Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
2020, Vol. 31(4) 294–302

DOI: 10.1177/0956462419898612
journals.sagepub.com/home/std


Persistent *Chlamydia trachomatis*, *Neisseria gonorrhoeae* or *Trichomonas vaginalis* positivity after treatment among human immunodeficiency virus-infected pregnant women, South Africa

Andrew Medina-Marino[1,2], Maanda Mudau[1], Noah Kojima[3], Remco PH Peters[4,5,6], Ute D Feucht[7,8,9], Lindsey De Vos[1], Dawie Olivier[1], Christina A Muzny[10], James A McIntyre[4,11] and Jeffrey D Klausner[3,12]

Abstract

The objective of this study is to assess the predictors and frequency of persistent sexually transmitted infection (STI) positivity in human immunodeficiency virus (HIV)-infected pregnant women treated for *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) or *Trichomonas vaginalis* (TV) infection. We enrolled HIV-infected pregnant women attending their first antenatal care visit and tested them for urogenital CT, NG and TV infection using Xpert® CT/NG and TV assays (Cepheid, Sunnyvale, CA). Those testing positive were treated. Participants either notified partners to seek treatment or were given extra medication to deliver to partners for treatment. Repeat testing was conducted approximately 21 days post-treatment or treatment initiation. Among 427 participants, 172 (40.3%) tested positive for any STI. Of the 136 (79.1%) that returned for repeat testing, 36 (26.5%) tested positive for the same organism: CT = 27 (26.5%), NG = 1 (6.3%), TV = 11 (16.7%). Persistent CT positivity was independently associated with having more than one sex partner in the preceding 12 months (adjusted-prevalence ratio [aPR] = 3.03, 95% CI: 1.44–6.37) and being newly diagnosed with HIV infection during the first antenatal care visit compared to those currently on antiretroviral therapy (aPR = 3.97, 95% CI: 1.09–14.43). Persistent TV positivity was associated with not knowing if a partner sought treatment following STI disclosure (aPR = 12.6, 95% CI: 2.16–73.5) and prior diagnosis of HIV but not currently on antiretroviral therapy. (aPR = 4.14; 95% CI: 1.25–13.79). We identified a high proportion of HIV-infected pregnant women with persistent CT or TV positivity after treatment. To decrease the risk of re-infection, enhanced strategies for partner treatment programmes are needed to improve the effectiveness of STI screening and treatment in pregnancy. The relationship between not being on antiretroviral therapy and persistent STI positivity needs further study.

[1]Research Unit, Foundation for Professional Development, East London, South Africa
[2]The Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa
[3]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
[4]Anova Health Institute, Johannesburg, South Africa
[5]Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[6]Department of Medical Microbiology, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre, Maastricht, The Netherlands
[7]Department of Health, Tshwane District, Gauteng, South Africa
[8]Department of Pediatrics, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[9]Research Centre for Maternal, Fetal, Newborn and Child Health Care Strategies, University of Pretoria, South African Medical Research Council, Pretoria, South Africa
[10]Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL, USA
[11]School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
[12]Department of Epidemiology, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA, USA

Corresponding author:
Jeffrey D Klausner, Division of Infectious Diseases, University of California Los Angeles, 10920 Wilshire Blvd, Suite #350, Los Angeles, CA 90024, USA.
Email: JDKlausner@mednet.ucla.edu

Keywords
Chlamydia (*Chlamydia trachomatis*), trichomoniasis (*Trichomonas vaginalis*), gonorrhoea (*Neisseria gonorrhoeae*), screening

Date received: 8 September 2019; accepted: 4 December 2019

Introduction

Chlamydia trachomatis (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) infections are important causes of morbidity among human immunodeficiency virus (HIV)-infected pregnant women and are associated with adverse pregnancy and birth outcomes[1,2]; CT and NG infections have been shown to increase the risk of mother-to-child transmission of HIV infection.[1,2] Additionally, mothers may transmit untreated sexually transmitted infections (STIs) to a newborn at delivery, resulting in nasopharyngeal and/or conjunctival colonization which may progress to pneumonia and/or conjunctivitis.[3] Consequently, routine screening and treatment of STIs during pregnancy may decrease the risk of maternal transmission of HIV infection and infectious complications in infants.[3,4]

In South Africa, like other resource limited settings, syndromic management of STIs in pregnancy is the current standard of care.[5] In syndromic STI management, clinicians treat patients based on defined symptoms, without an etiologic diagnosis. Given that most STIs are asymptomatic, syndromic management leaves a significant number of infections undiagnosed and untreated.[6,7] The adoption of new point-of-care diagnostic tests, which have been found to be highly acceptable and feasible, offers a more accurate method to detect and treat patients with CT, NG or TV infection.[8]

Though CT, NG and TV infections are curable, several studies have reported persistent positivity after appropriate therapy.[9,10] Persistent positivity may be due to treatment failure, slow clearance of detectable CT, NG or TV nucleic acids, or re-infection.[11,12] However, few studies have sought to describe treatment outcomes for CT, NG and TV among HIV-infected pregnant women and predictors of persistent positivity.[10,13] To that end, we determined the frequency and predictors of persistent positive CT, NG and TV test results among HIV-infected pregnant women in Tshwane District, South Africa.

