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USE OF A NOVEL TECHNOLOGY TO TRACK ADHERENCE TO PRODUCT USE IN A MICROBICIDE TRIAL OF SHORT DURATION (MTN-007)

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Abstract

Adherence measurement in microbicide trials is challenging. To decrease recall and social desirability bias, we used an Interactive Voice Response system (IVR) in a rectal microbicide trial. Forty-six participants were asked to report product use daily for one week. Participants received an incentive per call plus a bonus for calling every day. We examined adherence to calling the IVR and to gel use; we compared the latter to applicator counts.

Adherence to calling the IVR daily was high (mean=89.9%, sd=20.7%). Adherence to gel use per IVR was very good (mean=90.7%, sd=19.1%), and consistent with applicator counts in 80.4% of cases. Neither adherence to calling nor gel use were associated with temporal factors like day calls started, number of days since first call, or weekday vs. weekend. Daily reporting allowed identification of irregular product use. IVR appears useful for daily reporting in brief trials.

Keywords

IVR; adherence; microbicides; phone reporting system

Introduction

The safety and efficacy of a microbicide is highly contingent on its correct and timely use. Accurate measurement of adherence during microbicide trials will allow us to estimate safety and efficacy more precisely and also to understand challenges to using microbicides that may need to be addressed. (1).

Adherence measurement of microbicide use continues to be a major challenge. To address it, researchers have used a variety of tools ranging from self-reports (e.g., computer-assisted self-interview or CASI questionnaires, paper and pencil diaries, and face-to-face or phone interviews exploring product use) (2) to applicator counts (e.g., tallies of used and unused applicators returned to the pharmacy) to electronic adherence monitoring tools (Wisebags, Wisepills, Med-eMonitor) (3–5) and biomarkers (e.g., detection of drugs in blood and hair, use of dye tests on the applicator to determine vaginal insertion, or breath tests for gel use

which employ ester taggants) (6–8). However, all of these methods have limitations. Adherence data collected via diary, interview, or questionnaire at the end of the trial period may be subject to recall and/or social desirability bias (9); counts of returned applicators may result in overestimates of product use, since empty returned applicators or unreturned ones are assumed to be used; electronic adherence monitoring tools may have technical failures or participants may open them for reasons other than to use the study product (3–5); and biomarkers may not provide information on occasionally skipped doses, whether the product was used prior to sex, or whether the product was delivered as intended after insertion of the applicator. (10)

Consequently, development of new methods to measure adherence continues to be crucial to microbicide trial success; furthermore, the comparison of two or more adherence measurements within a trial has been proposed as a way to enhance accuracy.(1,10,11) In the case of self-reports of repeated behaviors, such as daily use of a microbicide, use of an interactive voice response system (IVR) can offer considerable advantage. The IVR combines computerized self-interviewing with touch-tone telephone technology. Participants respond to prerecorded questions by pushing numbers on the telephone keypad that correspond to their answers or by leaving voice messages. Participants' responses and additional metadata such as the date, time, and duration of the call are stored remotely on a server connected to a telephone network.(12) Since data are timestamped, if participants in a trial are asked to call shortly after product use, the time of the call can also serve as a proxy for time of product use. Prior research has also shown that participants may be highly adherent to using the IVR;(13) that data collection of frequent, sensitive behaviors via phone is acceptable to participants (13,14); and that the use of an IVR may lead to more accurate reporting of behaviors.(15–17) In addition, since calls are made to an automated system, greater confidentiality of the IVR may also reduce social desirability bias that may be present in face-to-face interviews.(13,18) Finally, the IVR may also encourage adherence to product use by serving as a reminder.(19,20)

We present data from a phase I rectal microbicide trial in which participants were randomized to use tenofovir 1% gel, hydroxyethylcellulose (HEC) placebo gel, Nonoxynol-9 gel, or no gel. Safety and acceptability results from this trial have been reported elsewhere.(21) Participants in gel arms were instructed to use the gel once daily for 7 days and to report at-home gel use to an IVR. In addition, participants returned used and unused applicators to the clinic, and applicator counts served as an additional measure of adherence. We report here the level of adherence to calling an IVR daily to report gel use as well as adherence to gel use during a seven-day trial. We also examined whether adherence (to calling the IVR and to gel use) varied by participants' socio demographic variables, day of the week calls started, number of days since the first call, or whether it was a weekday (vs. weekend). Finally, we compared the number of gel applications reported to the IVR to those inferred from returned used/unused applicator counts.

