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The influence of bacterial vaginosis on the response to *Trichomonas vaginalis* treatment among HIV-infected women

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Abstract

Objective—*Trichomonas vaginalis* (TV) is common in HIV+ women, and host factors may play a role in TV treatment outcomes. The purpose of this study was to examine the influence of bacterial vaginosis (BV) on the response to TV treatment among HIV+ women.

Methods—A secondary analysis was conducted of a clinical trial which randomised HIV+/TV+ women to metronidazole (MTZ) treatment: 2 g (single-dose) versus 7 day 500 mg twice daily (multidose). BV was classified using Nugent scores from baseline Gram stains. Women were recultured for TV at test-of-cure (TOC) and again at 3 months if TV-negative at TOC. Repeat TV infection rates were compared for women with a baseline TV/BV coinfection versus baseline TV infection only, and stratified by treatment arm.

Results—Among 244 HIV+/TV+ women (mean age=40.3, ±9.5; 92.2% African–American), the rate of BV was 66.8%. Women with BV were more likely to report douching and ≥1 recent sex partners. HIV+ women with baseline TV/BV coinfection were more likely to be TV-positive at TOC than women with baseline TV infection only (RR 2.42 (95% CI 0.96 to 6.07; p=0.05)). When stratified by treatment arm, the association was only found in the single-dose arm (p=0.02) and not in the multidose arm (p=0.92). This interaction did not persist at 3 months.

Conclusions—For HIV+/TV+ women, the rate of BV was high, and BV was associated with early failure of the MTZ single-dose treatment for TV. Biological explanations require further investigation.

INTRODUCTION

Trichomonas vaginalis (TV), a common sexually transmitted infection among HIV-positive women,[1–7] has been associated with increased genital HIV shedding.[89] Effective TV

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treatment has been shown to reduce genital shedding[10,11] and may therefore be an important HIV prevention strategy. However, high rates of repeat TV infections among HIV-infected women have been reported (9% to 36%).[2,12–16] While the source of these repeat infections is not known, evidence is mounting that most of the repeat infections can be attributed to clinical treatment failure rather than organism-related metronidazole (MTZ) resistance[13,17] or reinfection from an untreated partner.[13,17]

Our recent randomised clinical trial (RCT) found the multidose MTZ (500 mg twice a day for 7 days) to be more effective than the single-dose MTZ (2 g) for the treatment of TV among HIV-infected women.[14] The reason for the failure of the single-dose needs further elucidation. The present study is a secondary analysis of that RCT.

One clinical factor could be the presence of bacterial vaginosis (BV) which is also treated with MTZ. In prior research with HIV-positive women, we found the prevalence of TV/BV coinfection to be 17.5%, and the rate of BV among HIV-positive/TV-infected women to be 61.0% with many of the women not having discharge (40.6%).[18] The Centers for Disease Control and Prevention recommends the MTZ 2 g single-dose as a treatment regimen for TV; however, this dosage is inadequate for the treatment of BV.[19] HIV-positive/TV-positive women who are coinfected with asymptomatic or undiagnosed BV may remain inadequately treated for BV, and the influence of BV on TV treatment outcomes merits investigation. The purpose of this study, therefore, was to examine the influence of BV on the response to TV treatment among HIV-infected women to determine if BV could be a factor in MTZ single-dose treatment failure.

METHODS

Participants

Data were collected during our previously reported phase IV RCT comparing two doses of MTZ for the treatment of TV among HIV-infected women. This study was conducted from May 2006 to July 2009; detailed methods have been published elsewhere.[14] In brief, HIV-infected women were tested for TV by culture during routine gynaecological examinations. Women were patients attending selected public HIV outpatient clinics in New Orleans, Louisiana; Houston, Texas; and Jackson, Mississippi. Inclusion criteria were: HIV infection (confirmed by Western Blot), ≥18 years old, English-speaking, TV positive by culture and willing to take the MTZ treatment. Exclusion criteria were: pregnancy, incarceration, taking disulfiram or treated with MTZ within the previous 14 days. Other exclusion criteria, per provider discretion, were: diagnosis of symptomatic BV, medical contraindications to MTZ or unable to provide informed consent. This study was approved by Tulane University Institutional Review Board (Tulane IRB# K0231).