Methods

Study design

This is a sub-analysis of a larger cohort study of HIV-infected pregnant women which aimed to determine the acceptability and feasibility of integrating point-of-care molecular diagnostic testing for CT, NG and TV infections into antenatal care services.[7,14] Briefly, we incorporated same-day point-of-care diagnostic testing and treatment for urogenital CT, NG and TV infections into routine antenatal care provided to HIV-infected pregnant women.[14] We found antenatal STI screening to be highly acceptable to women and feasible. Participants who tested positive for CT, NG and/or TV during their antenatal care visit were treated and invited for repeat testing 21 days later. Eligibility criteria included: (1) enrolment during a participant's first antenatal care visit, (2) age $\geq$18 years, (3) currently pregnant and (4) estimated gestational age $<$34 weeks. Using audio computer-assisted self-interview (ACASI) technology, study nurses and research assistants collected socio-demographic, self-reported genitourinary symptoms (e.g. abnormal vaginal discharge or bleeding or pain during intercourse or dysuria), mental health and sexual behaviour data. Study staff abstracted clinical data from participant's antenatal medical records.

Specimen collection, testing and management

Participants self-collected vaginal swab specimens using Xpert® CT/NG Vaginal/Endocervical Specimen Collection kits (Cepheid, Sunnyvale, California, USA) as previously described.[14] Trained staff at each clinic tested swabs for CT, NG and TV per the manufacturer's instructions (Xpert® CT/NG and Xpert® TV assays, Cepheid, Sunnyvale, California, USA). The Xpert® assays have greater than 99% sensitivity and specificity for the organisms tested.[15,16] Study nurses gave participants who tested positive for CT, NG and/or TV infection treatment per South African guidelines.[5] Participants with CT infection were treated with a 1 g oral stat dose of azithromycin. Those with NG infection were treated with a 250 mg intramuscular injection of ceftriaxone in addition to a 1 g oral dose of azithromycin. Those with TV infection were treated with oral metronidazole 400 mg twice daily for seven days. Study nurses directly observed treatment for CT and NG infection. Nurses gave TV treatment to participants to take at home. Nurses counselled participants with CT, NG or TV infection on safer sex practices and gave women the option to either take home (1) a partner referral letter for treatment or (2)

a pill packet with the relevant medications for their sex partner(s). For cases of gonorrhoea, the partner pill packet included tablets of cefixime 400 mg and azithromycin 1 g.

Test-of-cure visits

Staff asked participants who tested positive for CT, NG and/or TV infection to return to the clinic 21 days after treatment initiation for repeat testing. Staff used a structured questionnaire to collect data from participants regarding disclosure of STI diagnosis and sexual behaviour between time-of-diagnosis and the test-of-cure visit. Staff provided re-treatment and repeat testing until the repeat test(s) were negative or a birth outcome was documented.

Data analysis

We categorized as 'persistently positive' those participants who tested positive at a repeat visit for the same organism(s) for which treatment was previously provided. We summarized categorical variables using percentages and included the 95% confidence intervals (CIs) as appropriate. We used Chi square or Fisher's exact test to determine statistical significance of differences in categorical variables between individuals with positive and negative test-of-cure results. A P-value <0.05 was considered statistically significant. We used multivariate Poisson regression analysis to calculate adjusted-prevalence ratios (aPRs) and identify determinants of positive CT, NG and TV results at test-of-cure. Any variable associated ($P < 0.20$, univariate analysis) with a positive CT, and TV result at the repeat visit was included in the multivariate model; analysis for each organism was conducted separately. Maternal and gestational ages at enrolment (trimester) were included, a priori, in the multivariate models. Additionally, we assessed whether pre-treatment PCR cycle threshold values – a measure of organism load – were predictive of persistent test positivity.

Ethical considerations

Informed consent was obtained from all participants. Facility managers and the Tshwane District Department of Health Research Committee provided permission to conduct this study at selected antenatal care clinics. Ethical approval and oversight were provided by the Institutional Review Board of the University of Pretoria, Faculty of Health Sciences, Research Ethics Committee (reference number: 401/2015) and the University of California Los Angeles (reference number: 15-001351). The committees agreed with the provision of patient-delivered partner therapy.

