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Patient-Delivered Partner Treatment and *Trichomonas vaginalis* Repeat Infection Among Human Immunodeficiency Virus-Infected Women

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Abstract

Background—Repeat infections with *Trichomonas vaginalis* (TV) among human immunodeficiency virus (HIV)-infected women are common and may increase the risk of HIV transmission. Patient delivered partner treatment (PDPT) has been shown to reduce repeat infections of other sexually transmitted diseases. The purpose of this study was to evaluate adherence to PDPT and possible causes of repeat TV infection among HIV-infected women.

Methods—A multicentered cohort study was conducted in 3 US cities. Women coinfectd with HIV and TV were treated with metro-nidazole and given treatment to deliver to all reported sex partners. A test-of-cure visit was conducted 6 to 12 days post index treatment completion and behavioral data were collected.

Results—Of 252 women (mean age = 40 years, s.d. 9.1) enrolled, 92.5% were black, 26.2% had CD4 cell counts <200/mm³, 34.1% had plasma viral loads >10,000 copies, 58.3% were taking antiretroviral therapy, and 15.1% had multiple partners. Of the 183 women with partners at baseline, 75.4% provided PDPT to all partners and 61.7% reported they were sure all of their partners took the medication. Factors associated with not giving medications to all partner(s) were multiple sex partners, being single, and having at least one partner unaware of the index woman's HIV status. At test-of-cure, 10.3% were TV-positive and 16.7% reported having sex since baseline. Of the 24 repeat infections, 21 (87.5%) reported adherence to medication and no sexual exposure.

Conclusion—HIV-infected women with TV reported high adherence to PDPT, and treatment failure was the most common probable cause of repeat infection.

Trichomonas vaginalis (TV) is a common parasitic sexually transmitted infection found among human immunodeficiency virus (HIV)-infected women with prevalence rates ranging from 6% to 44% in this population.^{1–6} TV in women is associated with vaginitis, cervicitis,

urethritis, and pelvic inflammatory disease.⁷ Among HIV-infected women, the presence of TV infection may amplify HIV transmission through increased shedding of HIV in vaginal fluids^{8,9} implicating TV infection as a source of sexual and perinatal transmission of HIV.^{10–12} Two studies have shown that treatment for TV can result in a reduction of HIV vaginal shedding.^{13,14} Therefore, prevention of TV infections, including repeat infections, among HIV-infected women can provide not only a clinical, but also a public health benefit.¹⁵

The rates of repeat TV infections among HIV-infected women range from 18% to 36%,^{4,16,17} which is much higher than the 8% repeat infection rate for non-HIV infected women.¹⁸ Repeat TV infections can result from nonadherence to treatment by the index patient, reinfection by an untreated sexual partner, infection by a new sexual partner, or treatment failure.^{16,19} Expedited partner therapy (EPT) is the practice of treating the sex partners of persons with curable sexually transmitted infections without requiring the partners to first obtain a medical evaluation.²⁰ EPT generally consists of a practice called patient-delivered partner therapy or treatment (PDPT), where the patient is given a medication or prescription to deliver to their sex partner(s). PDPT has been recommended for the prevention of recurrent infections with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* among women and heterosexual men. However, the Centers for Disease Control and Prevention has declared that there is insufficient evidence to support recommending PDPT for partner management among patients with TV.²¹

We found some evidence that PDPT may be helpful among HIV-infected women. In our prior cohort of HIV-infected women with TV who were given PDPT, we found that most repeat infections (55%) were attributed to treatment failure¹⁶ suggesting that PDPT does prevent reinfection. The purpose of the current study was to evaluate in more depth adherence to PDPT, and possible causes of repeat TV infection in a different cohort of HIV-infected women to determine whether our prior findings are reproducible.

METHODS

The study population consisted of HIV-infected women with TV infection from an on-going multicenter randomized treatment trial of 2 doses of metronidazole. Study participants were patients at public HIV clinics in New Orleans, LA, Houston, TX, and Jackson, MS.

