

Update on Trichomoniasis

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Disclosures/Acknowledgements

- Susan Tuddenham is a consultant for Biofire Diagnostics
- Thank you to Khalil Ghanem, and Anne Rompalo for many of these slides!

A woman with vaginal discharge...

Case 1: A woman with vaginal discharge

HPI: A 43 year old **HIV-infected** woman (CD4 780 cells/mm³; HIV RNA undetectable) presents complaining of a **vaginal discharge** for 5 days associated with dyspareunia, itching. No dysuria, hematuria, abdominal pain, fevers or chills

PMHx: HIV diagnosed in 2013; nadir CD4 420 cells/mm³. Papanicolou smear 4 months earlier was normal

Medications: Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy).

Allergies: NKA

Social: Administrative assistant; no recent travel; 2 sex partners in the past year (one new HIV- male partner she met 3 months earlier); unprotected receptive oral and vaginal sex

Case 1

Physical Examination: GI/GU: Copious thin greenish vaginal discharge; vagina and cervix without lesions; no abdominal, cervical motion, or adnexal tenderness

POC Laboratory Testing: Wet Mount: pH **5.5**; no clue cells and no amine odor with the addition of KOH; **motile trichomonads** noted on microscopy; urine pregnancy test was negative.

Laboratory Testing: throat swab for GC/CT; vaginal swab for GC/CT; syphilis serologies.



Which of the following medications would you prescribe at this time?

- A. Metronidazole 2g orally X 1 dose
- B. Metronidazole 500mg orally twice daily for 7 days
- C. Tinidazole 2g orally X 1 dose
- D. Metrogel 0.75% topical for 5 days

Which of the following medications would you prescribe if she were **not** HIV-infected?

- A. Metronidazole 2g orally X 1 dose
- B. Metronidazole 500mg orally twice daily for 7 days
- C. Tinidazole 2g orally X 1 dose
- D. Metrogel 0.75% topical for 5 days