Table 1. Count and proportion of sexually transmitted infections among HIV-infected pregnant women attending their first antenatal care visit, Tshwane District, South Africa.

	N = 427			
	Positive	%	95% CI	
Any STI (CT/NG/TV)	172	40.3	35.7	45.0
CT infection	126	29.5	25.4	34.0
NG infection	24	5.6	3.8	8.3
TV infection	86	20.1	16.6	24.2

CT: *Chlamydia trachomatis*; NG: *Neisseria gonorrhoeae*; STI: sexually transmitted infection; TV: *Trichomonas vaginalis*.

Results

Between 1 June 2016 and 29 September 2017, we enrolled 430 participants at three primary healthcare facilities in Tshwane District, South Africa. Three participants were subsequently determined to have pseudo-pregnancies, and thus ineligible for the study. Consequently, 427 HIV-infected pregnant women were included in the final analysis.

All 427 participants were tested for CT, NG and TV at their first antenatal care visit, of which 172 (40.3%) tested positive for CT, NG and/or TV; CT = 126 (29.5%), NG = 24 (5.6%) and TV = 86 (20.1%) (Table 1). Among those with a positive test result, 171 (99.4%) received treatment; one participant had received syndromic STI treatment six days prior to enrolment and was not provided additional treatment.

Among those with a positive STI test result, 136 (79.1%) returned for test-of-cure. Of 126 individuals initially treated for CT, 102 (81.0%) returned for test-of-cure, of which 27 (26.5%) tested positive. Among the 24 individuals treated for NG at their first visit, 16 (66.7%) returned for test-of-cure, of whom one (6.3%) tested positive. Among 86 individuals initially treated for TV, 66 (76.7%) returned for a test-of-cure, of whom 11 (16.7%) tested positive (Table 2).

Of 136 participants returning for the first test-of-cure, 133 (97.8%) completed a post-treatment interview. Of those, 122 (91.7%) reported they disclosed their STI test results to their partner(s) (Table 3). Among those 122 participants, 12 (9.8%) reported that their partner sought medical care, 67 (54.9%) reported that their partner accepted the partner treatment pill packet, 30 (24.6%) reported their partner(s) did not seek medical care, and 13 (10.7%) were unaware whether their partner had sought care. Of the 75 individuals (67.6%; 75/111) who reported engaging in sexual intercourse following their initial STI diagnosis, 42 (56.6%) said they always used condoms and 20 (26.7%) said that they never used condoms (Table 3).

Table 2. Sexually transmitted infection positivity at repeat test-of-cure visits among human immunodeficiency virus-infected pregnant women, Pretoria, South Africa.

	First test-of-cure (ToC1)		Second test-of-cure (ToC2)		Third test-of-cure (ToC3)	
	Tested at ToC1 N	Positive at ToC1 n (%)	Tested at ToC2 N	Positive at ToC2 n (%)	Tested at ToC3 N	Positive at ToC3 n (%)
Any CT, NG or TV at baseline	136	36 (26.5%)	29	14 (48.3%)	9	7 (77.8%)
CT positive at baseline	102	27 (26.5%)	22	10 (45.5%)	5	3 (60.0%)
NG positive at baseline	16	1 (6.3%)	1	0	0	0
TV positive at baseline	66	11 (16.7%)	9	5 (55.6%)	4	4 (100%)

CT: *Chlamydia trachomatis*; NG: *Neisseria gonorrhoeae*; TV: *Trichomonas vaginalis*.

Table 3. Interview responses on treatment disclosure and sexual activity among human immunodeficiency virus-infected pregnant women, Pretoria, South Africa.

Test-of-cure interview response	n	%
Disclosed STI diagnosis to sexual partner(s)		
No	11	8.3
Yes	122	91.7
Time taken to disclose results to partner(s)		
Within 24 h	105	86.1
After 24 h	17	13.9
Partner sought medical care after being informed of result		
No	30	24.6
Yes	12	9.8
No, but accept expedited partner treatment	67	54.9
Don't know	13	10.7
Sexual intercourse since STI diagnosis		
No	36	32.4
Yes	75	67.6
Sexual partner since STI diagnosis		
Regular partner	74	98.7
Other partner	1	1.3
Condom use since STI diagnosis		
All the time	42	56.6
Sometimes	13	17.3
Never	20	26.7

STI: sexually transmitted infection.

Among participants treated for CT infection at their first antenatal care visit, those who reported having more than one sex partner in the preceding 12 months were more likely to have a persistent positive test compared to those who reported having only one sex partner (52.6% versus 20.7%; aPR = 3.03, 95% CI: 1.44–6.37). Furthermore, persistent CT positive test results were higher among participants diagnosed with HIV infection during their first antenatal care visit compared to those with a known HIV infection status and on antiretroviral therapy (ART) (40.0% versus 9.3%; aPR = 3.97, 95% CI: 1.09–14.43).

