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Incident *Trichomonas vaginalis* is associated with partnership concurrency: a longitudinal cohort study

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Abstract

Background—Sexual partner concurrency (PC) has been shown to be a risk factor for a number of sexually transmitted infections but it is unknown if it is a risk factor for *Trichomonas Vaginalis* (TV).

Objective—We assess if there is an association between partner concurrency and incident TV infection.

Study design—We used mixed effects logistic regression to assess the association between partner concurrency and incident TV in the Longitudinal Study of Vaginal Flora, a cohort study of 3620 women followed quarterly for five visits.

Results—TV was more common in those reporting definite/possible/unknown PC (15.6%/15.0%/18.3%) than those reporting no PC (5.2% – $P < 0.001$ for all three comparisons). After controlling for a range of confounders, incident TV remained associated with reporting that one's partner definitely (adjusted Odds ratio [aOR] 5.4; 95% Confidence Interval [CI], 3.7–8.0) and possibly (aOR 3.4; 95% CI, 2.2–5.1) engaged in partner concurrency in the preceding time period.

Conclusion—Partner concurrency was associated with incident TV infection.

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Background

With an estimated 142 million cases per year, *Trichomonas vaginalis* (TV) is the most common curable sexually transmitted infection [1]. It has been associated with a range of adverse outcomes including, symptomatic vaginitis and urethritis, pelvic inflammatory disease and adverse pregnancy outcomes [2]. Of increasing concern is its effect on the vaginal microbiome/susceptibility to bacterial vaginosis (BV) [3, 4] and enhanced acquisition and transmission of HIV [5–7].

The prevalence of TV varies dramatically between populations [8]. In a nationally representative sample of the United States (USA) for example, the prevalence of TV was 10.3 times higher in African American than non-Hispanic white and Mexican American women [9]. Although TV infection is associated with a number of demographic and behavioral factors such as number of sexual partners, douching and socioeconomic status, controlling for all these factors does not eliminate the large ethnic/racial differences in TV prevalence in the USA [9, 10]. Differences in the prevalence of sexual partner concurrency (partnerships that overlap in time) are one possible explanation. Studies with other STIs such as chlamydia, HIV, HSV-2 and syphilis have found that differences in network structure, including differences in partner concurrency, can explain a large part of the ethnic/racial differences in STI prevalence [11–15]. An ecological study found a positive association between the prevalence of male partner concurrency and female TV in ethnic/racial groups within the USA and in a cross country comparison [16].

Sexual partner concurrency is thought to enhance STI transmission via a number of mechanisms that include enhancing *network-connectivity* and removing the protective effect of *partner-sequencing* [17]. These effects are illustrated in Figure 1, which contrasts the TV transmission possibilities between hypothetical sexual networks where concurrency (left) and serial monogamy (right) are the norm. Whereas all relationships run concurrently in the concurrency network, none do in the monogamy network. Instead, in the monogamy network, two new relationships form after a 7-week gap between the ending of a partnership and the commencement of a new one. Both scenarios commence with individual ‘B’ and her partner ‘A’ having TV (red used to depict TV). In the concurrent network the ‘A–D’ and ‘C–D’ partnerships offer pathways for TV to spread to all the partnerships of this network (enhanced *network-connectivity*). These connections are not present in the serial monogamy network, where TV is contained within ‘A–B’ until ‘B’ commences a partnership with ‘C’ which may provide an opportunity for TV to infect ‘C’.

The approximately ten-fold longer duration of colonization of TV in women as opposed to men (58 to 72 weeks for women and 6 weeks for men [18–21]) offers a further mechanism for concurrency to enhance the spread of TV. Because TV is rapidly cleared by men this produces a buffer to transmission in the serial monogamy network, particularly if the duration between old and new partnerships exceeds this duration. This is illustrated in Figure 1 where in the serial monogamy - but not the concurrency network - ‘D’ would be protected from TV acquisition during her partnership with ‘A’ because the gap between partnerships is 7 weeks. Concurrent partnering offers a means for TV to bypass this ‘*rapid-clearance-in-*

males-buffer [22]. At the end of the scenario, TV prevalence is higher in the concurrency network despite a lower total number of partnerships.

