Trich and Treat

Satellite Conference and Live Webcast
Wednesday, July 25, 2012
10:00 a.m. - 12:00 p.m. Central Time

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

Faculty

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Disclosures

- **Research support from BD Diagnostics, Gen-Probe Inc.**

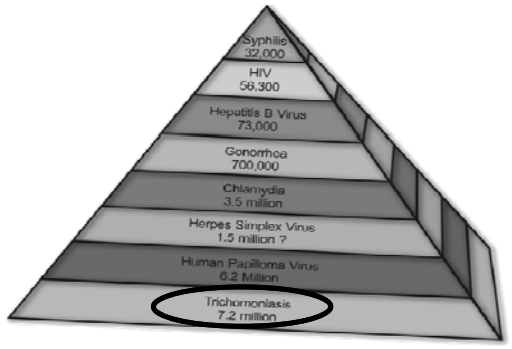
Trichomoniasis

- **Vaginal infections caused by *T. vaginalis* among most common conditions in women attending reproductive health care centers**
- **Most prevalent in age group 20-45**
- **Based on WHO estimates, approximately 5 million new cases annually in U.S. (Cates 1999)**

Trichomoniasis

- **Worldwide, over 180 million cases**
- ***T. vaginalis* accounts for 15-20% of all vaginitis**
- ***T. vaginalis* may be significantly underdiagnosed in the U.S. due to reliance on wet mount for diagnosis**

Estimates of Sexually Transmitted Infections in the U.S.



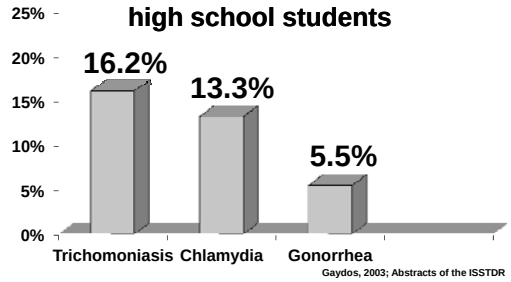
Studies Comparing the Prevalence of Trichomonas Vaginalis Infection with that of Other STDs Among AA Women in the U.S.

Year	City	Trichomonas (%)	Chlamydia (%)	Gonorrhea (%)
1996	New York	51	9	5
1994	New York	27	7	2
1994	New York	20	15	No data
1992	Baltimore	26	21	14
1990-94	New York	22	6	1
1985	San Francisco	28	25	No data

Sorvillo et al Emerg Inf Dis 2001

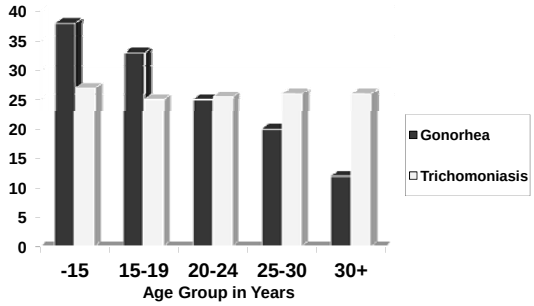
Prevalence of STDs Among a High School Population

n = 1,220 male and female high school students

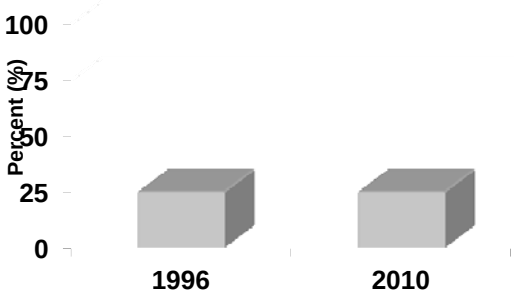


Gaydos, 2003; Abstracts of the ISSTDR

Rates of Gonorrhea and Urogenital Trichomoniasis in Different Age Groups (n = 29,239)



Prevalence of Trichomoniasis JCDH STD Clinic (1996-2010)