Among individuals treated for TV at their first antenatal care visit, those who did not know if their partner (s) sought treatment had a higher probability of having a persistent positive TV test result compared to women whose partner(s) accepted expedited partner treatment (42.9% versus 12.1%; aPR = 12.6, 95% CI: 2.16–73.5). Moreover, participants diagnosed with HIV infection prior to the first visit but not currently taking ART were more likely to have persistent TV positivity compared to those who were on ART (25.0% versus 9.7%; aPR = 4.14; 95% CI: 1.25–13.79) (Table 4). Finally, participants who had pre-treatment PCR cycle threshold values consistent with a higher burden of infection (Ct value = $\leq$29) had a higher frequency of both CT and TV persistent positivity compared to those with a lower burden of infection, however these findings were not significant (Table 4).

We could not assess determinants of persistent NG positivity due to the limited sample size.

Discussion

Our study investigated the frequency and predictors of persistent positive CT, NG and/or TV tests after locally recommended treatment in HIV-infected pregnant women. We found more than 25% of women returning for their test-of-cure visit had a persistent positive STI test. Among our participants, the frequency of persistent positive CT results following treatment (26.5%) was higher than previously reported in studies among pregnant women from the United States (15.4%) and Peru (14.0%).[17,18] In comparison, the 16.7% persistent TV positivity was only slightly higher than the 6–15% persistent TV positivity reported by others.[19]

Although more than 90% of women in our study reported disclosing their STI diagnosis to sex partners, nearly a quarter reported that their sex partner(s) did not seek medical care, and another 10% were unaware if their sex partner(s) sought medical care. Lack of

Table 4. Associations of study participant characteristics and test-of-cure results among human immunodeficiency virus-infected pregnant women, Pretoria, South Africa.

	CT									TV									
Characteristic	Number returned for ToC	Number with persistent CT positivity at ToC	Percent with persistent CT positivity at ToC	PR	(95% CI)		p-value	Adjusted PR (95% CI)	p-value	Number returned for ToC	Number with persistent TV positivity at ToC	Percent with persistent TV positivity at ToC	PR	(95% CI)		p-value	Adjusted PR (95% CI)	p-value	p-value
Age group																			
<25 years	21	6	28.6	1.10	0.51	2.39	0.806			14	4	28.6	2.12	0.72	6.29	0.174			
25–35 years	63	18	28.6	1.24	0.62	2.49	0.548			41	5	12.2	0.51	0.17	1.51	0.222			
>35 years	18	3	16.7	0.58	0.20	1.74	0.333			11	2	18.2	1.11	0.27	4.50	0.883			
Gestational age																			
1st Trimester (1–12 weeks)	22	3	13.6	0.45	0.15	1.38	0.163			12	1	8.3	0.45	0.06	3.24	0.282			
2nd Trimester (13–27 weeks)	67	22	32.8	2.30	0.95	5.57	0.065			45	8	17.8	1.24	0.36	4.26	0.728			
3rd Trimester (28–34 weeks)	13	2	15.4	0.55	0.15	2.06	0.373			9	2	22.2	1.41	0.36	5.55	0.625			
Gravidity																			
1	13	3	23.1	0.86	0.30	2.46	0.772			7	1	14.3	0.84	0.12	5.72	0.861			
2	31	14	45.2	2.47	1.31	4.63	0.005			23	4	17.4	1.07	0.35	3.30	0.909			
3	29	2	6.9	0.20	0.05	0.80	0.023			20	4	20.0	1.31	0.43	4.02	0.632			
>3	29	8	27.6	1.06	0.52	2.15	0.872			16	2	12.5	0.69	0.17	2.92	0.619			
Last known CD4 T cell count (cells/μl)																			
<200	11	3	27.3	1.28	0.43	3.79	0.656			5	2	40.0	2.80	0.75	10.46	0.126			
200–349	18	2	11.1	0.43	0.11	1.72	0.233			7	0	0.0							
350–499	20	8	40.0	2.60	1.12	6.02	0.026			12	3	25.0	1.75	0.48	6.33	0.394			
>500	23	3	13.0	0.49	0.15	1.57	0.231			23	3	13.0	0.63	0.17	2.36	0.489			
Last known HIV viral load																			
Detectable	33	12	36.4	Ref						18	6	33.3	Ref						
Undetectable	25	6	24.0	0.66	0.29	1.53	0.331			25	2	8.0	0.24	0.05	1.07	0.062			
Knowledge of HIV status at first ANC																			
Known HIV on ART	43	4	9.3	Ref						31	3	9.7	Ref						
Known HIV not on ART	14	5	35.7	3.84	1.19	12.42	0.025			12	3	25.0	2.58	0.60	11.19	0.205	4.14 (1.25–13.79)	0.020	
Diagnosed at ANC	45	18	40.0	4.30	1.57	11.74	0.004	3.97 (1.09–14.43)	0.036	23	5	21.7	2.25	0.59	8.54	0.235			
Partner HIV status																			
Known	32	4	12.5	Ref						31	4	12.9							
Unknown	55	19	34.5	2.76	1.02	7.45	0.045			27	5	18.5	1.44	0.42	4.86	0.562			
Depression (first ANC visit)																			
No depression (PHQ <10)	93	25	26.9	Ref						59	10	16.9	Ref						
Depression (PHQ ≥10)	8	2	25.0	0.93	0.27	3.25	0.910			6	1	16.7	0.98	0.15	6.51	0.986			
STI-associated symptoms (first ANC visit)																			
Asymptomatic	79	22	27.8	Ref						49	9	18.4	Ref						

