Doxycycline Prophylaxis to Reduce Incident Syphilis among HIV-Infected Men Who Have Sex With Men Who Continue to Engage in High-Risk Sex: A Randomized, Controlled Pilot Study

Robert K. Bolan, MD, Matthew R. Beymer, MPH,*† Robert E. Weiss, PhD,‡ Risa P. Flynn,* Arleen A. Leibowitz, PhD,§ and Jeffrey D. Klausner, MD, MPH¶*

Background: Incident syphilis infections continue to be especially prevalent among a core group of HIV-infected men who have sex with men (MSM). Because of synergy between syphilis and HIV infections, innovative means for controlling incident syphilis infections are needed.

Methods: Thirty MSM who had syphilis twice or more since their HIV diagnosis were randomized to receive either daily doxycycline prophylaxis or contingency management (CM) with incentive payments for remaining free of sexually transmitted diseases (STDs). Participants were tested for the bacterial STDs gonorrhea (*Neisseria gonorrhoeae*), chlamydia (*Chlamydia trachomatis*) and syphilis at weeks 12, 24, 36, and 48 and completed a behavioral risk questionnaire during each visit to assess number of partners, condom use, and drug use since the last visit. Generalized linear mixed models were used to analyze differences between arms in STD incidence and risk behaviors at follow-up.

Results: Doxycycline arm participants were significantly less likely to test positive for any selected bacterial STD during 48 weeks of follow-up (odds ratio, 0.27; confidence interval, 0.09–0.83) compared with CM arm participants ($P = 0.02$).There were no significant self-reported risk behavior differences between the doxycycline and CM arms at follow-up.

Conclusions: Daily doxycycline taken prophylactically was associated with a decreased incidence of *N. gonorrhoeae*, *C. trachomatis*, or syphilis incident infections among a core group of HIV-infected MSM at high risk for these infections. Safe and effective biomedical tools should be included in the efforts to control transmission of syphilis, especially in this population. A randomized clinical trial should be conducted to confirm and extend these findings.

From the *Los Angeles LGBT Center (The Center), Los Angeles, CA; and †Department of Community Health Sciences, Fielding School of Public Health, ‡Department of Biostatistics, Fielding School of Public Health, §Luskin School of Public Affairs, and ¶Geffen School of Medicine, University of California, Los Angeles

Conflicts of Interest: None declared for any authors.

Sources of funding: (1) R.K.B. and R.P.F. were supported by UCLA Center for HIV Identification, Prevention, and Treatment Services (Grant No. P30MH058107). (2) R.E.W. was supported by the Center for HIV Identification, Prevention, and Treatment (NIMH Grant No. MH58107) and the UCLA Center for AIDS Research (Grant No. 5P30AI028697, Core H.). (3) A.A.L. was supported by the UCLA Center for HIV Identification, Prevention, and Treatment Services, funded by a grant from the National Institute of Mental Health (Grant No. 3P30 MH058107-16); California HIV/AIDS Research Program of the University of California (Grant Nos. RP11-LA-020 and RP08-LA-602); UCLA Center for AIDS Research (Grant No. 5P30 A1028697); and National Center for Advancing Translational Sciences through the UCLA Clinical and Translational Science Institute (Grant No. UL1TR000124).

Correspondence: Robert Key Bolan, MD, Los Angeles LGBT Center, McDonald/Wright Building, 1625 Schrader Blvd, Room 351, Los Angeles, CA 90028-6213. E-mail: bbolan@lalgbtcenter.org.

Received for publication May 14, 2014, and accepted October 16, 2014.
DOI: 10.1097/OLQ.0000000000000216

The US Centers for Disease Control and Prevention reported that the prevalence of primary and secondary syphilis was 2.6% among HIV-uninfected men who have sex with men (MSM) and 10.1% among HIV-infected MSM seen at sexually transmitted disease (STD) clinics in 2011.[1] In 2012, 75% of primary and secondary syphilis cases occurred in MSM.[2] A 2009 study among a population of 4376 HIV-infected MSM found that 43.6% of the cases of syphilis were diagnosed in only 3.8% of the patient population.[3] Based on these data, it is reasonable to consider the presence of a core group of HIV-infected MSM who disproportionally contribute to the current epidemic of syphilis and to target that population for interventions.[4]

