Electronic Monitoring: Adherence Assessment or Intervention?

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Purpose: Electronic-monitored adherence is often used as the primary outcome measure for evaluating adherence interventions. However, electronic monitoring may not only measure adherence, but may also improve or impede adherence, making it difficult to assess the extent to which the observed effect size is attributed to the intervention versus electronic monitoring. This study examined whether electronic monitoring and patient diaries alter as well as measure adherence. **Method:** A sample of 180 patients on highly active antiretroviral therapy (HAART) were randomized to one of three adherence surveillance methods (electronic monitoring caps, patient medication diaries, no surveillance control group) for 4 weeks, with adherence measured by a structured interview at baseline and study endpoint; 173 (96%) participants completed the study. **Results:** After controlling for baseline adherence, a univariate analyses of adherence at study endpoint revealed no significant differences across groups, $F(2, 169) = 0.32$, $p = .73$, with mean adherence rates of 91.4, 92.4, and 93.8 for the electronic monitoring, diaries, and control group, respectively. Similarly, the proportion of participants with good adherence (≥95%) did not differ significantly from baseline to week 4 among all three subgroups. **Conclusion:** These results suggest that electronic monitoring caps and medication diaries do not alter adherence and can be used as outcome measures of interventions without the need to adjust the observed effect size. **Key words:** *adherence, diaries, electronic monitoring*

Highly active antiretroviral therapy (HAART) has contributed to dramatic declines in both mortality and morbidity rates among people with HIV in the United States.[1] Medication adherence is crucial to the success of HAART, as poor adherence contributes to incomplete viral suppression, development of drug resistance and loss of treatment options, and transmission of multidrug-resistant viral strains.[2–4] These personal and public health consequences of poor adherence have resulted in substantial research efforts and funding aimed at developing effective adherence interventions, many of which are evaluated using electronic monitoring as the primary outcome measure. However, electronic monitoring may not only measure adherence, but may also change pill-taking behavior, which makes it difficult to assess the effect size of the designed intervention independent from the effects of electronic monitoring. We conducted a randomized, controlled methodological study to determine whether electronic monitoring and medication diaries (another adherence measure that may alter adherence) simply measure adherence or whether they alter pill-taking behavior and thus also constitute interventions.

Although there is no gold standard measure of adherence, electronic monitoring caps are considered by most researchers to be the best available method of measuring adherence. This methodology utilizes microelectronic technology to record the date and time of each medication bottle opening; this provides a precise, objective assessment of the timing of each dose and the patient's pattern of pill-taking behavior. In measuring adherence, this methodology assumes that each bottle opening represents an actual ingested full dose at the approximate time that the bottle is opened and that only one dose is removed at each opening of the bottle. A limitation to electronic monitoring is that it precludes the use of common adherence strate-

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gies including "pocketed" doses and use of a pill box to organize the medication monitored by the electronic cap. This may lead some patients to miss doses or to remove more than one dose per bottle opening to avoid carrying around the medication bottle when leaving home, with the latter resulting in an underestimation of the patient's actual adherence. Electronic-monitored adherence rates consistently range between 10%–20% lower than rates assessed by other methods including self-reports,[5–7] yet these lower rates are considered more accurate because adherence is most predictive of clinical outcome when measured by electronic monitoring.[5,8]

Most ongoing and newly funded studies are using electronic monitoring as the primary outcome measure for evaluating interventions aimed at improving adherence to HAART. A potential downfall of this research strategy is that electronic monitoring may not only measure adherence, but may also change pill-taking behavior, which would impede its ability to accurately assess the independent effects of an experimental intervention. Patients are aware that the caps monitor their adherence; therefore, electronic monitoring may improve adherence by increasing the patients' conscious awareness of their treatment regimen and their desire to be seen as good patients. Conversely, electronic monitoring may interfere with adherence because of the restrictions associated with the use of the caps, as described earlier. We are unaware of any published studies that have systematically addressed this question.

Another method of measuring adherence that may change pill-taking behavior is the patient medication diary. Patients are instructed to record the time they ingest the medication, as well as the dosage. Medication diaries are often used to monitor patients' treatment adherence, particularly in studies of illnesses such as diabetes and asthma where the frequency and accuracy of dosing are important to minimize physical symptoms.[9–11] The advantages of diaries are their low cost and unobtrusive nature, while disadvantages include the reliance on patients to remember to complete the diaries and to complete them accurately and prospectively. Studies show that diaries overestimate adherence compared to electronic monitoring, but they indicate rates similar to those of self-reports or pill counts.[12–14] Like electronic monitoring, daily completion of medication diaries may improve adherence by increasing the patient's awareness of the treatment regimen. We were able to find one published study that addressed this question. Straka et al.[12] studied medication adherence in patients with heart disease and found that completion of daily medication diaries resulted in a significant increase in adherence from 46% to 55% as measured by electronic monitoring and adherence improved in 60% of the sample. However, there was no control group in this study to control for other variables that may have contributed to an increase in adherence.