Methods

Sample

Participants were recruited from clinics and the surrounding communities using media advertisements, fliers and lists of previous research participants who agreed to be contacted again. The study took place at three clinical research sites: Alabama Microbicides Clinical Research Site, Birmingham, AL; Fenway Clinic, Boston, MA; and Pittsburgh Clinical Research Site, Pittsburgh, PA between November 2010 and July 2011. To be eligible for the study, participants had to be healthy, HIV-uninfected adults (male and female) aged 18 or older at time of screening with a history of consensual receptive anal intercourse (RAI) at least once in the prior year. Written informed consent was obtained from all participants and the study was reviewed and approved by the Institutional Review Boards of all of the aforementioned participating institutions and at the HIV Center for Clinical and Behavioral Studies at NY State Psychiatric Institute and Columbia University, where behavioral measures were designed and analyzed.

Procedures

Following written informed consent, participants were screened to determine eligibility. Eligible candidates were invited to return for an enrollment visit. At enrollment, participants completed a baseline behavioral questionnaire via Web-based Computer Assisted Self-Interview (CASI) including a demographic questionnaire, underwent a baseline medical evaluation, and were randomized to one of three blinded study regimens or to no treatment. Participants returned to the clinic between one and four weeks later to receive their first, observed dose of study product, with a follow-up phone assessment 24 hours later to inquire about adverse events. The second treatment visit was scheduled at least one week later, and treatment arm participants received a 7-day supply of study gel for daily self-administration plus an extra applicator in case any of the applicators were unusable, for a total of eight applicators. Participants were instructed to insert the entire contents of one applicator rectally at night before bed or the longest period of rest and to abstain from RAI for the duration of study participation. Also, participants were instructed to call the IVR each night after inserting the gel. Calling the IVR following each episode of gel use was mandatory; nevertheless, participants received a small monetary incentive (US\$2.00) for each call regardless of their report of product use or lack of use. Furthermore, to encourage adherence to calling the IVR, a bonus (US\$10.00) at the end of the seven days was accrued by those who had not missed any day in calling the system. The cutoff time for calling the IVR each day was midnight. Figure 1 summarizes the prerecorded questions presented via the IVR. Upon completion of the 7-day at-home regimen, participants returned for their final clinic visit in which they underwent a medical screening, returned both used and unused gel applicators to the pharmacy, and completed a product acceptability questionnaire via Web-based CASI. Adherence data were not collected via Web-based CASI.

Assessment of Adherence to Calling the IVR and to Gel Use

Adherence to calling the IVR was measured by examining whether or not a participant made a call to the IVR on each day he/she was expected to call the system during the seven-day gel use period. We created two new variables: "Day Number," corresponding to the day of

the seven-day gel use period for which the call counted (1–7); “Called IVR,” in which a 0 was entered if no call was made that day and a 1 was entered if a call was made that day so that adherence to calling the IVR on each day could be clearly defined. The team discussed “questionable” phone calls (such as calls placed after midnight, dropped calls, etc.) to make final determinations on adherence to calling the IVR. If the data could not be clearly interpreted, we used as default the exact time and date of the original report.

Daily adherence to product use (or lack thereof) was tallied based on the IVR report for each given day. However, if a call was missed, participants could still report their gel use since the prior call, even if more than 24 hours had passed. If participants failed to call for 48 hours, an alert was automatically generated and sent by email to a staff member who then contacted the participant to inquire about missed calls and adherence to the study product regimen. This additional information was integrated to properly determine adherence to gel use. For example, if a participant had not called for 2 days and then reported using the gel twice since the last call, we could assign one gel use to each of the 2 prior days. In another example, someone may have called on a Monday, and then made the following call shortly after midnight on Tuesday (i.e., early Wednesday morning), and made a third call on Wednesday evening; although technically the second call would count as a Wednesday call, we could infer that it was a report on Tuesday’s events.

At the end of the week-long trial participants returned both used and unused applicators to the pharmacy where they were counted. This tally was used for cross-validation of numbers of gel applications reported through the IVR.