Although it is believed that most of new HIV infections originate from individuals who do not know they are HIV infected, it is clear that many HIV-infected individuals who do know their status continue to engage in sexual behaviors capable of transmitting HIV and other STDs.[5] There is bidirectional biological synergy between HIV and syphilis. Risk for increased transmission of HIV is evidenced by a transient but significant increase in plasma viral load in HIV-infected individuals who have primary and secondary syphilis, even among those whose HIV viral loads had previously been controlled.[6,7] On the other hand, HIV acquisition is increased 2- to 9-fold when syphilis is already present.[8] It remains unclear whether there is an increased biological susceptibility to HIV infection when HIV is transmitted at the same time as syphilis.

From a behavioral standpoint, it is doubtful that further exhortations for HIV-infected MSM to practice safer sex to avoid STDs will be successful, at least for the "core transmitters" described above. Although several investigators have remarked upon a sharp decline in HIV and STD transmission risk behavior after an HIV diagnosis, Gorbach and others have shown that after 9 months, there is a rebound in unprotected anal intercourse with serodiscordant or unknown serostatus partners.[9,10] Reducing rates of syphilis incidence among HIV-infected MSM, especially the core group of transmitters, theoretically could lower HIV transmission rates and importantly, syphilis transmission. Novel strategies are needed to accomplish those goals in such persistently high-risk subpopulations for whom the usual messages to practice safer sex have failed.

This pilot study investigated the feasibility of conducting a randomized trial to determine if daily prophylactic doxycycline was efficacious in reducing STDs among high-risk, HIV-positive MSM when compared with those who were provided contingency management (CM) incentives. The objectives of this study were 4-fold: (1) measure adherence to study visits; (2) measure adherence to the prophylaxis regimen; (3) measure any changes in risk

behaviors, such as drug use, condom use, and number of partners; and (4) to the extent possible in a brief pilot study, compare the effectiveness of doxycycline with that of a monetary incentive for remaining STD-free.

MATERIALS AND METHODS

Thirty-seven participants drawn from the Los Angeles LGBT Center (the Center) HIV Clinic were screened and underwent informed consent. Participants were required to meet the following inclusion criteria: (1) 18 years or older, (2) HIV-infected MSM or transgender women who have sex with men, and (3) at least 2 documented and adequately treated episodes of syphilis since HIV diagnosis. Participants were excluded from participation if either (1) had a known allergy or intolerance to doxycycline and/or (2) abused alcohol or other substances, which, in the opinion of the investigators, would jeopardize adherence to study procedures. Of the 37 participants screened for participation, 30 participants satisfied all inclusion criteria and were enrolled into the study.

Participants were block randomized to 1 of 2 groups with a 1:1 allocation ratio: (1) doxycycline hyclate, 100 mg once daily for 36 weeks, or (2) an incentive-based financial CM arm for remaining STD-free. Although all participants were compensated $25 per visit, participants in the CM arm received an additional $50, $75, and $100 if they tested STD-free at weeks 12, 24, and 36, respectively. No allocation concealment measures or specific measures for implementation were used; neither the researchers nor the analysts were blinded to the study group assignment.

The single daily dose of 100 mg was chosen to help adherence by conforming to the increasingly common use of once daily regimens for HIV treatment and because dosing as infrequent as once weekly was shown to be effective as prophylaxis against leptospirosis, another spirochetal disease.[11] Doxycycline is a well-absorbed antibiotic with a half-life of about 12 hours and a steady-state level of 1000 to 4000 ng/mL based on 100 mg daily dosing.[12] Adherence to doxycycline was defined as a blood concentration of at least 1000 ng/mL at a given visit.

The primary outcome measure was contraction of syphilis, gonorrhea, and/or chlamydia at or between study visits. A new case of syphilis was defined as a 4-fold or greater increase in rapid plasma reagin titer.[1] We regularly reminded participants that we had no knowledge about whether doxycycline would prevent syphilis and that condoms should be consistently used. Doxycycline prescriptions in the doxycycline arm and financial incentives in the CM arm were stopped after the 36-week visit. Participants were followed up for an additional 12 weeks to allow sufficient follow-up time to ascertain whether there were cases of subclinical syphilis that were not prevented by doxycycline but were incompletely treated.

