AIDS Behav (2011) 15:389–395
DOI 10.1007/s10461-010-9822-9

ORIGINAL PAPER

Notes on the Frequency of Routinely Collected and Self-Reported Behavioral Data in HIV Prevention Trials

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Published online: 19 October 2010
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Abstract HIV prevention trials typically randomize thousands of participants to active or control intervention arms, with regular (e.g. monthly) clinic visits over one or more years of follow-up. Because HIV infection rates are often lower than 3 per 100 person-years even in high prevalence settings, tens of thousands of clinic visits may take place before the number of infections required to achieve adequate study power has been observed. In addition to clinical outcomes, the multitude of study visits provides an opportunity to assess adherence and related participant behaviors in great detail. These data may be used to refine counseling messages, gain insight into patterns of behavior, and perform supporting analyses in an attempt to obtain more precise estimates of treatment efficacy. Exploratory analyses were performed to assess how our understanding of participant behaviors and their relationships to biological outcomes in two recent prevention trials might have been impacted had the frequency of routine behavioral data collection been reduced from monthly to just months 1, 3, 6, 9, and 12. Results were comparably informative in the reduced case, suggesting that unnecessarily extensive amounts of routine behavioral data may be collected in these trials.

Keywords Adherence · Microbicide · Trajectory analysis

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Background

In the absence of an effective vaccine, considerable interest has focused on the development of new technologies to reduce the risk of HIV infection in settings where programs to promote abstinence, being faithful, and consistent use of condoms have proven inadequate. Recently investigated products have included diaphragms [1], anti-retroviral based prophylaxis [2], and topical microbicides [3–5].

Because HIV infection is typically a rare outcome, well-powered effectiveness trials of HIV prevention methods may require thousands of participants and many thousands of person-years of follow-up [6]. Subjects make frequent (often monthly) clinic visits for HIV testing and risk-reduction counseling, management of adverse events (AEs), and the withdrawal of product when required by protocol (e.g. if a participant becomes pregnant and regulatory approval has not been obtained to use the product during pregnancy [7]). Since adherence to most interventions is in the hands of participants, frequent adherence counseling is also essential. The resulting tens of thousands of clinic visits provide an opportunity to assess self-reported product adherence and related behaviors in great detail.

Challenges surrounding the collection and interpretation of behavioral data in HIV prevention trials are well documented. In particular, concerns for recall and social desirability biases can undermine confidence in the accuracy of self-reported behaviors [8, 9]. Nevertheless, valid behavioral data would enhance the interpretation of results: behaviors that could have diluted the effectiveness of a product [10, 11] may be identified, lest an otherwise promising intervention be dropped from future consideration when the primary intention-to-treat analysis fails to identify an effect; adherence measures may allow for refined estimates of efficacy when the intention-to-treat analysis establishes an effect; and patterns in adherence and acceptability can be used to inform counseling messages in ongoing and future trials as well as to gain insight into which populations may ultimately benefit from an efficacious product.

Given that the time and costs associated with collecting, processing, and analyzing data in an HIV prevention trial are substantial, however, it is essential to understand how much data are necessary to robustly assess a study's objectives and interpret its findings. With this in mind, exploratory analyses were performed to assess how our understanding of self-reported behaviors and their relationship to biological outcomes might have been impacted had the frequency of behavioral data collection been reduced from monthly to just months 1, 3, 6, 9, and 12 in two prevention trials. Although the focus here is on routine questions about adherence and related behaviors like condom use, such deliberations should not be restricted to non-clinical outcomes when planning a study. In one of the example trials, for instance, the decision was made to perform HIV testing at month 1 and quarterly thereafter—rather than at all monthly clinic visits—to reduce participant burden in sites where blood draws were out of the social and cultural norm.

Motivating Examples

The Cellulose Sulfate (CS) Gel Trials

Two randomized, double-blind, placebo-controlled trials of the candidate vaginal microbicide CS were conducted in India, Benin, Uganda, and South Africa by CONRAD [12] and in Nigeria by FHI [13]. Both studies were halted when the multi-country trial found interim evidence of potential increased risk of HIV infection among women randomized to CS. Ultimately, however, neither study demonstrated a statistically significant increased risk, nor did a composite analysis of both studies combined (crude risk ratio: 1.2; 95% CI: 0.7, 2.0).

