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Clinical Evaluation of the Cepheid Xpert® TV Assay for detection of *Trichomonas vaginalis* with Prospectively Collected Female and Male Specimens

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Running Head: Xpert TV Assay in Female and Male Specimens

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Abstract

Trichomoniasis is the most prevalent curable sexually transmitted disease (STD). It has been associated with preterm birth and acquisition/transmission of HIV. Recently, nucleic acid amplification tests (NAAT) have been FDA-cleared in the United States for detection of *Trichomonas vaginalis* (TV) in specimens from both women and men. This current study reports the results of a multicenter study recently conducted using the Xpert TV Assay to test specimens from both men and women. On-demand results were available in as little as 40 minutes for positive specimens. A total of 1867 women and 4791 men were eligible for inclusion in the analysis. In women, the performance of the Xpert TV Assay was compared to a patient infected status (PIS) derived from results of InPouch TV broth culture and Aptima NAAT for TV. Diagnostic sensitivity and specificity of the Xpert TV Assay for the combined female specimens (urines, self-collected vaginal swabs, and endocervical swabs) ranged from 99.5 - 100% and 99.4 – 99.9%, respectively. For male urines, diagnostic sensitivity and specificity was 97.2% and 99.9% respectively, compared to a PIS derived from results of broth culture for TV and bi-directional gene sequencing of the amplicons. Excellent performance characteristics were seen using both female and male specimens. The ease of using the Xpert TV Assay should result in opportunities for enhanced screening for TV in both men and women and hopefully improved control of this infection.

Introduction

Trichomonas vaginalis (TV) is a flagellated protozoan parasite that causes genitourinary infections in women and men. It is the most prevalent curable sexually transmitted disease (STD) and is easily treated with inexpensive antibiotics (1, 2). Trichomoniasis causes distressing symptoms such as vaginal discharge and irritation and urethritis in men (3, 4). It is also significantly associated with an increased risk of preterm birth and acquisition/transmission of STDs, including HIV, as well as being associated with infertility (5-8). Currently, however, there is no national control program for this infection. Until recently, available tests were relatively insensitive (direct microscopy, antigen detection) or not widely available (culture) for detection of the parasite (9, 10). The advent and FDA clearance of nucleic acid amplification tests (NAAT) for diagnosis of TV in women (urine [UR] , endocervical swabs [ES], vaginal swabs, self-collected vaginal swabs [SC-VS]) has greatly improved our diagnostic capability but until now there was no FDA cleared test for detection of TV in male urine (11). The GeneXpert System (Cepheid, Sunnyvale, CA) is already used to diagnose other STDs such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (12). We now report on the performance of this assay for the detection of TV in specimens from women and men.

Results

Results for Female Subjects

A total of 1876 female subjects were initially enrolled in this clinical study, of which 1867 (99.5%) were eligible for inclusion. The nine ineligible subjects consisted of three

66 subjects with a history of hysterectomy, two subjects with improper or incomplete
67 informed consent, two subjects previously enrolled in the study, and two subjects who
68 had been treated with antibiotics within the 21 days prior to study enrollment. Of the
69 1867 eligible study participants, 714 (38.2%) were symptomatic and 1153 (61.8%) were
70 asymptomatic. The average age among eligible study participants was 33.5 years (range
71 = 18 to 78 years).

72 From the 1867 eligible female study subjects, 1799 (96.4%) ES specimens, 1791 (95.9%)
73 PC-VS specimens, and 1793 (96.0%) UR specimens were included in the final data set.
74 The reasons for exclusion of each specimen type are shown in Figure 1.

75 Results of the Xpert TV assay for 98.4% (5306/5391) of the samples from eligible female
76 subjects were successful on the first attempt. The 85 indeterminate results included 74
77 ERROR*, nine INVALID†, and two NO RESULT‡. Eighty-three of the 85 indeterminate
78 cases were retested; two samples were not retested. Seventy-seven of 83 indeterminate
79 cases retested yielded valid results upon repeat assay. The overall rate of assay success
80 was 99.9% (5383/5391).

