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Is It Time to Stop Using Single Dose Oral Metronidazole for the Treatment of Trichomoniasis in Women?

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Abstract

The 2015 Centers for Disease Control STD Treatment Guidelines currently recommend a single 2-gram dose of oral metronidazole (MTZ) as the preferred regimen for treatment of trichomoniasis in HIV-negative women. Mounting recent evidence has shown that the 7-day oral MTZ dosing regimen is more efficacious than the single 2-gram dose. This commentary reviews the implications associated with these new data and discusses issues surrounding it that should be considered moving forward.

Short Summary:

This commentary reviews the implications associated with new trichomonas treatment data in women, which suggests that all women should be treated with 7-days of oral metronidazole.

Trichomonas vaginalis is the most common curable, non-viral sexually transmitted infection (STI) worldwide.[1] It is associated with multiple adverse outcomes including premature rupture of membranes, preterm birth, low-birthweight infants, infertility, and increased risk of human immunodeficiency virus (HIV) acquisition.[2–5] Despite its high prevalence and substantial morbidity, it is considered a neglected STI [6–8] due to a limited public health response.[9–11]

Per the 2015 CDC STD treatment guidelines [12], first line treatment for trichomoniasis in HIV-negative women and men includes a single 2-gram dose of oral metronidazole (MTZ) or tinidazole (TIN). Oral MTZ 500 mg twice daily for 7 days is an alternative therapy. These recommendations were based on several small trials conducted over 30 years ago that found no difference between the two doses but were not powered for equivalency. A meta-analysis of these studies showed that women receiving the 7-day regimen of oral MTZ were 50% less likely to be positive at test of cure (TOC) compared to those receiving single-dose.[13] In addition, a prior randomized controlled trial (RCT) of HIV-infected women with *T. vaginalis* found that the 2-gram dose of oral MTZ was less effective than 7-days.[14] High rates of

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concurrent bacterial vaginosis (BV) may be one factor interfering with single-dose therapy, as the vaginal environment associated with BV may partially protect *T. vaginalis* from the effects of single-dose MTZ.[15] Thus, it is recommended to treat HIV-infected women with trichomoniasis with 7-days of oral MTZ, which also treats BV.[12] However, it is important to note that this recommendation is independent of BV status.

We recently conducted a randomized controlled trial of the single 2-gram dose of oral MTZ versus the 7 day dose for treatment of trichomoniasis in HIV-uninfected women.[16] Of 623 women randomized, those in the 7-day arm had 45% fewer treatment failures than those receiving the single dose. In contrast to the prior RCT in HIV-infected women [14], risk for *T. vaginalis* at TOC was similar by BV status in this study. Self-reported medication adherence was >95% in both arms. We concluded that the 7-day regimen of oral MTZ should be the preferred treatment for trichomoniasis among HIV-negative women.

The implications of this RCT prompted us to write this commentary to readers of the *Sexually Transmitted Diseases* journal, the official publication of the American STD Association, as many are thought leaders with expert opinions in this field. In particular, should the next version of the CDC STD treatment guidelines be changed to recommend the 7-day oral MTZ regimen as the first-line treatment regimen for all women with trichomoniasis? Will adherence with the 7-day regimen become an issue ‘in the real world’ if this becomes the preferred treatment? How will a change to the 7-day regimen in women impact the treatment of men with *T. vaginalis* or who are a contact to a female partner with *T. vaginalis*, as men are still receiving the single 2-gram dose of oral MTZ? And how will this change impact expedited partner therapy (EPT) of trichomoniasis, as it is currently permissible in the majority of U.S. states? [17] These discussions recently came up at our monthly meeting with physician colleagues at our local health department STD clinic in Birmingham, AL and there were no easy answers. Our STD clinic sees a large number of HIV-negative *T. vaginalis*-infected women and men (primarily African American) [18] and is currently providing the single 2-gram oral MTZ dose for therapy for HIV-negative women and men with trichomoniasis per standing orders.

In addition to better efficacy than single-dose MTZ in our recent RCT, another reason advocating for a change in the preferred treatment regimen for *T. vaginalis*-infected women to 7-days is the large, ongoing burden of *T. vaginalis* infection among U.S. women. According to the most recent NHANES data (2013–2014 cycle), *T. vaginalis* infection prevalence was 1.8% among U.S. women ages 18–59 years.[19] It was almost 5 times higher among U.S. African American women (8.9%), signifying a pronounced racial disparity that continues to exist. Further interventions are needed to reduce this high and disproportionate burden of *T. vaginalis* infection, particularly in African American women, one of which could be more highly efficacious treatment. Although our RCT had several limitations (enrollment was lower than planned and the study population consisted mainly of symptomatic African American women from urban areas), we do not believe that these limitations would dampen enthusiasm for a change in guidelines.