The studies enrolled women who reported multiple sex partners and who were willing to use CS or placebo gel for each act of vaginal intercourse over a period of 1 year. Participants attended monthly follow-up visits for gel supply, condom and safer-sex counseling, AE diagnosis and management, the administration of a behavioral questionnaire, and pregnancy testing. Rapid HIV testing was performed monthly in the Nigeria trial and at months 1, 3, 6, 9, and 12 in the multi-country trial. Routine behavioral data collected monthly in both trials included the numbers of sex partners in the 7 and 30 days prior to each visit, as well as the total numbers of sex acts, acts with condoms, acts with gel, and acts with neither gel nor condom in the week prior to each visit.

Descriptive demographic and follow-up information on the 2,627 women contributing data to our analyses is provided in Table 1 (the Indian sites in the multi-country trial are excluded because they contributed no HIV endpoints and only 2 pregnancies). Women reported a median of 4 sex partners in the month prior to enrollment and 5 vaginal sex acts in the week prior to enrollment. Only a small proportion (15%) reported using highly effective contraception at baseline, and most (85%) had previously been pregnant. There were 21,780 monthly visits completed prior to termination of the trials, with a median of nine visits per woman. During follow up 2.4 and 19.2% of participants, respectively, became infected with HIV and tested positive for pregnancy.

Methods

In order to assess how our understanding of adherence, risk-taking and their relationships to biological outcomes might have been impacted had the frequency of behavioral data collection been reduced, we defined two analysis scenarios: complete-case analyses based on all 21,780 monthly behavioral assessment records and reduced-case analyses based on the subset of 9,218 records from assessments made at months 1, 3, 6, 9, and 12. Month 1 data were included in the reduced-case scenario to mirror the HIV testing schedule in the multi-country trial, and because an early assessment of adherence was deemed prudent for a prevention trial.

Time-Varying Behaviors and Risks of Clinical Outcomes

Proportional hazards regression models were used to assess associations between time-varying reports of risk-taking behaviors and two clinical outcomes: HIV infection and pregnancy. Attention was restricted to the numbers of vaginal sex acts without condoms reported in the week

Table 1 Baseline demographic and summary follow-up information for the CS trials [12, 13] data

Characteristic	Nigeria trial		Multi-country trial[a]			Pooled
	Lagos ($N = 754$)	Port Harcourt ($N = 751$)	Benin ($N = 227$)	South Africa ($N = 592$)	Uganda ($N = 303$)	($N = 2627$)
>24 years of age (*n*, %)	255 (33.8)	238 (31.6)	146 (64.3)	399 (67.3)	159 (52.4)	1197 (45.5)
Living with a man (*n*, %)	46 (6.1)	7 (0.9)	13 (5.7)	170 (28.7)	24 (7.9)	260 (9.8)
>9 years of education (*n*, %)	381 (50.5)	582 (77.4)	58 (25.5)	366 (61.8)	68 (22.4)	1455 (55.3)
Highly effective contraception (*n*, %)[b]	14 (1.8)	11 (1.4)	9 (3.9)	263 (44.4)	92 (30.3)	389 (14.8)
Ever pregnant (*n*, %)	605 (80.2)	615 (81.8)	206 (90.7)	534 (90.2)	269 (88.7)	2229 (84.8)
STI at baseline (*n*, %)[c]	43 (5.7)	21 (2.7)	29 (12.7)	55 (9.2)	42 (13.8)	190 (7.2)
Anal or oral sex in month prior to enrollment (*n*, %)	97 (12.8)	202 (26.8)	6 (2.6)	81 (13.6)	1 (0.3)	387 (14.7)
Median sex partners in month prior to enrollment	4	4	56	3	78	4
Median vaginal sex acts in week prior to enrollment	4	4	17	5	15	5
Median vaginal sex acts with condoms in week prior to enrollment	4	3	16	3	15	4
HIV infection at follow-up (*n*, %)	11 (1.4)	12 (1.6)	9 (4.0)	27 (4.6)	5 (1.6)	64 (2.4)
Pregnancy at follow-up (*n*, %)	191 (25.3)	117 (15.6)	52 (22.9)	60 (10.1)	85 (28.0)	505 (19.2)
Median number of follow-up visits	7	11	8	8	12	9
End of study status (*n*, %)						
Completed final visit	388 (51.4)	477 (63.5)	85 (37.4)	279 (47.1)	217 (71.6)	1446 (55.0)
Early termination of study	178 (23.6)	108 (14.3)	89 (39.2)	253 (42.7)	69 (22.7)	697 (26.5)
Lost to follow-up	187 (24.8)	165 (21.9)	46 (20.2)	51 (8.6)	13 (4.2)	462 (17.5)
Other	1 (0.1)	1 (0.1)	7 (3.0)	9 (1.5)	4 (1.3)	22 (0.8)

