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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

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Abstract

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). Subjects were tested for the bacterial STDs gonorrhea (NG), chlamydia (CT) 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 subjects were significantly less likely to test positive for any selected bacterial STD during 48 weeks of follow-up (OR: 0.27; CI: 0.09-0.83) compared to CM arm subjects ($p = 0.02$). 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 NG, CT, 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

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to control transmission of syphilis, especially in this population. A randomized clinical trial should be conducted to confirm and extend these findings.

Keywords

Syphilis; men who have sex with men; doxycycline prophylaxis; HIV

Introduction

The U.S. Centers for Disease Control and Prevention (CDC) 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 clinics in 2011.¹ In 2012, 75% of primary and secondary syphilis cases, occurred in MSM.² A 2009 study among a population of 4,376 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 disproportionately contribute to the current epidemic of syphilis and to target that population for interventions.⁴

Although it is believed that a majority 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 sexually transmitted diseases (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 two to nine 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 following an HIV diagnosis, Gorbach and others have shown that after nine 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 to those who were provided contingency management incentives. The objectives of this study were four-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 subjects, drawn from the Los Angeles LGBT Center (the Center) HIV Clinic, were screened and underwent informed consent. Subjects were required to meet the following inclusion criteria: 1) 18 years of age or older; 2) HIV-infected MSM or transgender women who have sex with men and 3) at least two documented and adequately treated episodes of syphilis since HIV diagnosis. Subjects were excluded from participation if they 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 subjects screened for participation, 30 subjects satisfied all inclusion criteria and were enrolled into the study.

Subjects were block randomized to one of two groups with a 1:1 allocation ratio: 1) doxycycline hyclate, 100 mg once daily for 36 weeks or 2) an incentive-based financial contingency management (CM) arm for remaining STD-free. While all subjects were compensated \$25 per visit, subjects 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 100mg 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 1000-4000 ng/mL based on 100 mg daily dosing.¹² Adherence to doxycycline was defined as a blood concentration of at least 1,000 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 four-fold or greater increase in rapid plasma reagin titer.¹ We regularly reminded subjects 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. Subjects were followed 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, 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*

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

gonorrhoeae (NG) and *Chlamydia trachomatis* (CT) nucleic acid amplification tests (NAAT), pharyngeal swab for NG NAAT, a blood draw for rapid plasma reagin, and for subjects 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. Due to cost considerations, we did not measure doxycycline in CM subjects. 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

Subjects 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 ten year increments from 20-29 up to 50 and over. The year diagnosed with HIV was subtracted from each subject'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 subject 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 subject 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 (URAI/UIAI) for regular partners; 2) URAI/UIAI for casual partners; 3) meth use at any point in the past three months; 4) sex without a condom at any point in the past three months; 5) sex with an anonymous partner at any point in the past three 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 (SGIRB) (IRB Number: 00004474; Project Number: 11-001869-CR-00003). The trial was subsequently registered with ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02257658).

Results

Subjects were recruited between September 6th, 2011 and January 30th, 2012. Subjects 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 of fifteen (80%) individuals from the Doxycycline arm and eleven of fifteen (73%) from the CM arm completed the study through 48 weeks (Figure 1). All visits attended were analyzed for both the Doxycycline arm (53 of 60) and the CM arm (49 of 60). The study ended when the final subject completed their 48 week study visit on January 23rd, 2013.

Subject 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 symptoms resolved. This subject had not had any STDs at Weeks 12 and 24 but did have rectal CT at the Week 36 visit.

A majority of subjects in the Doxycycline arm were adherent to the medication at Weeks 12, 24, and 36, with doxycycline serum levels exceeding 1,000 ng/mL in 24 out 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 ($p = 0.02$; OR = 0.27, 95% CI 0.09-0.83), though not in the analysis through Week 36, with subjects in the Doxycycline arm less likely to test positive for NG, CT, or syphilis (6 visits with STDs out of 53 total visits) compared to the CM arm (15 visits with STDs out 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 three months ($p = 0.10$), sex with an anonymous partner ($p = 0.45$) in the past three 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 to 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 five STDs in the Doxycycline group and 12 STDs in the CM group. When looking

specifically at syphilis, there were only two cases in the Doxycycline group compared to six cases in the CM group through 36 weeks, a threefold difference. Although the difference through 36 weeks was not statistically significant, there was a significant reduction in the incidence of any STD among subjects in the Doxycycline arm compared to the CM arm through 48 weeks.