81 Overall, relative to the PIS, the Xpert TV Assay demonstrated an initial sensitivity and
82 specificity of 98.4% and 99.7%, respectively, for urine; 98.9% and 98.9% for
83 endocervical swabs, respectively; and 96.4% and 99.6% for patient-collected vaginal

*Test failed possibly because the reaction tube was filled improperly, a reagent probe integrity problem was detected, pressure limits were exceeded, or a valve positioning error was detected.
† SPC and/or the SAC failed. The sample was not properly processed, PCR was inhibited or the sample was not properly collected.
‡ Tests were aborted.

swabs, respectively (Table 1). There were no statistically significant differences in performance with respect to symptomatic status (Table 2).

Homogeneity analysis by site indicated that the results across sites were poolable for specificity. For diagnostic sensitivity, female ES specimens demonstrated non-homogeneity; however, the overall sensitivity was high (99.5%), with all sites but one having 100% sensitivity. The one site with less than 100% sensitivity demonstrated a sensitivity of 83.3% [(10/12), 95% CI 51.6%, 97.9%]. Though the upper Confidence Interval (CI) includes the Null Hypothesis, the sample size was too small for meaningful analysis. Some site-to-site variation can be expected, as well as some amount of sampling variation. Keeping this site in the pooled analysis, although it may have a slightly lower sensitivity than the other sites, was considered conservative.

Results for Male Subjects

Figure 1 illustrated specimen accountability for male subjects. A total of 4798 male subjects were enrolled in the study, of which 4791 (99.9%) were eligible for evaluation. The seven ineligible subjects consisted of one subject with improper or incomplete informed consent, two subjects previously enrolled in the study, two subjects who had been treated with antibiotics within the 21 days prior to study enrollment, one subject who was not sexually active, and one subject <14 years of age. The average age among eligible male study participants with valid test results was 36.2 years (range = 16 to 78 years). Of these 4611 study participants, 1088 (23.6%) were symptomatic and 3523

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(76.5%) were asymptomatic. The prevalence of TV in males across all study sites was 2.7%.

In all, a total of 4626 (96.6%) specimens from eligible male subjects were tested by the Xpert TV Assay. The urine specimens excluded consisted of 96 for shipping delays, 36 tested >72 hours after collection, 21 GeneXpert modules out of calibration, and 12 not tested. Xpert TV assays for 97.7% (4521/4626) of the samples from eligible subjects were successful on the first attempt. The 105 indeterminate results included 84 ERROR, 12 INVALID results, and 9 NO RESULT. One hundred of the 105 (95.2%) indeterminate cases were retested; five samples were not retested. Ninety of 100 (90%) indeterminate cases that were retested yielded valid results upon repeat assay. Thus, the overall rate of Xpert TV assay success was 99.7% (4611/4626).

Overall, relative to the PIS, the Xpert TV Assay demonstrated an initial diagnostic sensitivity and specificity for male urine specimens of 89.6% and 99.3%, respectively (Table 3). Secondary sequencing was performed on specimens with discordant results. The validated bi-directional sequencing procedure demonstrated that the sequencing LoD was similar to the Xpert TV Assay male urine analytical LoD, resulting in similar frequency of random dropouts with specimens with low level TV organisms. There were no statistically significant differences in performance with respect to symptomatic status.

Discussion

Trichomoniasis is a highly prevalent STD and presents with a spectrum of symptoms or with no symptoms (3). In women, the prevalence of infection spans the reproductive years and beyond with some studies showing high rates in older women (13). The

epidemiology is less well understood in men, although a recent study showed that age over 40 years was also associated with TV-associated STIs (14). Accurate identification of trichomoniasis is important for several reasons including optimizing treatment, realizing the need for treatment of the sexual partner(s) (15), and potential for prevention of associated public health consequences, such as preterm birth and acquisition/transmission of HIV (6-8). The CDC has recently recommended NAAT are the preferred diagnostic modality in light of their superior sensitivity compared to direct microscopy or culture-based methods for detecting TV (16). Diagnostic testing is recommended for symptomatic women and screening should be considered for individuals with multiple sex partners, persons who exchange sex for payment, use drugs, and/or have a history of STDs, and for women in high prevalence settings, such as STD clinics and correctional facilities (2). Annual screening is recommended for women with HIV infection due to the high rates of TV infection in this population (17). Rescreening is recommended within 3 months of the initial diagnosis due to high recurrence rates (18). Currently, there are no firm screening recommendations for men due to the fact that an FDA-cleared test has only recently become available. However, men attending STD clinics should be considered for screening (2). A recent study showed a prevalence rate of nearly 10% among men attending an STD clinic in Birmingham, AL (14).