[a] Indian sites in the multi-country trial are excluded because they contributed no HIV endpoints and only 2 pregnancies

[b] Reported sterilization, IUD, hormonal implant or injectable use at screening

[c] Gonorrhea or chlamydial infection

prior to each follow-up visit, a variable intrinsically related to both HIV and pregnancy risk. All models were stratified on site and treatment group.

A total of 2,622 women and 59 endpoints are included in the HIV analyses (five endpoints identified after behavioral data collection had ended were excluded, as were five women who contributed no follow-up data prior to the date that investigators began withdrawing product) and 2,233 women with 459 endpoints are included in the pregnancy analyses (389 women who were sterilized, used an IUD, or used an injected or implanted hormonal contraception method at baseline were excluded because they were presumed to be at low risk for pregnancy, regardless of condom use. Of these, 31 (8%) became pregnant, with all but one reporting use of injectable contraception at baseline).

All participants were tested monthly for pregnancy, with the corresponding monthly reports of condom use used as time-varying covariate values in the complete-case analysis. Although participants were tested monthly for HIV in the Nigeria trial, women were only tested for HIV at months 1, 3, 6, 9, and 12 in the multi-country trial. Hence, for women in the multi-country trial, the average numbers of acts without condoms reported between HIV test visits were used as time-varying covariates in the complete-case analysis of HIV, thereby incorporating all available condom use data. For reduced-case analyses of both HIV and pregnancy, behavioral responses reported at months 1, 3, 6, 9, and 12 were carried forward to each HIV and pregnancy test result. For example, the numbers of sex acts without condoms reported at month 1 visits were used as time-varying covariate values for pregnancy tests conducted at months 1 and 2, the numbers of acts without condoms reported at month 3 were used as covariates values for pregnancy tests conducted at months 3, 4, and 5, etc. This mimicked analyses that could have taken place had behavioral data only been collected at the reduced schedule.

Patterns in Behavior Over Time

Identifying patterns in participant behavior over time can be used to gain insight into product acceptability, refine

counseling messages for future studies, and assess what factors may be associated with better product adherence and lower risk-taking. To this end, latent class trajectory analysis [14] was used to identify patterns in the proportion of sex acts with gel use (a measure of adherence) and the proportion of acts with condoms (a measure of risk-taking) reported in the weeks prior to clinic visits. Although the results of trajectory analysis should not be construed to imply that only a small number of distinct patterns exist, trajectory analysis does provide a data-driven means of identifying predominant patterns and has previously been used to assess adherence in HIV prevention trials [15]. The procedure was implemented using the TRAJ Procedure [16] in SAS version 9.1 [17]. Bayesian Information Criteria were used to determine whether two, three, or four patterns best described the data, with each pattern based on a third-order polynomial (from experience it was deemed unlikely that fewer than two or more than four patterns would be meaningfully distinguishable).

In addition to identifying predominant patterns of behavior, trajectory analysis methods provide the predicted probabilities that each participant is a member of each pattern. In order to assess what baseline factors appear associated with pattern membership, we assumed that each participant belonged to the class for which they had the highest predicted probability and used logistic regression to model multi-level responses. Baseline factors assessed included: site, age > 24, cohabitation with male partner, >9 years of education, previous pregnancy, diagnosis with STI, history of anal and/or oral sex, vaginal sex partners in 30 days prior to enrollment, number of vaginal sex acts in the week prior to enrollment, number of condoms used for vaginal sex in the week prior to enrollment, and use of highly effective contraception. Odds ratios and descriptive 95% confidence intervals, adjusting for site and treatment group, were computed using the SAS LOGISTIC procedure [17], weighting the analysis according to each participant's probability of membership in her assigned pattern.

