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A post-trial assessment of factors influencing study drug adherence in a randomized biomedical HIV-1 prevention trial

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Abstract

High adherence and maintenance of blinding are critical for placebo-controlled efficacy trials of HIV-1 biomedical prevention strategies. We assessed adherence to study drug and factors affecting adherence, including perceived randomization group, in a post-trial questionnaire of participants who completed HPTN 039, a randomized, placebo-controlled trial of HSV-2 suppression with twice-daily acyclovir to reduce HIV-1 acquisition. Of the 3172 trial participants, 2003 (63%) completed the post-trial questionnaire. Of these 2003, 72% reported missing a dose of study drug less than twice a week. Study drug adherence was not compromised by perceived randomization or genital ulcer symptoms during the study. Alcohol use was cited as an adherence barrier in some populations. Assessment of study drug adherence during and at the end of trials can evaluate perceptions of randomization and adherence by randomization arm, help to better understand barriers to and motivations for adherence, and develop interventions to increase adherence for future trials.

Keywords

Adherence; Biomedical prevention; HIV-1; Clinical trials

INTRODUCTION

Despite concerted efforts over the past 20 years to implement HIV-1 prevention and scale-up treatment, 2.7 million new HIV-1 infections occurred during 2007, emphasizing the need to identify additional effective HIV-1 prevention strategies¹. Biomedical prevention interventions, including antiretroviral-based topical vaginal microbicides and pre-exposure prophylaxis (PrEP), are under evaluation in efficacy trials. Many of these biomedical prevention strategies require daily or coitally-dependent use of a study product for which ongoing adherence is critical for efficacy. Adherence has been suboptimal in some recent HIV-1 prevention trials, including studies of the cervical diaphragm, vaginal microbicides, and daily acyclovir suppressive therapy for genital herpes^{2–4}. For these user-dependent interventions, there are no gold-standard measurements of adherence⁵. Many studies have used self-report or pill counts to evaluate adherence. These methods are subject to possible social desirability bias, particularly in the context of a trial with frequent contact with research staff and intensive adherence counseling⁶.

Insights into patterns of adherence during biomedical HIV-1 prevention trials might increase understanding of effective adherence measurement methods, improve the ability to measure adherence in future biomedical prevention studies, and maximize the effectiveness of the intervention for implementation of interventions demonstrated to be efficacious. Post-trial assessment of randomization perceptions are rarely done in biomedical HIV-1 prevention trials but are important as unmasking could potentially lead to differential adherence across study arms, which could threaten the internal validity of the study and lead to biased trial results. In order to assess adherence behaviors in a manner less influenced by social desirability reporting, we conducted a post-trial assessment of self-reported adherence to twice-daily study drug (acyclovir or placebo) in an HIV-1 prevention trial [HIV Prevention Trials Network (HPTN) 039]. Given that the intervention being evaluated in HPTN 039, acyclovir, suppresses symptomatic genital ulcer disease (GUD), we hypothesized that GUD symptoms during the study could influence participants' perception of randomization arm and levels of adherence to study drug. In this report, we summarize self-reported adherence, perceived randomization assignment, and the relationship between perceived randomization, GUD symptoms, and other factors with self-reported adherence in this post-trial assessment among HPTN 039 participants.

METHODS

HPTN 039 was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of twice-daily acyclovir suppressive therapy for herpes simplex virus type 2 (HSV-2) for the prevention of HIV-1 acquisition⁷. Between March 2004 and November 2007, 3172 HIV-1 seronegative women and men who were seropositive for HSV-2 were enrolled, including 1581 women from southern Africa (Johannesburg, South Africa; Harare, Zimbabwe; and Lusaka, Zambia) and 1591 men who have sex with men (MSM) from the United States (New York, San Francisco, and Seattle) and Peru (Iquitos, Lima, and Pucallpa). During the trial, participants were seen monthly for study drug distribution, return of unused pills, GUD screening and adherence counseling. Adherence aids (e.g., pill boxes) were offered to study participants. Participants completed up to 18 months of follow-up with the last participant visit in November 2007.