The reason for this finding is not clear, but differences in behavior between the arms do not appear to explain it. Since we did not measure doxycycline levels at Week 48 we do not know whether some subjects continued to take doxycycline, whether unused study drug or from another source. When analyzing syphilis alone, the non-significant OR of 0.24 for syphilis incidence in the Doxycycline arm compared to 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 about 12 hours and serum levels indicative of recent dosing will be 1000-4000 ng/mL.¹³ Given this, eight of thirteen subjects (62%) took doxycycline during two of three study visits and four of thirteen subjects (31%) did so at all three visits.

There was one subject in the doxycycline arm who reported gastroesophageal reflux. No rashes, photosensitivity or 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 due to 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 non-drug 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 subjects probably had unused drug at home. For these reasons, a future study should measure doxycycline levels in both drug and non-drug 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 subjects enrolled, further study with a much larger sample size is needed to determine if these results are reproducible. Lastly, 1,000 ng/mL was set as a minimum protective doxycycline serum level, but the literature is unclear if levels less than 1,000 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 non-drug arms, eliminating the CM arm.

Doxycycline is often prescribed for a variety of common conditions but usually for durations of two 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 four 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 *Neisseria gonorrhoeae*, doxycycline is not used for treatment and there is little evidence for *Chlamydia trachomatis* resistance to the tetracycline class of antibiotics. Treatment for *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.¹⁴ There are choices other than tetracyclines for treatment of community acquired methicillin-resistant *Staphylococcus aureus* (MRSA), and they are not used for hospital treatment of complicated skin and soft tissue infections with this organism.¹⁵ 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. Further, 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.

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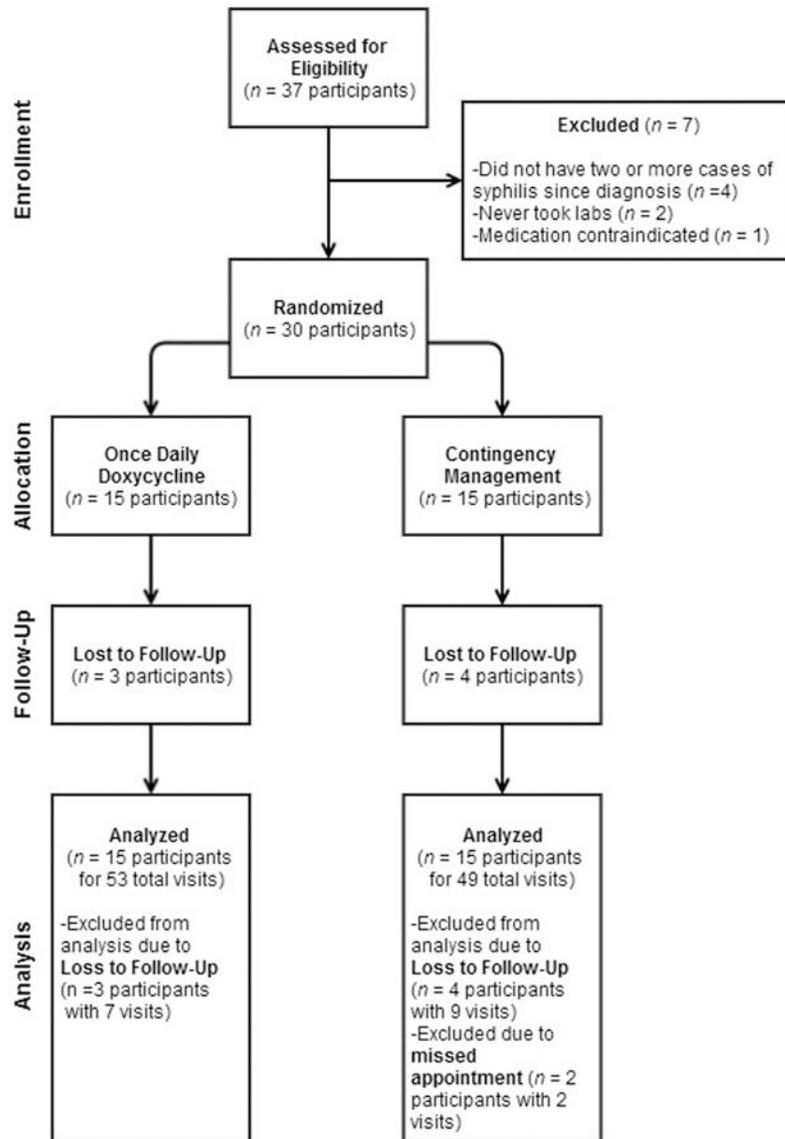


Figure 1.

Table 1

Baseline Demographics of Study Participants for the Doxycycline and Contingency Management Arms (n=30).