(continued)

Table 4. Continued.

Characteristic	CT									TV									
	Number returned for ToC	Number with persistent CT positivity at ToC	Percent with persistent CT positivity at ToC	PR	(95% CI)		p-value	Adjusted PR (95% CI)	p-value	Number returned for ToC	Number with persistent TV positivity at ToC	Percent with persistent TV positivity at ToC	PR	(95% CI)		p-value	Adjusted PR (95% CI)	p-value	p-value
Symptomatic	23	5	21.7	0.78	0.33	1.84	0.571			17	2	11.8	0.64	0.15	2.70	0.544			
STI-associated symptoms (test-of-cure visit)																			
Asymptomatic	88	24	27.3	Ref						55	8	14.5	Ref						
Symptomatic	12	2	16.7	0.61	0.16	2.28	0.464			10	3	30.0	2.06	0.65	6.53	0.218			
Disclosed STI diagnosis to sexual partner(s)																			
No	4	2	50.0	Ref						7	2	28.6	Ref						
Yes	96	24	25.0	0.50	0.18	1.42	0.193			58	9	15.5	0.54	0.14	2.05	0.367			
Time taken to disclose results to partner(s)																			
After 24 h	14	5	35.7	Ref						5	1	20.0	Ref						
Within 24 h	82	19	23.2	0.65	0.29	1.46	0.295			53	8	15.1	0.75	0.11	4.96	0.769			
Partner sought medical care after being informed of result																			
No	23	6	26.1	1.06	0.48	2.36	0.890			15	2	13.3	0.82	0.19	3.56	0.790			
Yes	10	1	10.0	0.37	0.06	2.50	0.311			3	0	0.0							
No, but accepted expedited partner treatment	55	14	25.5	1.04	0.51	2.12	0.906			33	4	12.1	0.61	0.18	2.05	0.420			
Don't know	8	3	37.5	1.57	0.59	4.16	0.363			7	3	42.9	3.64	1.16	11.49	0.027	12.6 (2.16–73.5)	0.005	
Sexual intercourse since STI diagnosis																			
No	26	7	26.9	Ref						21	6	28.6	Ref						
Yes	59	15	25.4	0.94	0.44	2.05	0.885			36	5	13.9	0.49	0.17	1.41	0.185			
Condom use since STI diagnosis																			
All the time	35	12	34.3	2.74	0.86	8.78	0.089			20	2	10.0	0.53	0.10	2.88	0.465			
Sometimes	10	0	0.0	–						4	0	0.0							
Never	14	3	21.4	0.80	0.26	2.47	0.703			12	3	25.0	3.00	0.56	15.98	0.198			
More than one sex partner in the past 12 months																			
No	82	17	20.7	Ref						49	7	14.3	Ref						
Yes	19	10	52.6	2.54	1.39	4.64	0.002	3.03 (1.44–6.37)	0.003	16	4	25.0	1.75	0.58	5.26	0.319			
Pre-treatment cycle threshold (Ct) value																			
Strong positive (≤29)	40	13	32.5							40	10	25.0							
Moderate positive (>29≥37)	37	8	21.6	0.67	0.31	1.426	0.295			12	0	0.0							
Weak positive (>37)	25	6	24.0	0.74	0.32	1.70	0.475			14	1	7.1	0.29	0.04	2.07	0.215			

ANC: antenatal care; ART: antiretroviral therapy; CT: *Chlamydia trachomatis*; HIV: human immunodeficiency virus; NG: *Neisseria gonorrhoeae*; PHQ: Patient Health Questionnaire; STI: sexually transmitted infection; TV: *Trichomonas vaginalis*.

knowledge of whether their sex partner(s) received treatment was significantly associated with persistent TV positivity. Among those with persistent CT positivity, having more than one sex partner in the preceding 12 months was a significant risk factor. Together, these finding suggest that the elevated frequency of persistent TV and CT positivity may be due to increased risk of re-exposure/re-infection by sexual partners and sexual networks. Others have described possible reasons for persistent positivity including delayed clearance of non-viable microbial nucleic acids, treatment failure due to antimicrobial resistance and re-infection by sex partners.[20] Similarly, our results suggest that persistent CT and TV test positivity may be due to multiple factors.