To assess whether electronic monitoring and medication diaries change pill-taking behavior, we conducted a study in which participants on HAART were randomized to one of three adherence surveillance methods (electronic monitoring caps, medication diaries, no surveillance control group) for 4 weeks, with self-reported adherence assessed at baseline and study endpoint. If electronic monitoring is found not to alter adherence behavior, its validity as a gold standard measure of adherence and an outcome measure for the efficacy of interventions will be enhanced. If such methodology does alter adherence, the data will inform other studies when assessing the proportion of improved adherence attributable to electronic monitoring versus the intervention being studied. If diaries are found to improve adherence, then this methodology provides a simple, inexpensive method for helping patients monitor and improve their adherence.

METHOD

Participants

Participants were recruited via postings and staff referrals at community-based organizations and clinics in Los Angeles (e.g., AIDS Project Los Angeles, Minority AIDS Project), through advertisements in HIV community newsletters, and through word of mouth. Eligibility criteria included being HIV-seropositive, on a three-drug antiretroviral regimen for at least 1 month, English speaking, and at least 18 years of age. Participants were required to bring their antiretroviral medications to the baseline interview to confirm their eligibility.

Procedures

Study participants were screened briefly on the phone to assess preliminary eligibility and to

schedule a baseline interview. After the completion of the baseline interview, eligible participants were then randomized to one of three adherence surveillance conditions: (1) to use an electronic cap to monitor one of their antiretroviral medications; (2) to complete daily medication diaries; or (3) to continue their pill-taking behavior as usual (control group). After the baseline interview, participants returned at week 4 for the final interview assessment. All participants were paid $15 at baseline and $45 at week 4.

Participants who were assigned to use the electronic caps were asked to transfer the medication with the most complex regimen, termed the "selected medication," into a container provided by the project with an attached electronic monitoring cap. Participants were informed that the cap houses a microelectronic chip that records the date and time of each bottle opening. Participants were told to follow their normal regimen but to: (1) open the bottle that contained the selected medication only when they were about to take a dose, and (2) to remove only one dose at a time. They were also instructed to refill the container when removing the last remaining pills and prior to placing the cap back on the bottle and to return the container and cap at the week 4 visit.

Participants randomized to complete medication diaries were instructed to complete a diary form each day, indicating the time they took each antiretroviral medication, how many pills they ingested at each dose taken, and the time that they ate food if their antiretroviral regimen had to be taken with or without food. Participants were instructed to document doses taken in the diary either after each dose was taken or at the end of each day. Diaries were submitted at the week 4 visit.

Participants randomized to the control group were told to continue to take their medication as usual, with no added requirements or instructions.

Adherence Measures

At baseline and week 4, a retrospective medication recall interview reconstructed for each of the previous 3 days when and what the patient ate, what time each antiretroviral medication was taken, and the number of pills taken per dose. Errors related to missed doses, failure to follow food requirements, and timing errors (interval between doses) were scored, with missed doses weighted more than other errors. The 3-day adherence score is 1 minus the proportion of the sum of errors for the 3 days divided by the total possible number of errors. This score is then multiplied by 100 and is represented as a percentage, with 100% considered perfect adherence. The medication diaries were scored using the same weighting strategy and scoring system as the medication recall interview.

At week 4, participants randomized to use the electronic monitoring cap were asked if their pill-taking behavior was influenced by the knowledge that their adherence was being monitored by the cap and, if so, whether this influence was helpful or harmful to their adherence. A parallel set of questions was administered to participants completing diaries with regard to the influence of daily diaries on adherence.

Data Analysis

Univariate analysis of variance statistics were used to detect significant differences between the three groups with regard to change in adherence from baseline to week 4 as measured by the medication recall interview. McNemar and Fisher's exact tests were used to compare group differences with regard to change in adherence when the self-reported adherence score was converted to a dichotomous variable using a cutoff of 95% to differentiate poor adherence from good adherence. If electronic monitoring caps or medication diaries do change pill-taking behavior, participants assigned to these methodologies should report significantly different rates of adherence at week 4 compared to the control group, with the control group not expected to exhibit change in adherence during the study period.