In this study, we assess, for the first time, the association between partner concurrency and incident TV in a longitudinal cohort.

Methods

This represents a secondary data analysis of the Longitudinal Study of Vaginal Flora (LSVF). The study recruited 3620 15 to 44 year old women between 1999 and 2003 when they presented for a routine health assessment at 12 clinics in the Birmingham, Alabama area. Women were excluded if they were pregnant or had significant medical or gynaecological conditions. All participants provided informed consent and the study was approved by Review Boards of the Jefferson County, Alabama Department of Health, the University of Alabama at Birmingham and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Local Institutional Review Boards (OH-99-CH-N023).

Participants were seen at an initial visit then quarterly for a further 4 visits. At each visit women followed a structured interview performed in private. They were asked a range of questions including a number relating to their sexual behavior and that of their partners since their last visit. For the baseline and follow up visits, these questions typically referred to the 6 and 3-month time period preceding the interviews, respectively [23, 24].

Partner concurrency

Women were asked ‘Do you think that any of your sex partners had sex with anyone other than you in the past 6 months (baseline visit)/ 30 days (visits 2–5)?’ They were asked to choose between the following options which were read out to them: ‘Yes, definitely’, ‘Yes, possibly’, ‘Do not think so’, ‘Definitely not’. If women were unable to answer the interviewer could classify their answer to this question ‘Unknown’ or ‘Refused to answer.’ Only on one occasion did a person refuse to answer and we recoded this event as missing.

TV and other STIs

At each study visit, each woman had vaginal and endocervical swabs collected at the time of pelvic examinations. A diagnosis of *T. vaginalis* infection was made if either the culture (In-Pouch) was positive or motile trichomonads were seen on microscopy. Vaginal smears were used to diagnose BV via the Nugent method and by Amsel’s clinical criteria [25]. Results were not affected when analyzed by Amsel criteria (data not shown) and thus we restrict the results shown to those using the Nugent method. BV was defined in this study as a Nugent score of 7 or more.

Race/ethnicity

Only 51 women in the cohort were not white or African American. They were classified in 5 other racial/ethnic categories. To simplify the analyses these 51 women were dropped from the analyses.

Statistical analysis

Categorical and continuous variables were compared between groups with the chi square and Kruskal-Wallis tests, respectively. Mixed effects logistic regression was used to assess the association between incident TV and partner concurrency. The analysis was limited to study intervals where the woman was TV negative at the beginning of the period and thus at risk of TV acquisition. The first study visit was excluded as we did not know when TV found at this visit was acquired. Any consecutive study visits where the woman was positive for TV at the first visit of these visits were also excluded.

Potential confounders

Factors that could confound the relationship between incident TV and reported PC were controlled for. These were identified based on a literature review and biological plausibility. These include the frequency and type of sex, age, number of sex partners, the use of douching, receipt of metronidazole at the previous visit, race, education attained, use of hormonal and barrier contraception and the presence of BV at the previous and current visits.

All analyses were done using Stata version 13. A *P*-value of less than 0.05 was considered statistically significant. Intervals with missing data were dropped from the analyses.

Results

Characteristics of the study population

A total of 3519 out of the 3620 LSVF participants were included in this analysis. They were mainly African American (80.6%) and young (mean age 25.4, Standard Deviation 6.95). Participant characteristics by reported partner concurrency status at baseline visit are detailed in Table 1. Respondents reporting partner concurrency (definite or possible) had a higher mean number of sex partners, and were more likely to report rectal and oral sex than women reporting no PC/unlikely PC. Women reporting PC were also more likely to be African American, report douching and always using condoms. They were less likely to use hormonal contraception. TV was more common in those reporting definite/possible PC (15.6%/15.0%) and unknown PC (18.3%) than those reporting no PC (5.2% - $P < 0.001$ for all three comparisons).

