Papinicolau smears have a low sensitivity (57%) and should not be used for TV screening or diagnosis.¹⁵ Point of care tests that are available and FDA-approved for the diagnosis of TV include the OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Massachusetts) and the Affirm VP III (Becton Dickinson, San Jose, California).³⁸ The Gen-Probe APTIMA Combo2 nucleic acid amplification test for detection of *N. gonorrhoeae* and *C. trachomatis* can be augmented with TV Analyte Specific Reagents (ASR) in order to detect TV.³⁹ PCR and point of care tests have increased sensitivity and detection over culture or microscopy, especially in men.^{12–15,28} However, these methods are associated with increased cost and equipment for analysis, which are not available in developing countries or low resource settings in the United States.

Treatment of TV infection is affordable and effective. The preferred therapies for TV are a single 2000 mg dose of metronidazole or tinidazole.^{15,27,38,40} Extended therapy using metronidazole 500 mg twice daily for 7 days may be more effective in treating males and HIV positive women.^{41,42} Untreated partners may serve as a reservoir for re-infection of treated patients.¹⁹ It has been demonstrated that sexual transmission rates of TV are high. 85–100% of female partners of TV infected men and 45–70% of men with infected female partners are noted to be concurrently infected.^{14,43–46} Rates of resistance to metronidazole are relatively low (2–5%) and do not differ based on HIV status.²⁷ Ineffective treatment of both partners due to non-compliance or non-disclosure of infection to partners may explain the observed rates of recurrence, 5–8% in HIV negative patients versus 30% in HIV positive patients.^{15,21,27} Due to high rates of recurrent TV infection, the recent Center for Disease Control (CDC) 2010 Sexually Transmitted Diseases Treatment Guidelines now recommend repeat TV testing 3 months following an initial infection.³⁸ Tests of cure are not currently recommended following TV treatment; however, due to high rates of recurrence and asymptomatic carriage, especially in HIV infected patients, this may be reasonable to assure effective therapy has been delivered.¹³

Diagnosis and treatment of TV infections in

HIV susceptible patients and HIV positive patients with susceptible partners may have a significant impact on healthcare costs. TV increases a women's risk of HIV acquisition by 1.5–3 fold. It is estimated that TV is associated with 6% of the 12,000 newly diagnosed HIV infections in the United States each year. These TV-associated HIV cases account for a lifetime cost of \$167 million dollars.^{15,16} Given high rates of asymptomatic carriage, a screening approach in at risk men and women is best in order to impact HIV infection rates.^{13,19,37} The CDC recommends annual TV screening in HIV positive women with repeat screening 3 months following infection due to high rates of recurrence. There are no recommendations for TV screening in HIV positive men, most likely due to poor sensitivity in non-PCR diagnostic methods in males.^{27,38,47} Currently, there is no recommendation for screening in other at risk populations. In the United States, African Americans are at significant risk for both TV and HIV infections.²⁴ African Americans have 1.5–10x higher rates of TV infection than any other racial or ethnic group and are disproportionately affected by the HIV pandemic.^{15,24,26} Associated risk factors that have been suggested to increase rates in African Americans over other racial groups include: poverty, early initiation of sexual activity, increased number of lifetime sexual partners infected with TV, infrequent condom use, and low level of education.^{13,15,20,24,48–50} Other risk factors for TV infection include: illicit drug use, tobacco use, incarceration, prostitution, vaginal douching, intact foreskin, vaginitis, and concurrent STIs.^{3,7,13,14,18,26,30,36,37} Given the identified risk factors and at risk populations, it is in the hands of health care providers to embrace screening and treatment of TV infections.

The evidence supporting increased risk of HIV acquisition and transmission in patients with TV infection is substantial. Risk factors and populations at risk for both infections are well defined. However, complacency and a lack of urgency regarding TV diagnosis and treatment in asymptomatic carriers, particularly males, is commonplace. Even in STI clinic settings where providers are screening for TV, diagnosis is most often made by microscopy, which is inferior to culture and PCR. TV is the second most common STI, diagnostic techniques are available in most settings, and treatment is affordable and effective. Given the high probability of current partner infection and recurrent infections, expedited partner therapy and return visits for tests of cure before the recommended 3 months should be considered. By actively identifying and treating TV, not only is there the potential to impact the spread of HIV infection but also rates of pelvic inflammatory disease, bacterial and viral STI acquisition, post-operative infection, and pregnancy complications. TV screening in

at risk populations, especially HIV positive patients, should be embraced by health care providers.

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