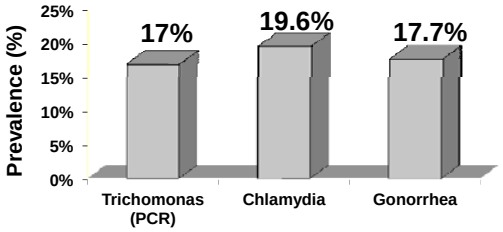
Trichomoniasis Prevalence Rates: Men

- 11% in men at risk for STDs in Seattle (Krieger, 1995)
  - Urethral, urine, coronal sulcus cultures
- 12% of symptomatic men attending a California STD clinic (Borchardt, 1995)
  - Urine sediment culture

Trichomoniasis Prevalence Rates: Men

- 3% of men at a Denver STD clinic (Joyner, 2000)
  - Urine sediment culture
- 58% of Washington, D.C. men at high risk for STDs (Saxena, 1991)
  - Urethral and urine culture, DFA urethral swab, urine sediment microscopy, urethral pap

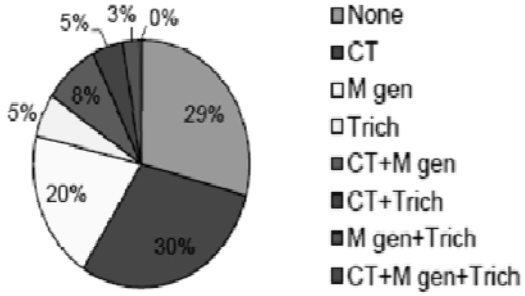
Prevalence of *Trichomonas,* Chlamydia, and Gonorrhea Among Men at an STD Clinic
n = 300 men



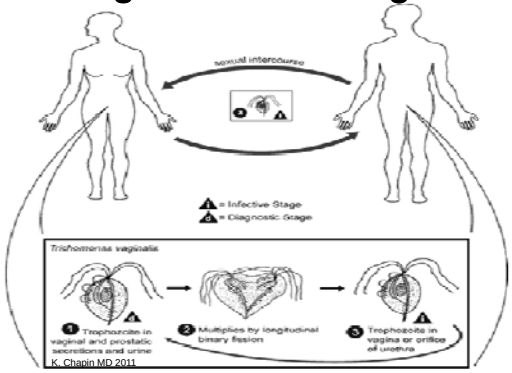
Schwebke and Hook, 2003 JID

Baseline Pathogens Among Men with NGU

Schwebke et al CID 2011

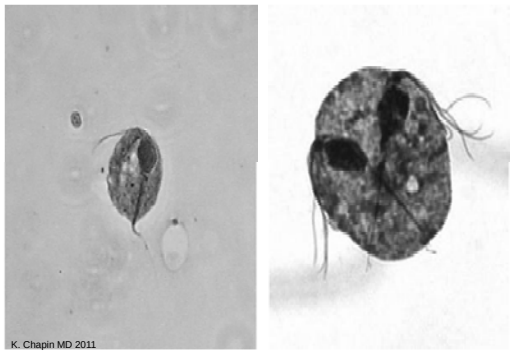


Pathogenesis of T. Vaginalis



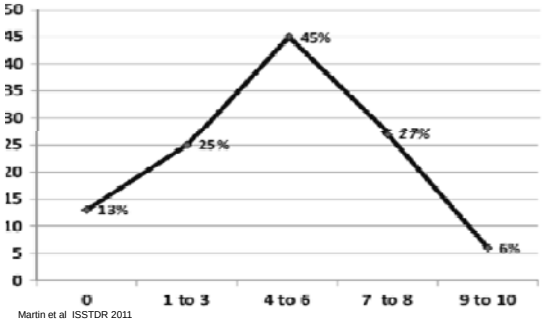
K. Chapin MD 2011

Pathogenesis of T. Vaginalis



K. Chapin MD 2011

Association of Nugent Score and Prevalence of Trichomonas



Martin et al ISSTDR 2011

Relationship of Nugent Score at Prior Visit to Incident STD

	0 – 3 (normal)	p-value AHR (95% CI) 4-6 (intermediate)	p-value AHR (95% CI) 7 -10 (BV)
Gonorrhea	REF	0.05 1.51 (1.00-2.28)	0.07 1.43 (0.98-2.08)
Chlamydia	REF	<0.001 1.58 (1.20-2.08)	<0.001 1.75 (1.37-2.23)
Trichomonas	REF	0.05 1.39 (1.00-1.92)	<0.001 1.95 (1.48-2.57)
Any Incident STD	REF	<0.001 1.41 (1.12-1.76)	<0.001 1.73 (1.42-2.11)