Data Analysis

Descriptive statistics were generated for demographic variables. We examined the association between adherence to calling the IVR and key study variables such as participants’ socio demographic characteristics, day of the week calls started, number of days since the first call, and whether it was a weekday (vs. weekend). Data were analyzed using Generalized Linear Model with logit link function. We employed Generalized Estimating Equation (GEE) to account for the within-subject correlations introduced by repeated measures from the same participant, and an over-dispersion parameter to account for the unexplained variance due to the between-subject heterogeneity. Similar analyses were conducted for adherence to gel use. In addition, we compared the adherence of gel use reported by IVR with the applicator counts. While the odds ratio (OR) was used to measure the strength of the association, the intraclass correlation coefficient (ICC) was reported to measure the reliability between the two measures of adherence (i.e., IVR and applicator counts). Analyses were conducted using SPSS v.18.0.

Results

There were 46 participants randomized to the gel arms. Their mean age was 36 years (range=19–57 years). Among these 46 subjects, 74% were male, 61% were gay/lesbian/homosexual, and 64% were white/European American. The majority of the sample was employed (74%) with at least partial college education (85%). The mean income was between US \$20,000 to \$40,000

Out of 322 expected calls included in the analysis, 289 were made by participants. We made 83 adjustments on those 289 calls as part of data cleaning (See Table I). Most of the adjustments (66.3%) were made because participants called the IVR after midnight but analysis of the report pattern indicated that the reported event corresponded to a prior day. The second most frequent adjustment (25.3%) was made because participants misunderstood the question about number of times of gel use and entered the total number of gel applications to date (i.e., 1 for the first day, 2 for the second day, etc. up to 7 for the last day). The study staff was able to contact 4 of the participants and confirmed that this question was misunderstood and that they were using one applicator per day. We counted these calls as one gel use per day.

Adherence to Calling the IVR

Mean adherence to calling the IVR was 89.9% with a standard deviation of 20.7%. Of 46 study subjects, 69.6% (32/46) called every day, and 15.2% (7/46) missed one day.

Adherence to calling the IVR was not associated with any of the covariates we examined, including socio demographic characteristics (data not shown).

Adherence to Gel Use

Mean adherence to gel use based on IVR reports was 90.7% with a standard deviation of 19.1%. Among the 46 participants in the gel arms, 65.2% (30/46) reported 100% adherence, and 23.9% (11/46) missed only one gel use. No association was found between adherence to gel use and the key study covariates, including socio demographic characteristics (data not shown).

Comparison of IVR and Applicator Counts

Among 46 participants, 89.1% (42/46) returned 7 or 8 “used” applicators with an average of 6.91 (sd=0.73) “used” and 1.07 (sd=0.74) “unused” applicators. The number of gel applications reported through the IVR was consistent with returned applicators counts in 80.4% of cases with an intraclass correlation coefficient (ICC) equal to 0.75 (95% CI 0.54–0.86). However, discrepancies existed (See Table III). For example, one participant returned 8 “used” (i.e., empty) applicators but indicated via the IVR that he/she did not use two of the applicators due to dropping them. In addition, one participant returned 7 “used” applicators but the IVR data indicated that the gel was used 0 times on the first day and twice on the seventh day of the study period.

Discussion

We found that a self-initiated call to an IVR paired with staff reminders when no call is received within 48 hours results in high levels of reporting adherence. Furthermore, the close monitoring provided by the IVR allows for a nuanced assessment of adherence to product use. Although self-reports of product use via the IVR corresponded to returned applicator counts in most cases, in others the IVR proved valuable to ensure we did not overestimate adherence to product use. This suggests that using only returned applicator counts may not be sufficient to accurately measure adherence to gel use. In all cases of inconsistent data, returned applicator counts suggested a higher number of gel applications;

yet, in many cases the IVR provided additional information that allowed a potentially more accurate evaluation of product adherence. For example, the IVR allowed participants to report problems with gel use during the trial and gel application since the last call. This led to the identification of some slight deviations from protocol, e.g., starting product use a day early, using two gels in one day, or using more than one applicator to deliver one dose of gel.

Compared to other self-report adherence measures such as CASI used at the end of a study period, the use of an IVR appears advantageous as a measurement when daily product use is required. Furthermore, IVR for daily data collection may present advantages over CASI or Audio-CASI (ACASI) given that a telephone is all that is required as interface with the participant, and it allows for low literacy levels and a high level of confidentiality due to the private nature of the call and a response system based on keying in digits (22). In addition, since the IVR collects time-stamped data, it is also be preferable to paper diaries, which may be filled in by participants shortly before the study visit, thereby relying on a longer recall period. Finally, research has shown that written diaries had a higher rate of missed items when compared to daily phone calls (15) and that an automated telephone diary is more accurate for collecting behavioral data than either a written diary or a biweekly timeline followback method (16,17) and is preferred by participants to a written diary (16). One limitation is that IVR may not work as well in resource-constrained settings where access to a telephone may be limited, and it may restrict the sample to those who have access to a telephone. This can be avoided if cell phones are provided to the participant by the research organizations.