Twice daily acyclovir suppression did not prevent HIV-1 acquisition overall or in subgroup analyses⁷. After the results of HPTN 039 were reported at an international scientific meeting in February 2008, participants were invited to individual ‘unblinding visits’ at the study sites between March and October 2008, during which a research staff member discussed the trial results with the participant and the participant’s randomization assignment was disclosed. Prior to hearing about the trial results and their randomization assignment, participants were asked to complete a questionnaire about their study drug adherence. The questionnaire was administered using either an interviewer-administered paper-based format (at Seattle and Lusaka) or computer-assisted self interview (CASI) format (at San Francisco, New York, and Harare); at the Johannesburg and Peru sites, both methods were used depending on CASI availability, but individual participants completed only one format. In an effort to minimize potential social desirability bias at sites using the interviewer-administered format, staff members administering the questionnaire were different from the primary counselor for the participant during the study.

Written informed consent was obtained from all HPTN 039 participants who returned for the post-trial assessment and completed the questionnaire. The study protocol was approved by institutional review boards at the University of Washington and at local institutions affiliated with each study site.

Adherence Measurement

During the trial, adherence was measured by monthly pill count of unused study drug in returned bottles. For this analysis, months where pill count data were missing due to missed clinic visits or failure to return empty bottles were not incorporated in calculations of average measured adherence.

In the post-trial questionnaire, reported adherence was assessed by asking participants to identify, on average, how frequently they missed study drug during the course of the study: i.e., once daily, twice weekly, once weekly, twice monthly, once monthly, less than once monthly, or never. Based on data describing the length of treatment necessary to achieve suppression of genital HSV reactivation, the self-reported frequency of missed study drug was collapsed into two groups for this analysis: less than 2 times per week and at least 2 times per week⁸. The relationship between self-reported adherence and factors potentially affecting adherence to study drug, including perception of randomization arm, GUD symptoms during the study, and other factors (e.g., forgetting, travel, and use of drugs and alcohol) that may have affected adherence, was assessed.

Statistical Analysis

All analyses were done using SAS version 9.1. Chi-square and Mann-Whitney U tests were used to compare proportions and medians between groups, respectively. Multiple logistic regression was used to determine whether randomization arm or GUD during the study predicted perceived randomization. A separate multiple regression analysis was performed to assess whether perceived randomization after the study or GUD during the study were independent predictors of missing drugs at least 2 times per week; the analysis was adjusted for study site.

RESULTS

Of 3172 participants enrolled in HPTN 039, 2003 (63%) returned for the post-trial adherence assessment, with a higher proportion returning at the Peruvian (908/1355, 67%) and African sites (867/1358, 64%) compared to the US sites (228/459, 50%). Characteristics of the returning participants are detailed in Table I. The median time between participants’

final HPTN 039 visit and the post-trial visit was 22 months (IQR 15–28). Approximately one-third of participants had heard about the results of HPTN 039 prior to completing the post-trial assessment. Participants who returned were generally similar to the overall HPTN 039 study population. Compared to participants who did not return, however, participants who returned for the post-trial adherence assessment were slightly older (31 vs. 29 years, $p<0.001$) and, among Peruvian MSM, more likely to report unprotected anal receptive sex (58% vs. 51%, $p=0.01$).

Self-reported Adherence

Most participants (1355/1874, 72%) reported missing a dose of study drug an average of less than twice a week (Table II). Of the 519 participants who reported missing doses at least twice a week, 327 (63%) reported missing doses on a daily basis. A majority (77%) of these participants, however, reported making up missed doses by doubling pills with their next dose, as was instructed by the trial protocol.

We compared the level of self-reported adherence from the post-trial assessment with adherence measured during the trial using monthly pill count. Median adherence based on monthly pill count was high, measuring greater than 90% in the majority of visits⁷. Participants who reported missing doses at least twice a week had slightly lower median adherence, as measured by pill count during their entire study participation, compared to those who reported missing doses less than twice a week (97.7% vs. 98.4%, Mann Whitney $p=0.0014$).

We asked participants whether, during the study, they had been comfortable reporting non-adherence to study staff. Most participants (74%) reported that they were comfortable reporting non-adherence to study staff. A larger proportion of Peruvian participants (42%), however, reported reluctance to tell study staff when they missed study drug compared to participants from the African (14%) and US (9%) sites.

Perceived Randomization to Study Drug

Two-thirds (1318/1998, 66%) of participants were uncertain whether they had been randomized to acyclovir or placebo (Figure 1). Among the one-third ($n=680$) of participants who thought they knew their randomization assignment, most (496/680, 73%) thought they were randomized to the acyclovir arm. This preference to guess being randomized to the acyclovir arm occurred among participants truly randomized to acyclovir as well as those randomized to placebo. Guessing they were randomized to acyclovir occurred more frequently in participants truly randomized to acyclovir than participants randomized to placebo (28% vs. 22%, $p=0.002$); however, this difference in the proportion correctly guessing randomization arm represents less than 5% of study participants.