RESULTS

Sample Description

The total number of participants enrolled was 180, with 61, 60, and 59 participants randomized to electronic monitoring, completion of medication dairies, or the no surveillance control group, respectively. Attrition was very low, with 173 (96%) participants completing the 4-week study; of the seven who dropped out, four were randomized to the diary condition, two were in the control group, and one was assigned to use the electronic moni-

Table 1. Baseline demographic and medical characteristics by subgroup

Characteristics	Electronic monitoring	Diaries	Control
n	61	60	59
Mean age (years)	41	42	40
Female	9 (15%)	12 (20%)	11 (19%)
Ethnicity			
Caucasian	18 (30%)	22 (37%)	18 (31%)
Latino	9 (15%)	9 (15%)	11 (19%)
African American	33 (54%)	26 (43%)	30 (51%)
At least some college	30 (49%)	30 (50%)	31 (53%)
Employed	11 (18%)	6 (10%)	12 (20%)
In a relationship	26 (43%)	27 (45%)	22 (37%)
Living in temporary/transitional housing	9 (15%)	11 (18%)	12 (20%)
Self-identified as gay/bisexual	38 (62%)	28 (47%)	34 (58%)
No health insurance	13 (21%)	14 (23%)	23 (39%)
Antiretroviral regimen			
Twice-a-day dosing	52 (85%)	52 (87%)	51 (86%)
Three-times-a-day dosing	9 (15%)	8 (13%)	8 (14%)
Self-reported mean CD4 count (cells/mm^3)	417	389	412
Self-reported viral load <400 copies	27 (48%)	24 (42%)	21 (40%)
Mean months since tested HIV+	112	111	94
Mean months since started current regimen	12	16	12
AIDS diagnosis	42 (69%)	41 (68%)	33 (56%)

toring caps. Table 1 lists the demographic and medical characteristics of the sample. The three subgroups did not differ with regard to any of these background characteristics.

Self-Reported Adherence Rates

Adherence rates were similar across all three subgroups at baseline, $F(2, 177) = 0.11$, $p = .90$, with a mean rate of 92.6% ($SD = 14.1$) for the whole sample. Table 2 lists the mean self-reported adherence rates and proportion of patients with at least 95% adherence at baseline and week 4 among study completers in each subgroup and the whole sample. There was no significant change in adherence from baseline to week 4 within each subgroup; after controlling for baseline adherence, we found that the subgroups did not differ significantly with regard to adherence at week 4, $F(2, 169) = 0.32$, $p = .73$.

Data from the continuous self-reported adherence variable used in the univariate analysis de-

Table 2. Mean self-reported adherence rates and proportion with at least 95% adherence at baseline and week 4 among study completers

		Baseline		Week 4	
	n	Mean (*SD*)	≥95%	Mean (*SD*)	≥95%
Total sample	173	93.0% (12.4)	118 (68%)	92.5% (16.5)	121 (70%)
Electronic monitoring	60	92.9% (12.5)	41 (68%)	91.4% (12.2)	34 (57%)
Patient diaries	56	94.5% (10.5)	40 (71%)	92.4% (22.9)	46 (82%)
Control group	57	91.7% (14.1)	37 (65%)	93.8% (12.5)	41 (72%)

Table 3. Number of completers reporting "good" (≥95%) and "poor" (< 95%) adherence at baseline and week 4 by subgroup

		Week 4 adherence		
		Poor	Good	p^a
		Electronic monitoring		
Baseline adherence	Poor	10	9	
	Good	16	25	.16
		Medication diaries		
Baseline adherence	Poor	4	12	
	Good	6	34	.16
		Control		
Baseline adherence	Poor	7	13	
	Good	9	28	.39

[a]*p* values are from McNemar tests.

scribed previously were highly skewed to the left and were not normally distributed; 61% of the sample reported 100% adherence at baseline, and only 32% of the sample reported less than 95% adherence. Due to the lack of spread in the continuous variable, the data were dichotomized using 95% adherence as the cutoff mark to classify participants as having "good" (≥95%) or "poor" (< 95%) adherence. We chose 95% as the cutoff because of reported findings that adherence above this level is a significant predictor of complete viral suppression.[4] Table 3 lists the number of study completers reporting poor and good adherence at baseline and at week 4 within the three subgroups. The cells on the diagonal represent participants whose adherence classification did not change from baseline to week 4, whereas the cells on the off-diagonal represent the participants whose adherence classification did change.

The proportions of participants in the electronic monitoring (58%), diary (68%), and control (61%) groups whose classification of adherence was unchanged from baseline to week 4 were similar, as were the proportions of participants whose adherence improved from poor at baseline to good at week 4 (15%, 21%, and 23% for the electronic monitoring, diary, and control groups, respectively). Adherence declined from good at baseline to poor at week 4 among 11% and 16% of participants in the diary and control groups, respectively, compared to 27% of those using the electronic monitoring caps. Overall, classification of adherence as poor or good did not change significantly from baseline to week 4 within each group separately (see *p* values of McNemar tests in Table 3), nor were there significant differences across groups (Fisher's exact test = 0.23).