Although other NAAT in addition to the Xpert TV Assay have also been recently FDA cleared for the diagnosis of TV in women (11, 19), the Xpert TV Assay can provide on-demand results in 63 minutes or less, with early termination for positive results within 40 minutes. This quicker turn-around-time makes the GeneXpert platform ideal for use in

high risk settings where diagnosis and treatment could ideally take place in real time for optimal public health control of this STD.

The platform is easy to use and thus suitable for in-clinic testing at the point-of-care (POC). Furthermore, the equally high diagnostic sensitivity and specificity demonstrated here for urine, self-collected vaginal swabs, and endocervical swabs in symptomatic and asymptomatic patients makes the assay an important diagnostic screening tool for patients in high risk settings such as STI clinics and emergency departments as well as gynecology clinics with laboratory facilities. Of note, the majority of men were asymptomatic suggesting that screening for trichomoniasis should be considered for high-risk men such as those attending STD clinics.

The availability of NAATs testing for TV in men is a welcome addition from a public health perspective and has been a key element missing for the control of this STD. The sensitivity and specificity of the Xpert TV Assay were both high relative to the PIS, 97.2 and 99.9%, respectively. However, it should be noted that InPouch cultures for this study followed the current manufacturer's package insert at the time of the study (Biomed Diagnostics document no. 100-001, revision K) which instructed users to incubate and read cultures up to 3 days. A study conducted by Rivers and colleagues showed that 17.2% additional positive cultures were identified when cultures are incubated and read up to 5 days. Thus, a study comparing the Xpert TV Assay directly to InPouch cultures incubated for 5 days would need to be conducted in order to determine if the sensitivity of the Xpert assay would be slightly lower.

In summary, TV is a highly prevalent STI associated with increased risk of HIV acquisition/transmission as well as preterm births. The availability of an FDA cleared test for men is especially welcome. Recent advances in molecular diagnostics for this highly prevalent infection, if implemented, should begin to reduce the burden of disease.

Materials and Methods

This multi-center study evaluated test performance in prospectively collected first catch urine (UR) from both women and men, endocervical swab specimens (ES), clinician-collected vaginal swab specimens (CC-VS), and patient-collected vaginal swabs (PC-VS) in a clinical setting. The sites participating in this study were academic medical centers, STD clinics, family planning clinics, public health departments, and clinical trial offices. The sites were located across the United States including the west coast, the Midwest, southern states, and the east coast. Subjects were eligible for enrollment regardless of the presence or absence of genital symptoms. Seventeen diverse geographic sites participated in collection of the specimens. Institutional Review Board approval was obtained for each of the collection sites.

To be eligible for study enrollment participants needed to be sexually active, ≥14 years of age, and provide informed consent and minor assent if needed. Subjects were excluded if they had been previously enrolled in the study, had received antimicrobial therapy within 21 days prior to enrollment, had undergone a hysterectomy, or had urinated less than one hour prior to specimen collection. Female study participants were classified as symptomatic if they reported any of the following symptoms: itching, burning, redness,

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196 soreness or irritation of the genitals, unusual odor, abnormal vaginal discharge, coital
197 pain, and/or dysuria. Males were classified as symptomatic if they reported any of the
198 following signs and/or symptoms: urethral discharge, dysuria, or urethral itching or
199 burning, burning after ejaculation and/or dysuria. Study participants not reporting any of
200 the above symptoms were classified as asymptomatic.