We assessed whether self-reported GUD symptoms during the study influenced participants' perceived randomization assignment. Participants with GUD symptoms were no more likely to hazard a guess (36.7% vs. 34.7%, $p=0.52$) at their randomization assignment than participants without GUD. Among the subset of participants who did guess, however, participants without GUD were more likely to guess they had been randomized to the acyclovir arm compared to those with GUD (77.0% vs. 68.3%, $p=0.01$). In a step-wise multiple logistic regression model (Table III) among those who guessed at their randomization assignment and using perceived randomization arm as the outcome, controlling for GUD only slightly attenuated the effect of randomization arm [odds ratio (OR) 1.67, $p=0.004$ vs. OR 1.74, $p=0.002$ without GUD in the model], suggesting that the occurrence of GUD symptoms during the study did not explain the differential perception of randomization assignment between the two arms. In this model, having GUD during the

study remained associated with a modest decrease in likelihood of guessing randomization to the acyclovir arm (OR 0.68, $p=0.03$). When asked about other factors that may have influenced impression of randomization, such as pill appearance, interactions with the study staff, and discussions with other study participants, less than 10% of participants reported each of these factors as influencing their impression of randomization assignment.

Factors Influencing Adherence

Most participants who thought they knew their randomization assignment (479/680, 70%) reported this perception did not influence their adherence to study drug. Of the 201 participants who reported that perception of randomization influenced their adherence, the majority (70%) reported that their perception resulted in increased adherence. Participants who guessed they were randomized to placebo were no more likely to report that they missed doses less than 2 times per week than those who guessed they were randomized to acyclovir [OR 1.19, 95% confidence interval (CI) 0.79–1.80, $p=0.4$]. In a multiple logistic regression model of all participants in the post-trial assessment (Table IV), neither perceived randomization to study drug [OR 1.21, 95% CI 0.80–1.82] nor GUD symptoms during the study [OR 0.94, 95% CI 0.76–1.16] were significantly associated with higher adherence (i.e., reporting missing a dose of study drug less than 2 times per week at the post-trial assessment).

We also assessed how perceived randomization and GUD symptoms were related to median adherence measured using pill count during the trial. Among participants randomized to the placebo arm, participants who perceived their randomization to be the acyclovir arm had slightly greater median adherence than those who perceived that they were randomized to the placebo arm [98.8% vs 97.2%, Mann-Whitney $p=0.03$]. In contrast, among participants randomized to the acyclovir arm, there was no significant difference in adherence measured during the trial using monthly pill count of unused study product for those guessing randomization to acyclovir versus placebo arm [98.3% vs 97.5%, Mann-Whitney $p=0.7$]. In addition, there was no significant difference in median adherence during the trial, as measured by pill count, between participants with or without GUD symptoms [98.1% vs 98.7%, Mann-Whitney $p=0.5$].

Participants reported that the most common reasons for missing doses were forgetting (66%), travel (30%), and running out of doses between study visits (12%). Less than 10% of participants reported missing doses because of losing study drug, concern about drug interactions and side effects, or fear of others knowing they were in an HIV prevention study. Approximately two-thirds of participants stated they used strategies to help them remember taking the study drug (78% of African women, 68% of US MSM, and 54% of Peruvian MSM). The most common strategies included utilization of pill boxes (33%) and incorporation of taking the study drug into a daily routine (33%).

Overall, behaviors related to study drug adherence across sites were similar. Participants infrequently (<10%) reported throwing away study drug or sharing study drug with a sexual partner or someone else, which could have compromised the validity of monthly pill counts as the primary measure of adherence during the study. Most participants reported that they did not hide their study drug from their partners (91%), including the women from the African sites (92%), the majority of whom were in stable partnerships. One difference observed was that Peruvian participants more frequently reported they missed doses due to alcohol use than US and African participants (36% versus 8% and 4%, respectively). Peruvian men reported that missing doses due to alcohol use was related to forgetting to take study drug (73%) rather than fear of potential study drug interactions with alcohol (26%).