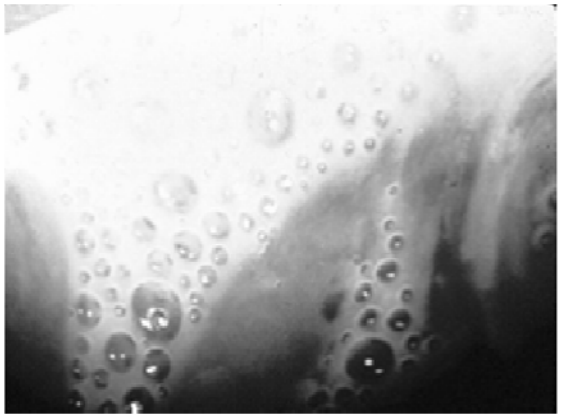
Brotman, Klebanoff, Nansel, Yu, Andrews, Zhang, Schwebke. JID 2010

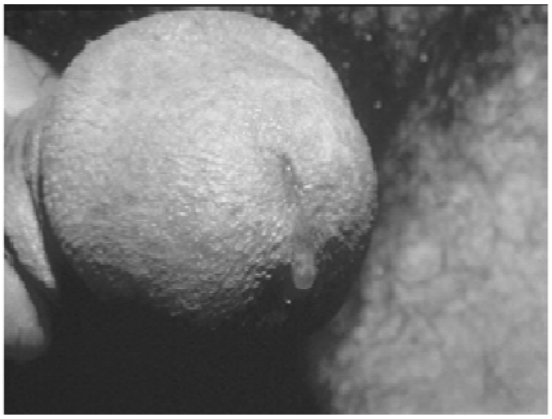
Resolution of Trichomonas in Men with NGU

Last available result for subjects who were positive at baseline	Doxycycline	Doxycycline+ Tinidazole	Azithromycin	Azithromycin + Tinidazole
Trichomonas swab/urine (PCR) - n				
Positive	3	0	2	1
Negative	6	9	5	4
Missing	2	3	2	3

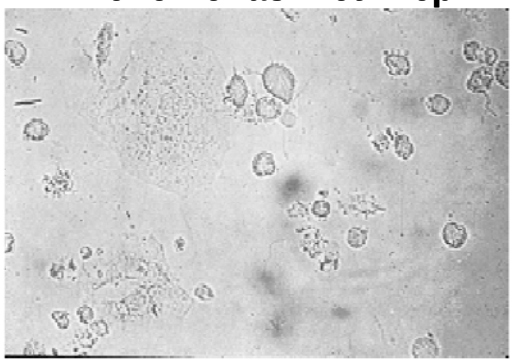
Schwebke et al CID 2011

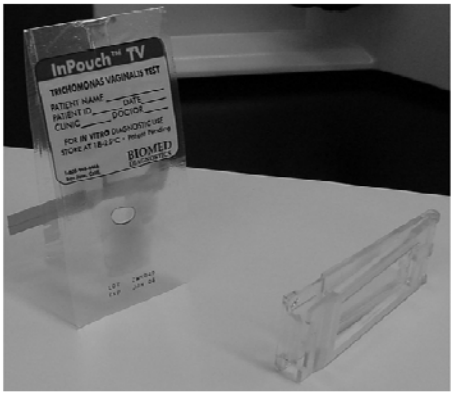
Table 3: Microbiologic Cure Rate (UPDATED); DMID Protocol Number 05-0120; * Missing values excluded from the denominator of prevalence (%) calculations