This study allowed us to learn valuable lessons about the utility of the IVR that can be applied to future research. First, creating a system in which the cut-off time for each day is later than midnight (e.g., 3:00 a.m.) may work better for many participants, given that several participants called after midnight to report gel use for the previous day (especially since they were asked to use the gel before bedtime). An option would be to set the IVR to call the participants at the same time daily (at a time chosen by the participant), rather than waiting for the participants to call the system; this could increase adherence to reporting via IVR and simultaneously serve as a reminder for product use. Prior research has shown that respondents who were expected to initiate daily calls had a higher rate of missed days than those who received calls initiated by project staff (15). Future studies should test whether a system in which participants receive a call from the IVR rather than initiating it themselves results in better adherence to reporting.

Second, daily calling, rather than less frequent, may be necessary to preserve consistency in reporting. In our study, most participants were adherent to calling the system daily for a seven-day period. However, adherence to calling may not be as high during longer trials in which participants are expected to call once per week instead of daily.

Third, calls to the IVR lasted between one and three minutes except for two longer calls (one lasted 4 minutes and the other one lasted 6 minutes). Given that participants were asked to refrain from RAI and none of them reported RAI through the IVR, they were able to skip most of the questions regarding gel use with sex and partner reaction. Longer questionnaires

administered via the IVR may be counterproductive in that participants may try to guess skip patterns so as to complete the questionnaire more quickly and collect the reward.

Fourth, data cleaning required careful review of information collected by IVR (such as the time of calling and participants' comments); adequate staff effort should be allocated for longer trials and/or studies with larger sample size.

In conclusion, our findings show high adherence to calling the IVR and to gel use in this particular trial and population. Daily reporting allowed identification of a few irregular uses of the product. The system seems to be useful for brief trials that require daily reporting of behavior. The fact that reported gel use was mostly consistent with returned applicator data contributes to validation of the utility of the IVR as a data collection method. To a certain degree, the use of an IVR may contribute to gel use adherence (by serving as a reminder to use); however, more research is needed to determine the utility of the IVR in longer trials.

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Figure 1.
IVR System Call Flow

Table I

Adjustments made to the original IVR data prior to the analysis

Reason for adjustment	Action	# of calls (% of adjusted calls)
Called after midnight	Counted as called the day before	55 (66.3)
Summed total number of times used gel	Counted as 1 gel use per day	21 (25.3)
Called on the eighth day	Call removed from data	3 (3.6)
Technical problems	Call removed from data	2 (2.4)
Started the call a day early*	Counted as called on the first day	1 (1.2)
Call dropped and called again	Dropped call removed from the data	1 (1.2)

* Participant was instructed to skip the first day and continue to call the day after.

Table II

Summary of adherence to calling the IVR and to Gel use

Adherence to Calling the IVR	
(N=46, M=89.9%, SD=20.7%)	
	% (n)
Called every day	69.6% (32)
Missed only 1 day	15.2% (7)
Missed 2 to 6 days	13.0% (6)
Never called	2.2% (1)
Adherence to Gel Use	
(N=46, M=90.7%, SD=19.1%)	
	% (n)
Used every day	65.2% (30)
Missed only 1 day	23.9% (11)
Missed 2 to 6 days	8.7% (4)
Never used	2.2% (1)

Table III

Examples of data discrepancies based on comparison of returned applicators and IVR product use data

Ppt ID	# of Returned Applicators	Valid # of Gels Used per IVR	Additional Information from IVR
102	7	6	Participant missed one day of calling the IVR and did not report two gels used since the last call the next time a call was made.
305	7	6	Participant called to report no gel use on first day and reported two gel uses on the seventh day.
208	7	6	Participant reported difficulty understanding the IVR and reported no gel use on the first day and one gel use each subsequent day.
241	7	6	Participant initiated gel use one day early, skipped first day, and continued on second day. Missed last call to IVR.
326	8	6	Participant reported no gel use the first day and reported having a problem with the gel.
225	8	5	Participant reported dropping two applicators in the toilet and skipping a day of gel use, per IVR.