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Monitoring microbicide gel use with real-time notification of the container's opening events: results of the CAPRISA Wisebag study

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Abstract

Accurate estimation of the effectiveness of a microbicide for HIV prevention requires valid measurement of adherence to product use. A microbicide gel applicator container (Wisebag), fitted with cell phone technology to transmit opening events and text message reminders, was developed to monitor each opening event of the container as a proxy for gel use and adherence. Ten women were enrolled in a pilot study and followed for up to 4 months. Wisebag opening (WBO) dates and times were recorded and correlated with self-reported sex acts and gel applicator returns. During the 33 monthly follow-up visits, 47.8% (77/161) of the recorded number of WBO events were concordant with the number of empty (used) applicators returned. The discrepancies were likely due to removal of more than one applicator during a single opening event. When the date and time of the WBO event data was assessed in relation to three different self-report adherence measures, agreement was fairly modest. The Wisebag was found to be acceptable as a storage container and the cell phone reminders generated were useful in supporting the dosing strategy. We recommend that the Wisebag be considered for larger scale and lengthier testing in microbicide trials.

Keywords

adherence; electronic monitoring; microbicides; clinical trials; HIV prevention

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Conflicts of interest

All authors report no conflicts of interest

BACKGROUND

The effectiveness of HIV prevention interventions such as microbicides depends substantially on a participant's ability to adhere to the prescribed product and dosing instructions. Imperfect adherence may reduce the test products' effectiveness (1) and make study results difficult to interpret, particularly if adherence is not accurately monitored and assessed (2). Most adherence assessment methods in microbicide trials rely on participant self-report of gel use, i.e., reliance on accurate participant recall (3, 4). Data from antiretroviral therapy trials show that participant self-reporting overestimates adherence when compared to more objective measures such as electronic drug monitoring (5, 6). The limitations of self-report include inaccurate recall, social desirability bias, and the time-consuming nature of assisted recall (6, 7).

In the CAPRISA 004 trial, where the effectiveness of 1% tenofovir gel in preventing HIV infection in young women was investigated (1), adherence was assessed by both subjective and objective measures when participants attended monthly study clinic visits. Subjective measures included participant self-report of gel use and objective data was obtained by pharmacy reconciliation of empty and unused applicators returned by participants at each study visit.

Other studies assessing HIV treatment adherence have demonstrated that wireless technologies with real-time event monitoring (8) or stored events for comparison and reconciliation with self-report at a later time (9, 10) are useful for providing objective estimates of adherence, useful for assessing self-report data and facilitate early intervention as problems arise. Wireless technology to monitor adherence to treatment has been effectively extended to other chronic diseases such as cystic fibrosis (11) and diabetes (12). Pilot studies have also been undertaken on electronic monitoring of adherence to oral hygiene practices using special toothbrushes (13) and monitoring hand hygiene in a hospital setting (14). This nested pilot study assessed the feasibility, acceptability and usefulness of real-time event monitoring of a coitally-dependent, vaginally administered antiretroviral microbicide in a resource limited setting.

METHODS

The CAPRISA 004 trial was conducted from May 2007 to March 2010 at both an urban and a rural site in KwaZulu-Natal, South Africa. This two-armed randomized, double-blind placebo controlled trial assessed the effectiveness and safety of 1% tenofovir gel in preventing HIV infection in sexually active women aged 18 to 40-years. Women were requested to insert one dose of gel within 12 hours before sex and a second dose of gel as soon as possible within 12 hours after sex with no more than two doses of gel inserted in a 24-hour period. This dosing strategy was termed BAT 24. Gel requirements for the month were assessed by the study clinician in conjunction with the study participant, where a minimum of 10 and up to a maximum of 60 applicators could be prescribed per month. Participants were requested to return their used (from October 2007 onward) and unused applicators at every visit. The applicators returned by women as used and unused were counted and reconciled against the number dispensed at the study pharmacy at each study

visit (1). An adherence support program was designed to assist participants with the mechanics of applicator use, timing and dosing, avoidance of gel sharing, and incorporation of gel use into their daily routines.