Women were considered eligible for study participation if they were HIV-infected (confirmed by Western Blot), at least 18 years of age, tested positive for TV by wet preparation which was confirmed by culture using InPouch (Biomed Diagnostics white City, OR) or tested positive for TV by culture only, were willing to take metronidazole treatment, and agreed to refrain from drinking alcohol 24 hours after taking oral metronidazole. Women were excluded from participation if they were pregnant, symptomatic for bacterial vaginosis (which would require a higher dose of metronidazole), incarcerated at the time of the study visit, taking disulfiram at baseline, or treated with metronidazole within the previous 14 days. Other exclusion criteria, per discretion of the medical provider, were: alcoholism or known liver damage, medical contraindications to metronidazole, or cognitively impaired and unable to provide informed consent.

Data were collected on demographics and partner-specific information, including sexual exposure and partner treatment, using a computer assisted self-administered interview format (CASI) created with Questionnaire Development Software (Nova Research Company, Bethesda, MD). Those who refused or were unable to take the CASI were interviewed using a computer-assisted personal interview format which was conducted by the study staff.

Women were given either a single dose of metronidazole (2 g, taken as directly observed therapy) or a 7-day dose of metronidazole (500 mg twice daily for 7 days) according to randomization. Women in the 7 day arm were further counseled to take all of their medication. All women were instructed to refrain from unprotected sex for 24 hours after completion of medication, and until all partners had completed their medications.

All women were given a 2 g single dose of metronidazole to deliver to each of their identified sex partners. Women were asked to identify their sex partners by initials, which were used only for the purposes of tracking women's responses to partner treatment questions during study follow-up visits. The medicine was dispensed in a child-proof container, with clear and visible instructions to avoid drinking any alcohol for 24 hours after taking the medicine and to take the medication with food. A 24-hour pager number for the study nurse was provided in case the partner had any side-effects or questions. Women were also provided with informational documents about TV and the medication to give to their partners. Medication warnings were also included indicating that partners should not take the medication and go to the sexually transmitted disease clinic of their choice for care if they were taking disulfiram, have known allergies to the medicine, have liver problems, or were unable to refrain from alcohol use. Contact information for public sexually transmitted disease clinics was provided.

A test-of-cure (TOC) visit was scheduled for 6 to 12 days after the index woman completed her medication dose, and this follow-up timeframe was used for women in both treatment arms. At this visit, women were asked to provide a self-collected vaginal swab for TV culture. Women were instructed to insert the swab into the vagina, rotate the swab 3 times, place it in a sterile cup and give it to the study staff. The verbal instructions were accompanied by a diagram. The specimen was then immediately placed in the InPouch medium, incubated and read according to BioMed Diagnostics protocol.²² Women were again interviewed using CASI or computer-assisted personal interview to elicit information on sexual exposure, partner treatment, and adherence to treatment. Sexual exposure between the baseline and TOC visits was classified as: women who reported sexual exposure with a baseline partner and women who reported sexual exposure with a new partner.

Women who tested positive for TV at the TOC visit were considered a repeat infection. Based on self-reported sexual behavior with all sexual partners and self-reported adherence to treatment, 4 categories of repeat infection were determined: lack of treatment adherence (for women who reported not taking all of their metronidazole dose), probable reinfection (for women with sexual exposure to an untreated baseline partner), probable infection by a new sexual partner (for women with no sexual exposure to the baseline partner, but unprotected sex with a new partner), and probable treatment failure (for women with no sexual exposure).

Statistical Analysis

All statistical analyses were conducted using SAS version 9.1. There were 2 units of analyses: (1) the women, and (2) the partners. Univariate analyses were conducted to examine characteristics of the women, as well as characteristics of the partners. Bivariate analyses were conducted to examine the factors associated with providing or not providing PDPT to all partners. At the participant (woman) level, factors were assessed using χ^2 tests. At the partner level, generalized estimating equation was used to accommodate for multiple partnerships for some women in assessing factors associated with a partner receiving or not receiving PDPT. For probable causes of repeat infection, the number and percent of women in each category was assessed.