Results

Time-Varying Behaviors and Risks of Clinical Outcomes

For the complete-case analysis, each additional vaginal sex act without a condom was associated with a 5% increase in HIV risk, although the result was not statistically significant (hazard ratio (HR) 1.05; 95% CI: 0.95, 1.16). The reduced-case analysis led to similar findings (HR 1.02; 95% CI: 0.89, 1.17). For pregnancy, each additional act without a condom was associated with a significant increase in pregnancy risk, with the complete-case (HR = 1.08: 95% CI: 1.06, 1.10) and reduced-case (HR 1.10; 95% CI: 1.06–1.13) analyses providing comparable results. A sensitivity analysis which included the 285 women using injectable hormonal contraception at baseline led to HR 1.08 (95% CI: 1.06–1.10) and HR 1.10 (95% CI: 1.07–1.14) for the complete- and reduced-case, respectively, with use of injectables associated with a significant reduced risk of pregnancy in each case.

Patterns in Behavior Over Time

Predominant patterns in self-reported rates of gel and condom use identified using trajectory analysis are presented in Figs. 1 and 2, respectively. Only two patterns of gel use were identified: a large percentage of women (88 and 84% in the complete- and reduced-case, respectively) who tended to report consistently high gel adherence levels and a smaller percentage of women (12 and 16%) whose gel adherence tended to decrease over time. Likewise there were only two predominant patterns of condom use: a large percentage of women (78 and 86% in the complete- and reduced-case, respectively) who tended to report consistently high rates of condom use and a smaller percentage of women (22 and 14%) with rates that tended to decrease over time.

The identified patterns in gel adherence were nearly the same for both complete- and reduced-case analyses. The estimated trajectories of decreasing condom use differed by 10–20% between the two analyses, but both patterns exhibit qualitatively similar trends and provide comparable

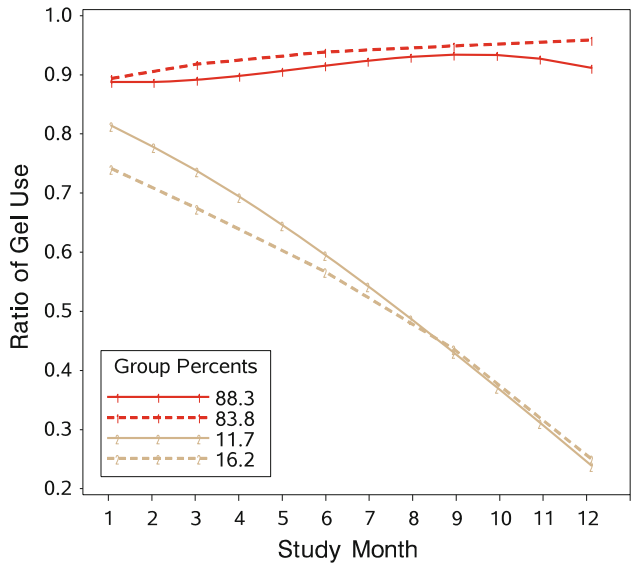

Fig. 1 Predominant patterns of gel use rates identified using complete-case (*solid lines*) and reduced-case (*dotted lines*) analyses (group percents represent proportions of participants predicted to fall in each pattern)