A total of 2926 women contributed 9053 visits to the multivariable model (Table 2). A diagnosis of TV was associated with both reporting that one's partner definitely (adjusted Odds ratio [aOR] 5.4; 95% Confidence Interval [CI], 3.7–8.0) and possibly (aOR 3.4; 95% CI, 2.2–5.1) engaged in partner concurrency in the preceding time period. Reporting 'I don't think so' to this question was weakly associated with TV (aOR 1.5; 95% CI, 1.1–2.0). The presence of BV at the prior and current visits were both positively associated with the presence of TV (aOR 1.4; 95% CI, 1.1–1.7 and aOR 2.0; 95% CI, 1.6–2.5, respectively).

A number of sensitivity analyses were run. Firstly, because BV may be in the causal pathway between PC and TV, we reran the models removing the presence of BV at the current visit from the analysis. This did not alter the strength of the association between TV

and PC (data not shown). Secondly, the models were rerun using prevalent TV at each of the 5 visits as the outcome variable. This made little difference to the results (data not shown).

Discussion

A strong association was found between incident TV and self-reported PC after controlling for a range of possible confounders. This association has only been found at an ecological level before [16]. Although this is the first time that this association has been established at an individual level, this may be because, as far as we can establish, this association has not been assessed before. Few studies prospectively collect data on both incident STIs and partner concurrency, making the LSVF a particularly valuable resource. We cannot exclude the possibility that unconsidered confounders, such as variations in the vaginal microbiome not captured by Nugent's BV categorization, may explain the relationship. The relationship between sexual behavior, TV and other constituents of the genital microbiomes is extremely complex [23]. A number of longitudinal studies have found that BV is a risk factor for subsequent TV infection [24]. In a previous analysis of the LSVF, we found that PC is correlated with BV [26]. Controlling for the presence of BV at the previous and current visits did not, however, attenuate the relationship between TV and PC. This combined with the findings that TV was an independent risk factor for incident BV in the LSVF (data not shown) and BV a risk factor for TV [24] suggests that PC may play a role in the transmission of both these conditions and that they may in turn enhance the susceptibility to one another. We were however unable to exclude the possibility that innate differences in vaginal microbiomes may have played a role [27]. A further methodological issue is that more sensitive diagnostic tests (such as Nucleic Acid Amplification Tests) are currently available for the diagnosis of TV. The use of less sensitive diagnostic tests in the LSVF would, however, likely have resulted in a nondifferential misclassification bias which would be expected to bias the association between TV and PC toward the null hypothesis. Further limitations include the age of the dataset, the possibility of social desirability bias in the reporting of PC and the large number of women dropped from the analysis due to missing data.

PC is thought to play a particularly important role in the transmission of infections like HIV that have a peak of infectivity in a relatively short seroconversion-type period [28]. This is partly related to the fact that in a serial monogamy network, there is a smaller chance that infected persons will still be in the highly infectious acute phase when they start a new partnership [28–30]. In a concurrent network, there is a higher probability that a recently infected individual will have sex with another individual during the acute period [28].

A similar phenomenon may be taking place with STIs, such as TV, with a dramatically shorter duration in men compared to women. This '*rapid-clearance-in-males-bottleneck*' may operate as a marked impediment to transmission in a serial monogamy network. Male concurrency enables TV to bypass this bottleneck – provided that the man's gap between sex with each of his partners is less than the 6 weeks duration of TV. In sexual networks characterized by high male concurrency rates, there may be a higher prevalence of TV (and other STIs influenced by concurrency).