DISCUSSION

This post-trial assessment of study drug adherence among African women and MSM from Peru and the US who participated in a randomized, placebo-controlled trial of twice daily acyclovir for HIV-1 prevention indicates high self-reported adherence to study drug. Almost 75% reported missing pills less than twice a week, and among the 28% of participants who retrospectively reported missing pills at least twice a week, most reported making up missed doses by taking two pills once daily when they missed a dose, as was instructed by the study protocol. High accuracy of adherence measurements is critical to evaluating efficacy in HIV-1 prevention trials⁹. Poor adherence to use of a study product in an HIV-1 biomedical prevention trial that fails to demonstrate efficacy may make it impossible to differentiate “method failure” (in which the intervention, when used as prescribed, does not prevent HIV-1) from “user failure” (in which suboptimal adherence undermines the assessment of whether the intervention truly prevents HIV-1 infection).

In this trial of acyclovir suppressive therapy for HIV-1 prevention, a specific concern was the potential for unblinding and decreased adherence if participants perceived the frequency or severity of GUD as an indication of their randomization arm. Only a minority of participants (one-third) thought they knew their randomization arm. Although perceived randomization to the acyclovir arm was greater in participants who were randomized to the acyclovir arm compared to the placebo arm, this excess represented less than 5% of participants. Moreover, while a small but statistically significant difference in study drug adherence was identified in participants randomized to the placebo arm, participants’ perceptions of randomization were associated with unchanged or higher study drug adherence. GUD symptoms reported during the trial minimally influenced participants’ perception of their randomization assignment and their adherence to study drug. Thus, the integrity of randomization and the internal validity of the study appeared to be largely maintained in spite of the potential for unmasking of treatment randomization due to less frequent GUD symptoms in the acyclovir arm. Future biomedical prevention trials should evaluate perceptions of randomization, including assessment of potential side effects that might lead to unmasking.

Limitations of this study include that one-third of the trial participants did not return for the assessment. Although we found few differences in those who did and did not return, selection bias may have occurred with more motivated participants returning for the post-trial assessment. In addition, since participants were asked at the post-trial study visit about adherence behaviors by site staff, desirability bias could still influence accuracy of their responses if they were reluctant to admit a disparity in their reporting of non-adherence, even after trial completion. We reported a significant but small difference in median adherence during the trial, as measured by monthly pill count of returned study drug, with respect to level of adherence reported in the post-trial assessment. However, with an average of 22 months between trial exit and the post-trial visit, direct comparisons between adherence measurements during the trial, based primarily on pill counts of returned drug, and the post-trial assessment were limited by participants’ ability to recall and accurately report average adherence over their 18 month trial participation. Future studies could administer this type of adherence evaluation at the final study visit in order to potentially reduce potential recall bias.

A recent study conducted after the completion of a Tanzanian trial of HSV-2 suppression to prevent HIV-1 acquisition among high-risk women qualitatively assessed how participants’ beliefs about study drug may have influenced adherence behavior during the trial¹⁰. The insight into adherence behavior obtained from this type of assessment, particularly regarding participant misunderstanding about the study drug and placebo, study drug adherence and

barriers to adherence introduced by unsupportive partners, travel or familial illness, could complement the type of quantitative data we obtained during and after HPTN 039 to arrive at a more comprehensive understanding of study drug adherence during a biomedical HIV-1 prevention trial.

CONCLUSION

The findings of this post-trial assessment of adherence to a study drug in a randomized, placebo-controlled trial of a biomedical HIV-1 prevention intervention illustrate the ability to capture additional information about adherence behaviors when participants are less likely to be affected by social desirability bias. Factors, such as alcohol use, which impact study drug adherence and may differ by region and population, should be carefully monitored in order to provide targeted interventions that could help to increase adherence. Biomedical HIV-1 prevention trials should incorporate qualitative and quantitative assessments of study drug adherence and randomization perception during and at the end of trials in order to understand barriers to and motivations for adherence and to develop interventions to increase adherence for future trials.