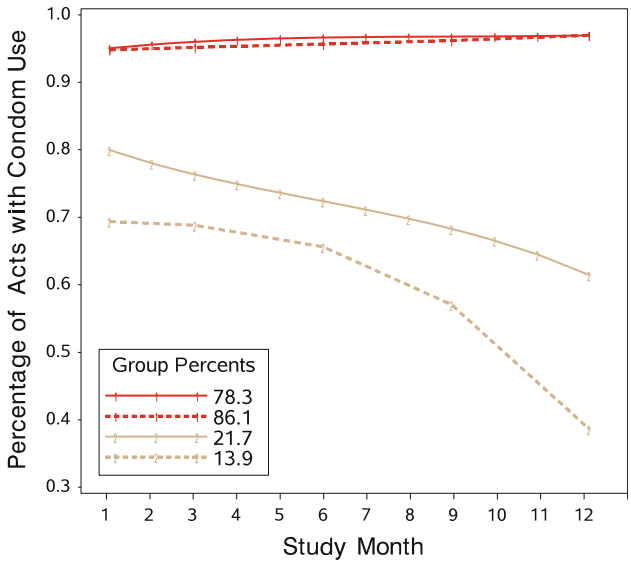

Fig. 2 Predominant patterns of condom use identified using complete-case (*solid line*) and reduced-case (*dotted line*) analyses (group percents represent proportions of participants predicted to fall in each pattern)

insight into condom use over time. The percentages of women predicted to fall in each gel and condom use trajectory differed by as much as 8% between the complete- and reduced-cases, but no meaningful differences in the associations between baseline characteristics and gel or condom use pattern membership were identified between the complete- and reduced-case analyses (Table 2). Nigerian and South African women were less likely to fall in the consistently high condom use trajectory, whereas women from Benin and South Africa were more likely to report consistently high gel use. Numbers of sex partners, frequency of vaginal sex, and baseline condom use were associated with consistently high condom but not gel use, and history of anal and/or oral sex was associated with decreasing condom use over time.

Discussion

We found that routine behavioral data collected monthly provided no important additional information in terms of describing the relationship between condom use and the risks of HIV and pregnancy than data collected only at months 1, 3, 6, 9, and 12 in two HIV prevention trials. We did not assess the relationship between self-reported gel use and clinical outcomes because there was no evidence that the active gel was effective in primary analyses reported elsewhere [12, 13]. However, reduced data collection had no meaningful impact on identifying predominant patterns of gel adherence or condom use over time. All identified patterns were substantially linear, regardless of data intensity. Further, most participants were predicted to fall in consistently high gel adherence and condom use trajectories, as might be expected in a setting where frequent counseling and social desirability factors encouraged consistently high self-report of product use over time. Together, these analyses suggest that collecting routine behavioral data from all participants at all visits may have added unnecessary burden to staff and participants in the example trials.

Microbicide effectiveness trials typically measure adherence according to either the last sex act or all sex acts in a specified time period prior to study visits. This requires accurate recall of one or more specific sexual events and, due to extensive adherence counseling, is prone to social desirability bias. Even in the absence of such biases, however, self-reported data have inherent limitations. Participants cannot identify which if any sex acts led to HIV exposure when the infection status of one or more partners is unknown. Likewise, a participant cannot identify which sex act led to his or her infection when multiple acts took place between HIV test visits. As a consequence, investigators must generally assume that typical behaviors reported by participants are representative of behaviors where exposure to, and ultimate infection with, HIV took place. This questionable assumption leaves any adherence-based effectiveness analysis vulnerable to unknown confounding and measurement error.

Our finding that routine behavioral data collection in the reported studies was unnecessarily extensive may not extrapolate to other HIV prevention trials. For example, the nature of the study populations considered here (women with multiple partners and high coital frequency) may have posed unique challenges to accurate assessment of behavioral data. Further, more accurate estimation of the effects of adherence and risk-taking on clinical outcomes might be achieved in studies where the timing of biological outcomes is more precise (e.g. using monthly HIV PCR testing rather than rapid antibody tests to define the infection window period).

Our results should not be construed to imply that behavioral data are unessential to the interpretation of prevention trials. They do argue, however, that some resources applied to routine data collection may be better directed towards related activities like enhanced adherence support that have the potential to increase product effectiveness [8] and study power. Consideration could also be given to prioritizing less frequent but potentially more informative means of assessing behaviors like triangulating multiple data sources [18] (e.g. drug supply counts, biomarkers, in-depth interviews, etc.). The validity of such methods in the current setting is beyond the scope of this paper, but it should be noted that investigators for the first microbicide study to demonstrate a statistically significant

Table 2 Odds Ratios (OR) for falling in consistently high condom use and high gel use trajectories, according to baseline demographic characteristics in the CS trials [12, 13] data