Participants were seen monthly where they underwent face-to-face standardized behavioral interviews with research nurses and had their used and unused applicator return counts recorded at the study pharmacy. At the beginning of the CAPRISA 004 trial the adherence counselling and adherence measurements were conducted by the same staff; however from October 2008 (and throughout the Wisebag study) these procedures were conducted by different staff. Interview data on self-reported sexual behavior included the date and time of last sex act prior to the study visit and 24 hour gel coverage for that sex act, seven day recall of total sex acts in that period and the number of these acts with gel coverage, as well as 30 day recall of cumulative gel use. Pharmacy data included counting the applicators returned as used and unused (as determined by applicator appearance) for the period since the last study visit when these applicators were dispensed, which was usually in the range of 28 to 30 days.

The nested CAPRISA 004 Wisebag pilot study was conducted in the five month period between July 2009 and November 2009 of the CAPRISA 004 trial. Participants active in the CAPRISA 004 study were randomly selected for screening. After screening for participants' interest, availability of a personal cell phone and willingness to be interviewed, a separate written informed consent was obtained for the pilot study at the study pharmacy. A structured Wisebag acceptability questionnaire was administered at enrollment into the Wisebag study, at month 1, at month 3 and finally at their CAPRISA 004 study exit. Wisebag participants were scheduled to be followed for a minimum of 4 months.

The acceptability questionnaire completed at enrollment assessed the participant's opinion of the Wisebag's appearance; whether they preferred this bag, a storage bag given to all CAPRISA 004 participants or their own bag; feelings about others seeing them carry the Wisebag; and feelings about the text message service (SMS) dosing reminder. At follow-up visits, including the study exit, the same questionnaire was repeated, and in addition storage, access difficulties and helpfulness of the SMS reminder was assessed.

Participants were only recruited into this study if they provided informed consent specifically developed for this study, as it included agreement to receive text message reminders each time the bag was opened. Participants received the text message in either English or Zulu sent to their cell phone at each opening event with the text "Hello, please remember to insert the gel as you were taught at the clinic. Remember to use only two gels in 24 hours." The text message generated at each opening of Wisebag was meant to serve dual purposes. First, it provided a BAT24 dosing reminder to participants and secondly it enables assessment of the acceptability and potential social consequences of adherence based text messaging within a prevention trial.

Participants were also instructed to retrieve a single applicator at each Wisebag opening, to zip the bag closed after each retrieval, and to bring the bag to each follow-up visit for gel

reconciliation and battery re-charging. This instruction was reinforced each time they met the study pharmacist.

The Wisebag dispenser (developed by CAPRISA and Wisepill® Technologies) is a soft bag that has a built-in pocket which houses an electronic unit that senses each opening event when a reed-switch in the electronic box breaks its contact with a magnet sewn into the lid of the bag. The unit transmits a cellular signal via General Packet Radio Service (GPRS) to a central Wisepill® server in Cape Town, South Africa and generates a text message to a designated participant's cell phone number each time the bag is opened (Figure 1). If there is no cell phone reception, the unit stores data on the opening events and transmits them as soon as cell phone reception is restored. The Wisebag unit switches off completely between openings and therefore has battery life of up to 3 months. A previous study using a Wisepill electronic unit to monitor daily antiretroviral treatment had difficulties with battery life prior to a system improvement (8). The Wisebag electronic units used in this study were fitted with the upgraded batteries at the start of this pilot study, which reduced potential difficulties with limited battery life. Two of the limitations of the Wisebag were that the bag had to be closed after opening in order to record the next opening event and there is no mechanism to indicate how many applicators are removed at each opening event. The date and time of each opening event was recorded and accessed from the central Wisepill database.

At the end of the CAPRISA 004 trial, the opening events generated by Wisebag were compared with study collected data on self-reported gel use, self-reported date of last sex and protected sex acts for the last sex day, sex days in last seven days and the last 30 days as well as the numbers of used applicators returned to the study pharmacy for the month. These data were summarized for the total number of Wisebag study visits. Pharmacy generated Wisebag opening events are excluded from the analysis.