Differential Diagnosis: Vaginal discharge

CERVICITIS

Gonorrhea

Chlamydia

?Mycoplasma genitalium

VAGINITIS

Trichomonas

Bacterial Vaginosis

Vulvovaginal Candidiasis

Non infectious causes of vaginitis symptoms

Atrophic vaginitis

Erosive lichen planus

Lichen sclerosis

Desquamative inflammatory vaginitis

Pemphigoid

Contact/Irritant Dermatitis

Seborrheic or eczematoid dermatitis

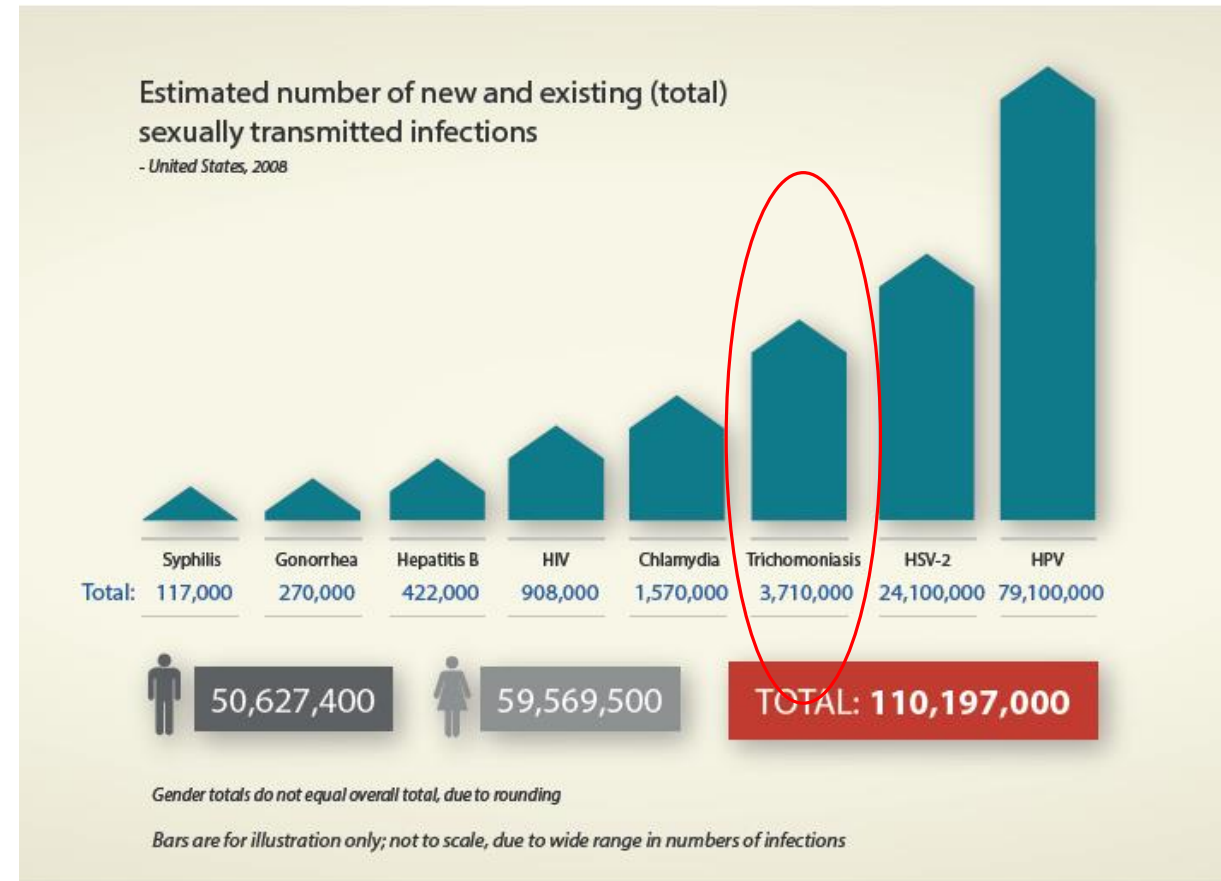
Psoriasis

Vulvodinia

- Vaginal symptoms: irritation from Herpes Simplex Virus

Trichomonas vaginalis

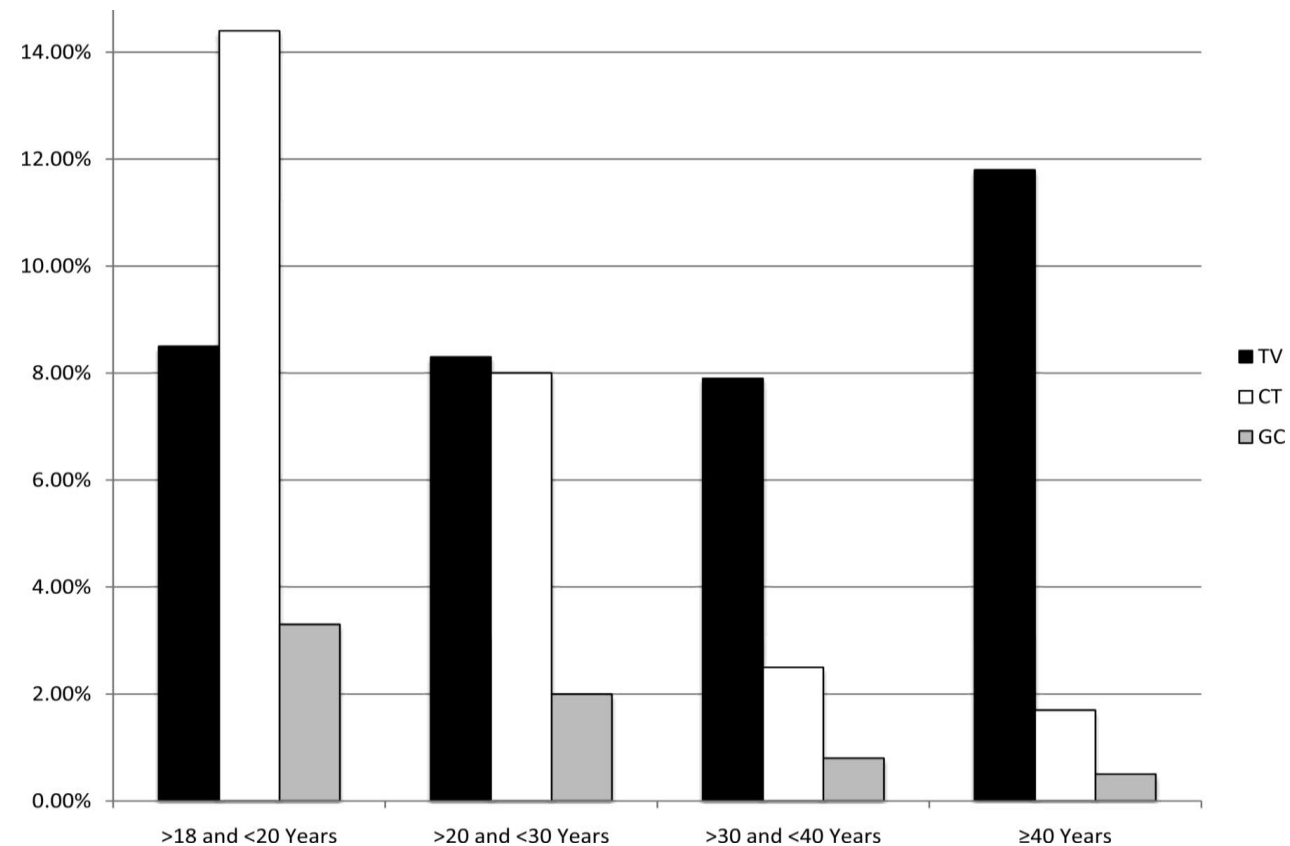
- Parasite
- Transmission is almost exclusively sexual
- Most common non-viral STI!