Study visits (baseline and weeks 12, 24, 36, and 48) included (1) a self-administered computerized behavioral risk assessment; (2) collection of adverse events and concomitant medications; (3) a physical examination limited to skin, mucous membranes, lymph nodes, and anogenital areas; (4) collection of rectal swabs and urine samples for *Neisseria gonorrhoeae* (*NG*) and *Chlamydia trachomatis* (*CT*) nucleic acid amplification tests (NAATs), pharyngeal swab for *NG* NAAT, a blood draw for rapid plasma reagin, and, for participants randomized to the doxycycline arm, a blood draw at 12, 24, and 36 weeks to measure doxycycline serum levels; and (5) pill counts and self-report of pill taking history since last visit. Because of cost considerations, we did not measure doxycycline in CM participants. GC NAATs were performed using APTIMA Combo 2 Assay (Hologic Gen-Probe, San Diego, CA), a transcription-mediated amplification test that detects RNA.

Statistical Methods

Participants were asked to report their race (white, African American, Asian/Pacific Islander, and/or Native American), ethnicity (Hispanic or non-Hispanic), age, and year diagnosed with HIV at the baseline visit. An age group variable was subsequently created in 10-year increments from 20 to 29 years up to 50 years and older. The year diagnosed with HIV was subtracted from each participant's baseline visit date to create the number of years since HIV-positive diagnosis. Fisher exact tests were used to assess independence of study arm at baseline with the demographic variables (race, ethnicity, age group, and years since HIV positive diagnosis) and loss to follow-up.

All analyses were intent to treat. Two-sample t tests were used to determine differences in the number of regular sex partners at baseline (count of partners with whom the participant has had sex more than twice and with whom they plan on having further sexual encounters) and casual partners at baseline (count of partners with whom the participant has had sex once or a few times and with whom they are not planning on having further sexual encounters). Poisson random intercept generalized linear mixed models (GLMMs) were used to compare differences at follow-up between the doxycycline and CM arms in the number of regular and casual partners. Logistic random intercept GLMMs were used to assess differences between the doxycycline and CM arms at follow-up on (1) receptive or insertive anal intercourse without condoms for regular partners, (2) receptive or insertive anal intercourse without condoms for casual partners, (3) meth use at any point in the past 3 months, (4) sex without a condom at any point in the past 3 months, (5) sex with an anonymous partner at any point in the past 3 months, and (6) identification of a primary sexual partner. Similarly, logistic random intercept GLMMs were used to compare (1) any new syphilis infection, (2) any new *NG* or *CT* infection, or (3) any *NG*, *CT*, or syphilis infection (any STD) through both 36 and 48 weeks of follow-up between the doxycycline and CM arms. All GLMM analyses were performed using PROC GLIMMIX in SAS version 9.3 (SAS Institute, Cary, NC).

Ethics

The study received approval from the University of California, Los Angeles South General Institutional Review Board (IRB No. 00004474; Project No. 11-001869-CR-00003). The trial was subsequently registered with ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02257658).

RESULTS

Participants were recruited between September 6, 2011, and January 30, 2012. Participants at baseline were comparable across treatment groups on race ($P = 0.31$), ethnicity ($p = 1.0$), age group ($P = 0.63$), and years since HIV positive diagnosis ($P = 0.46$; Table 1). Twelve (80%) of 15 individuals from the doxycycline arm and 11 (73%) of 15 from the CM arm completed the study through 48 weeks (Fig. 1). All visits attended were analyzed for both the doxycycline arm (53/60) and the CM arm (49/60). The study ended when the final participant completed their 48-week study visit on January 23, 2013.

Participant 08 (doxycycline arm) experienced an adverse event of gastroesophageal reflux that was found to be related to the drug. The doxycycline was discontinued at week 29, and the

[1]For clarification, there is a 2-titer increase between 1:4 and 1:16 (i.e., the progression is 1:4, 1:8, and 1:16), but this represents a 4-fold increase in titer (referring to the numerical difference between 4 and 16).