Treatment and follow-up

HIV+/TV+ participants were randomised to receive the MTZ 2 g single-dose or the MTZ 500 mg twice-daily 7-day multidose. The entire single-dose (four pills) and the first pill (500 mg) of the multidose were given under direct observation. Women in both treatment arms were also provided with MTZ 2 g single doses to deliver to their sex partner(s).

A test-of-cure (TOC) visit was scheduled for 6–12 days after the participant completed her medication dose. Women with positive TV results at the TOC visit were considered an early repeat infection and were retreated. Women who tested negative for TV at the TOC visit, or who did not complete a TOC visit, were scheduled for a follow-up visit at 3 months after enrolment. This visit was done to include women with possible persistent, undetected TV at the TOC visit.[20,21]

T vaginalis culture

Participants were tested for TV at all study visits using the InPouch culture (Biomed Diagnostics, White City, Oregon). Specimens were processed and stored per the manufacturer's protocol.

BV classification

A provider-collected vaginal swab was carefully rolled over a predefined area of a glass slide and placed in a cover to air dry. After participant enrolment, the slide was sent to the core laboratory for subsequent staining and reading. Gram stains were scored using Nugent criteria,[22] with a score ≥7 considered BV.

Data collection

At baseline, participants completed an audio computer-assisted self interview, or computer-assisted personal interview, depending on the participant's comfort with computers. The baseline survey elicited information about participants' sociodemographics, substance use, douching practices and sexual behaviour. Study staff also abstracted information on prescribed antiretrovirals, CD4 cell count and plasma viral load from participants' clinic charts.

Statistical analysis

All statistical analyses were conducted using SAS version 9.1. HIV+ women with TV and BV (TV/BV coinfection) were compared with HIV+ women with TV infection only. Baseline associations between BV status and selected sociodemographic, behavioural, and clinical characteristics were examined using the χ^2 or Fisher exact test as appropriate. The outcome of interest was repeat TV infection. The measure of association at TOC and 3 months was calculated as an RR with 95% CI, to examine the relationship between TV/BV coinfection status and repeat TV infection status. Results were then stratified by treatment arm.

RESULTS

Of the 270 HIV+/TV+ women in the RCT, 244 (90.3%) participants had complete Gram stain results and were included in this analysis. The majority of these women were African–American (92.2%, n=225), and the mean age was 40.3 years (±9.5).

Signs associated with BV were present, with 52.2% of women having a positive whiff test (121/232) and 31.5% of women having clue cells present on wet preparation (73/232). Median vaginal pH was 5.3 (range 3–7, total n=173) and 85.6% of the women had a vaginal pH>4.5 (n=148). The distribution of Nugent scores was: 8.2% with scores of ≤3 (n=20), 25.0% with scores of 4–6 (n=61) and 66.8% with scores ≥7 (n=163). Therefore, 66.8% of HIV+/TV+ women also had BV (n=163). The rate of BV did not differ by treatment arm (68.8% (86/125) in the single-dose vs 64.7% (77/119) in the multidose arm: p=0.50).

At baseline, HIV+/TV+ women with BV were more likely to report douching (p=0.04) and having ≥1 sex partners in the past 3 months (p=0.02) compared with the HIV+/TV+ only women (table 1). No other differences were found by BV status.

Table 2 presents TV culture results by follow-up and treatment arm. At TOC, women with a baseline TV/BV coinfection were more likely to be positive for TV compared with those with a baseline TV infection only (RR 2.42 (95% CI 0.96 to 6.07; p=0.05)). When TOC results were stratified by treatment arm, this association was evident in the single-dose arm

(RR 4.16 (95% CI 1.02 to 16.89; p=0.02)) but not in the multidose arm (RR 1.07 (95% CI 0.28 to 4.04; p=0.92)).

Repeat infections were also examined at 3 months, excluding participants who were TV-positive at TOC and treated or those who received MTZ for any other reason during the interim. At 3 months, women with a baseline TV/BV coinfection were just as likely to test positive for TV compared with women with a baseline TV infection only for both arms combined and when stratified by arm.

DISCUSSION

Our recent RCT found that the MTZ multidose was superior to the single dose for the treatment of TV among HIV-infected women.[14] The current study used data from the trial to examine the possible influence of BV on the response to treatment of TV infection. Among those given a single-dose treatment, women with baseline TV/BV coinfection were 4.2 times more likely to be TV-positive at TOC than those with baseline TV infection only. This difference was not seen among women given the multidose and was not observed for either dose at 3 months.