<https://www.cdc.gov/std/stats/sti-estimates-fact-sheet-feb-2013.pdf>

Trichomonas-epidemiology

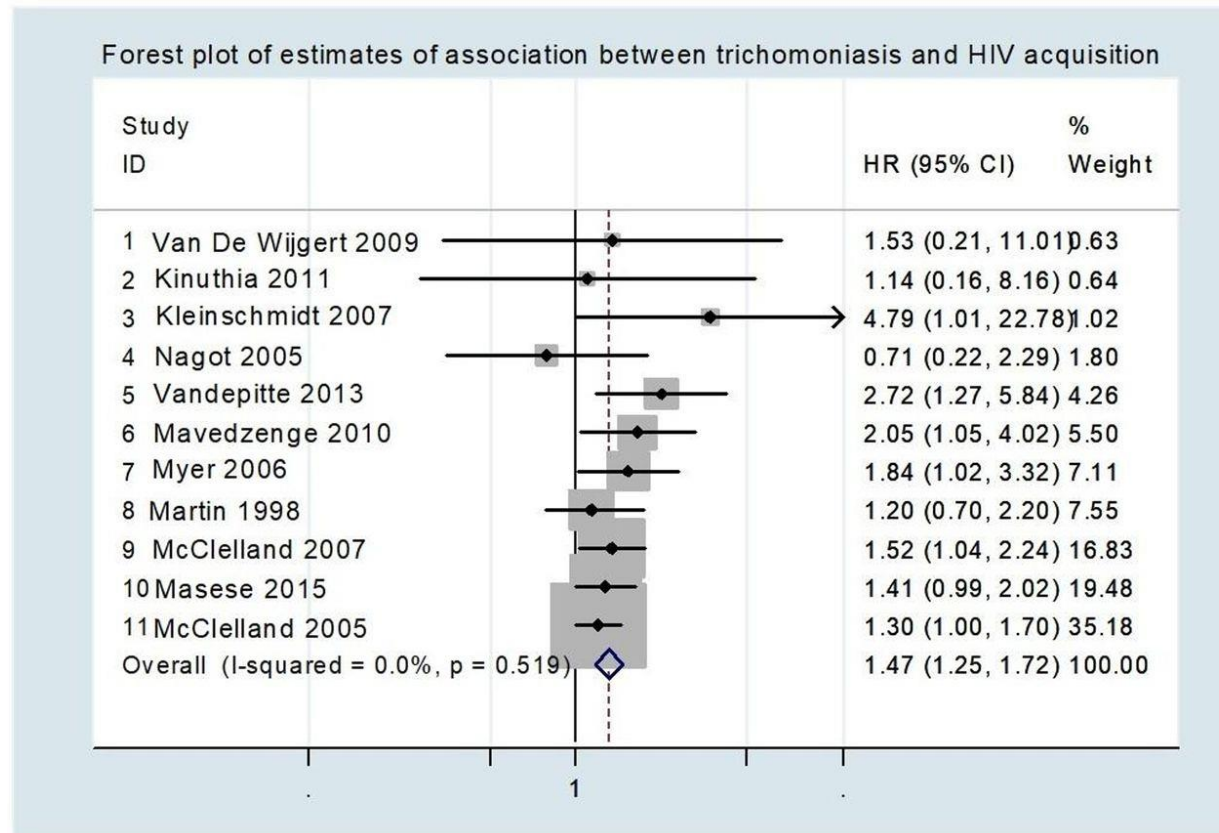
NAAT prevalence of TV, CT and GC infections among 7593 US women age 18-89, by age group.



Trichomonas-epidemiology

- 13.3% prevalence in African American women, 1.3% in Caucasian Women, 1.8% in Mexican American women (Sutton et al. CID 2007)
- NHANES data: 0.5% in men, 1.8% in women, 8.9% in African American women, 4.2% in African American men (Patel et al CID 2018)
- 10-43% in HIV+ women, recent study at HIV clinic: 17.4% of women tested were positive via NAAT. (Muzny et al. STD 2016)

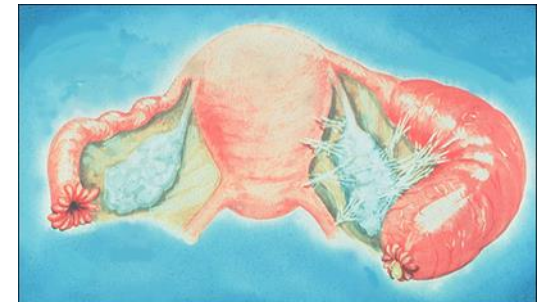
Trichomonas: Increases HIV risk



Trichomonas infection enhances HIV acquisition by **50%**. HR: 1.5 (95% CI: 1.3-1.7)

Trichomonas-Symptoms

- Majority **asymptomatic** (85% of women)
- Women: Vaginal discharge (may be with odor), pruritis and pain with urination or sex.
 - Pelvic Inflammatory Disease in **HIV+** women
- Men: Urethritis (MSW)



Trichomonas-Diagnosis



- pH usually > 5,
- May see frothy greenish or yellowish discharge, strawberry cervix; can cause a cervicitis.
- Wet prep: Motile trichomonads (sensitivity 51-65%)
- Nucleic acid amplification (NAAT)
 - >95% sensitive and > 95% specific
 - Several assays FDA-cleared for vaginal, endocervical or urine specimens from women and urine or urethral swabs from men if lab is CLIA certified to run
- CLIA waved Point of care tests for women:
 - OSOM Trich Rapid test (10 minutes with 82-95% sensitivity and >97% specificity; self-testing is an option)
 - Affirm VP III (45 minutes, with sensitivity 63% and specificity 99%)
- NO for PAP tests: too many false negatives and positives.