TABLE 1. Baseline Demographics of Study Participants by Study Arm, HIV-infected MSM, Los Angeles (n = 30)

	Doxycycline		Incentive	
Demographic	**n**	**%**	**n**	**%**
Race ($P = 0.31$)				
White	14	93.3	15	100.0
African American	1	6.7	0	0.0
Ethnicity ($P = 1.0$)				
Hispanic	9	60.0	9	60.0
Non-Hispanic	6	40.0	6	40.0
Age group ($P = 0.63$)				
20–29 y	1	6.7	2	13.3
30–39 y	4	26.7	5	33.3
40–49 y	6	40.0	7	46.7
50+ y	4	26.7	1	6.7
Years since HIV positive diagnosis ($P = 0.46$)				
<5 y	3	20.0	5	33.3
5–10 y	3	20.0	4	26.7
11–15 y	6	40.0	2	13.3
16–20 y	1	6.7	3	20.0
>20 y	2	13.3	1	6.7
Study completion ($P = 0.66$)				
Yes	12	80.0	11	73.3
No	3	20.0	4	26.7
Total	15	100	15	100

symptoms resolved. This participant had not had any STDs at weeks 12 and 24 but did have rectal *CT* at the week 36 visit.

Most participants in the doxycycline arm were adherent to the medication at weeks 12, 24, and 36, with doxycycline serum levels exceeding 1000 ng/mL in 24 of 39 visits (Table 2). There were no significant differences between arms in only syphilis incidence or only *NG*/*CT* incidence at either the 36-week visits (the end of on-drug phase for the doxycycline arm and incentive payments for the CM arm) or the 48-week follow-up analysis. However, there was a significant difference between the doxycycline and CM arms on incidence of any STD in the follow-up analysis that included week 48 ($P = 0.02$; odds ratio [OR], 0.27; 95% confidence interval [CI], 0.09–0.83), although not in the analysis through week 36, with participants in the doxycycline arm less likely to test positive for *NG*, *CT*, or syphilis (6 visits with STDs of 53 total visits) compared with the CM arm (15 visits with STDs of 49 visits; Table 3). Follow-up analysis included data from all visits up to week 48, although doxycycline administration was stopped at week 36.

There were no differences between study arms in either self-reported number of regular partners ($P = 0.14$) or casual partners ($P = 0.29$) at follow-up (Table 4). There were also no differences between study arms in self-reported condom use for regular partners ($P = 0.55$), condom use for casual partners ($P = 0.30$), meth use ($P = 0.78$), sex without a condom in the past 3 months ($P = 0.10$), sex with an anonymous partner ($P = 0.45$) in the past 3 months, or having a main/primary partner ($P = 0.14$).

DISCUSSION

We completed a randomized, controlled pilot study designed to investigate the feasibility of conducting a definitive study to determine whether daily doxycycline prophylaxis compared with a financial incentive could impact incident syphilis infections in HIV-infected MSM who have had syphilis twice or more since their HIV diagnosis. The 76.7% overall retention rate in this pilot study suggests that a clinical trial in a persistently high-risk group of HIV-infected MSM is feasible.

In this small study, we did not expect to find significant differences in the incidence of STDs between the study arms. Considering only the on-drug study visits (through week 36), there were 5 STDs in the doxycycline group and 12 STDs in the CM group. When looking specifically at syphilis, there were only 2 cases in the doxycycline group compared with 6 cases in the CM group through 36 weeks, a 3-fold difference. Although the difference through 36 weeks was not statistically significant, there was a significant reduction in the incidence of any STD among participants in the doxycycline arm compared with the CM arm through 48 weeks.

The reason for this finding is not clear, but differences in behavior between the arms do not seem to explain it. Because we did not measure doxycycline levels at week 48, we do not know whether some participants continued to take doxycycline, whether unused study drug or from another source. When analyzing syphilis alone, the nonsignificant OR of 0.24 for syphilis incidence in the doxycycline arm compared with the CM arm is suggestive of a lower incidence possibly attributable to doxycycline. A larger study may have the power to detect an association.

There is no established doxycycline concentration level which is known to prevent syphilis. However, the half-life of doxycycline in most patients is approximately 12 hours and serum levels indicative of recent dosing will be 1000 to 4000 ng/mL (B. J. Guglielmo, personal communication, 2013). Given this, 8 (62%) of 13 participants took doxycycline during 2 of 3 study visits and 4 (31%) of 13 participants did so at all 3 visits.