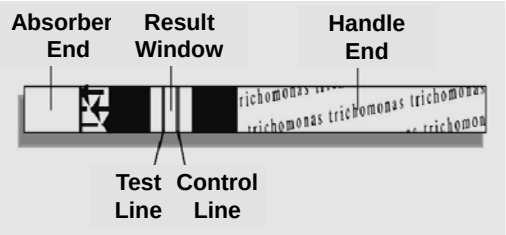


Trichomonas Wet Prep





OSOM® Test Stick



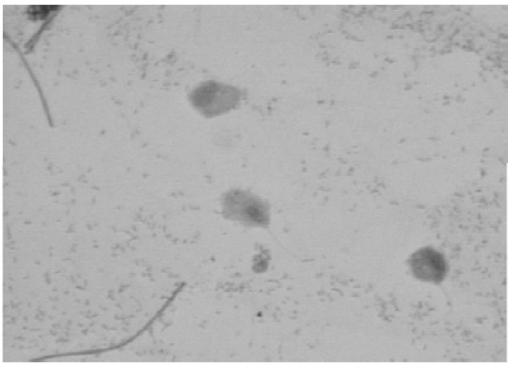
Positive test result

A blue Test Line and a red Control Line is a positive result for the detection of Trichomonas antigen.

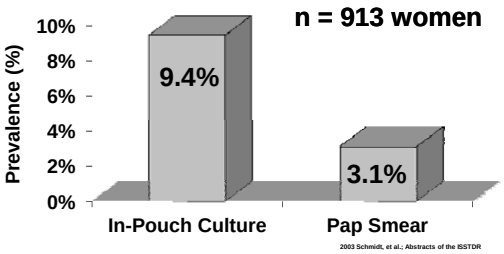
OSOM® Test Stick

- Positive test result
  - A blue Test Line and a red Control Line is a positive result for the detection of Trichomonas antigen

Trichomonas: Pap Smear



Comparison of Culture vs. Pap Smear for the Detection of *Trichomonas*



*Pap smear highly underestimates TV prevalence (31% sensitive, 99.9% specific)

Clinical Evaluation of the APTIMA® *Trichomonas vaginalis* Assay on the TIGRIS® DTS® System in Asymptomatic Female Subjects

- J. Schwebke
  - Department of Infectious Diseases, University of Alabama at Birmingham
- M. Hobbs
  - Department of Medicine/Microbiology and Immunology, University of North Carolina, Chapel Hill

Clinical Evaluation of the APTIMA® *Trichomonas vaginalis* Assay on the TIGRIS® DTS® System in Asymptomatic Female Subjects

- S. Taylor
  - Department of Medicine/Section of Infectious Diseases, Louisiana State University Health Sciences Center, New Orleans, Louisiana

Clinical Evaluation of the APTIMA® *Trichomonas vaginalis* Assay on the TIGRIS® DTS® System in Asymptomatic Female Subjects

- M. Catania, B. Weinbaum, A. Johnson, D. Getman
  - Gen-Probe Inc., San Diego, California
- C. Gaydos
  - Division of Infectious Diseases, Johns Hopkins University, Baltimore, Maryland

Study Aim

- To evaluate the clinical performance of the APTIMA *Trichomonas vaginalis* (ATV, Gen-Probe Incorporated) Assay, a nucleic acid amplification test for the diagnosis of *Trichomonas vaginalis* (TV) infection, in asymptomatic and symptomatic women in the United States as compared with wet mount and culture

Methods

- This was a prospective, multicenter clinical trial which enrolled 1,025 women attending U.S. OB-GYN, adolescent, family planning, or sexually transmitted disease clinics

Methods

- Four specimen types were collected from each subject:
  - Physician-collected vaginal swab
  - Endocervical swab
  - ThinPrep specimen
  - First-catch urine

Methods

- Of three vaginal swabs collected from each subject:
  - One was used for wet mount microscopic examination, one for culture, and one for molecular testing for TV
    - Collection was randomized