Strawberry Cervix



Diagnostic Criteria	Vaginitis Syndrome			
	Normal	Bacterial vaginosis	Candida vulvovaginitis	Trichomonas vaginitis
Vaginal pH	3.8-4.2	>4.5	≤4.5 (usually)	>4.5
Discharge	White, clear, flocculent	Thin, homogeneous, white, gray, adherent, often increased	White, curdy, “cottage Cheese” like, sometimes increased	Yellow, green, frothy adherent, increased
Amine odor (KOH “whiff test)	Absent	Present (fishy)	Absent	Present (fishy but not always)
Microscopic exam	Lactobacilli	Clue cells, coccoid bacteria, no WBCs	Mycelia, budding yeast, pseudohyphae with KOH	Trichomonads, WBCs >10/hpf
Main patient complaints	None	Discharge, bad odor, itching	Itching/burning discharge	Frothy discharge, bad odor, vulvar pruritis, dysuria

Trichomonas-Treatment

- Metronidazole 2 g PO in a single dose OR
- Tinidazole 2 g PO in a single dose

- Alternate Regimen: Metronidazole 500 mg PO BID for 7 days
- Expedited Partner Therapy: Metronidazole 2 g PO in a single dose

- No alcohol (24 hours MTZ; 72 hours TNZ);
- Metronidazole gel is not recommended...does not reach therapeutic levels in the urethra/perivaginal glands
- Tinidazole is not recommended in pregnancy (animal studies)

Trichomonas and HIV infection

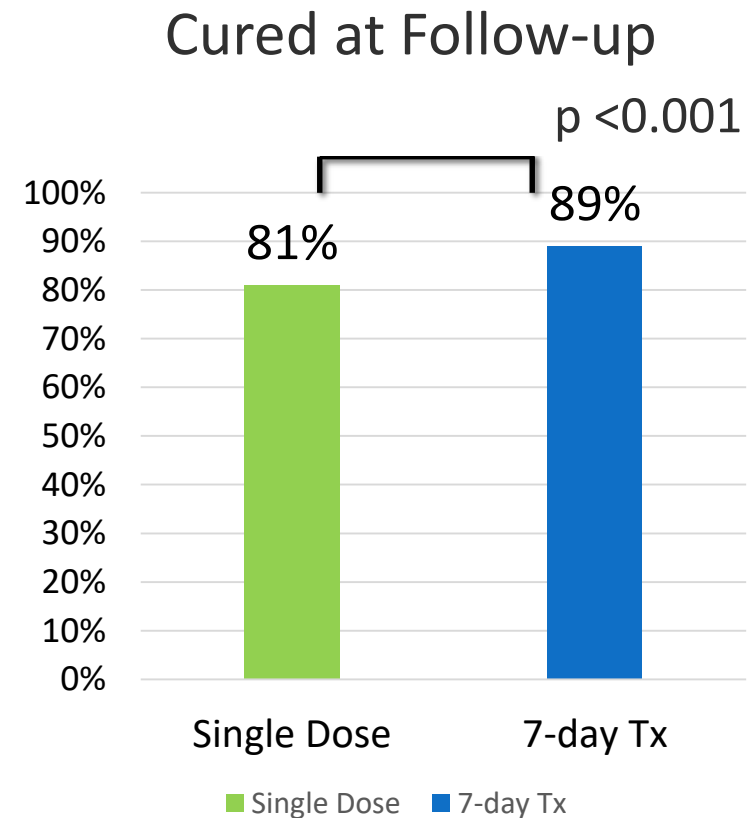
- Women with HIV infection should receive **screening** at entry to care and **annually if sexually active**
 - Associated with PID (Moodley 2002)
 - Treatment reduces genital HIV shedding (Kissinger 2009, Anderson 2012)
- **Longer treatment course better in HIV+ women**
 - Metronidazole 500mg BID x7d (vs. 2g)-less TV at TOC/3 mo RR 0.46, CI:0.21–0.98 (*Kissinger, 2010*)
 - Potential factors - BV infection, ART, changes in vaginal ecology
- No data to recommend extended treatment in men

HIV+ women: Metronidazole (Flagyl) 500mg po BID X 7 days

New treatment Consideration: Is 2g Single Dose Metronidazole Good Enough in HIV-?