For each of the recall periods described above, every Wisebag study visit was assessed for agreement with WBO event data. If the self-report of date of last sex day corresponded with the last WBO event date (the date that the participant reported was concordant if it corresponded with the WBO date up to 12 hours before the first sex act of the last sex day and up to 12 hours after this act), then it was regarded as agreement for this measure. Assuming that each sex act has two corresponding WBO events, sex acts covered by two corresponding WBO events for the 7 day time period were regarded as agreement for the seven day recall period.

For the returned applicators collected in each 30 day period, returned used applicator numbers concordant with WBO opening events was regarded as agreement for that study visit. Finally, Wisebag acceptability data captured at the study pharmacy was descriptively assessed. No test statistics were used in the analysis due to the small sample size.

Ethics approval for this pilot study was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE016/09), and the FHI Protection of Human Subjects Committee (study #10149).

RESULTS

Twenty-four CAPRISA 004 trial participants were screened for the pilot study and 10 participants (six rural and four urban) were enrolled during the period July to August 2009 at the two study clinic pharmacies. The reasons cited for not enrolling into the Wisebag study were: time constraints (n=4), wanting more time to think about the research (n=2), did not own a cell phone (n=1), was concerned about Wisebag being stolen from the home (n=1), was not willing to receive the dosing reminder text message (n=1), was not able to complete informed consent procedure (n=1) and the last four screened women were eligible but were not enrolled because the target sample size had been reached.

The age of the 10 women in this study ranged from 22 to 39 years (mean 29.5 years). Four of the participants were married and the remaining women were unmarried but were in a regular relationship with a stable partner. Most (n=8) had a monthly income less than R1000 (\pm \$100) per month. Four participants completed four months of follow-up. For five participants the third follow-up visit, and for 1 participant the second follow-up visit, coincided with the exit visit from the parent study and by default exit from the Wisebag pilot study. For this reason, 6 of the women had to exit the study prior to anticipated completion. A total of 33 follow-up visits of the 40 expected were completed by the 10 participants. There were no missed study visits.

There were a total of 161 Wisebag opening events transmitted to the server for the ten participants. For each follow-up visit, the corresponding WBO events were matched to returned used applicator count data for each participant: e.g. 8 WBO events and 8 returned used applicators was regarded as concordance at that follow-up visit. Assuming that each opening event corresponds with the retrieval of a single applicator, 77 (47.8%) WBO events were concordant while 84 (52.2%) WBO events were discordant when compared to returned used applicator counts. The majority of the discordant events had a higher number of used applicators returned compared with WBO events. It was not possible to verify if multiple applicators were retrieved at a single opening.

Three types of data were compared (last sex day with self-reported gel use, self-reported protected sex acts in the last seven and the last 30 days as well as 30 day returned used applicator counts) with WBO events and are summarized for the 33 study visits in Table 1. For the last sex day prior to a Wisebag study visit participants reported gel insertion from up to 20 days before the last recorded WBO event to seven days after the last recorded opening event. There was a difference in WBO dates compared to self-report dates in 12 (36.4%) of the 33 study visits.

There were 28 self-reported sex acts in the last seven days that were covered by gel and 38 corresponding WBO events. In accordance with the dosing strategy, each sex act should be covered by two applicators and no more than two applicators should be in used in 24 hours. It is not possible to tell from the data whether the 28 sex acts were adequately covered by the recommended number of gels as there could have been more than one sex act in a day. In 14 (42.4%) of the 33 study visits there was concordance with self-reported sex acts and WBO for the seven day recall measure.

Assuming a single gel is retrieved per WBO, agreement was higher (87.9%) between cumulative WBO events (161) and numbers of used gels returned (183) in the last 30 days. However, when individual study visits are examined for concordance between WBO events and returned used gel, again only 14 (42.4%) of the 33 study visits match. Self-reported gel use in the last 30 days and applicators returned for this same period showed high concordance in 30 (90.9%) of the 33 study visits. In spite of this, self-reported gel use and WBO events show agreement in only 12 (36.3%) of the 33 study visits.