Methods

- Each specimen was tested by the ATV assay using the automated TIGRIS DTS system at 3 different sites

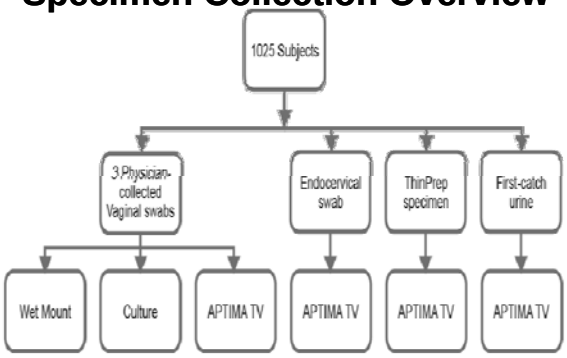
Data Analysis

- Infected Status Determination:
  - Infected status was positive if the culture and/or wet mount was positive
  - Infected status was negative if both culture and wet mount were negative

Data Analysis

- **Discordant Analysis**
  - **Supplemental testing of discordant samples was performed with:**
    - **Real-time TV PCR assay**
    - **Alternate amplification TMA assay (Alt TMA) targeting a different region of the rRNA**
    - **Results were not used to calculate sensitivity or specificity**

Specimen Collection Overview



Subject Age: n = 933

Age, years	
Mean (SD)	27.9 (9.50)
Median	24
Min-Max	14-67
Age groups, n (%)	
14-17	81 (8.7%)
18-20	177 (19.0%)
21-25	284 (30.4%)
26-30	136 (14.6%)
31-35	88 (9.4%)
36-40	76 (8.1%)
>40	91 (9.8%)

Subject Symptomatic Status

Symptomatic Status	N (%)[1]
Symptom Status	
Asymptomatic	374 (40%)
Symptomatic	559 (60%)

[1] Subjects may report multiple symptoms.

Subject Symptomatic Status

Symptomatic Status	N (%)[1]
Reported Symptom (Symptomatic subjects)	
Vaginal odor	242 (43%)
Vaginal discharge	420 (75%)
Vaginal/vulvar itch	184 (33%)
Pain/discomfort during sexual intercourse	33 (6%)
Lower abdominal discomfort	99 (18%)
Pain/discomfort during urination	54 (10%)
Other	89 (16%)

[1] Subjects may report multiple symptoms.

Performance of the ATV Assay in Urine and Vaginal Swab Specimens

ATV Assay specimen	n	Prev %	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Urine	735	11.4	95.2 (88.4-98.1)	98.9 (97.8-99.5)	92.0 (85.1-96.4)	99.4 (98.5-99.8)
Vaginal swab	875	12.7	100 (96.7-100)	99.0 (97.9-99.5)	93.3 (87.6-97.0)	100 (99.5-100)

Performance of the ATV Assay in Endocervical Swab and ThinPrep Specimens

ATV Assay specimen	Age group (years)	n	Prevalence %	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Endo-cervical swab	All	920	12.4	100 (96.7-100)	99.4 (98.6-99.7)	95.8 (90.7-98.6)	100 (99.6-100)
ThinPrep	All	813	11.4	100 (96.0-100)	99.6 (98.8-99.9)	96.9 (91.4-99.3)	100 (99.5-100)