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References

1. Status of the global HIV epidemic. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2008. 2008 Report on the global AIDS epidemic. Available at: http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp
2. Padian NS, van der Straten A, Ramjee G, et al. Diaphragm and lubricant gel of prevention of HIV acquisition in southern African women: a randomized controlled trial. *Lancet*. 2007; 13:251–261. [PubMed: 17631387]
3. Watson-Jones D, Weiss HA, Rusizoka M, et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. *N Engl J Med*. 2008; 368:1560–1571. [PubMed: 18337596]
4. Skoler-Karpoft S, Ramjee G, Ahmed K, et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008; 372(9654):1977–87. [PubMed: 19059048]
5. Chesney MA. The elusive gold standard: future perspectives for HIV adherence assessment and intervention. *J Acquir Immune Defic Syndr*. 2006; 43(S1):S149–S155. [PubMed: 17133199]
6. Lagakos, SW.; Gable, AR., editors. *Methodological Challenges in Biomedical HIV Prevention Trials*. Washington, DC: National Academies Press; 2008. Design considerations: adherence; p. 5.1-5.24.
7. Celum C, Wald A, Hughes J, et al. Effect of acyclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2008; 371:2109–2119. [PubMed: 18572080]
8. Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. *J Infect Dis*. 2004; 190:1374–81. [PubMed: 15378428]
9. Weiss HA, Wasserheit JN, Barnabas RV, Hayes RJ, Abu-Raddad LJ. Persisting with prevention: the importance of adherence for HIV prevention. *Emerg Themes Epidemiol*. 2008; 5(8):1–7. [PubMed: 18173854]

10. Plummer ML, Watson-Jones D, Lees S, et al. A qualitative study of participant adherence in a randomized controlled trial of herpes suppressive therapy for HIV prevention in Tanzania. *AIDS Care*. 2010; 22(4):499–508. [PubMed: 20140794]

Randomized to Acyclovir (n=980)

Randomized to Placebo (n=1018)

Figure 1.
Participants' perceived randomization to study arm categorized by actual study arm
(n=1998)

Table I

Characteristics of participants who returned for the post-trial adherence assessment

	African women (n=867)	US MSM (n=228)	Peru MSM (n=908)	Total (n=2003)
Demographics				
Age (median, min-max)	32 (17–66)	44 (20–79)	28 (18–66)	31 (17–79)
Education at least secondary school	534 (62%)	228 (100%)	868 (96%)	1630 (81%)
Any monthly income of own	176 (20%)	196 (86%)	695 (77%)	1067 (53%)
Behavioral characteristics, at the time of trial enrollment				
Sex partners in the prior month				
Any HIV-1 positive sex partner	9 (1%)	27 (12%)	12 (1%)	48 (2%)
Any HIV-1 unknown sex partner	514 (59%)	65 (29%)	663 (73%)	1242 (62%)
Any HIV-1 negative sex partner	291 (34%)	123 (54%)	229 (25%)	643 (32%)
Sexual behaviors with last 3 sex partners in last 3 months				
Any unprotected vaginal ^a	781 (90%)	..	..	781 (90%)
Any unprotected anal receptive ^b	..	78 (34%)	525 (58%)	603 (53%)
Any unprotected anal insertive ^b	..	98 (43%)	183 (20%)	281 (25%)
Alcohol use with sex	15 (2%)	85 (37%)	468 (52%)	568 (28%)
Drug use with sex	0 (0%)	87 (38%)	42 (5%)	129 (6%)
Exchange of money, drugs, or shelter for sex	12 (1%)	10 (4%)	241 (27%)	263 (13%)
Clinical characteristics, at the time of trial enrollment^c				
Self-reported GUD in past 3 months	271 (31%)	66 (29%)	149 (16%)	486 (24%)
GUD on exam	141 (16%)	5 (2%)	26 (3%)	172 (9%)
Characteristics at the time of post-trial adherence assessment				
Heard results of HPTN 039 prior to post-trial assessment	306 (35%)	107 (47%)	308 (34%)	721 (36%)
Months between final HPTN 039 visit and post-trial assessment (median, min-max)	19 (13–25)	23 (16–31)	24 (20–31)	22 (15–28)

MSM=Men who have sex with men; HIV-1=Human immunodeficiency virus, type 1; GUD=Genital ulcer disease;

^aDenominator represents women from Africa;^bDenominator represents MSM from US and Peru;^cEver during follow-up

Table II

Reported frequency of missed doses among participants within randomization arm who returned for the post-trial adherence assessment