On the other hand, one could argue that treatment adherence could become a problem if the 7-day regimen becomes the preferred regimen. The 2-gram oral MTZ dose is attractive as it

can be given to patients as directly observed therapy. In contrast, the 7-day regimen will require patient adherence over a period of time. Non-adherence to medication is well-known to lead to decreased treatment effectiveness and potential worsening of a patients' condition.[20] With respect to STIs, this could lead to ongoing STI transmission and drug resistance. Treatment adherence was high and not significantly different between arms in our recent *T. vaginalis* RCT [16] and in the prior *T. vaginalis* RCT of HIV-infected women.[14] However, these were highly controlled clinical trials in which participants received monetary compensation and were not 'real world' situations, as mentioned by Keizur and Klausner in their editorial to our RCT.[21] In a study of 91 predominately African America women prescribed multi-dose oral therapies for pelvic inflammatory disease, participants took approximately 70% of their twice daily doses, took the medications for less than half of their outpatient days, took an unscheduled drug holiday almost 25% of the time, and took only 16.9% of their doses within the optimal timing interval.[22] In light of these suboptimal treatment adherence rates, data on patient adherence to the 7-day oral MTZ regimen for trichomoniasis in 'real world' situations is needed. The most logical population in which to obtain these data is HIV-infected women with trichomoniasis, as guidelines currently recommend the 7-day oral MTZ dose.[12]

Another issue that will arise if providers change to the 7-day oral MTZ regimen is how will this impact the treatment of men who are their sexual contacts and/or who are diagnosed with *T. vaginalis*? Will we continue to treat them with the single 2-g dose of oral MTZ? To our knowledge, a RCT comparing the efficacy of the single 2-g dose of oral MTZ with the 7-day regimen for trichmoniasis in men has not been conducted; our recent RCT only included women. And how would the spontaneous resolution of trichomoniasis in men factor into this situation? In a RCT of non-gonococcal urethritis (NGU) treatment among men [23], 11/16 (69%) not receiving treatment for trichomoniasis had apparent spontaneous resolution of their infection during follow-up. Also, from a practical standpoint, if a woman is treated with the 7-day regimen but her male partner(s) are treated with the single 2-gram dose, there could be a conflict in the timing of abstinence from sex, which could put the couple at risk for re-exposure. These questions should be taken into consideration when counseling patients on *T. vaginalis* treatment.

Enhanced counseling messages should be provided to women receiving the 7-day oral MTZ dose to try to head off these potential issues. Counseling messages should include the need to take the entire 7 days of medication (preferably with non-dairy foods such as crackers to reduce nausea and vomiting), use cell phone alarms to set medication reminders, do not share the medication, and do not have sex until both the patient and her partner(s) have been treated. Anecdotally, there is an additional issue that has come up in our HIV clinic practice. Women receiving the 7-day regimen for a current episode of trichomoniasis may know that in the past a single 2-gram dose of oral MTZ was used. Because of this, they may take a single 2-gram dose when given the 7-day dose. They may share also their medication with their partner(s), since there are three possible 2-gram doses in a 7-day pill bottle. Enhanced counseling services should be provided to women receiving the 7-day oral MTZ regimen to try to avert this potential issue.

Finally, how will changing to the 7-day oral MTZ treatment regimen in all women with trichomoniasis impact EPT in states allowing this practice? While most states allow for EPT, uptake has been relatively low for chlamydia and gonorrhea.[24,25] It is currently unclear how often EPT is prescribed for partners of patients with trichomoniasis. Moving forward, should providers give women the 7-day oral MTZ regimen for their male partner(s)? And what about female sexual partners? These important topics should be addressed in the next version of the CDC STD treatment guidelines.

In conclusion, new RCT data strongly suggest that the 7-day oral MTZ regimen should be the preferred *T. vaginalis* treatment regimen in all women. We advocate for this change in the next version of the CDC STD treatment guidelines. However, this change must be accompanied by effective counseling messages that describe how to mitigate the side effects of oral MTZ as well as stress the importance of adherence to therapy and partner treatment.

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