201 The following samples were collected from females: one PC-VS (collected in a clinical
202 setting) for testing by the Xpert TV Assay, followed by two CC-VS for testing by
203 InPouch TV culture-based methods (BioMed Diagnostics, White City, OR) and the
204 Aptima TV NAAT (Hologic, Bedford, MA) (specimens alternated), three ES (the first
205 swab for In Pouch, while the second and third swabs were alternated for Aptima and
206 Xpert assays), and 35-50 mL of first catch UR for InPouch, Xpert, and Aptima assays.
207 For males, 35-50 mL of first catch urine was collected for InPouch, bi-directional gene
208 sequencing of amplicons, and Xpert testing. For "collection-only" participating sites, the
209 specimens designated for Xpert testing and reference assay testing were shipped to
210 designated testing laboratories on the same day as collection, whenever possible. All
211 Xpert testing was performed within 72 hours of collection.

212

213 Assay Procedures

214 Each trial specimen was collected by using the Cepheid specimen collection device (swab
215 or urine) and tested by the Xpert TV Assay. Transport reagent containing the specimen
216 was gently inverted 3 to 4 times followed by transferring 0.5 mL of the sample to the
217 Xpert cartridge, using the supplied transfer pipet. Aptima assay testing was performed

218 according to the manufacturer's package insert. For InPouch, CC-VS and ES were
219 inoculated at each collection site. For UR cultures in InPouch, 10-15 mL of the urine
220 specimen was centrifuged at 500 x g for 5 minutes and the sediment inoculated into the
221 culture pouch on-site within one hour of collection. Culture pouches were shipped to the
222 reference testing laboratory within 24 hours of collection with receipt of specimens
223 occurring within 48 hours of collection. These specimens were shipped at ambient
224 temperature with two warming packs per shipping box. At the reference laboratory
225 cultures were incubated at 37 °C and read daily on weekdays for 3 days to look for the
226 presence of motile protozoan with characteristic morphology per the InPouch package
227 insert instructions.

228 Results of the reference tests (InPouch and Aptima for female specimens and InPouch
229 and a validated sequencing method (bi-directional amplicon sequencing of the excess
230 urine remaining from Xpert testing for male specimens)) were used to determine the
231 patient infected status (PIS). The PIS was used to designate a subject as infected or not
232 infected. The subject was considered infected if either of the reference test results were
233 positive for TV, while the subject was considered not infected when both reference test
234 results were negative for TV. Bi-directional nucleic acid sequencing was performed on
235 specimens from women with discrepant results between Xpert and the PIS, as well as
236 from an equal number of specimens from women who were determined to be uninfected
237 (i.e., true negatives). For male specimens, secondary sequencing was performed on any
238 specimens with discrepant results between Xpert and the PIS. Quality control for the
239 Xpert TV Assay consisted of one TV-negative and one TV-positive external control, with
240 both controls being run on each day that study specimens were tested. Study specimens

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were not run until valid test results were obtained for both the negative and positive controls. Additionally, several internal controls are built-in the assay to monitor all aspects of the analytical process with each specimen run: a Sample Processing Control (SPC) a Sample Adequacy Control (SAC), and a Probe Check Control (PCC). The SPC is present to control for adequate processing of the target Trichomonads and to monitor the presence of inhibitors in the PCR reaction. The SAC reagents detect the presence of a single copy human gene and to monitor whether the specimen contains human cells. The PCC verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity and dye stability. Only those study specimens with valid control results available for all study test methods were included in the data analyses.

Statistical analyses were performed using SAS.

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Table 1 Xpert TV vs. InPouch, Aptima & PIS for Female Subjects