There was 1 participant in the doxycycline arm who reported gastroesophageal reflux. No rashes, photosensitivity or

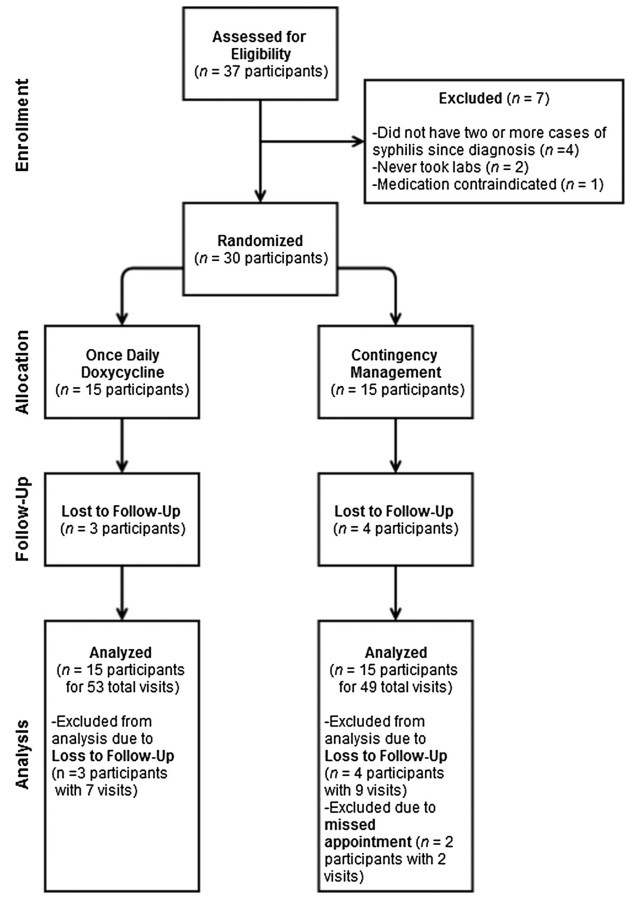

Figure 1. Enrollment and randomization schema.

TABLE 2. Sti Incidence by Visit for the Doxycycline and CM Arms

Doxycycline Arm

Participant No.	Week 12	Doxy Blood Levels	Week 24	Doxy Blood Levels	Week 36	Doxy Blood Levels*	Week 48
S01	None	Missing[†]	LTFU		LTFU		LTFU
S03	None	1630	None	1600	None	196	None
S05	None	459	None	3610	None	2450	None
S06	None	2160	None	1780	None	1390	None
S08	None	1890	None	<50	Rectal chlamydia	0	None
S10	None	3330	None	2260	Early latent syphilis	2200	None
S11	None	<50	Rectal gonorrhea[‡]	72	None	87.6	None
S13	Early latent syphilis	1970	None	1640	None	2120	None
S18	None	Missing	LTFU		LTFU		LTFU
S19	None	457	None	1180	None	1030	None
S22	None	1840	None	1230	None	145	Rectal chlamydia
S25	None	493	None	1160	None	714	None
S28	None	3520	Pharyngeal gonorrhea	1300	None	1970	None
S29	None	4510	None	52.7	None	83.8	LTFU
S36	None	1050	None	<50	None	<50	None

CM Arm

Participant No.	Week 12	Week 24	Week 36	Week 48
S02	None	None	None	None
S07	None	Rectal chlamydia[‡]	None	None
S14	Rectal chlamydia	Early latent syphilis	None	Urethral gonorrhea/rectal gonorrhea
S15	Early latent syphilis	Rectal chlamydia[‡]	Early latent syphilis	None
S17	None	None	Urethral gonorrhea	LTFU
S20	None	None	Missed	Early latent syphilis
S24	None	LTFU	LTFU	LTFU
S26	LTFU	LTFU	LTFU	LTFU
S27	None	None	None	None
S30	Early latent syphilis	Missed[§]	None	LTFU
S32	None	Early latent syphilis	Early latent syphilis	None
S33	Rectal chlamydia	Urethral chlamydia	None	None
S34	None	None	None	None
S35	None	None	None	Urethral chlamydia
S37	None	None	None	None

*Doxycycline administration was stopped at 36 weeks.