RESULTS

Baseline Characteristics

Of the 252 women enrolled at the baseline visit, 92.5% ($n = 233$) were black, with a mean age of 40.0 years (SD 9.1). More than half of study participants were taking ART (58.3%, $n = 147$), 26.2% had CD4 cell counts $<200/\text{mm}^3$ ($n = 66$), and 34.1% ($n = 86$) had plasma viral loads $>10,000$ copies (median = 2185 copies). In the past 3 months, 22.6% of participants reported no sex partners ($n = 57$), 62.3% reported 1 sex partner ($n = 157$), and 15.1% reported more than 1 partner ($n = 38$). At baseline, 60.9% ($n = 154$) of participants completed the CASI interview with no or minimal assistance from study staff, and 68.0% of participants did the same at TOC ($n = 159$).

Adherence to PDPT at TOC Visit

Of the 183 women who reported having partners at baseline, 75.4% ($n = 138$) provided PDPT to all of their partner(s), 61.7% ($n = 113$) reported that they were “sure” that all of their partner(s) took the medication, though only 51.9% ($n = 95$) reported actually seeing all partners take the medicine. Of the 45 women who did not provide PDPT to all partners, 8 provided PDPT to some partners but not all, and 37 did not provide PDPT to any partners.

From the women who did not give medication to all of their partners ($n = 45$), the main reason was not being able to get in touch with a partner (46.8%), followed by being afraid of a partner’s reaction (10.6%), not wanting to see a partner again (8.5%), not wanting to give a partner meds (4.3%), a partner got meds from another place (4.3%), and the medication was lost (2.1%). Factors associated with not giving medications to all partner(s) were multiple sex partners in the past 3 months before baseline ($P = 0.03$), being single ($P = 0.006$), and having at least one partner who did not know the index woman’s HIV status ($P = 0.02$). The mean age of women who did not give medications to all of their partners was 37.2 years, which was younger ($P = 0.05$) than the mean age of women who provided PDPT to all of their partners (40.2 years). Race, education level, and employment status were not associated with giving meds to all partners.

In Table 1, partner characteristics are presented on the 218 partners from 183 women at the TOC visit. Almost all of the partners were male, and very few (6.4%, $n = 14$) were reported by the woman to have symptoms for TV. A majority of the partners were delivered meds by the woman (76.6%, $n = 167$) but only 50.5% of the partners were witnessed taking the meds ($n = 110$) by the index woman.

Table 2 presents partner factors associated with PDPT, using generalized estimating equation to accommodate for multiple partnerships for some women. Casual sex partners and partners who did not know the woman’s HIV status were less likely to receive PDPT, with respective P -values of <0.0001 and 0.002. If the woman anticipated that talking to the partner about her TV infection and the need for both of them to take medications would be very or somewhat difficult, partners were less likely to receive PDPT ($P < 0.0001$). Partners with whom women were living with or reinitiated sex with were more likely to receive PDPT ($P = 0.003$ and $P = 0.05$, respectively).

Sexual Exposure at TOC Visit

Of the 234 women who returned for the TOC visit, 16.7% ($n = 39$) reported sexual exposure since the baseline visit with a majority of these women having used condoms all (48.7%, $n = 19$) or most (15.4%, $n = 6$) of the time. Among the women reporting sexual exposure with baseline partners ($n = 33$), 39.4% reported having sex before a partner took their medication ($n = 13$), 21.2% reported having sex before finishing all of their own medication ($n = 7$),

18.2% reported having sex before they and a partner took the medication ($n = 6$), and only 1 woman had a repeat TV infection. Of the women who had sex with an untreated partner ($n = 13$), 53.8% reported using condoms all of the time ($n = 7$) and 30.8% reported using condoms most of the time ($n = 4$). Among the women reporting sexual exposure with a new partner since baseline ($n = 6$), all reported taking their own medication as instructed and 4 women reported not having sex before finishing their medication.

Repeat Infections at TOC Visit

Of the 234 women who returned for the TOC visit, 96.6% reported taking all of their medicine, 10.3% were positive for TV ($n = 24$). Of the 24 women with repeat infection, only 2 reported sexual exposure since the baseline visit. The repeat infections were categorized as follows: 1 (4.2%) was classified as lack of treatment adherence, 1 (4.2%) was classified as a probable case of reinfection, 1 (4.2%) was classified as a probable case of infection by a new sexual partner, and 21 (87.5%) were classified as probable cases of treatment failure (Table 3). There was no difference in median time to follow-up (TOC visit) for women with a repeat infection versus women with no repeat infection (10.5 vs. 8.0 days, $P = 0.53$).