Sample Type	Comparator Test	Total (n)	Sensitivity	95% CI	Specificity	95% CI	Prevalence (%)	PPV (%)	NPV (%)
Endocervical Swab	InPouch	1799	98.7% (153/155)	95.4%-99.8%	97.6% (1604/1644)	96.7%-98.3%	8.6%	89.3%	99.9%
	Aptima	1799	100% (175/175)	98.3%-99.3%	98.9% (1606/1624)	98.3%-99.3%	9.7%	90.7%	100%
	PIS	1799	98.9% (175/177)	96.0%-99.9%	98.9% (1604/1622)	98.3%-99.3%	9.8%	90.7%	99.9%
Patient Collected-Vaginal Swab	InPouch	1791	96.9% (156/161)	92.9%-99.0%	97.7% (1593/1630)	96.9%-98.4%	9.0%	80.8.%	99.7%
	Aptima	1791	97.4% (186/191)	94.0%-99.1%	99.6% (1593/1600)	99.1%-998%	10.7%	96.4%	99.7%
	PIS	1791	96.4% (186/193)	92.7%-98.5%	99.6% (1591/1598)	99.1%-99.8%	10.8%	96.4%	99.6%
Urine - Female	InPouch	1793	97.7% (148/150)	95.3%-99.8%	97.7% (1606/1643)	96.9%-98.4%	8.4%	80.0%	99.9%
	Aptima	1793	99.4% (178/179)	96.9%-100%	99.6% (1607/1614)	99.1.%-99.8%	10.0%	96.2%	99.9%
	PIS	1793	98.4% (180/183)	95.3%-99.7%	99.7% (1605/1610)	99.3%-99.9%	10.2%	97.3%	99.8%

Table 2 Xpert TV vs PIS by Symptomatic Female Status

Sample Type	Status	Total (n)	Sens	95% CI	Spec	95% CI	Prev (%)	PPV (%)	NPV (%)
Endocervical Swab	Symp	685	100% (71/71)	94.9%-100%	98.5% (605/614)	97.2%-99.3%	10.4%	88.8%	100%
	Asymp	1114	98.1% (104/106)	93.4%-99.8%	99.1% (999/1008)	98.3%-99.6%	9.5%	92.0%	99.8%
	Overall	1799	98.9% (175/177)	96.0%-99.9%	98.9% (1604/1622)	98.3%-99.3%	9.8%	90.7%	99.9%
	Difference	P-Value	P=0.517	-0.70%, 4.48%	P=0.331	-1.69%, 0.54%			
Patient Collected – Vaginal Swab	Symp	682	98.6% (73/74)	92.7%-100%	99.5% (605/608)	98.6%-99.9%	10.9%	96.1%	99.8%
	Asymp	1109	95.0% (113/119)	89.3%-98.1%	99.6% (986/990)	99.0%-99.9%	10.7%	96.6%	99.4%
	Overall	1791	96.4% (186/193)	92.7%-98.5%	99.6% (1591/1598)	99.1%-99.8%	10.8%	96.4%	99.6%
	Difference	P-Value	P=0.254	-1.04%, 8.42%	P=1.000	-0.77%, 0.59%			
Urine - Female	Symp	688	98.6% (71/72)	92.5%-100%	99.8% (615/616)	99.1%-100%	10.5%	98.6%	99.8%
	Asymp	1105	98.2% (109/111)	93.6%-99.8%	99.6% (990/994)	99.0.%-99.9%	10.0%	96.5%	99.8%
	Overall	1793	98.4% (180/183)	95.3%-99.7%	99.7% (1605/1610)	99.3%-99.9%	10.2%	97.3%	99.8%
	Difference	P-Value	P=1.000	-3.25%, 4.08%	P=0.655	-0.27%, 0.75%			

Table 3 **Xpert TV vs. PIS Initial Results based on Symptomatic Status**

Sample Type	Status	Total (n)	Sens	95% CI	Spec	95% CI	Prev (%)	PPV (%)	NPV (%)
Male Urine	Symp	1088	87.5% (28/32)	71.9%-95.0%	99.8% (1054/1056)	99.3%-99.9%	2.9%	93.3%	99.6%
	Asymp	3523	90.3% (84/93)	82.6%-94.8%	99.2% (3401/3430)	98.8%-99.4%	2.6%	74.3%	99.7%
	Overall	4611	89.6% (112/125)[a]	83.0%-93.8%	99.3% (4455/4486)[b]	99.0%-99.5%	2.7%	78.3%	99.7%
	Difference		P=0.738	-15.8%, 10.1%	P=0.020	0.25%, 1.06%			

[a]Testing results by secondary sequencing: 9 of 13 false negatives were TV negative; 4 of 13 were TV positive
[b]Testing results by secondary sequencing: 27 of 31 false positives were TV positive; 4 of 31 were TV negative.

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Figure 1 – Specimen Accountability from Eligible Female and Male Participants