This generates a parsimonious theory to explain the considerable differences in STI prevalence between populations. Populations with high network transmissibility index (NTI; as defined by parameters such as high concurrency prevalence, high rate of partner change, short partnership gaps, age-mixing, low condom usage and circumcision) have a more rapid and extensive spread of TV, BV and HSV-2. BV then enhances the susceptibility to TV [24] and HSV-2 [31, 32], TV to BV, and HSV-2 to BV [33]. They also each enhance the susceptibility to and transmission of other STIs [24, 34]. This enhanced susceptibility/transmission is depicted by broader links/edge weights between nodes in Figure 1. This heightened transmission will mean that high NTI networks will be not only more connected but also more likely to transmit STIs than low NTI networks. This could help explain the fact that a African American woman from the USA with one lifetime sex partner has a four-fold higher probability of being HSV-2 positive than a non-Hispanic white woman with the same partner number [35]. The relationship between number of partners and BV prevalence has been shown to vary in a similar fashion by ethnic group in the USA [36].

The relationship between partner concurrency and TV needs to be replicated in other studies. It would be instructive to do so in a prospective cohort that includes high and low STI prevalence subpopulations and regularly characterizes the participants' microbiomes/STIs and relates these to individual, partnership and network-level behavior. Ideally a proportion of the cohort should be included prior to sexual debut. This would provide a more rigorous way to assess the role that partnership and network level characteristics such as PC and the related *rapid-clearance-in-males-buffer* play in the spread of TV and other STIs. If PC is established as a risk factor for TV acquisition then this would provide further rationale to ask about PC when taking sexual histories. It could also contribute extra motivation to efforts to reduce the prevalence of PC [37].

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Figure 1.

Trichomonas vaginalis (TV) is able to spread further in a sexual network characterized by concurrent partnering (left) as compared to one characterized by serial monogamy (right). The scenarios commence with individual B infected with TV (squares: men, circles: women, red: TV infected, beige: TV uninfected, black bars/edges: sexual partnership, breadth of black border or box/circle is proportional to number of other STIs present; edge weight $\approx$ transmission rate -dependent on the number of STIs they have; see text for further explanation. There is a 7-week gap between old and new partnerships as this exceeds TV's 6-week duration of colonization in males. Figure based on figure in Kenyon et al. [16]).

Table 1

Characteristics of 3445 women according to self-reported partner concurrency at baseline visit

	Definitely yes	Possibly yes	Do not think so	Definitely not	Unknown	Total N	P-value [#]
N	384	433	1114	1339	175	3445	
Mean Age [SD – years]	25.5 [6.6]	25.6 [7.0]	25.4 [7.0]	25.4 [7.1]	25.5 [6.3]	-	0.761
Education							0.122
<12 years completed	140 (36.6)	170 (39.3)	397 (35.7)	438 (32.7)	68 (39.1)	1213	
12 years completed	139 (36.4)	163 (37.6)	470 (42.3)	497 (37.1)	78 (44.8)	1347	
>12 years completed	103 (27.0)	100 (23.1)	245 (22.0)	403 (30.1)	28 (16.1)	879	
Respondent race							<0.001
White	46 (12.0)	40 (9.2)	231 (20.7)	340 (25.4)	12 (6.9)	669	
African American	338 (88.0)	393 (90.8)	883 (79.3)	999 (74.6)	163 (93.1)	2776	
Mean no. sex partners last 6 months [SD] *	1.9 [1.9]	1.5 [0.8]	1.1 [0.4]	0.7 [0.5]	1.2 [0.4]	-	<0.001
Douched *	198 (51.7)	259 (60.0)	548 (49.2)	583 (43.6)	95 (54.3)	1683	<0.001
Hormonal contraception	166 (43.2)	189 (43.7)	553 (49.6)	689 (51.5)	73 (41.7)	1670	<0.001
Rectal sex *	33 (8.7)	32 (7.4)	39 (3.5)	55 (4.1)	4 (2.3)	163	<0.001
Oral Sex (receptive) in last 6 months *	203 (53.0)	218 (50.6)	425 (38.3)	417 (31.2)	59 (34.3)	1322	<0.001
Vaginal sex 4 x per week *	67 (17.6)	62 (14.4)	199 (18.1)	207 (15.6)	21 (12.2)	556	0.134
Always use condoms *	113 (29.4)	141 (32.6)	299 (26.9)	177 (13.2)	64 (36.6)	794	<0.001
T. vaginalis diagnosis at baseline visit #	60 (15.6)	65 (15.0)	91 (8.2)	70 (5.2)	32 (18.3)	318	<0.001

