Antiretroviral Therapy Adherence and Viral Suppression in HIV-Infected Drug Users: Comparison of Self-Report and Electronic Monitoring

Julia H. Arnsten,[1–3] Penelope A. Demas,[1] Homayoon Farzadegan,[6] Richard W. Grant,[1] Marc N. Gourevitch,[1–3] Chee-Jen Chang,[1,4] Donna Buono,[1] Haftan Eckholdt,[5] Andrea A. Howard,[1,2] and Ellie E. Schoenbaum[1,2]

[1]AIDS Research Program, Department of Epidemiology and Social Medicine, [2]Department of Medicine, [3]Division of Substance Abuse, Department of Psychiatry and Behavioral Sciences, [4]Division of Biostatistics, Department of Epidemiology and Social Medicine, and [5]Division of Biometry, Department of Neurology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; and [6]Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

To compare electronically monitored (MEMS) with self-reported adherence in drug users, including the impact of adherence on HIV load, we conducted a 6-month observational study of 67 antiretroviral-experienced current and former drug users. Adherence (percentage of doses taken as prescribed) was calculated for both the day and the week preceding each of 6 research visits. Mean self-reported 1-day adherence was 79% (median, 86%), and mean self-reported 1-week adherence was 78% (median, 85%). Mean MEMS 1-day adherence was 57% (median, 52%), and mean MEMS 1-week adherence was 53% (median, 49%). One-day and 1-week estimates were highly correlated ($r > .8$ for both measures). Both self-reported and MEMS adherence were correlated with concurrent HIV load ($r = .43–.60$), but the likelihood of achieving virologic suppression was greater if MEMS adherence was high than if self-reported adherence was high. We conclude that self-reported adherence is higher than MEMS adherence, but a strong relationship exists between both measures and virus load. However, electronic monitoring is more sensitive than self-report for the detection of nonadherence and should be used in adherence intervention studies.

The use of potent antiretroviral combinations has provided unprecedented opportunities for effectively treating HIV disease and led to a dramatic decline in HIV mortality [1, 2]. Highly active antiretroviral therapy (HAART) can profoundly inhibit viral replication and delay disease progression, but achieving this potential in clinical practice requires adherence to complex regimens. Nonadherence with antiretroviral therapy may result not only in reduced treatment efficacy but also in the selection of drug-resistant HIV strains [3, 4].

Virologic failure may result from low adherence, lack of antiretroviral potency, drug resistance, or a combination [4–8]. An accurate measure of adherence would therefore be of great value in the assessment of virologic failure. Despite this, little is currently known about how best to measure adherence, particularly among drug users and others not usually enrolled in clinical trials. Self-report, which is widely used in both trials [4, 9] and community settings [10–13], has been shown to produce higher adherence estimates than electronic monitoring [14–16], but electronic monitors may un-

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Reprints or correspondence: Dr. Julia H. Arnsten, AIDS Research Program, Montefiore Medical Center, 111 East 210 St., Bronx, NY 10467 (jarnsten@montefiore.org).

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derestimate adherence when patients do not carry the monitors with them. Further research is needed to compare adherence measures, including different approaches to self-report.

Drug users account for a substantial proportion of AIDS cases in the United States, yet they have achieved disproportionately less benefit from HAART than non–drug users. Several recent reports [17–20] have shown that HAART is underutilized among drug users, largely because of clinicians' concerns about nonadherence [21–23]. Few studies of adherence have been conducted in drug users [23, 24], and none have compared different adherence measures or systematically examined the relationship between adherence and virus load.

Our objective was to describe antiretroviral adherence in HIV-infected current and former drug users. We compared electronically monitored (Medication Event Monitoring Systems [MEMS]; Aprex Corporation) and self-reported measures of adherence, including assessments of adherence for both 1 day and 1 week prior to each research visit. In addition, we determined the impact of both MEMS and self-reported adherence on HIV load.

MATERIALS AND METHODS

Recruitment. Subjects were recruited from the Bronx HIV Epidemiologic Research on Outcomes Study (HEROS), an ongoing cohort of drug users at Montefiore Medical Center, Bronx, New York, that began in 1985 [25, 26]. Eligibility criteria for the adherence study included current prescriptions for antiretroviral therapy and willingness to use MEMS caps for each antiretroviral medication. Subjects who used other medication dispensing devices, such as pillboxes, were ineligible. MEMS caps fit standard-sized medication bottles and record the time and date of each opening as a presumptive dose.