- N=623 women randomized 1:1 to single dose vs 7 day therapy
- Culture for test of cure (TOC), 6-12 days post treatment

Kissinger, 2018 Lancet Infect Dis



Stay tuned...

- Current recommendations: Metronidazole 2 g PO OR Tinidazole 2 g PO X 1 for HIV- women.
- However: In the future will we recommend 7 days of treatment for all women with trichomonas?
 - Will patients adhere to treatment?
 - What about partners? Implications for EPT?

Back to our case...

- A 43 year old **HIV-infected** woman (CD4 780 cells/mm³; HIV RNA undetectable) presents complaining of a **vaginal discharge** for 5 days associated with dyspareunia, itching, found to have *Trichomonas vaginalis* on wet prep.
- Treated with 500mg Metronidazole po BID X 7 days.
- She presents 10 days later with **persistent symptoms**; she says she felt no improvement in her symptoms after taking the metronidazole; she has not had any sexual contacts since her symptoms began and her partner was treated with 2g of metronidazole X 1 (she says she “broke up with him” in any case and is not having sex.
- Her GC/CT/syphilis testing from the previous visit is negative; HIV RNA was undetectable; CD4 count 822 cells/mm³
- A repeat wet mount on this visit demonstrates **motile trichomonads**.
- She broke up with her male partner (he had other female partners) when she was diagnosed by you, and has not been sexually active since before she started the metronidazole.

Which of the following medications would you prescribe now?

- A. Metronidazole 500mg orally twice daily for 7 days
- B. Metronidazole 2g orally daily for 7 days
- C. Tinidazole 2g orally X 1 dose
- D. Tinidazole 2g orally daily for 7 days

Case 1

- The patient is treated with metronidazole 2g orally daily for 7 days
- Her symptoms persist and she denies any additional sexual contacts.
- She is seen in clinic again and she is treated with Tinidazole 2g orally for 7 consecutive days

- On follow-up two weeks later, the patient **still has symptoms, wet prep reveals motile trichomonads again...**She has now been dealing with these symptoms for several months and is getting very frustrated.

WHAT DO YOU RECOMMEND NOW??

What now?

- A. Treat with oral tinidazole 2g daily for 7 days plus metrogel twice daily for 7 days.
- B. Treat with oral metronidazole 2g po X1 and have her take it in front of you (DOT).
- C. Send a sample to the CDC for antimicrobial susceptibility testing.
- D. Refer her to Dr. Tuddenham! (Infectious Diseases at Johns Hopkins Bayview).
- E. Give up and tell her this condition is likely incurable.

Her sample is sent to the CDC and reveals...

Sexually Transmitted Diseases Treatment Guidelines, 2015

and tinidazole susceptibility is recommended (693). CDC has experience with susceptibility testing for nitroimidazole-resistant *T. vaginalis* and treatment management of infected persons and can provide assistance (telephone: 404-718-4141; website: <http://www.cdc.gov/std>). Higher dose tinidazole at

Nitroimidazole Susceptibility Testing Results



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

Meingassner's technique. Results listed below are minimum lethal concentrations (MLC). The performance characteristics of this test were determined by the Elimination and Control Laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration.

Aerobic MLC
Patient isolate

Metronidazole
>400 ug/ml

Tinidazole
>400 ug/ml

Based on the *in vitro* susceptibility testing, this isolate shows a very high level of resistance to metronidazole and tinidazole. Despite the *in vitro* antimicrobial

Which of the following regimens would you prescribe at this time?