[†]Missing = visit attended, but data missing.

[‡]STD occurred between visits (S11 occurred on 3/5/2012, S07 occurred on 2/2/2012).

[§]Missed = missed appointment.

LTFU indicates lost to follow-up.

TABLE 3. Results of GLMMs for STDs (n = 30)*

Outcome	No. Visits With Outcome		Follow-Up Analysis (Through 48 wk)		On-Drug Analysis (Through 36 wk)	
	Doxy Arm	CM Arm	*P*	OR (95% CI)	*P*	OR (95% CI)
STI contraction						
Gonorrhea or chlamydia only	4	8	0.18	0.36 (0.08–1.56)	0.25	0.42 (0.09–1.89)
Syphilis only	2	7	0.10	0.24 (0.04–1.33)	0.16	0.27 (0.04–1.73)
Any STD (gonorrhea, chlamydia, syphilis, or any combination thereof)	6	15	0.02	0.27 (0.09–0.83)	0.07	0.30 (0.08–1.09)

*ORs or rate ratios below 1 indicate the decreased odds/rates in the doxycycline arm compared with CM arm; OR or rate ratios above 1 indicate increased odds/rates in the doxy arm compared with the CM arm.

other adverse events were reported. It is important to note that the daily administration of doxycycline during this study was in combination with other medications taken for HIV and other medical diagnoses.

Our study has several limitations. Drug levels were measured only for the doxycycline arm because of cost considerations. Doxycycline drug levels are important for documenting medication adherence and for determining serum levels that would be protective against syphilis. However, doxycycline is a commonly prescribed antibiotic for a diversity of conditions, and it is possible that individuals in the nondrug arm may intermittently have taken it for these other indications, or even that individuals in the drug arm continued to take it after the 36-week on-drug phase of the study. Pill count and self-reported drug taking data are not shown but suggest that some participants probably had unused drug at home. For these reasons, a future study should measure doxycycline levels in both drug and nondrug study arms and at all visits, including those that are unscheduled due to a suspected STD. This would serve to document potential contamination effects and to query drug taking at any time STD testing is done.

Given the inclusion criteria of this pilot study, the results generalize to those MSM in HIV care who have elevated sexual risk profiles but are likely not generalizable to all MSM. Because this was a pilot study with only 30 participants enrolled, further study with a much larger sample size is needed to determine if these results are reproducible. Lastly, 1000 ng/mL was set as a minimum protective doxycycline serum level, but the literature is unclear if levels less than 1000 ng/mL confer a modest amount of protection. A larger study may determine the protection conferred at other concentrations of the drug. We further recommend that a future study be simplified to include only drug and nondrug arms, eliminating the CM arm.

Doxycycline is often prescribed for a variety of common conditions but usually for durations of 2 weeks or less. Exceptions to this would include longer courses for prostatitis or even chronic use for acne suppression. Concerns about antimicrobial resistance among various organisms, whether sexually transmitted or not, are legitimate. However, for 4 organisms that may be of special public health concern in this core transmitter group, there is perhaps reason to be less concerned about doxycycline resistance. For *N. gonorrhoeae*, doxycycline is not used for treatment and there is little evidence for *C. trachomatis* resistance to the tetracycline class of antibiotics. treatment of *Mycoplasma genitalium* relies on azithromycin and newer fluoroquinolones, and although there is concern over resistance to these agents, doxycycline has not been considered very effective treatment despite absence of demonstrated in vitro resistance.[13] There are choices other than tetracyclines for treatment of community-acquired methicillin-resistant

TABLE 4. Results of GLMMs for risk behaviors (n = 30)*

Outcome	No. Visits With Outcome Reported		Follow-Up Analysis (Through 48 wk)	
	Doxy Arm	CM Arm	*P*	OR (95% CI)
Drug use				
Meth use only	8	7	0.78	1.17 (0.38–3.57)
Behaviors in the past 3 mo				
Sex without a condom	33	24	0.10	2 (0.88–4.54)
Sex with an anonymous partner	10	13	0.45	0.69 (0.27–1.79)
Identifies a main sex partner/primary partner	14	21	0.14	0.53 (0.23–1.23)
Regular partners				
No. regular partners (total)	40	25	0.14	1.45 (0.88–2.38)
Receptive or insertive anal sex without condoms(reference= condom use)	11	10	0.55	0.63 (0.13–2.94)
Casual partners				
No. casual partners (total)	25	26	0.29	1.32 (0.79–2.22)
Receptive or insertive anal sex without condoms(reference = condom use)	10	7	0.30	2.86 (0.38–20)