Study visits. Subjects were enrolled in the adherence study for 6 months, during which research visits were scheduled at 4-week intervals. Prior to the first visit, subjects were assisted with transferring their medications to MEMS pill bottles and were instructed to open these bottles only to withdraw doses at the time of ingestion and not to transfer medications to other containers. Subjects were further instructed to carry the MEMS bottles with them while away from home. At each follow-up visit, MEMS software (MEMS View, version 161; Aprex Corporation) was used to download adherence data. Replacement MEMS caps were issued for lost caps or if medications were changed. If a subject stopped using MEMS caps but continued to take medications, the dates of nonuse were recorded and excluded from analysis.

Self-reported adherence was assessed by interviewer-administered questionnaire for both 1 day and 1 week preceding each visit. We assessed 1-day adherence because it is clinically feasible and efficient, although it may overestimate adherence because of increased medication-taking in the day preceding a clinic or research visit. We assessed 1-week adherence in order to include weekends, during which medication schedules may be disrupted [16]. Obtaining 2 measures of self-reported adherence enabled us to compare them with each other and to compare both with MEMS.

Blood was drawn at each visit for virus load quantification (Version 3.0 b-DNA Quantiplex assay; Bayer Diagnostics). Subjects received monetary reimbursement for each visit and a cash incentive for returning the MEMS caps.

Adherence indices. The period of analysis began the day after the baseline interview and ended the day of the 6th follow-up interview (or final interview, if the subject withdrew). The dates and times of every pill bottle opening for all medications were exported into the SAS system (SAS Proprietary Software Release 6.11; SAS Institute). This allowed the combining of data for subjects who were given replacement caps for the same medication and the exclusion of data for subjects who did not use the MEMS caps for defined periods of time.

Exporting all of the MEMS data into the SAS system allowed in-depth analysis of medication-taking behavior, including calculation of the following adherence indices. (1) Adherence in the day preceding each research visit (1-day adherence). This was defined as percentage of medication doses taken as prescribed during the previous day [(no. doses taken)/(no. doses prescribed) $\times$ 100] and was calculated by use of both self-reported and MEMS data from all 6 follow-up visits. (2) Adherence in the week preceding each research visit (1-week adherence). This was defined as percentage of medication doses taken as prescribed during the 7 days preceding each follow-up visit. (3) Adherence during the entire study period. Because self-reported data only captured medication-taking behavior for 1 week before each research visit, we used MEMS data to calculate adherence during the entire study period as (total no. doses taken)/(total no. doses prescribed) $\times$ 100. (4) Dose interval adherence. The percentage of days on which $\geq$1 dose was taken, the percentage of days on which the correct number of doses was taken, and the percentage of days on which all medication doses were taken within 25% of the correct dosing interval (e.g., within 9–15 h of the previous dose for a twice-per-day medication) were all calculated by use of MEMS data from every monitored day. (5) Medication-specific adherence. Because MEMS caps were used for each antiretroviral medication, medication-specific adherence rates (percentage of doses taken as prescribed) were calculated by using both MEMS and self-reported data.

Statistical analysis. For each of the adherence indices described above, adherence was analyzed as a continuous variable measured at each research visit. HIV load, also measured at each visit, was analyzed both continuously (as $\log_{10}$ HIV RNA copy number) and dichotomously (more than or less than 500

copies/mL). Associations between continuous variables were assessed by Pearson correlation coefficients and by repeated-measures analyses that used mixed-effects models. For the mixed-effects models that compared different adherence indices, dependent variables were created that represented the difference between adherence rates. For example, to compare self-report to MEMS, a variable was created to represent the difference between 1-day self-reported adherence and 1-day MEMS adherence, and it was then determined whether this variable was significantly different than zero.

