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Trichomonas vaginalis Infection: Can We Afford to Do Nothing?

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For more than a century following its initial description in 1836, *Trichomonas vaginalis* was considered to be either a harmless vaginal colonizer or simply a minor nuisance [1]. This view may have been sustained by the observation that women with trichomoniasis vaginalis were usually either asymptomatic or had only mild symptoms. More recently, it has been recognized that *T. vaginalis* infection may be associated with a range of adverse reproductive health outcomes, including preterm birth [2–4], cervical neoplasia [5, 6], posthysterectomy infection [7], atypical pelvic inflammatory disease [8, 9], and infertility [10]. Perhaps most concerning, in the context of the global HIV-1 epidemic, is the emerging recognition that *T. vaginalis* infection may increase women's susceptibility to HIV-1 infection. Two prospective analyses, both conducted in populations of female sex workers, have demonstrated significant associations between trichomoniasis vaginalis and HIV-1 acquisition [11, 12]. Several additional longitudinal studies have suggested that trichomoniasis vaginalis increases a woman's risk of acquiring HIV-1 by 1.2–2.4-fold [13–18], although these findings were not statistically significant. Of note, the majority of studies have been underpowered to demonstrate an association of this magnitude.

While there is continued debate about the causal linkage between *T. vaginalis* infection and obstetrical, gynecological, and infectious complications, it is generally recognized that the incidence of this sexually transmitted infection (STI) has reached epidemic levels throughout much of the world. In 1999, the World Health Organization (WHO) estimated the global incidence of *T. vaginalis* infection to be 173 million cases annually, making this the most common nonviral STI [19]. The greatest burden of disease was observed in less developed regions, but a high incidence was also found in North America (8 million cases annually) and western Europe (11 million cases annually).

In response to evidence that *T. vaginalis* infection is highly prevalent and may lead to serious complications, there have been numerous calls for control strategies, including screening, centralized reporting, treatment, and partner notification [20–23]. Two articles in this issue of the *Journal of Infectious Diseases* provide additional evidence supporting the need to reconsider public health responses for control of trichomoniasis vaginalis [24, 25].

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In the first article, Van Der Pol et al. [24] report findings from a nested case-control study conducted in a general population cohort of women recruited in Uganda and Zimbabwe. A total of 213 HIV-1 seroconverters were compared to 419 women who remained HIV-1 seronegative throughout the follow-up period. Polymerase chain reaction (PCR) analysis detected *T. vaginalis* at the visit prior to HIV-1 acquisition in 24 seroconverters (11.3%) and at the matched visit in 19 nonseroconverters (4.5%) (odds ratio, 2.41; 95% confidence interval [CI], 1.28–4.53). These findings remained statistically significant in analyses that adjusted for individual-level demographic, behavioral, and biological confounding factors, as well as for primary sex partner–associated risk.

Two features of this study were unique in comparison to prior prospective studies that have demonstrated significant associations between *T. vaginalis* infection and HIV-1 acquisition [11, 12]. First, these findings were from a general population cohort, confirming that the association is not restricted to high-risk women. Second, this study used PCR for detection of *T. vaginalis*. The increased sensitivity of this technique, compared with that of vaginal saline wet mount microscopy, may have provided a more precise estimate of the association between trichomoniasis vaginalis and the risk of HIV-1 infection.

In the second article, Miller et al. [25] describe a study of the prevalence, incidence, and correlates of *T. vaginalis* infection in a population of African American women who reported active drug use. Among 135 women recruited through a combination of street outreach and chain-referral methods in Brooklyn, New York, PCR revealed a baseline prevalence of *T. vaginalis* infection of 38%. Women who did not have trichomoniasis vaginalis at baseline had a remarkably high incidence of this infection during follow-up (35 cases per 100 person-years). There was a strong association between incident infection and having >1 sex partner (hazard ratio, 4.3; 95% CI, 2.0–9.4). The majority of participants with *T. vaginalis* infection denied having had symptoms and were unaware of the infection, highlighting the importance of screening in asymptomatic women. While nearly 20% of participants in this cohort were HIV-1 seropositive at baseline, no HIV-1 seroconversions occurred during follow-up, and this study was not designed or powered to examine the relationship between trichomoniasis vaginalis and HIV-1 infection.

In considering the case for an expanded public health response to reduce the incidence of *T. vaginalis* infection, it is important to recognize that although these new data are compelling, observational studies cannot definitively establish the presence of a causal link between trichomoniasis vaginalis and an increased risk of HIV-1 infection. Both infections share a common transmission route, so associations between them may be related to shared high-risk sexual exposures. Carefully controlled studies, such as the one presented by Van Der Pol and colleagues, may reduce the risk of identifying spurious associations, but they cannot eliminate this risk entirely. A randomized, controlled trial of a highly effective strategy for reducing the rate of *T. vaginalis* infection in women at risk for HIV-1 infection would provide the strongest evidence to prove or disprove a causal association. However, no such trial is currently under way, and financial, logistical, and ethical considerations make it unlikely that such a study will be completed in the near future.

Despite the inherent limitations of observational data, the studies by Van Der Pol et al. [24] and Miller et al. [25] highlight several important points. *T. vaginalis* infection may be epidemic in populations at risk for HIV-1 infection in resource-limited countries and in the developed world. The association between *T. vaginalis* infection and HIV-1 acquisition, previously demonstrated only among sex workers, has now been confirmed in a general population cohort. Taken together, these findings offer important new evidence to support the assertion that control of *T. vaginalis* could provide a cost-effective strategy for reducing the spread of HIV-1 in areas where both infections are common. Indeed, a recent study estimated that 6.2% of all HIV-1 infections in US women might be attributable to *T. vaginalis* infection [26]. The proportion of HIV-1 infections attributable to trichomoniasis vaginalis could be much higher in settings where this STI is more common.

What, then, is an appropriate response to the global epidemic of *T. vaginalis* infection? A brief review of available evidence may provide some guidance. First, a modest but highly consistent association with HIV-1 acquisition has been demonstrated in 9 prospective studies [11–18, 24]; the association was statistically significant in 3 [11, 12, 24]. A causal association is biologically plausible and could be mediated through a number of mechanisms, including recruitment of activated CD4-bearing target cells [27, 28], mechanical disruption of the genital mucosa [29], degradation of secretory leukocyte protease inhibitor [30], and interactions with other genital tract conditions [31]. *T. vaginalis* may also promote HIV-1 infectivity in both women and men by increasing genital HIV-1 shedding [32, 33]. Finally, in addition to its potential importance in promoting the spread of HIV-1, *T. vaginalis* has been associated with a range of adverse reproductive health outcomes [2–10].

In considering how a public health response to *T. vaginalis* might be implemented, a number of important questions must be addressed. For example, who would be screened and at what intervals? What type of testing should be used? What approaches would be most effective for case reporting and ensuring partner treatment? While the answers to these questions are beyond the scope of this article, it is worth noting that the essential tools for *T. vaginalis* control are already available. A range of diagnostic tests, including vaginal saline wet mount microscopy, culture, rapid antigen testing, and nucleic acid amplification and detection, provide alternatives that could be used in a variety of settings. Oral metronidazole and tinidazole offer inexpensive, effective, and generally well-tolerated treatment options that are widely available. Given the finite resources of STI control programs both in the United States and internationally, questions will undoubtedly be raised about whether we can afford to undertake a comprehensive program to address the epidemic of *T. vaginalis* infection. In light of the accumulating evidence, we must also consider the question of whether we can afford not to.

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