We also report that HIV-infected women not on ART had a higher frequency of persistent TV positivity. That finding is in contrast to a Kenyan study which reported that HIV-infected women on nevirapine-based ART had a higher frequency of persistent TV infection after treatment compared to HIV-infected women not on ART.[21] In that study, a 2 g single dose of metronidazole had a lower success rate in TV-infected women who were on ART compared to those who were not on ART. Adamski et al.[22] corroborated those findings in a study of 226 HIV-infected women with TV on a variety of antiretroviral regimens. In that study, those on ART had a higher frequency of persistent TV positivity after treatment than those not on ART, with more treatment failures occurring among women receiving the 2 g single dose of metronidazole compared to a seven-day 500 mg twice daily regimen. The authors suggested that ART is a marker of some other biological factor that interferes with metronidazole treatment of TV infection. However, what this other biological factor(s) may be is unknown. Reasons for the discrepancy between our findings and those of previous studies are unknown. To elucidate the interaction between ART and metronidazole investigators should conduct pharmacokinetic studies.

Similar to women with persistent TV positivity, we found that women not on ART were more likely to also be persistently positive for CT. Whether that observation is due to HIV-related immune dysregulation in women with untreated HIV infection or due to drug–drug interactions is unknown. Similar to metronidazole, the exact mechanism by which ART may alter azithromycin efficacy is also unclear. Efavirenz, emtricitabine and tenofovir-diphosphate, the three drugs which make up South Africa's first line fixed dose combination ART, do not seem to have significant interactions with azithromycin.[23] A slight increase in the maximum serum concentration of azithromycin has been reported when used in combination with efavirenz.[24] Though antiretroviral medications are known to have an effect on the constitution of the gut microbiome,[25] evidence suggests that antiretroviral medications on their own do not lead to reconstitution of the gut microbiome from dysbiosis to a healthy state similar to HIV-uninfected individuals.[26] Further studies are needed to investigate the causal pathway between ART, immune dysregulation and STI treatment outcomes, as well as the role of the vaginal microbiome and STI clearance.

Some sexual behaviours and partner characteristics were also associated with persistent STI positivity in our study. In multivariate analysis, we found that women who reported more than one sex partner in the preceding 12 months were more likely to test persistently positive for CT compared to women who did not have multiple partners. That finding is consistent with prior studies that found higher rates of CT persistent positivity among women in multiple concurrent partnerships.[27,28] We also found that participants who were unsure whether their partner(s) sought STI treatment had a higher probability of persistent TV positivity compared to those who knew their partner sought treatment. That strongly suggests re-infection due to lack of partner treatment related to complex partner dynamics and poor communication which may influence the risk of acquiring repeat STIs.[29,30]

Nucleic acid amplification tests to detect infections, similar to the one used in our study, cannot distinguish between nucleic acids from viable or non-viable organisms.[31] Cell culture has been used to assess whether detected DNA represents viable infectious microorganisms. When used in combination with high resolution molecular typing methods, cell culture may provide key information regarding persistent positivity. A limitation in our current study is the lack of culture and molecular typing data. However, we previously reported on a sub-study involving TV culture in a subset of women with persistent positive TV results.[32] In that study we found that 50% of participants with a positive test-of-cure results had viable organisms. That study also found that test-of-cure PCR cycle threshold value from test-of-cure specimens was predictive of *T. vaginalis* culture positivity, and thus viable infection.

In a study conducted among non-pregnant women in the Netherlands, Versteeg et al.[33] found that women with PCR cycle threshold values consistent with a higher burden of infection were more likely to be culture positive as well. Similarly, we found pre-treatment PCR cycle threshold values were predictive of persistent test positivity. However, those results were not statistically significant. Given that specimens were self-collected, variations in the amount of material collected on a swab for testing may not have been well standardized, and thus impacted cycle threshold values.

Social desirability response bias to survey questions on sexual behaviour, sexual history and alcohol use may also have contributed to study limitations. Specifically, the sensitivity of survey questions may have not been sufficient to capture behavioural factors associated with re-infection. We also did not ascertain from partners themselves their treatment exposure, a challenge not unique to our study.[34] Finally, we did not have specific measures other than self-report to confirm medication adherence with the multiday regimen for TV treatment. Consequently, we could not determine if adherence was associated with TV persistence.