*ORs or rate ratios below 1 indicate the decreased odds/rates in the doxycycline arm compared with CM arm; OR or rate ratios above 1 indicate increased odds/rates in the doxy arm compared with the CM arm.

Staphylococcus aureus, and they are not used for hospital treatment of complicated skin and soft tissue infections with this organism.[14] Nevertheless, antibiotic resistance is becoming an increasingly important issue and a future study of doxycycline syphilis prophylaxis could include monitoring resistance among a selected panel of organisms. Finally, the use of daily doxycycline prophylaxis against syphilis would not be an appropriate prevention tool for most HIV-infected MSM but only for a relatively small, yet epidemiologically important population, where its use may outweigh the theoretical resistance risks. As for any prophylactic intervention, if shown to be effective, it would only be recommended after careful review of the individual clinical circumstances.

Population-based efforts to control the HIV and STD epidemics must recognize the synergy between the spread and infectiousness of the various organisms, and the importance of core transmitter groups. Furthermore, it is important to investigate whether well tolerated and safe pharmacologic agents can be added to our prevention tools, thus giving us more options in populations where behavioral prevention has not worked and is not likely to work.

REFERENCES

1. Centers for Disease Control and Prevention. 2011 Sexually transmitted diseases surveillance—Syphilis [CDC Web site]. January 15, 2013. Available at: http://www.cdc.gov/STD/Syphilis2011/default.htm. Accessed September 1, 2013.
2. Centers for Disease Control and Prevention. 2012 Sexually transmitted diseases surveillance—syphilis [CDC Web site]. January 10, 2014. Available at: http://www.cdc.gov/STD/Syphilis2012/default.htm. Accessed February 1, 2014.
3. Bolan RK, Rudy ET, Cheng KJ, et al. Sexually transmitted infections among HIV positive persons before and after entry into HIV care: The need for priority interventions. Presented at: National HIV Prevention Conference, 2009, Atlanta.
4. Yorke JA, Nold A, Hethcote HW. Dynamics and control of the transmission of gonorrhea. *Sex Transm Dis* 1978;5:51–6.
5. Hall HI, Holtgrave DR, Maulsby C. HIV transmission rates from persons living with HIV who are aware and unaware of their infection. *AIDS* 2012;26:893–6.
6. Jarzebowski W, Caumes E, Dupin N, et al. Effect of early syphilis infection on plasma viral load and CD4 cell count in human immunodeficiency virus-infected men: Results from the FHDH-ANRS CO4 cohort. *Arch Intern Med* 2012;172:1237–43.
7. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS* 2004;18:2075–9.
8. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: The contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Trans Infect* 1999;75:3–17.
9. Marks G, Crepez N, Senterfitt JW, et al. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States—Implications for HIV prevention programs. *J Acquir Immune Defic Syndr* 2005;39:446–53.
10. Gorbach PM, Weiss RE, Jeffries R, et al. Behaviors of recently HIV-infected men who have sex with men in the year postdiagnosis: Effects of drug use and partner types. *J Acquir Immune Defic Syndr* 2011;56:176–82.
11. Takafuji ET, Kirkpatrick JW, Miller RN, et al. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. *N Engl J Med* 1984;310:497–500.
12. Vu B, Nguyen C, Nguyen T, et al. Sex affects the steady-state pharmacokinetics of primaquine but not doxycycline in healthy subjects. *Am J Trop Med Hyg* 2009;81:747–753.
13. Taylor-Robinson D. Diagnosis and antimicrobial treatment of *Mycoplasma genitalium* infection: Sobering thoughts. *Expert Rev Anti Infect Ther* 2014;12:715–22.
14. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant S*taphylococcus Aureus* infections in adults and children. *Clin Infect Dis* 2011;52:E18–E55.