Among the 59 study completers who were randomized to use the electronic monitoring caps, 35 (59%) reported that their adherence was influenced by the cap and its recording of the doses they took and missed. All but 1 of these 35 participants reported that this influence was beneficial. Participants reported that knowing the cap was monitoring their adherence helped them to remember their doses, because it made them more conscious of their regimen and it increased their motivation to show that they could adhere well. However, the self-report adherence data do not support this perception, as adherence rates decreased numerically from baseline (mean = 94.2%, *SD* = 12.2) to week 4 (mean = 88.9%, *SD* = 14.3), albeit not significantly ($t = 1.5_{33}$, $p = .14$), among the 34 who reported that the cap helped their adherence.

Among the 56 study completers in the diary group, 26 (46%) reported that daily completion of medication diaries influenced their adherence. All 26 reported that completing the diaries helped their adherence; however, this subgroup's self-reported adherence did not change significantly from baseline (mean = 92.2%, *SD* = 13.8) to week 4 (mean = 91.4%, *SD* = 24.8; $t = 0.1_{25}$, $p = .9$).

DISCUSSION

With the importance of adherence to the success of HAART becoming increasingly evident, several clinical trials evaluating adherence interventions have been recently funded and are currently in the field. Almost all of these studies use electronic monitoring to test the intervention's efficacy. Results from this study bolster the validity of electronic-monitored data as an outcome measure for adherence interventions. Self-reported adherence over the previous 3 days did not differ from baseline to week 4 for those randomized to use the electronic monitoring caps, nor did this group differ significantly from the control group with regard to change in adherence. Similar findings were found for those completing daily medication diaries. Likewise, the proportion of participants with good adherence (≥95%) did not differ significantly from baseline to week 4 among all three subgroups. These results suggest that electronic monitoring and daily medication diaries do not significantly alter the pill-taking behavior that they measure. Hence, when electronic monitoring or medication diaries are used as outcome measures for evaluating adherence interventions, the observed effect size can be interpreted as independent from the measurement procedures.

Although the study data indicate that electronic monitoring do not alter adherence in general, there was some evidence that electronic monitoring may have interfered with the adherence of some participants. The self-reported adherence of 27% of the group using electronic caps declined from good (≥95%) at baseline to poor (< 95%) at week 4. This proportion is not much greater than what was found in the control group (16%), but it raises concerns about the potential harmful effects of restricting the use of common adherence strategies such as pill boxes and "pocketing" doses, which are requirements associated with electronic monitoring.[15] This issue may become less of a concern as more and more drugs are taken once or twice a day, rather than three times a day.

The use of self-report methodology to assess change in adherence between baseline and week 4 poses some study limitations. Consistent with other studies,[5,6] our self-report measure overestimated adherence and produced data that were skewed and restricted in range. The self-reported adherence mean of 93% in the subgroup of participants using the electronic monitoring caps was considerably higher than the adherence rate (76%) measured by the caps over the same time period (last 3 days of the 4-week study period). These two methods were significantly correlated (r = .53) in their assessment of adherence during this time period, which validates the self-report measure. Nonetheless, the inflated self-report data may have created a "ceiling effect" that made it difficult to detect significant changes with regard to improved adherence, and therefore may have masked actual group differences. We might have found intervention effects associated with the use of electronic monitoring or diaries if lower adherence rates had been reported at baseline. Even though self-reports may not be the most accurate measure of change in adherence, the limits of this methodology were equivalent across the three subgroups. If we had examined whether the groups differed with respect to viral load changes from baseline to week 4, it would have helped to substantiate our findings, but the resources needed to conduct these assays were unfortunately not available.

The randomization controlled for other variables that could potentially contribute to group differences (or lack thereof) with regard to change in adherence; the three subgroups did not differ with regard to any demographic or medical variables. An added limitation of the self-report is that it only assessed adherence over a 3-day period, primarily because memory recall deteriorates significantly after 3 days. Hence, the self-report is representative of very recent adherence and may not be indicative of a patient's usual adherence pattern. However, electronic monitoring showed a moderately high correlation (r = .60) between adherence over 4 weeks with that of the 3 days prior to the week 4 assessment, which suggests that a 3-day "snap shot" of adherence is fairly indicative of a patient's usual adherence pattern.

CONCLUSION

Our findings suggest that electronic monitoring and patient medication diaries are methods of measuring adherence that do not significantly alter pill-taking behavior and therefore are not adherence interventions in and of themselves. Electronic monitoring is considered the most accurate measure of adherence currently available, and the va-

lidity of its use as the primary test of adherence interventions is strengthened by these results.

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