These data suggest that the vaginal environment associated with BV at the time of TV treatment in some way partially protects the organism (TV) from the effects of single-dose MTZ, but over a more prolonged period of time the effect is largely lost. These observations are of considerable interest because in the main results from the trial, the superiority of the MTZ multidose over the single-dose treatment was shown at TOC and very clearly persists at the 3-month visit.[14] One possible explanation for the TOC results could be that TV growth is more robust in the presence of BV resulting in higher parasite numbers in dually infected women at the time of treatment. If equal proportions of TV are killed by single-dose MTZ in the BV and non-BV-infected women, the number of surviving organisms in the latter group would have been higher than that in the former and could have resulted in the observed differences in apparent cure rate at the TOC visit. Alternatively, the vaginal flora associated with BV may have inactivated MTZ to the extent that treatment success was greater among women with TV alone. While there are no data in the literature to support the former hypothesis, there are such data in support of the latter.

The influence of the vaginal environment on TV treatment has been alluded to in other studies. Over 40 years ago, Nicol *et al*.[23] reported the possibility that inactivation of MTZ might be the cause of multiple treatment failures in a woman infected with a TV strain that was susceptible to the drug in vitro. A few years later, McFadzean *et al*.[24] described inactivation of MTZ by bacteria isolated from 16 samples taken from 84 women with TV vaginitis. Ten of the organisms were Gram-positive cocci including seven cases of *Streptococcus* (*Enterococcus*) *faecalis*. The six others were Gram-negative rods including *Escherichia coli, Proteus* spp and *Klebsiella* spp. More recently, several papers have reported that various members of the genus *Enterococcus* are capable of inactivating MTZ.[25–27] Deep sequencing studies have not found many of these organisms in patients with BV,[28–30] but it could be that even minor populations of certain organisms or combinations of organisms may have the ability to inactivate MTZ to a clinically significant degree.

Our findings shows that BV has no effect on TV treatment outcome in women taking the MTZ multidose treatment, clearly implying that drug inactivation, if in fact this occurs, by BV flora is not complete. In our previous studies, we proposed that MTZ treatment induces a state of latency in TV to the extent that some treatment failures may not be detectable by culture shortly following treatment but are detectable by culture after longer time

intervals.[1420] Our data suggest that by one mechanism or another, BV unmasks this effect, resulting in early detection of treatment failure. Among women without a BV single dose treatment, failures go undetected until a longer interval post-treatment has passed. The use of nucleic acid TV amplification assays in conjunction with culture as well as measurement of MTZ concentrations in vaginal fluid obtained from women with well-characterised vaginal flora will be necessary in order to test the various hypotheses raised by our observations.

There are a few limitations to the current study. Because Gram-stain specimens were not obtained at the TOC and 3-month visits, we do not know if BV was resolved. Also, symptomatic women meeting Amsel criteria for BV were excluded from the RCT; thus, the full spectrum of BV disease is not represented in this analysis. However, their exclusion is unlikely to have altered the outcome, as there is no evidence that symptomatic BV would have had less effect than asymptomatic BV on MTZ single-dose treatment outcomes for TV. Our findings are not generalisable to HIV-uninfected individuals and perhaps not even to younger HIV+ women. It will be of considerable interest to determine if the effect of BV on MTZ single-dose TV treatment, the current standard of care for TV infection, is a reproducible phenomenon in HIV-uninfected women who represent the vast majority of TV cases.

The rate of BV at baseline, per Nugent score, was high (66.8%) in this group of HIV+/TV+ women which is consistent with other screening studies.[20] In many clinical settings, women are inconsistently screened and underdiagnosed for BV. Amsel criteria, commonly used for diagnosing BV at the point of care,[31] have demonstrated low sensitivities among HIV+ women (34–37%).[432] In the current study, only 30% of TV/BV coinfected women had clue cells, and only 55% had a positive whiff test. In the absence of more sensitive point-of-care tests, a diagnosis of BV will be frequently missed among HIV+/TV+ women. Given the frequency of BV in HIV+/TV+ women, and the likelihood of underdiagnosis of BV, it may be more efficient to presumptively treat TV-infected women for BV, as is often done for urethritis and cervicitis.[19]

Our trial results show that the MTZ multidose treatment is tolerated as well as the single dose.[14] Therefore, the main conclusion of the RCT is not altered by the analyses presented here, that is, the MTZ 2 g single dose should no longer be recommended for the treatment of TV among HIV-infected women. The mechanism by which BV alters MTZ treatment outcome in TV-infected women requires further exploration.