To understand how the results would be impacted if assumptions on gel retrieval were changed, additional analysis presuming study visit agreement if one WBO event corresponded to the retrieval of two or more applicators for the seven day recall self-report measure, was performed. Study visit agreement then increased to 75.6% (for 25 of the 33 study visits) from 42.4%. Likewise, investigating WBO events in a 24 hour period around the date of when the last sex act was self-reported and ignoring any WBO opening events after that self-reported date of last gel insertion, agreement increased to 78.8% (26 of the 33 study visits).

Three study participants' opening event data were generated for an arbitrarily chosen time period in the study to illustrate the usefulness of Wisebag opening event data. Figures 2a, 2b and 2c show WBO events by date and time. Participant A (Fig 2a) presented to the study clinic on 18 August 2009 for her monthly study visit. Her Wisebag was opened by the study pharmacy which generated an opening event. Self-report of gel insertion date and time for last sex day was 17 August 2009 at 16:25 which matched the Wisebag opening event. She reported inserting her before-sex dose at 05:00 and a sex act at 06:00 on the same day. However, the Wisebag opening event data only records the after sex applicator retrieval dose that corresponds with this self-report. The last time the bag was opened prior to the self-reported sex act was seven days prior on 10 August 2009. It is possible in this scenario that the before sex dose was missed.

Participant B (Figure 2b) presented to the study clinic on 15 August 2009 and reported last inserting study gel earlier that morning at 06:00, a sex act at midnight the previous night with the prior dose inserted at 21:00. The Wisebag opening event data roughly corroborate the self-report.

Agreement between Wisebag data and self-report was poor for Participant C (Figure 2c) who visited the study clinic twice for the period 1 September 2009 to 30 September 2009. On 1 September 2009, she reported her last sex act to be on 19 August 2009, with her before-sex dose inserted at 20:00, a sex act at 21:00 and the after-sex dose at 22:00. WBO events indicate only one opening event at 20.30 on the 19 August 2010 and it is possible that the participant retrieved more than one applicator at this time. However, there are no self-reports of gel use for the two opening events that are subsequently recorded on 28 August 2009. On her next monthly visit on 30 September 2009, the participant reported last gel insertion on 27 September 2009 at 22:10, with the sex act on the same day at 22:00 and the before-sex dose at 21:00. WBO events record the last opening prior to reported sex to be seven days before the report.

During face-to-face interviews participants were specifically asked if they ever forgot to close the Wisebag and only one participant reported ever forgetting to zip the bag on a single occasion. Wisebag use continued throughout the study and was well-accepted by the participants. Nine of the ten women preferred the Wisebag to the CAPRISA 004 gel storage bag provided to all participants for gel transit and storage, due to its compact size, uniqueness, exclusivity and content anonymity. No storage difficulties were reported and none of the participants forgot to bring the bag to a scheduled visit. The SMS reminder on dosing was reported as 'very helpful' by eight participants. All participants reported always receiving SMS's on Wisebag opening, indicating that the forwarder system on receiving the signal at the Wisepill server which generated a SMS to the participants, was reliable. Two participants reported the reminder information as unhelpful. For the one participant, if the SMS arrived more than a few minutes after opening, it lost its helpfulness, and the other stated that it was not helpful because she did not require a dosing reminder. There were also no reports of social harms caused by the cell phone reminder messages.

DISCUSSION

In the CAPRISA Wisebag study, we pilot tested a real-time adherence monitoring and adherence support technology in 10 microbicide trial participants in Kwazulu-Natal, South Africa, and found its technical performance to be adequate and the electronic event-based monitoring feasible.