Conclusions

We observed a high frequency of CT and TV persistent positivity after treatment among a cohort of HIV-infected pregnant women in South Africa. However, we could not conclusively distinguish between treatment failure, re-infection, or slow clearance of CT and TV nucleic acids following treatment. More than one recent sex partner and lack of knowledge of uptake of partner treatment were independent determinants of persistent positivity, indicating that persistent positivity may be due to re-infection by partners. This may be particularly important in settings where CT is hyperendemic. That highlights the need to improve safer sex counselling among HIV-infected pregnant women diagnosed with STIs and to determine optimal cost-effective strategies for repeat screening and partner treatment. Effective partner treatment programmes are needed to improve the effectiveness of STI screening and treatment programmes, especially during antenatal care. The relationship between ART, HIV-related immunosuppression and STI treatment outcomes needs to be explored further.

Acknowledgements

The authors would like to acknowledge the Tshwane District Department of Health, clinic managers and facility staff, who gave permission to conduct the study at the respective sites and accommodated the study teams.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Christina A Muzny is currently a consultant for Lupin Pharmaceuticals, BioFire Diagnostics, and Cepheid. She also received honoraria from Roche Diagnostics. Jeffrey D Klausner has received advising fees and donated research supplies from Cepheid.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Eunice Kennedy Shriver Institute of Child Health and Human Development, National Institutes of Health (NIH), award R21HD084274 and the President's Emergency Plan for AIDS Relief through the United States Agency of the Cooperative Agreement AID 674-A-12-00017 funded this study. Noah Kojima was supported by the U.S. NIH Fogarty International Center (award number D43TW009343) and the University of California Global Health Institute. Christina A Muzny was supported by K23AI106957-01A1 from the National Institute of Allergy and Infectious Diseases. The content is solely the responsibility of the authors.

ORCID iDs

Remco PH Peters https://orcid.org/0000-0003-2124-7275
Dawie Olivier https://orcid.org/0000-0001-7654-1434
Jeffrey D Klausner https://orcid.org/0000-0002-6922-7364

References

1. Mayor MT, Roett MA and Uduhiri KA. Diagnosis and management of gonococcal infections. *Am Fam Physician* 2012; 86: 931–938.
2. Soper D. Trichomoniasis: under control or undercontrolled? *Am J Obstet Gynecol* 2004; 190: 281–290.
3. Hammerschlag MR. Chlamydial and gonococcal infections in infants and children. *Clin Infect Dis* 2011; 53: S99–S102.
4. Lewis DA. HIV/sexually transmitted infection epidemiology, management and control in the IUSTI Africa region: focus on sub-Saharan Africa. *Sex Transm Infect* 2011; 87: ii10–ii13.
5. National Department of Health RoSA. *Sexually transmitted infections management guidelines 2015*. Pretoria: National Department of Health, Republic of South Africa, 2015.
6. White RG, Moodley P, McGrath N, et al. Low effectiveness of syndromic treatment services for curable sexually transmitted infections in rural South Africa. *Sex Transm Infect* 2008; 84: 528–534.
7. Mudau M, Peters RP, De Vos L, et al. High prevalence of asymptomatic sexually transmitted infections among human immunodeficiency virus-infected pregnant women in a low-income South African community. *Int J STD AIDS* 2018; 29: 324–333.
8. Shannon CL, Bristow C, Hoff N, et al. Acceptability and feasibility of rapid chlamydial, gonococcal, and trichomonal screening and treatment in pregnant women in 6 low- to middle-income countries. *Sex Transm Dis* 2018; 45: 673–676.
9. Wijers J, van Liere G, Hoebe C, et al. Test of cure, retesting and extragenital testing practices for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* among general practitioners in different socioeconomic status areas: a