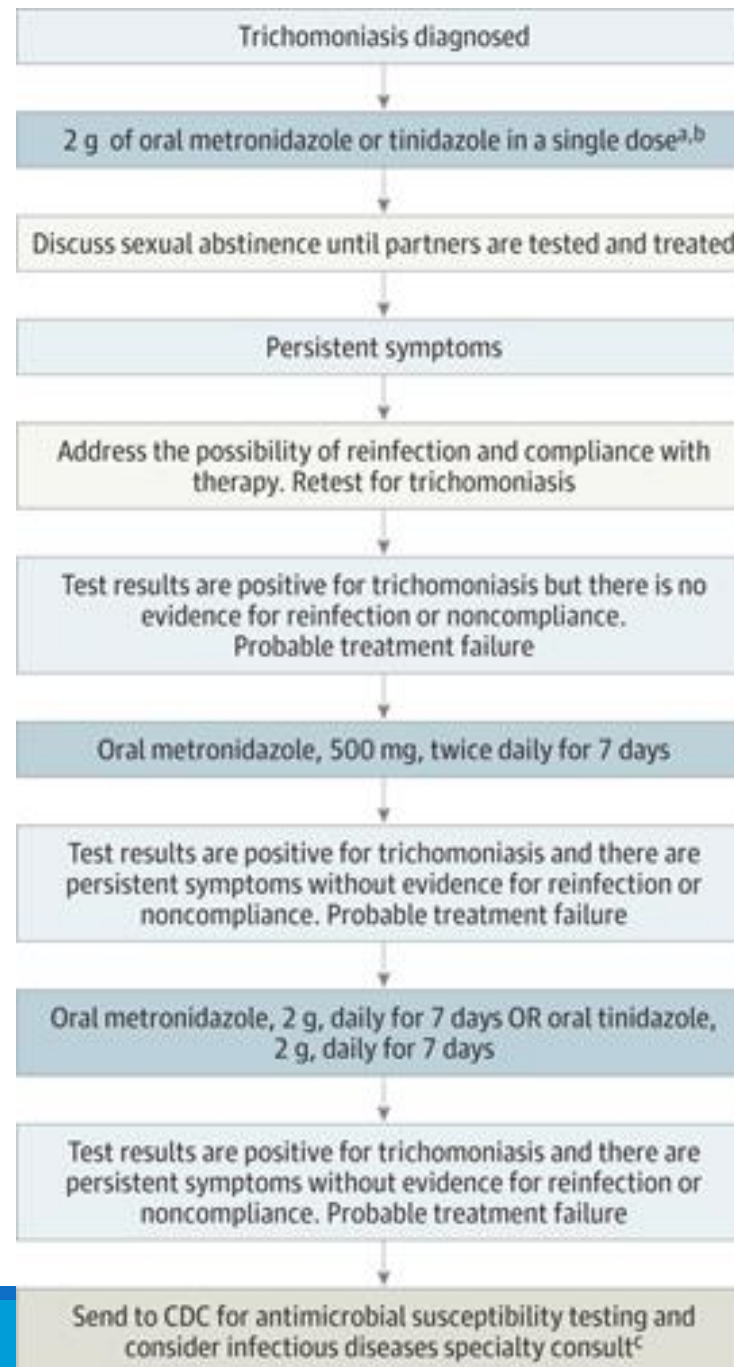
- A. Tinidazole 1g orally TID X 14 days
- B. Paromomycin 6.25% topical daily X 14 days
- C. Tinidazole 1g orally TID PLUS topical paromomycin 6.25% daily X 14 days
- D. Boric acid intravaginal capsules 600mg BID X 28 days
- E. Intravaginal betadine (povidone iodine) X 30 days



Based on the *in vitro* susceptibility testing, this isolate shows a very high level of resistance to metronidazole and tinidazole. Despite the *in vitro* antimicrobial resistance, in many instances utilizing higher doses of tinidazole over a prolonged duration can overcome *in vitro* resistance. I would suggest tinidazole 1 gram three times daily plus intravaginal paromomycin (see attached instructions for intravaginal compounding) for 14 days. If this regimen is ineffective, another option is boric acid vaginal capsules 600 mg bid for at least 28 days. One month after completion of treatment, a culture should be obtained to document eradication of the infection. I have also included some additional information including follow up forms that we ask be completed to document treatment response, a recent manuscript that describes our experience in the management of clinical treatment failure, and an article that describes the method used to compound paromomycin for intravaginal



Current suggested algorithm for Trichomonas treatment



Will our first line recommended regimens change soon, even for HIV- patients??