Demographic	Doxycycline		Contingency Management		
	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	1	6.7%	2	13.3%	
30-39	4	26.7%	5	33.3%	
40-49	6	40.0%	7	46.7%	
50+	4	26.7%	1	6.7%	
Years Since HIV Positive Diagnosis					p = 0.46
Less than 5 years	3	20.0%	5	33.3%	
5-10 years	3	20.0%	4	26.7%	
11-15 years	6	40.0%	2	13.3%	
16-20 years	1	6.7%	3	20.0%	
More than 20 years	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%	

Table 2

STI Incidence by Visit for the Doxycycline and Contingency Management Arms.

Doxycycline Arm									
Subject Number	Week 12	Doxycycline Blood Levels	Week 24	Doxycycline Blood Levels	Week 36	Doxycycline Blood Levels [†]	Week 48		
S01	None	Missing*	LTFU**	LTFU	LTFU	LTFU	LTFU		
S03	None	1,630	None	1,600	None	196	None		
S05	None	459	None	3,610	None	2,450	None		
S06	None	2,160	None	1,780	None	1,390	None		
S08	None	1,890	None	<50	Rectal Chlamydia	0	None		
S10	None	3,330	None	2,260	Early Latent Syphilis	2,200	None		
S11	None	<50	Rectal Gonorrhea ^{††}	72	None	87.6	None		
S13	Early Latent Syphilis	1,970	None	1,640	None	2,120	None		
S18	None	Missing	LTFU	LTFU	LTFU	LTFU	LTFU		
S19	None	457	None	1,180	None	1,030	None		
S22	None	1,840	None	1,230	None	145	Rectal Chlamydia		
S25	None	493	None	1,160	None	714	None		
S28	None	3,520	Pharyngeal Gonorrhea	1,300	None	1,970	None		
S29	None	4,510	None	52.7	None	83.8	LTFU		
S36	None	1,050	None	<50	None	<50	None		
Contingency Management Arm									
Subject Number	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	None					
S20	None	None	Missed	None					
S24	None	LTFU	LTFU	LTFU					
S26	LTFU	LTFU	LTFU	LTFU					

Doxycycline Arm	Week 12	Doxy Blood Levels	Week 24	Doxy Blood Levels	Week 36	Doxy Blood Levels [†]	Week 48
S27	None	None	None	None	None	None	None
S30	Early Latent Syphilis	Missed ^{***}	None	None	None	LTFU	LTFU
S32	None	Early Latent Syphilis	None	None	None	None	None
S33	Rectal Chlamydia	Early Latent Syphilis	Early Latent Syphilis	Urethral Chlamydia	Early Latent Syphilis	None	None
S34	None	None	Urethral Chlamydia	None	None	None	None
S35	None	None	None	None	None	None	Urethral Chlamydia
S37	None	None	None	None	None	None	None

* Missing = Visit attended, but data missing

** LTFU = Lost to Follow-Up

*** Missed = Missed Appointment

[†] Doxycycline administration was stopped at 36 weeks

^{††} STD occurred between visits (S11 occurred on 3/5/2012, S07 occurred on 2/2/2012)

Table 3

Results of Generalized Linear Mixed Models for Sexually Transmitted Diseases (n=30).[†]

Outcome	Number of Visits with Outcome				Follow-Up Analysis (thru 48 Weeks)		On-Drug Analysis (thru 36 Weeks)	
	Doxy Arm	CM Arm	p-value	OR (95% CI)	p-value	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)		

[†] Odds ratios (OR) or Rate ratios (RR) below 1 indicate the decreased odds/rates in the Doxycycline arm compared to Contingency Management (CM) arm; OR or RR above 1 indicate increased odds/rates in the Doxy arm compared to the CM arm

Table 4Results of Generalized Linear Mixed Models for Risk Behaviors (n=30).[†]

Outcome	Number of Visits with Outcome Reported		Follow-Up Analysis (thru 48 Weeks)	
	Doxy Arm	CM Arm	p-value	OR (95% CI)
Drug Use				
Meth Use Only	8	7	0.78	1.17 (0.38-3.57)
Behaviors in the Past Three Months				
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				
Number of Regular Partners (Total)	40	25	0.14	1.45 (0.88-2.38)
Receptive or Insertive Anal Sex without Condoms (REF = Condom Use)	11	10	0.55	0.63 (0.13-2.94)
Casual Partners				
Number of Casual Partners (Total)	25	26	0.29	1.32 (0.79-2.22)
Receptive or Insertive Anal Sex without Condoms (REF = Condom Use)	10	7	0.30	2.86 (0.38-20)

[†]Odds ratios (OR) or Rate ratios (RR) below 1 indicate the decreased odds/rates in the Doxycycline arm compared to Contingency Management (CM) arm; OR or RR above 1 indicate increased odds/rates in the Doxy arm compared to the CM arm