To examine the association of HIV load with both MEMS and self-reported adherence, adherence rates in each virus load group (<500 copies/mL or ⩾500 copies/mL) were compared. In addition, a series of logistic regression models was created with HIV load (<500 copies/mL or ⩾500 copies/mL) as the dependent variable and adherence (continuous), number of antiretroviral medications, and CD4 count as independent variables. Similar logistic models were created in which adherence was categorized according to quartiles of MEMS adherence.

RESULTS

From July 1998 through April 1999, 138 members of the Bronx HEROS cohort were screened, and 67 (68%) of 99 eligible subjects agreed to enroll. These 67 subjects provided 307 measures of MEMS 1-day and 1-week adherence, 332 estimates of self-reported 1-day and 1-week adherence, and 382 HIV load measurements. The mean length of follow-up was 155 days (5.1 months); 49 subjects (73%) completed all 6 months of follow-up. Of the 32 eligible subjects who did not enroll, 16 were unwilling to use MEMS caps, 6 were using other medication-dispensing devices (e.g., pillboxes), and the remainder died or were incarcerated prior to enrollment.

Sociodemographic and disease characteristics. Thirty-nine percent of subjects were women, and the vast majority were Hispanic or black, which reflects the HIV-infected population in the Bronx (table 1). Sixty-four subjects (96%) were on methadone maintenance, and one-third reported active drug use (smoking, snorting, or injecting heroin or cocaine) during the study. Most subjects were unemployed, and almost all were receiving public assistance. Subjects had been HIV-infected for a median of 7.3 years. Only 15% were antiretroviral naïve; the remainder had taken a mean of 2.7 (range, 1–10) antiretrovirals prior to their current regimen. Most subjects (84%) were taking ⩾3 antiretrovirals, and 79% were taking a protease inhibitor.

Use of MEMS caps. A total of 203 MEMS caps were dispensed, and data were analyzed from 165 caps (81%). Reasons that MEMS data were not analyzed included malfunction ($n = 11$), improper use ($n = 5$), study withdrawal ($n = 15$), medications discontinued before baseline ($n = 4$), and lost caps ($n = 3$). Most subjects (55 [82%]) remained on the same medications throughout the study. All 13 currently licensed antiretroviral medications were used in various combinations by study subjects.

Table 1. Sociodemographic characteristics of study subjects.

Characteristic	Study subjects
Sex	
Female	26 (39)
Male	41 (61)
Race	
Black	16 (24)
Hispanic	40 (60)
White	8 (12)
Median age, years (range)	43 (23–61)
Methadone maintenance	64 (96)
Marital status	
Married	21 (31)
Separated, divorced, or single	46 (69)
Active drug or alcohol use	33 (49)
Heroin	20 (30)
Cocaine	22 (33)
Alcohol use more than several days per week	15 (22)
Unemployed	64 (96)
Receiving public assistance	66 (99)
Median baseline CD4 count,[a] cells/mm^3	324
Baseline CD4 count,[a] cells/mm^3	
<50	8 (13)
50–200	14 (22)
201–500	29 (46)
>500	12 (19)
Baseline HIV RNA,[b] copies/mL	
<50	19 (29)
50–500	17 (26)
501–5000	10 (15)
5001–10,000	5 (8)
10,001–100,000	9 (14)
>100,000	6 (9)

NOTE. Data are no. (%) of subjects, unless otherwise indicated.
[a] CD4 counts available for 63 subjects.
[b] Baseline HIV RNA available for 66 subjects.

One-day and 1-week adherence. Mean self-reported adherence (percentage of doses taken as prescribed) for the day preceding each follow-up visit was 79% (median, 86%; interquartile range, 68–100), and mean self-reported adherence for the week preceding each visit was 78% (median, 85%; interquartile range, 66–93). One-day and 1-week self-reported adherence rates at each of the visits are reported in table 2, along with the correlation between the 2 measures at each time point. The overall correlation between 1-day and 1-week self-reported adherence was .81 ($P < .001$). The 1-day and 1-week estimates

Table 2. Correlation between 1-day and 1-week self-reported (SR) and electronically monitored (MEMS) adherence at each visit.