Baseline characteristic	High condom use				High gel use			
	Complete-case		Reduced-case		Complete-case		Reduced-case	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Site								
Lagos, Nigeria	0.43	(0.24, 0.77)	0.37	(0.17, 0.81)	0.49	(0.28, 0.86)	0.58	(0.37, 0.92)
Port Harcourt, Nigeria	0.12	(0.07, 0.21)	0.13	(0.07, 0.28)	0.49	(0.28, 0.85)	0.58	(0.37, 0.90)
Benin	0.99	(0.44, 2.21)	0.81	(0.29, 2.23)	2.93	(1.00, 8.60)	4.17	(1.63, 10.7)
South Africa	0.42	(0.23, 0.76)	0.29	(0.13, 0.61)	1.83	(0.91, 3.66)	2.59	(1.45, 4.64)
Uganda	Ref	–	Ref	–	Ref	–	Ref	–
>24 years of age	0.88	(0.69, 1.14)	0.73	(0.54, 0.99)	1.16	(0.83, 1.61)	1.06	(0.80, 1.40)
Living with a man	0.93	(0.59, 1.49)	0.94	(0.55, 1.61)	1.21	(0.61, 2.39)	1.07	(0.61, 1.90)
>9 years of education	0.79	(0.61, 1.03)	1.03	(0.76, 1.41)	0.91	(0.65, 1.28)	1.18	(0.88, 1.58)
Effective contraception at baseline[a]	0.85	(0.55, 1.32)	0.98	(0.59, 1.63)	0.82	(0.44, 1.50)	1.03	(0.61, 1.76)
Ever pregnant	0.78	(0.55, 1.09)	0.67	(0.44, 1.03)	0.81	(0.53, 1.26)	0.90	(0.63, 1.30)
STI at baseline[b]	1.05	(0.62, 1.79)	1.46	(0.72, 2.98)	0.71	(0.39, 1.31)	1.25	(0.67, 2.35)
Sex partners in month prior to enrollment[c]	1.01	(1.00, 1.02)	1.01	(1.00, 1.01)	1.00	(1.00, 1.00)	1.00	(1.00, 1.00)
Vaginal acts in week prior to enrollment[c]	1.02	(1.01, 1.04)	1.01	(0.99, 1.03)	1.00	(0.98, 1.01)	1.00	(0.99, 1.02)
Acts with condoms in week prior to enrollment[c]	1.05	(1.02, 1.07)	1.04	(1.01, 1.07)	1.00	(0.98, 1.01)	1.00	(0.99, 1.02)
Anal/oral sex in month prior to enrollment	0.65	(0.48, 0.87)	0.70	(0.50, 0.99)	0.81	(0.54, 1.20)	0.81	(0.57, 1.14)

[a] Reported sterilization, IUD, hormonal implant or injectable use at screening

[b] Gonorrhea or chlamydial infection

[c] Odds ratios for these characteristics correspond to one-unit changes in levels of baseline factor

protective effect [19] reported an apparent relationship between adherence and effectiveness of 1% Tenofovir gel based on a composite measure of self-report and applicator count data. More in-depth assessments of participants becoming infected during the trial might also provide greater insight into behaviors that can dilute study power [10, 20] but which are hard to capture in routine interviews. This could be done in the context of nested case-control studies as suggested in an Institute of Medicine report on methodological challenges in biomedical HIV prevention trials [21], although the impact of a positive HIV diagnosis on participant recall and possible confounding due to unknown HIV exposure among controls would need to be carefully explored.

Our conclusions regarding the frequency of data capture in some HIV prevention trials may be applicable to other situations where the effectiveness of an intervention is closely linked to unobservable participant behaviors, and where intensive counseling and social desirability pressures encourage consistently high self-report of product use. Possible examples include contraceptive trials, behavioral interventions for disease prevention, and HIV treatment trials. Secondary analysis of relevant datasets can be especially useful when planning for the optimal level of routine behavioral data collection in these settings.

Acknowledgments The authors thank Beth Raymond for her thoughtful review of an early version of this manuscript. The authors also express appreciation to Suniti Solomon and Marissa Becker (Indian site investigators for one of the CS trials) and the participants and staff who made the trials possible. The writing of this manuscript was supported in part by the United States Agency for International development (USAID) through Cooperative Agreement GPO-A-OO-05-00022-00; however, the views expressed do not necessarily reflect those of USAID.

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