Performance of ATV Assay in the Different Specimens by Symptom Status

ATV Assay specimen	Symptom status	n	Prevalence	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Urine	Asymptomatic	324	6.8	95.5 (78.2-99.2)	99.0 (97.1-99.7)	87.5 (71.4-96.9)	99.7 (98.4-100)
	Symptomatic	411	15.1	95.2 (86.7-98.3)	98.9 (97.1-99.6)	93.7 (85.7-98.1)	99.1 (97.7-99.8)
Vaginal swab	Asymptomatic	345	7	100 (86.2-100)	98.8 (96.8-99.5)	85.7 (70.3-95.6)	100 (98.9-100)
	Symptomatic	530	16.4	100 (95.8-100)	99.1 (97.7-99.6)	95.6 (89.5-98.8)	100 (99.2-100)
Endocervical swab	Asymptomatic	372	7	100 (87.1-100)	99.7 (98.4-99.9)	96.3 (82.4-99.9)	100 (99.0-100)
	Symptomatic	548	16.1	100 (95.8-100)	99.1 (97.8-99.7)	95.7 (89.6-98.8)	100 (99.2-100)
ThinPrep	Asymptomatic	353	6.5	100 (85.7-100)	100 (98.8-100)	100 (86.2-und)	100 (99.0-100)
	Symptomatic	460	15.2	100 (94.8-100)	99.2 (97.8-99.7)	95.9 (88.9-99.1)	100 (99.1-100)

Discordant Test Result Analysis with PCR and Alt AMP TMA TV Assays

Specimen Type	ATV Assay Results	Infected Status	Interpretation	N	TV PCR Results*		Alt-TMA Results*	
					Positive	Negative	Positive	Negative
Urine	Pos	Neg	FP	7	1	6	5	2
Urine	Neg	Pos	FN	4	0	4	0	4
Vaginal swab	Pos	Neg	FP	8	1	7	8	0
Endo-cervical swab	Pos	Neg	FP	5*	2	2	5	0
ThinPrep	Pos	Neg	FP	3	1	2	3	0

*One of the 5 false positive samples was not analyzed by PCR

Range of Performance of the ATV Assay in the Different Specimens Among the Collection Sites

ATV Assay specimen	Sensitivity % (95% CI)	Specificity % (95% CI)
Urine	83.3-100	92.3-100
Vaginal swab	100	97.9-100
Endocervical swab	100	93.3-100
ThinPrep	100	93.3-100

APTIMA Prevalence Study: Methods

- **IRB approval for using consecutive de-identified remnant APTIMA Combo 2 CT/NG samples from females was obtained by sites**

APTIMA Prevalence Study: Methods

- **Clinics**
  - **Obstetrics/gynecology, emergency departments, hospital in-patient, family practice clinics, internal medicine clinics, jails, STD clinics**

APTIMA Prevalence Study: Methods

- Samples from women ages 18-89 yr. in 21 States were tested retrospectively using the APTIMA Trichomonas vaginalis (ATV) assay on the TIGRIS DTS ® Instrumentation
  - Endocervical
  - Vaginal
  - Urine
  - PreservCyt liquid Pap

National Prevalence Study of Trichomonas Using Gen-Probe ATV

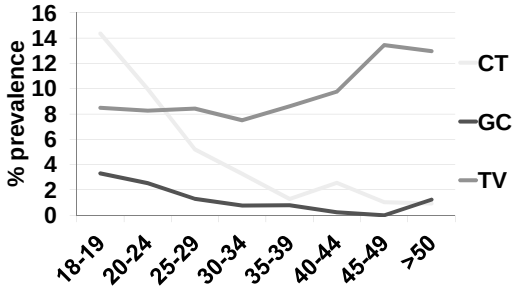
- n=7,593 women
  - Ages 18-89 years
  - 21 states
- Overall prevalence
  - TV: 8.7%
  - CT: 6.7%
  - NG: 1.7%

Prevalence of TV, CT, and NG Infections by Age

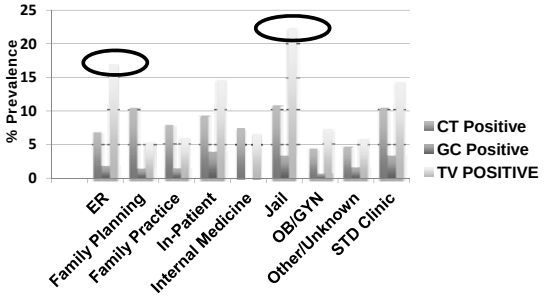
	N*	TV+	CT+	NG+
Overall Prevalence	7593	8.70%	6.70%	1.70%
% (n/N*)		(663/7593)	(508/7588)	(129/7579)
Age (yr)				
Mean		29.82	23.4	24.0
Median (min-max)		26 (18-82)	22 (18-65)	22 (18-53)
Prevalence (%)* by Age Group				
18-19	907	8.50%	14.40%	3.30%
20-29	3972	8.30%	8.00%	2.00%
30-39	1667	7.90%	2.50%	0.80%
40-49	720	11.30%	1.90%	0.10%
50+	324	13.00%	0.90%	1.20%

* In the calculations of prevalence, the denominator may be less than that the N shown due to missing or invalid assay data.