[#] P-value refers to comparison of 'Definitely yes'/'Possibly Yes' PC versus 'Do not think so'/'Definitely not' PC columns

* These refer to the numbers reporting ever having engaged in the specified activity in the last 6 months

Table 2

Multivariable model of the association between incident *Trichomonas vaginalis* (TV) and reported partner concurrency (adjusted Odds Ratios [95% Confidence Intervals] P-values *).

	No. without incident TV ^a	No. (%) with incident TV ^a	Incident TV ^d
Partner concurrency			
None	3813	119 (3.03)	Ref
Yes	430	74 (14.7)	5.4 (3.7–8.0) **
Possibly	471	47 (9.1)	3.4 (2.2–5.1) **
Don't think so	3387	154 (4.4)	1.5 (1.1–2.0) *
Unknown	524	34 (6.1)	1.9 (1.2–2.9) *
Age			
15–25	4818	226 (4.5)	Ref
26–35	2689	136 (4.8)	1.1 (0.8–1.4)
36–46	1118	66 (5.6)	1.2 (0.9–1.7)
No. sex partners ^b	-	-	0.9 (0.7–1.1)
Race/Ethnicity			
Non-Hispanic White	1566	23 (1.5)	Ref
African American	7059	405 (5.4)	2.8 (1.8–4.5) **
Douche			
No	5177	205 (3.8)	Ref
Yes	3448	223 (6.1)	1.3 (1.1–1.6) *
Rectal sex			
No	8414	422 (4.8)	Ref
Yes	211	6 (2.8)	0.6 (0.3–1.6)
Oral Sex (receptive)			
No	6137	330 (5.1)	Ref
Yes	2488	98 (3.8)	0.7 (0.5–0.9) *
Frequency of vaginal sex/week			
0–1	5117	260 (4.8)	Ref
2–3	2603	124 (4.6)	0.9 (0.7–1.1)
4	905	44 (4.6)	1.0 (0.7–1.5)
Hormonal contraception			
No	4417	283 (6.0)	Ref
Yes	4208	145 (3.3)	0.6 (0.5–0.7) **
Condom use			
Never	5380	234 (4.2)	Ref
Seldom	1366	87 (6.0)	1.1 (0.8–1.4)
Always	1879	107 (5.4)	0.9 (0.7–1.2)

	No. without incident TV ^a	No. (%) with incident TV ^a	Incident TV ^d
Education completed			
<12 years	2905	187 (6.1)	Ref
12 years	3277	170 (4.9)	0.8 (0.6–1.0) *
>12years	2443	71 (2.8)	0.5 (0.4–0.7) **
TV therapy^c			
No	7562	380 (4.8)	Ref
Yes	1063	48 (4.3)	0.5 (0.4–0.7) **
BV Previous visit			
No	5367	195 (3.5)	Ref
Yes	3258	233 (6.7)	1.4 (1.1–1.7) **
BV current visit			
No	5289	156 (2.9)	Ref
Yes	3336	272 (7.5)	2.0 (1.6–2.5) **

BV – bacterial vaginosis; TV – *Trichomonas vaginalis*

^aThese columns refer to the number (%) of visits where a respondent was or was not diagnosed with incident TV by each of the exposure variables. Only visits that were entered into the multivariable model were included.

^bNumber of sex partners in the preceding study interval. Continuous variable.

^cReceipt of metronidazole therapy at the previous visit. This could be metronidazole for BV or TV.

^dMixed effects logistic regression was used to test the association between TV and partner concurrency

* P<0.05,

** P<0.005