retrospective cohort study, 2011–2016. *PLoS One* 2018; 13: e0194351.
10. Hananta IPY, De Vries HJC, van Dam AP, et al. Persistence after treatment of pharyngeal gonococcal infections in patients of the STI clinic, Amsterdam, the Netherlands, 2012–2015: a retrospective cohort study. *Sex Transm Infect* 2017; 93: 467–471.
11. Kissinger P, Secor WE, Leichliter JS, et al. Early repeated infections with *Trichomonas vaginalis* among HIV-positive and HIV-negative women. *Clin Infect Dis* 2008; 46: 994–999.
12. Sena AC, Bachmann LH and Hobbs MM. Persistent and recurrent *Trichomonas vaginalis* infections: epidemiology, treatment and management considerations. *Expert Rev Anti Infect Ther* 2014; 12: 673–685.
13. Kissinger PJ, White S, Manhart LE, et al. Azithromycin treatment failure for *Chlamydia trachomatis* among heterosexual men with nongonococcal urethritis. *Sex Transm Dis* 2016; 43: 599–602.
14. Morikawa E, Mudau M, Olivier D, et al. Acceptability and feasibility of integrating point-of-care diagnostic testing of sexually transmitted infections into a South African antenatal care program for HIV-infected pregnant women. *Infect Dis Obstet Gynecol* 2018; 2018: 3946862.
15. Gaydos CA, Van Der Pol B, Jett-Goheen M, et al. Performance of the Cepheid CT/NG Xpert rapid PCR test for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *J Clin Microbiol* 2013; 51: 1666–1672.
16. Schwebke JR, Gaydos CA, Davis T, et al. Clinical evaluation of the Cepheid Xpert TV assay for detection of Trichomonas vaginalis with prospectively collected specimens from men and women. *J Clin Microbiol* 2018; 56(2). pii: e01091-17.
17. Hoover KW, Tao G, Nye MB, et al. Suboptimal adherence to repeat testing recommendations for men and women with positive Chlamydia tests in the United States, 2008–2010. *Clin Infect Dis* 2013; 56: 51–57.
18. Cabeza J, Garcia PJ, Segura E, et al. Feasibility of *Chlamydia trachomatis* screening and treatment in pregnant women in Lima, Peru: a prospective study in two large urban hospitals. *Sex Transm Infect* 2015; 91: 7–10.
19. Williams JA, Ofner S, Batteiger BE, et al. Duration of polymerase chain reaction-detectable DNA after treatment of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* infections in women. *Sex Transm Dis* 2014; 41: 215–219.
20. Pitt R, Alexander S, Ison C, et al. Phenotypic antimicrobial susceptibility testing of Chlamydia trachomatis isolates from patients with persistent or successfully treated infections. *J Antimicrob Chemother* 2018; 73: 680–686.
21. Balkus JE, Richardson BA, Mochache V, et al. A prospective cohort study comparing the effect of single-dose 2 g metronidazole on *Trichomonas vaginalis* infection in HIV-seropositive versus HIV-seronegative women. *Sex Transm Dis* 2013; 40: 499–505.
22. Adamski A, Clark RA, Mena L, et al. The influence of ART on the treatment of *Trichomonas vaginalis* among HIV-infected women. *Clin Infect Dis* 2014; 59: 883–887.
23. University of Liverpool. HIV Drug Interactions, https://www.hiv-druginteractions.org/ (1999, accessed 26 December 2019)
24. Joshi A, Fiske WD, Benedek IH, et al. Lack of pharmacokinetic interaction between efavirenz (DMP 266) and ethinyl estradiol in healthy volunteers. In: The 5th conference on retroviruses and opportunistic infections (CROI), Chicago, United States, 1998.
25. Pinto-Cardoso S, Lozupone C, Briceno O, et al. Fecal bacterial communities in treated HIV infected individuals on two antiretroviral regimens. *Sci Rep* 2017; 7: 43741.
26. Pinto-Cardoso S, Klatt NR and Reyes-Teran G. Impact of antiretroviral drugs on the microbiome: unknown answers to important questions. *Curr Opin HIV AIDS* 2018; 13: 53–60.
27. Mosure DJ, Berman S, Kleinbaum D, et al. Predictors of *Chlamydia trachomatis* infection among female adolescents: a longitudinal analysis. *Am J Epidemiol* 1996; 144: 997–1003.
28. Marrazzo JM, Fine D, Celum CL, et al. Selective screening for chlamydial infection in women: a comparison of three sets of criteria. *Fam Plann Perspect* 1997; 29: 158–162.
29. Daniels J, De Vos L, Mogos W, et al. Factors influencing sexually transmissible infection disclosure to male partners by HIV-positive pregnant women in Pretoria townships, South Africa: a qualitative study. *Sex Health*. Epub ahead of print 10 May 2019 DOI: 10.1071/SH18177.
30. Fox AM, Jackson SS, Hansen NB, et al. In their own voices: a qualitative study of women's risk for intimate partner violence and HIV in South Africa. *Violence Against Women* 2007; 13: 583–602.
31. Janssen KJ, Hoebe CJ, Dukers-Muijrers NH, et al. Viability-PCR shows that NAAT detects a high proportion of DNA from non-viable *Chlamydia trachomatis*. *PLoS One* 2016; 11: e0165920.
32. Price CM, Peters RPH, Steyn J, et al. Prevalence and detection of *Trichomonas vaginalis* in HIV-infected pregnant women. *Sex Transm Dis* 2018; 45: 332–336.
33. Versteeg B, Bruisten SM, Heijman T, et al. Monitoring therapy success of urogenital *Chlamydia trachomatis* infections in women: a prospective observational cohort study. *PLoS One* 2017; 12: e0185295.
34. Kissinger PJ. The challenges of implementing and evaluating prescription expedited partner treatment. *Sex Transm Dis* 2017; 44: 109–110.