The most challenging aspect of the Wisebag study proved to be event data interpretation in relation to self-reported gel use. When the date and time of the WBO event data was assessed in relation to three different self-report adherence measures, agreement was fairly modest. As the recall period interval increased from last sex day to seven and 30 days, agreement with Wisebag opening events appeared to decrease. One can only speculate whether the Wisebag event data is more accurate than recall measures, as interpretation was complicated by the CAPRISA 004 dosing schedule and the ability of the participant to potentially retrieve more than one applicator at an opening. When assumptions about applicator retrieval were modified, concordance increased, suggesting that participants did remove more than applicator per opening.

As with all technologies, incorrect operator use of the device makes outcome data difficult to interpret. High agreement was demonstrated between self-reported number of returned used gels and pharmacy applicator count, which can possibly be ascribed to the participant watching the pharmacist complete and log the applicator count prior to starting their clinic visit. The WBO event data could be used as an adjunct tool with participants during face-to-face interviews, possibly generating more accurate data on timing of actual gel insertion for a variety of dosing strategies as discrepancies may be resolved at the interview. This strategy would only be feasible if in fact all opening events had been captured, as estimates could be biased in favour of the technology. In addition non-judgemental interviewer techniques must be adopted to ensure that the process of corroboration of self-reported data with electronic data doesn't pressurise participants and ultimately lead to spurious adherence estimates. Data would also have to be easily accessible and interpretable to the researcher to afford this method any type of practical application.

The Wisebag was programmed to send dosing reminders by SMS text at opening events, and this feature was well-accepted. The bag can further be programmed to remind participants in cases when scheduled opening events (either daily or intermittent) have not occurred. It can also send messages to participants if opening events exceed pre-set limits for safe dosing. Concerns that social harms might stem from the SMS texts proved to be unfounded in this small cohort, although it remains important to verify that this method of adherence support is socially acceptable in larger numbers of participants. Cell-phone ownership/sharing has been documented in other settings that have been testing HIV care cell phone technology (15). Although cell-phone sharing was not assessed in this sample, none of the women indicated that her privacy could potentially be intruded. Of the 24 women initially screened, only one objected to the cell-phone dosing reminder.

There are several limitations to this Wisebag pilot study, the most important being the inability to identify the numbers of gels retrieved at opening events. Failure to zip the bag and re-set the system would undermine accurate opening event data, although it did not appear to occur in this pilot, except for one episode reported by a study participant. It is acknowledged that the potential for underreporting failure to re-zip the bag by study participants exists. Device failure is another obvious concern, however, when participants were interviewed, none reported missing a SMS notification after opening the bag, indicating that unit malfunction did not occur in this small cohort followed over a short time. It is still conceivable that system errors such as poor cell phone network coverage or unregistered opening events were not picked up, although battery signal strength as verified by the pharmacy team was invariably found to be adequate.

The Wisebag demonstrates a potential for application in adherence assessment and enhancement. If successful, this technology has the potential to reduce provider dependence on self-reported adherence data with its inherent biases. Real-time event monitoring would be a useful tool to support adherence assessment by researchers by providing an objective and more accurate measure of true adherence. It is important that this technology be tested for a longer period in a larger sample. Participants must be instructed about not retrieving more than one applicator at a time or opening the bag with no applicator retrieval. Follow-up interviews should assess if such situations have occurred. Additionally, the bag should be opened as close as possible to intended gel insertion for opening events to serve as a proxy for gel insertion. Alternately, modifications to the current Wisebag design that lends itself to single applicator retrieval and electronically captures each applicator retrieved would improve the usefulness of this technology.

Although no gold standard exists in the HIV prevention field when measuring adherence, utilizing 'triangulation methods' where several measures of adherence are combined (16, 17) shows promise in the microbicide field. Triangulation first identifies discrepancies between different measures (self-report, coital diaries, in-depth interviews, applicator counts), and secondly aims to resolve them in face-to-face interviews with participants. The time-consuming, technically difficult nature of this type of data synthesis and the potential for reduced precision of the final estimates are concerns that require further investigation of this methodology. For future work, Wisebag generated data may be of use to add as a triangulation component to increase objectivity and aid recall, bearing in mind the Wisebag

limitations described. The prototype bag would also need to be optimized by creating a means to count applicators removed at each opening. Another possible enhancement would be to program SMS text messages whenever the bag remains open for an unusually long period, indicating failure to re-zip it.