Case 1: Follow-up

The patient was treated with one month of boric acid 600mg intravaginal capsules BID with complete resolution of her symptoms and negative subsequent NAATs testing

Take-Home Messages: Trichomoniasis

Most cases of recurrent trichomoniasis are due to reinfection

Nitroimidazole resistance

- Metronidazole resistance seen in 4%-10% of isolates
- Tinidazole resistance seen in 1% of isolates
- In general, isolates have lower MICs to tinidazole than metronidazole

AVOID single-dose therapy when treating persistent infections

Treatment of persistent infections

- If 2g oral metronidazole used initially, use metronidazole 500mg twice daily for 7 days
- If persistent: Metronidazole or tinidazole 2g daily for 7 days
- If still persistent: Send for CDC Susceptibility Testing, Consider Referral to Infectious Diseases

Resources

- **Recurrent Vaginitis Clinic:** Johns Hopkins Bayview
 - Refer to Infectious Diseases at Johns Hopkins Bayview and specify Dr. Susan Tuddenham
 - Difficulties scheduling? 410-550-7330, studden1@jhmi.edu
- Trich/STIs Clinical Consultations: Send question via email to Elisabeth Liebow, elisabeth.liebow@maryland.gov, and copy Marcia Pearlowitz, marcia.pearl@maryland.gov. Do not include PHI unless sending secure message via Virtru.
- STD Treatment Guidelines
- PTC STD warmline www.stdccn.org

STD Treatment Guidelines Apps

STD Tx Guidelines



STD Clinical Toolbox



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Available on iTunes

STD Treatment Guidelines wall charts, pocket guides, and the full MMWR article at: www.cdc.gov/std/tg2015

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TV in pregnancy

STD treatment guidelines:

“One trial suggested the possibility of increased preterm delivery in women with *T. vaginalis* infection who received metronidazole treatment (706), yet study limitations prevented definitive conclusions regarding the risks of treatment. More recent, larger studies have shown no positive or negative association between metronidazole use during pregnancy and adverse outcomes of pregnancy (634,707-710). If treatment is considered, the recommended regimen in pregnant women is metronidazole 2 g orally in a single dose. Symptomatic pregnant women, regardless of pregnancy stage, should be tested and considered for treatment. Treatment of *T. vaginalis* infection can relieve symptoms of vaginal discharge in pregnant women and reduce sexual transmission to partners. Although perinatal transmission of trichomoniasis is uncommon, treatment also might prevent respiratory or genital infection of the newborn (711,712). Clinicians should counsel symptomatic pregnant women with trichomoniasis regarding the potential risks for and benefits of treatment and about the importance of partner treatment and condom use in the prevention of sexual transmission. The benefit of routine screening for *T. vaginalis* in asymptomatic pregnant women has not been established. However, screening at the first prenatal visit and prompt treatment, as appropriate, are recommended for pregnant women with HIV infection, because *T. vaginalis* infection is a risk factor for vertical transmission of HIV (713). Pregnant women with HIV who are treated for *T. vaginalis* infection should be retested 3 months after treatment. Data from studies involving human subjects are limited regarding use of tinidazole in pregnancy; however, animal data suggest this drug poses moderate risk. Thus, tinidazole should be avoided in pregnant women, and breastfeeding should be deferred for 72 hours following a single 2-g dose of tinidazole (<http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>).”