	SR adherence				MEMS adherence			
Visit	No. of subjects	One-day SR, mean ± SD	One-week SR, mean ± SD	r[a]	No. of subjects	One-day MEMS, mean ± SD	One-week MEMS, mean ± SD	r[a]
2	63	75.6 ± 34.1	80.9 ± 23.3	.66	60	66.4 ± 42.4	60.3 ± 35.9	.77
3	59	85.3 ± 28.3	78.3 ± 26.7	.70	58	57.1 ± 41.3	52.2 ± 37.0	.80
4	56	82.9 ± 31.0	80.1 ± 23.0	.56	54	54.2 ± 40.1	54.8 ± 35.8	.66
5	55	84.3 ± 31.8	81.1 ± 27.9	.62	49	63.9 ± 41.9	54.9 ± 39.6	.74
6	50	83.2 ± 30.8	86.6 ± 22.6	.86	45	56.3 ± 36.8	53.8 ± 41.2	.86
7	49	80.4 ± 33.9	81.1 ± 29.7	.79	41	56.1 ± 38.2	55.6 ± 43.6	.86
Total	63	79.1 ± 22.5	78.1 ± 22.1	.81	60	57.3 ± 31.9	53.4 ± 33.9	.91

[a] $P = .0001$ for all correlation coefficients.

of self-reported adherence did not differ significantly in a mixed-effects repeated-measures model ($P = .14$), nor did the estimates at different research visits differ significantly ($P = .10$).

Mean MEMS adherence for the day preceding each follow-up visit was 57% (median, 52%; interquartile range, 32–86), and mean MEMS adherence for the week preceding each follow-up visit was 53% (median, 49%; interquartile range, 24–90; table 2). The overall correlation between 1-day and 1-week MEMS adherence was .91 ($P < .001$). As with self-report, MEMS 1-day and 1-week estimates did not differ significantly in a mixed-effects repeated-measures model ($P = .08$), nor did the MEMS estimates vary over time ($P = .14$).

Although the self-reported and MEMS estimates were correlated with each other ($r = .49$ and $P < .001$, for 1-day; $r = .46$ and $P < .001$, for 1-week), self-reported adherence was significantly higher. The mean difference between self-reported and MEMS adherence was 31% for the 1-day estimates and 32% for the 1-week estimates ($P = .0001$ for the differences between self-report and MEMS with use of mixed-effects models). Thirty-five percent of subjects had MEMS 1-day adherence of ⩾80%, whereas twice that number (70%) reported 1-day adherence of ⩾80%. Furthermore, only 18% of subjects had near-perfect MEMS 1-day adherence (95%–100%), whereas 32% self-reported near-perfect adherence.

Other adherence indices. The following adherence rates were calculated using data from the entire period of MEMS monitoring (median, 165 days; range, 9–325 days). Mean adherence was 54% (median, 48%; interquartile range, 21–89); the correlations between this rate and MEMS 1-day and MEMS 1-week adherence were .87 and .98, respectively ($P < .001$). The mean percentage of days on which ⩾1 dose was taken was 64% (median, 75%; interquartile range, 29%–96%), and the mean percentage of days on which the correct number of doses was taken was 39% (median, 27%; interquartile range, 6–76). The mean percentage of days on which all medication doses were taken within 25% of the correct dosing interval was 26% (median, 14%; interquartile range, 1–42). These rates were highly correlated ($r = .8$; $P = .0001$) with all other MEMS measures.

Medication-specific adherence. Medication-specific adherence rates were calculated from both self-reported and MEMS data. There were no significant differences between medications, nor were there differences between different classes of medications or between medications taken 2 versus 3 times per day. Medications with a higher pill burden were not associated with reduced adherence. Most study subjects (64%) were taking 2 nucleoside reverse-transcriptase inhibitors plus 1 protease inhibitor.

Adherence and virus load. To investigate the relative validity of self-reported and MEMS adherence, we estimated the correlation between each adherence measure and mean ($\log_{10}$) HIV load (table 3). To calculate mean HIV load, we excluded the first 2 load measurements and included the last 5, because

Table 3. Association of HIV load (mean $\log_{10}$ viral load during study period) with self-reported and electronically monitored (MEMS) adherence.