The Wisepill technology has been used successfully in a pilot study to assess adherence to HIV treatment (8) and Wisebag performance was assessed in HIV negative women instructed to open the unit daily for two weeks (18), but this is the first microbicide trial to test electronic adherence monitoring of a coitally dependent dosing strategy using a test product. There is no standard to measure adherence in microbicide research, but technologies such as the Wisebag, if used correctly, could aid in more accurate generation of data to make comparisons. A larger and lengthier testing of the Wisebag in microbicide trials is therefore recommended.

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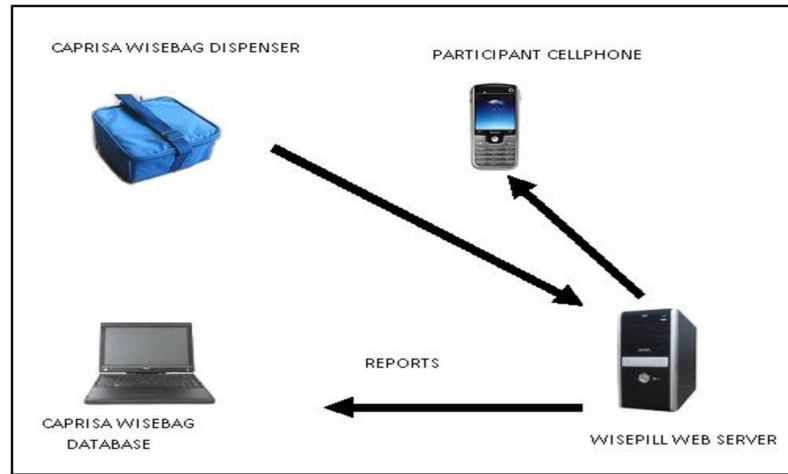


Figure 1.
The CAPRISA Wisebag dispensing unit and flow of communication

Figure 2a:

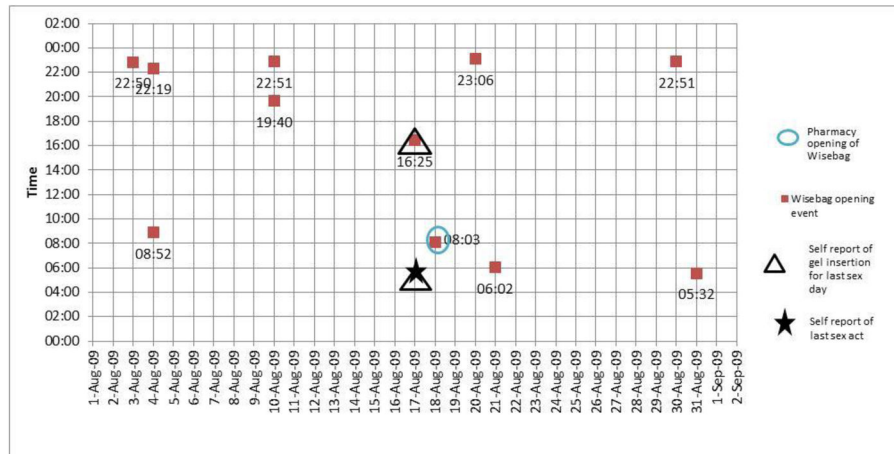


Figure 2b:

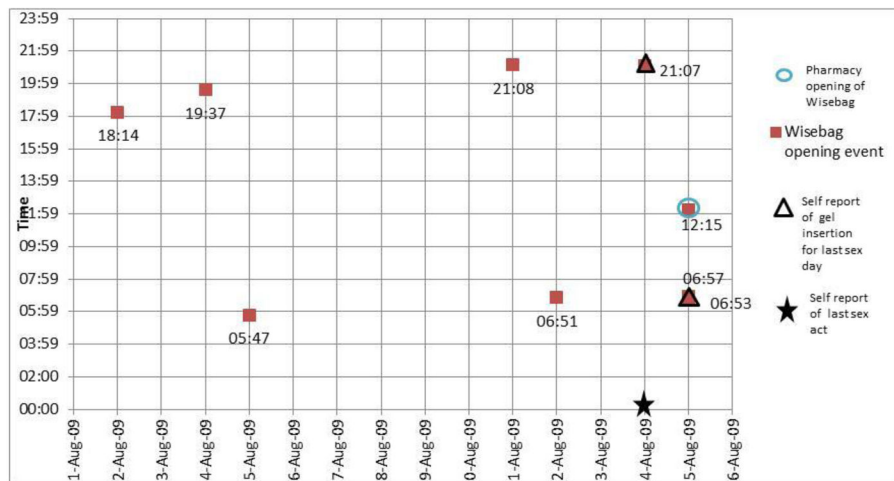


Figure 2c:

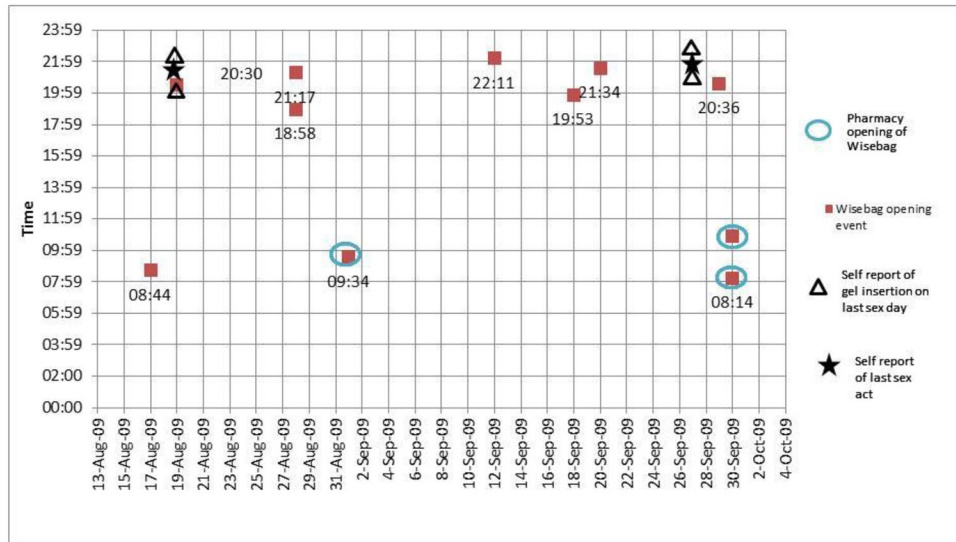


Figure 2.

Figure 2a: Participant A Wisebag opening events and self-reported data by date and time

Figure 2b: Participant B Wisebag opening events and self-reported data by date and time

Figure 2c: Participant C Wisebag opening events and self-reported data by date and time

Table 1
Recall measures, returned used applicators and Wisebag opening events for all 33 study visits

Recall period	Number of protected sex acts by self-reported	Number of gel used by self-report	Number of returned applicators*	Number of Wisebag openings	Number of study visits with agreement
Last sex day <i>Self-report of last sex day date compared to WBO date</i>	34	48	Not applicable	31	60.1% (20/33) [‡]
Last 7 days <i>Reported sex days compared to WBO openings for 7 day period</i>	28	Not measured	Not applicable	38	42.4% (14/33) [^]
Last 30 days <i>Reported sex days and returned used gels compared to WBO openings for 30 day period</i>	126	178	183	161	42.4% (14/33) [§]

* Gel applicator counts were available for 30 days periods only. Study visit agreement:

[‡] Date of last sex day corresponds with last WBO event date. Assuming 1 sex act has 2 WBO:

[^] Sex acts covered with 2 corresponding WBO events for the 7 day time period,

[§] Returned used applicators concordant with WBO opening events.