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Key messages

- HIV+ women with *Trichomonas vaginalis* (TV) infection had a high rate of bacterial vaginosis (BV).
- The women with TV and BV who were treated with the metronidazole 2 g single-dose were more likely to be culture positive for TV at the test-of-cure visit.
- Biological bases for the observation of BV altering MTZ treatment outcome of TV require further investigation.

Table 1

Baseline characteristics of HIV+/*T vaginalis* + women by bacterial vaginosis status (N=244)

	Percentage coinfection *T vaginalis*/ bacterial vaginosis (n=163)	Percentage single infection *T vaginalis* (n=81)	p Value
Demographic			
Africane–American	92.6	91.4	0.60
≥40 years of age	49.7	56.8	0.30
Married or cohabitating	26.4	25.9	0.94
Unemployed	71.2	67.9	0.55
Did not graduate from high school	45.4	35.8	0.14
Behavioural			
Regularly smokes cigarettes	46.6	35.8	0.11
Drank alcohol in past week	39.9	32.1	0.24
Douches	73.6	60.5	0.04
≥1 sex partner in past 3 months	81.0	69.1	0.02
HIV disease			
On antiretroviral therapy	67.5	59.3	0.21
CD4 cell count ≤200 mm^3	25.2	35.8	0.10
Plasma viral load >10 000 copies	33.1	39.5	0.40
Other infections			
Chlamydia †	2.1	2.8	0.66 *
Gonorrhoea †	1.4	2.8	0.60 *
Clinical			
Unusual vaginal discharge in past week by self-report	47.9	39.5	0.22
Unusual vaginal odour in past week by self report	35.0	29.6	0.40
Unusual vaginal itching or irritation in past week by self-report	42.3	43.2	0.90
Pain while urinating in past week by self-report	14.7	8.6	0.18
No vaginal symptoms in past week	31.3	30.9	0.95
Provider exam: discharge amount ‡			0.24
Scant	46.6	43.5	
Moderate	34.6	44.9	
Large	18.8	11.6	
Provider exam: discharge colour §			0.98
Clear	13.2	12.5	
White	65.9	67.2	
Yellow	20.9	20.3	
Provider exam: discharge consistency ¶			0.39
Thin	51.2	42.6	
Thick	35.6	45.6	
Frothy	13.2	11.8	

	Percentage coinfection *T vaginalis*/ bacterial vaginosis (n=163)	**Percentage single infection *T vaginalis* (n=81)**	**p Value**
Positive whiff test[¶]	55.1	46.0	0.19
Clue cells present on wet prep [**]	30.1	34.2	0.53
Vaginal pH>4.5[††]	87.7	81.4	0.26

[*] Fisher exact test.

[†] Total n=218.

[‡] Total n=202.

[§] Total n=193.

[¶] Total n=197.

[**] Total n=232.

[††] Total n=173.

Table 2

Post-treatment repeat *T vaginalis* (TV) infection rates at test-of-cure and 3 months by baseline bacterial vaginosis status and metronidazole treatment arm among HIV-positive women

	Percentage overall repeat infection rate TV+ (n)	Percentage baseline coinfection TV/bacterial vaginosis	Percentage baseline single infection TV	RR (95% CI)	p Value
Test-of-cure (N=230)	13.0 (30/230)	16.1 (25/155)	6.7 (5/75)	2.42 (0.96 to 6.07)	0.05
Single-dose	18.3 (21/115)	23.8 (19/80)	5.7 (2/35)	4.16 (1.02 to 16.89)	0.02
7-day dose	7.8 (9/115)	8.0 (6/75)	7.5 (3/40)	1.07 (0.28 to 4.04)	0.92
3 month (N=138)	16.7 (23/138)	19.1 (16/84)	13.0 (7/54)	1.47 (0.65 to 3.34)	0.35
Single-dose	22.2 (16/72)	25.6 (11/43)	17.2 (5/29)	1.48 (0.58 to 3.82)	0.40
7-day dose	10.6 (7/66)	12.2 (5/41)	8.0 (2/25)	1.52 (0.32 to 7.27)	0.70 Fisher exact test

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