Adherence measure	Correlation with HIV load[a]
Self-report	
One-day self-reported adherence	.43
One-week self-reported adherence	.52
MEMS	
One-day MEMS adherence	.46
One-week MEMS adherence	.55
MEMS adherence, entire study period	.57
MEMS dose interval adherence	
Days with correct no. of doses, %	.60
Days with all doses ⩽25% of correct interval, %	.52
Days with ⩾1 dose, %	.53

[a] $P < .001$ for all correlation coefficients.

a significant minority (15%) of study subjects were antiretroviral naïve prior to this study and experienced precipitous decreases in virus load during its first 2 months. Therefore, our virus load measure was an average of months 2 through 6. As shown, both self-reported and MEMS adherence were highly correlated with virus load ($P < .001$).

We further examined the relationship between HIV load and adherence by calculating the percentage of subjects with a virus load of <500 copies/mL in each quartile of MEMS adherence, using MEMS adherence during the entire study period to define quartiles. These data are presented in figure 1 and demonstrate that 79% of subjects with MEMS adherence of ⩾90% achieved virologic suppression, compared with only 62% of those with 1-week self-reported adherence of ⩾90%. The adjusted odds (adjusted for CD4 count and prior antiretroviral experience) of achieving a virus load of <500 copies/mL was 12.3 (95% CI, 2.8–52.6; $P = .0008$) if MEMS adherence was >90% and 8.2 (95% CI, 2.5–27.0; $P = .0006$) if self-reported adherence was >90%. These estimates were essentially unchanged when the analyses were unadjusted or when they were repeated with use of 1-week or 1-day MEMS adherence or 1-day self-report.

Finally, we constructed a series of multivariate models that included adherence, antiretroviral experience, and CD4 count as predictors and virus load (<500 copies/mL or ⩾500 copies/mL) as the outcome. For 1-day self-report, we found that a 10% increase in adherence was associated with an odds of 1.98 (95% CI, 1.19–3.32; $P = .009$), or an almost 2-fold likelihood, of achieving a virus load of <500 copies/mL. For 1-day MEMS, we found that a 10% increase in adherence was associated with an OR of 1.46 (95% CI, 1.18–1.82; $P = .006$) of achieving a virus load of <500 copies/mL. These estimates were not significantly different when CD4 count and antiretroviral experience were excluded or when we used 1-week estimates.

DISCUSSION

In this observational study of HIV-infected drug users, adherence was stable over time and across medications. Self-reported adherence was higher than MEMS adherence, but a strong relationship was observed between both measures and HIV load. MEMS, however, was found to be a more sensitive measure of clinically significant nonadherence.

We did not observe a significant increase in adherence in the day preceding the research visit, measured by either self-report or MEMS. One-day adherence estimates were comparable to 1-week estimates, and both were predictive of virologic suppression. This is the first study to show that 1-day adherence is correlated both with adherence over time and with concurrent virus load. This suggests that, for some populations, a careful assessment of adherence for the day preceding the visit may provide an efficient and reliable adherence measure.

We found that adherence did not vary during the 6 months of the study. Because most subjects were antiretroviral experienced, this may not reflect the natural history of adherence during antiretroviral initiation. In addition, although our population was characterized by high rates of ongoing drug use, all subjects were receiving comprehensive HIV care, often on site at their methadone clinics. Although our results may therefore not be generalizable to drug users without a usual source of care, they suggest that adherence is stable when drug users have access to treatment for both substance abuse and HIV.