Prevalence of TV, CT, and GC Infections by Age



Prevalence of TV, CT, and GC Infections by Collection Site



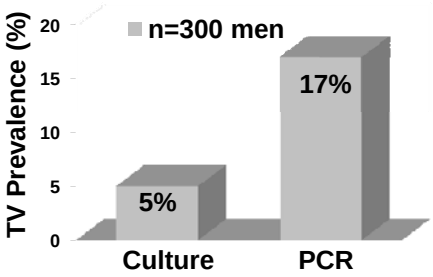
National Prevalence Study of Trichomonas Using Gen-Probe ATV

RACE/Ethnicity	Prevalence
Black	20.2%
White	5.7%
Hispanic	5.0%
Asian	3.8%

National Prevalence Study of Trichomonas Using Gen-Probe ATV

Region	Prevalence
Southeast	14.4%
Southwest	9.5%
Midwest	9.5%
Northeast	4.3%

Detection of T. Vaginalis in Males: PCR vs. Culture



Schwebke JR, and Lawing LF. J Clin Microbiol 2002

Objectives of Gen-Probe ASR Study

- Compare TMA (Gen-Probe APTIMA analyte specific reagents for *T. vaginalis*) to wet prep, culture, and PCR (B-tubulin, LabCorp)
- Evaluate various specimen types including vaginal endocervical, male urethral, and urine

Prevalence of TV in Men

Culture	4.0%	
Urine PCR	6.7%	ATV 11.5%
Urethral PCR	7.7%	ATV 16.6%

Comparison of Diagnostic Tests for TV in 299 Male Subjects

Diagnostic method and specimen	Number of Specimens: True positive	False positive	False negative	True negative	Sensitivity %	Specificity %
Infected patient status algorithm*						
Culture	12	0	13	274	48.00	100
ATV – Urethral swab	24	25	1	249	96.00	90.88
ATV – Urine	24	10	1	264	96.00	96.35
Molecular resolved algorithm**						
ATV – Urethral swab	40	9	2	248	95.34	96.5
ATV – Urine	31	3	11	254	73.81	98.83

*By infected patient status algorithm (+ urethral swab/urine culture, + urine or urethral swab PCR) there were 25 infected male subjects
**By molecular resolved algorithm there were 42 infected male subjects

Conclusions

- TV PCR increases detection of infection in males compared to culture
- Sampling of multiple sites increases yield
- TV may be as common as CT in certain populations

Conclusions

- Infection with TV in males may be associated with urethritis or may be asymptomatic
- Diagnosis and treatment of men with TV may be critical to controlling/eliminating disease in women

Trichomoniasis: Treatment

- Metronidazole or tinidazole 2 gm P.O.
  - Single dose
  - Treat partners
- Metronidazole resistance
  - Usually can be overcome with increased doses of metronidazole or tinidazole

Dosing for Resistance

- If fails single dose metronidazole
  - Tinidazole 2 gm stat OR metronidazole 500 mg BID for 7 days
  - Tinidazole or metronidazole 2 gm PO x 5 days OR tinidazole 2 gm per day for 14 days with or without intravaginal tinidazole (500 mg BID)

Dosing for Resistance

- If fails above can try paromomycin cream
  - 250 mg in 4 grams of cream base qhs x 7days

Partner Treatment of Trichomoniasis

- Female cure rates increased nearly 20% when male partner also treated (Lyng, 1983)
  - Tinidazole used for treatment
- Both patient and partner must be treated to prevent reinfection