Frequency of missed doses	African women (n=754)		US MSM (n=227)		Peru MSM (n=893)		Total (n=1874)	
	Acyclovir	Placebo	Acyclovir	Placebo	Acyclovir	Placebo	Acyclovir	Placebo
1 dose/day	60 (16.0%)	59 (15.6%)	0 (0%)	4 (3.5%)	105 (24.1%)	99 (21.7%)	165 (17.8%)	162 (17.0%)
2 doses/week	30 (7.9%)	14 (3.7%)	6 (5.4%)	7 (6.1%)	62 (14.2%)	73 (16.0%)	98 (10.6%)	94 (9.9%)
1 dose/week	24 (6.4%)	27 (7.1%)	9 (8.0%)	16 (13.9%)	65 (14.9%)	71 (15.5%)	98 (10.6%)	114 (12.0%)
2 doses/month	65 (17.3%)	70 (18.5%)	24 (21.4%)	29 (25.2%)	62 (14.2%)	67 (14.7%)	151 (16.3%)	166 (17.5%)
1 dose/month	81 (21.5%)	104 (27.5%)	31 (27.7%)	30 (26.1%)	78 (17.8%)	85 (18.6%)	190 (20.6%)	219 (23.0%)
< 1 dose/month	65 (17.3%)	59 (15.6%)	21 (18.8%)	18 (15.6%)	23 (5.3%)	23 (5.0%)	109 (11.8%)	100 (10.5%)
Never	51 (13.6%)	45 (11.9%)	21 (18.8%)	11 (9.6%)	41 (9.4%)	39 (8.5%)	113 (12.2%)	95 (10.0%)
TOTAL	376	378	112	115	436	457	924	950
≥ 2 doses/week	90 (23.9%)	73 (19.3%)	6 (5.4%)	11 (9.6%)	167 (38.3%)	172 (37.6%)	263 (28.5%)	256 (26.9%)
< 2 doses/week	286 (76.1%)	305 (80.7%)	106 (94.6%)	104 (90.4%)	269 (61.7%)	285 (62.4%)	661 (71.5%)	694 (73.1%)
TOTAL	376	378	112	115	436	457	924	950

MSM=Men who have sex with men

Table IIIStepwise logistic regression of correlates of randomization perception reported at the post-trial assessment ^a

OUTCOME = PERCEIVED RANDOMIZATION TO ACYCLOVIR ARM ^b			
	β (SE)	OR (95% CI)	p-value
Model 1 (n=680)^c			
Randomized to acyclovir arm ^d	0.55 (0.17)	1.74 (1.24–2.45)	0.002
Model 2 (n=680)^c			
Randomized to acyclovir arm ^d	0.51 (0.18)	1.67 (1.18–2.36)	0.004
Had GUD symptoms reported during the study	−0.39 (0.18)	0.68 (0.48–0.96)	0.03

 β =Beta estimate; SE=Standard error; OR=Odds ratio; CI=Confidence interval; GUD=Genital ulcer disease;

^a Coding variables: participants randomized to acyclovir arm were coded as 1 and those randomized to the placebo arm were coded as 0; participants who perceived their randomization to be the acyclovir arm were coded as 1 and those who perceived their randomization to be the placebo arm were coded as 0; participants who had GUD symptoms reported during the study were coded as 1 and those without GUD symptoms were coded as 0;

^b An additional model that included the interaction term between randomization arm and GUD found that the interaction was not statistically significant (p=0.7);

^c Sample size limited to the subset of participants who guessed at their randomization assignment;

^d Compared to participants randomized to the placebo arm.

Table IVStepwise logistic regression of correlates of high adherence (missed study drug doses < 2x/week) ^a

OUTCOME = REPORTED MISSED STUDY DRUG < 2 TIMES/WEEK^b			
	β (SE)	OR (95% CI)	p-value
Model 1 (n=1872)			
Perceived randomization to placebo ^c	-0.18 (0.21)	1.19 (0.79–1.80)	0.4
Unsure of perceived randomization ^c	0.11 (0.13)	1.33 (0.92–1.92)	0.1
Model 2 (n=1868)			
Perceived randomization to placebo ^c	-0.19 (0.21)	1.21 (0.80–1.82)	0.4
Unsure of perceived randomization ^c	0.10 (0.13)	1.34 (0.92–1.94)	0.1
Had GUD symptoms reported during the study	-0.063 (0.11)	0.94 (0.76–1.16)	0.6

β=Beta estimate; SE=Standard error; OR=Odds ratio; CI=Confidence interval; GUD=Genital ulcer disease;

^a Coding variables: participants missing study drug < 2 times/week were coded as 1 and those missing study drug 2 times/week were coded as 2; participants who were unsure of their randomization arm or who perceived their randomization to be the placebo arm were coded as 1 and those who perceived their randomization to be the acyclovir arm were coded as 0; participants who had GUD symptoms reported during the study were coded as 1 and those without GUD symptoms were coded as 0;

^b In an additional model, the interaction between perceived randomization and GUD symptoms was not statistically significant (p=0.08);

^c Compared to participants randomized to the acyclovir arm.