Although we found that adherence was not related to the

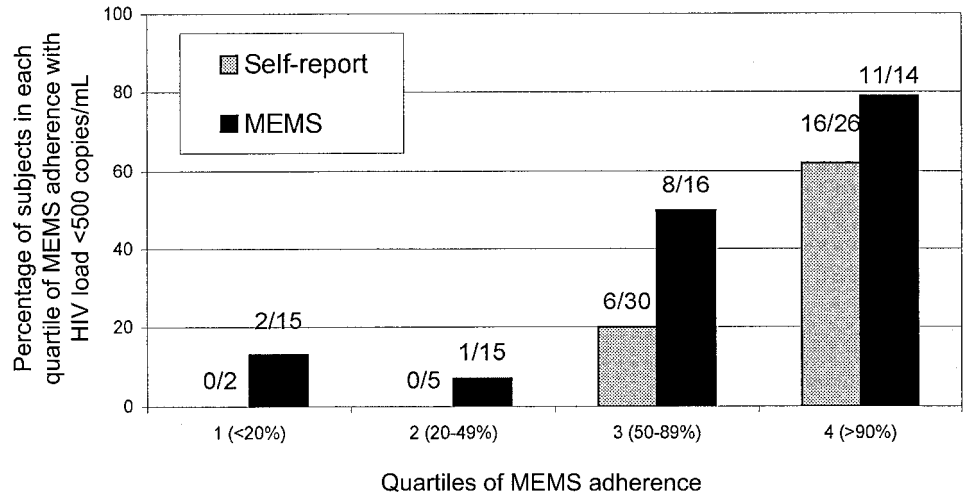

Figure 1. Subjects were categorized by quartile of electronic monitoring (MEMS) adherence: (1) <20%, (2) 20%–49%, (3) 50%–89%, and (4) ⩾90%. Among the 22 subjects with a virus load of <500 copies/mL, the number and percentage in each quartile by both MEMS and self-reported adherence are indicated.

number, class, or dosing frequency of medications, these results must be interpreted with caution. In the present study, medications were not randomly assigned, and the treating physicians may have chosen complex regimens only for patients they deemed "good adherers." In addition, study patients may have accepted prescriptions for complex regimens only if they felt able to adhere. However, among this group of antiretroviral-experienced patients who were engaged in HIV primary care, complex medication regimens were not associated with poor adherence.

As has been found elsewhere, self-reported adherence was higher than MEMS adherence [14–16]. The self-report rates we observed are consistent with the median self-reported adherence rate of 89% found by Bangsberg et al. [6] in a cohort of homeless and marginally housed subjects, and they were somewhat lower than the rates reported in clinical trials [4, 5]. Self-reported adherence was highly correlated with concurrent HIV load (r = .4–.5); these correlations are also similar to that reported by Bangsberg et al. (r = .6) [6]. These data demonstrate that self-report, although it overestimates adherence, is valid and reliable for use in research settings. To our knowledge, no other studies have demonstrated a strong relationship between self-reported adherence and virologic outcomes in drug users.

In contrast to self-report, our estimates of MEMS adherence were lower than were those that others have reported. Bangsberg et al. [6] found median MEMS adherence of 67% after adjustment for "pocket doses" (doses not taken directly from the MEMS bottle). An even higher MEMS adherence rate (82%) was observed in a study by Kastrissios et al. [27] that was nested within an AIDS Clinical Trials Group protocol. We believe that there are 2 reasons for the lower MEMS adherence rates we observed. First, we did not adjust the MEMS data for "pocket doses." Because we observed that the percentage of days on which ⩾1 MEMS dose was taken (mean, 64%; median, 75%) was higher than the percentage of days on which the correct number of doses was taken (mean, 39%; median, 27%), we concluded that subjects removed "pocket doses" on some days when they opened the bottle only once. However, both of these measures were similarly correlated with HIV load (r = .53 and .60, respectively), which indicates that the higher adherence estimate does not more-accurately predict virus load. We believe that the true mean adherence rate is somewhat higher than we found but not higher than 64% (the percentage of days on which ⩾1 dose was taken).

The other reason for the lower MEMS rates we observed is that our study was conducted in a "real world" population with high rates of poverty, unemployment, and active drug use. Despite this, the MEMS adherence rate we observed is comparable to the average adherence of 50% that has been reported in association with many chronic diseases [28]. This suggests that, with appropriate access to care, adherence among drug users is similar to that of other community-based populations.

MEMS adherence was strongly correlated with concurrent virus load. Ours is one of the few studies to date to have examined this relationship, and the correlations we observed are consistent with observations by Paterson et al. (r = .55) [7] and are slightly lower than those reported by Bangsberg et al. (r = .81) [6]. Because MEMS may underestimate adherence and self-report may overestimate adherence, we expect that the true relationship between adherence and virus load is stronger than we observed using either MEMS or self-report. Nonetheless, the likelihood of achieving virologic suppression was greater at high levels of MEMS adherence than it was at high levels of self-reported adherence. For future research, particularly studies of adherence-enhancing interventions, we recommend that MEMS continue to be used to augment self-reported adherence measures.

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