Partner Treatment of Trichomoniasis

- Cure rates exceed 90% when both partners treated (Sobel, 1997)
- Male therapy also impacts on spread of infection to other females (Eschenbach, 1991)
- CDC recommends partner treatment as TV is an STD

Complications Associated with Trichomoniasis

- Risk factor for acquisition/ transmission of HIV
- Associated with HSV-2 acquisition
- Increased risk of post-hysterectomy infection (Soper,1990)
- Associated with atypical PID
- Associated with preterm birth

T. Vaginalis as Risk Factor for HIV

- *T. vaginalis* may amplify HIV-1 transmission by increasing susceptibility in an HIV-1 negative person, and the infectiousness in an HIV-1 positive patient (Sorvillo, 1998)

T. Vaginalis as Risk Factor for HIV

- An association between *T. vaginalis* and HIV has been detected in women
  - OR: 1.8-3.0 (Laga, 1993)
  - OR: 2.26 (Dellabatta, 1993)

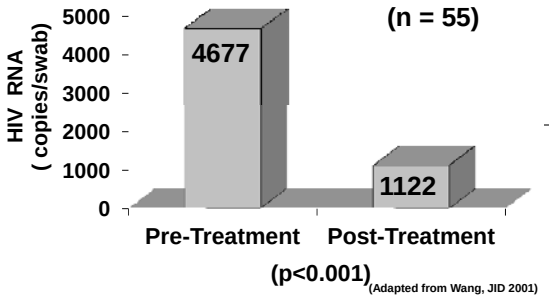
T. Vaginalis as Risk Factor for HIV

- Treatment of *T. vaginalis* resulted in a 4.2-fold reduction in the quantity of HIV-1 in vaginal secretions, but not in shedding of virus (Wang, 2001)
- Increase in HIV RNA in semen of HIV+ men w/ *T. vaginalis* (Hobbs, 1999)

Acquisition of HIV

- Prospective study in Kenya
- Monthly visits and lab testing
- 1,335 HIV negative women enrolled
- Trichomoniasis associated with 1.52-fold increased risk of HIV acquisition after adjusting for potential confounding factors

Metronidazole Treatment Effect on Vaginal HIV-1 RNA in Women with *T. Vaginalis*



Trichomoniasis and Pregnancy Risks

- Higher incidence of PROM reported ($p < 0.03$) (Minkoff, 1984)
- Associated with increased preterm delivery rates: OR = 1.4 (Cotch, 1997)
- LBW infants: OR = 1.3 (Cotch, 1997)

Use of Metronidazole in Pregnant Women with Asymptomatic Trichomoniasis

- Double-blind, placebo controlled trial of 2g metronidazole on day 1, and another 2g 48 hrs. later (n=320) or placebo (n=297) in pregnant women with asymptomatic trichomoniasis
- Treatments given at both 16-23 and 24-29 weeks gestation

Use of Metronidazole in Pregnant Women with Asymptomatic Trichomoniasis

- All sexual partners treated with single 2g metronidazole
- Of 31,157 women screened 2,377 (7.6%) were positive for *T. vaginalis* infection

Use of Metronidazole in Pregnant Women with Asymptomatic Trichomoniasis

- Of these, 617 women were eligible for participation in the trial
- Primary outcome was delivery < 37 weeks

– Klebanoff, et al. NEJM 2001; 345: 487-493.

Metronidazole in Pregnant Women with Asymptomatic Trichomoniasis

Outcome	Metronidazole (n=315)	Placebo (n=289)	OR
Delivery at < 37 weeks	60 (19%)	31 (10.7%)	1.8 (1.2-2.7)
Delivery at < 35 weeks	27 (8.6%)	19 (6.6%)	1.3 (0.7-2.3)
Delivery at < 32 weeks	16 (5.1%)	11 (3.8%)	1.3 (0.6-2.8)

Unresolved Issues

- Study was stopped prematurely by the DSMB
- Unusual dose of metronidazole
- Many women were treated "off study" by PMDs
- More studies are needed to resolve these questions

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