DISCUSSION

In this study, high rates of adherence to PDPT were found among HIV-infected women who were treated for TV. Despite the high rate of partner treatment, 10.3% of the women tested positive for TV at the TOC visit. This rate of repeat infection is similar to our prior study of HIV-infected women who were provided PDPT (18.3%)¹⁶ and lower than 2 other studies of HIV-infected women from the same site where PDPT was not provided (36% and 37%).^{2,17}

The Centers for Disease Control and Prevention has stated that there is not enough evidence to support recommending PDPT for partner management among patients with TV.²¹ Other than anecdotal evidence, only one randomized clinical trial of PDPT for TV among non-HIV infected women has been published which showed that whereas PDPT was less costly than standard partner referral, provision of PDPT to TV-infected women did not result in more partners taking the medicine or lower rates of repeat TV infection at test of cure.¹⁸ In the trial of PDPT for TV, all arms received counseling beyond the standard of care which may have diminished the effect of PDPT. Furthermore, the trial was conducted among non-HIV infected women, which may not be generalizable to HIV-infected women. The effectiveness of PDPT for partner management among HIV-infected women with TV has not yet been assessed, although the current study shows that these women are adherent to PDPT.

Similar to our prior study of repeat TV infections among HIV-infected women,¹⁶ the repeat infections in this study were largely due to probable treatment failure. The prevalence of metronidazole-resistant TV has been estimated to be 2.5% to 9.6%^{23–25} and is suspected to be on the rise.²⁶ The parent study to this substudy will determine which dose of metronidazole is superior and how much metronidazole-resistance exists among HIV-infected women.

Because all sexual and partner-related behavior was determined from women's self-report, it is possible that sexual exposure and partner treatment were misclassified. Future studies of repeat TV infections among HIV-infected women should include genotype testing, which may help to determine whether the repeat infection was from the original partner or not, irrespective of the woman's reported behavior.

One of the factors associated with not giving PDPT to a partner was having a partner who was thought to be unaware of the woman's HIV-positive status. This suggests that one of the

barriers to sexually transmitted infection partner treatment among HIV-infected women is fear of disclosure. For these women, the option of third party notification (such as a provider or a disease intervention specialist) should be considered.

This was not a randomized trial of PDPT, so it is not possible to say whether PDPT reduced the repeat infection rate. However, the overwhelming adherence to PDPT demonstrates that it is acceptable. Given the high rates of repeat TV infections among HIV-infected women and the findings that TV increases HIV shedding, the provision of PDPT or some form of EPT among HIV-infected women with TV needs further consideration and research.

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TABLE 1

Description of Sexual Partners and Partner Treatment Details From HIV+TV+Women (n =218, Number of Partners)

	N (%)
Partner is male	214 (98.2%)
Woman delivered meds to partner	167 (76.6%)
Woman saw the partner take the meds	110 (50.5%)
Woman delivered meds to partner * and very sure that partner took meds	132 (79.0%)
Partner given meds the same day woman received meds from clinic	127 (58.3%)
Partner was symptomatic for TV	14 (6.4%)

*
n = 167.

TABLE 2

Factors Associated With Patient (HIV+/TV+ Woman) Delivery of Medication to Partners (N = 183 Women; 218 Observations, Done by GEE)

	Delivered Medication to Partner (n = 167 Partners) %	Did not Deliver Medication to Partner (n = 51 Partners) %	P
Casual sex partner	17.7%	51.2%	<0.0001
Living with partner	41.6%	14.6%	0.003
Partner does not know woman's HIV positive status	21.1%	43.9%	0.002
Talking to partner about TV infection and meds will be very or somewhat difficult	23.4%	61.0%	<0.0001
Reinitiated sex with partner	18.4%	6.1%	0.05

TABLE 3

Possible Causes of Repeat TV Infections Among HIV+ Women (N = 24)

Repeat Infection Category	N (%)
Lack of treatment adherence	1 (4.2%)
Probable reinfection	1 (4.2%)
Probable new infection	1 (4.2%)
Probable treatment failure	21 (87.5%)