Impact of Active Drug Use on Antiretroviral Therapy Adherence and Viral Suppression in HIV-infected Drug Users

Julia H. Arnsten, MD, MPH, Penelope A. Demas, PhD, Richard W. Grant, MD, Marc N. Gourevitch, MD, MPH, Homayoon Farzadegan, PhD, Andrea A. Howard, MD, Ellie E. Schoenbaum, MD

Despite a burgeoning literature on adherence to HIV therapies, few studies have examined the impact of ongoing drug use on adherence and viral suppression, and none of these have utilized electronic monitors to quantify adherence among drug users. We used 262 electronic monitors to measure adherence with all antiretrovirals in 85 HIV-infected current and former drug users, and found that active cocaine use, female gender, not receiving Social Security benefits, not being married, screening positive for depression, and the tendency to use alcohol or drugs to cope with stress were all significantly associated with poor adherence. The strongest predictor of poor adherence and, in turn, failure to maintain viral suppression, was active cocaine use. Overall adherence among active cocaine users was 27%, compared to 68% among subjects who reported no cocaine use during the 6-month study period. Consequently, 13% of active cocaine users maintained viral suppression, compared to 46% of nonusers. Interventions to improve adherence should focus on reducing cocaine use, developing adaptive coping skills, and identifying and treating depression.

KEY WORDS: **adherence; drug users; antiretroviral therapy; electronic monitors.**
J GEN INTERN MED 2002;17:377–381.

Drug users account for a substantial proportion of AIDS cases in the United States,[1] yet have received disproportionately less benefit from highly active antiretroviral therapy (HAART) than have non–drug users. Several recent reports[2–4] have shown that HAART is underutilized among drug users, and that persons with a history of injection drug use may be less likely to achieve the level of adherence necessary to maintain viral suppression than non–drug users.[5–7] However, few of these studies have examined the impact of ongoing drug use on adherence and viral suppression, and none have utilized electronic monitors to quantify adherence. Because self-report of both adherence and drug use is likely to be influenced by social desirability, the use of an objective measure of adherence is particularly important to avoid differential misclassification of nonadherence.

Our objective was to describe the impact of ongoing illicit drug use on antiretroviral therapy adherence in HIV-infected drug users, using electronic monitors (Medication Event Monitoring Systems [MEMS]; Aprex Corporation, Menlo Park, Calif) to measure adherence. In addition, we determined the impact of active drug use on HIV viral load.

METHODS

Subjects were recruited from the Bronx HIV Epidemiologic Research on Outcomes (HERO) cohort, which began at Montefiore Medical Center's Substance Abuse Treatment Program in 1985, and is comprised of current and former opiate users. HERO cohort members were eligible for the adherence study if they had current prescriptions for combination antiretroviral therapy and were willing to use MEMS caps for each antiretroviral medication. Subjects using other medication dispensing devices, such as pillboxes, were ineligible. MEMS caps fit standard size medication bottles, and record the time and date of each opening as a presumptive dose.

Subjects remained in the adherence study for 6 months, attending research visits at 4-week intervals. At the first visit, the purpose of the MEMS caps was explained, and subjects were assisted with transferring their medications to pill bottles fitted with MEMS caps. They were also instructed to open the MEMS bottles only to withdraw doses at the time of ingestion, not to transfer medications to other containers, and to carry the MEMS bottles with them if they anticipated taking medication while away from home.

At each follow-up visit, adherence data were downloaded using MEMS software (MEMS View, version 161; Aprex Corporation), and blood was drawn for viral load quantification (b-DNA Quantiplex assay [version 3.0; Bayer Diagnostics, Emeryville, Calif]). Sociodemographic and laboratory data were obtained at research visits performed contemporaneously as part of the HERO protocol. Antiretroviral history and selected psychosocial variables were assessed at baseline, and use of drugs and alcohol was assessed at every visit. Subjects received monetary reimbursement for each visit and a

Received from the AIDS Research Program, Department of Epidemiology and Social Medicine (JHA, PAD, RWG, MNG, AAH, EES), the Department of Medicine (JHA, MNG, AAH, EES), and the Division of Substance Abuse, Department of Psychiatry and Behavioral Sciences (JHA, MNG), Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; and the Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health (HF), Baltimore, Md.

Presented in part at the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, Calif, January, 2000, and the 22nd annual meeting of the Society of General Internal Medicine, San Francisco, Calif, May, 2000.

Address correspondence and requests for reprints to Dr. Arnsten: AIDS Research Program, Montefiore Medical Center, 111 East 210 St., Bronx, NY 10467 (e-mail: jarnsten@montefiore.org).

Table 1. Sociodemographic, Behavioral, and Clinical Characteristics of Study Subjects

Variable	*n* (%)
Gender	
Female	34 (40)
Male	51 (60)
Race	
African American	19 (23)
Hispanic	51 (61)
White	11 (13)
Age (median = 42 y)	
≤30 y	4 (5)
31–40 y	29 (34)
41–50 y	38 (46)
>50 y	13 (15)
Marital status	
Married	31 (37)
Separated, divorced, or single	53 (63)
Unemployed	76 (91)
Housing	
Living in own apartment	70 (83)
Living in others' apartment	6 (7)
Hotel, shelter, or other temporary housing	8 (10)
Insurance	
Medicaid	82 (98)
Medicare	8 (10)
Benefits	
Social Security	61 (73)
Food stamps	62 (74)
Welfare	10 (12)
Methadone maintenance	81 (95)
Active drug use during study period	
Heroin	21 (25)
Cocaine (including crack)	24 (28)
Heroin or cocaine	32 (38)
Average alcohol use during study period	
None	49 (58)
0–1 drinks/wk	14 (16)
2–5 drinks/wk	12 (14)
>5 drinks/wk	10 (12)
Depression (CESD ≥16)	43 (51)
Alcohol/drug coping style*	26 (31)
Number of antiretroviral therapy drugs in current regimen†	
Two	9 (11)
Three	70 (82)
Four	4 (5)
Type of antiretroviral therapy drugs in current regimen	
Protease inhibitor	59 (69)
Nucleoside reverse transcriptase inhibitor	81 (95)
Non-nucleoside reverse transcriptase inhibitor	16 (19)
Length of time with known HIV infection (median = 7.9 years)	
< 3 y	13 (17)
3–5 y	9 (12)
5.1–8 y	17 (22)
8.1–11 y	23 (29)
>11 y	16 (21)
Median baseline CD4 count (cells/mm^3)‡	322
Baseline CD4 count (cells/mm^3)‡	
<50	8 (10)
50–200	18 (22)
201–500	36 (45)
>500	19 (23)
Mean HIV RNA (copies/mL)§	
<50	14 (19)
50–500	17 (22)
10,001–50,000	13 (17)
>50,000	10 (13)

* *Alcohol or drug coping style: When under stress or dealing with an upsetting problem, subject reported that "I use alcohol or drugs to help me get through it," or "I use alcohol or drugs to make myself feel better."*[8]

† *Combivir counted as two drugs.*

‡ *CD4 counts available for 81 subjects.*

§ *Mean HIV RNA available for 75 subjects.*

cash incentive for returning the MEMS caps at study end.

All data downloaded from the MEMS caps were exported into the SAS system (SAS Proprietary Software, Release 6.11; SAS Institute Inc., Cary NC). The period of analysis was defined as beginning at 2:00 AM on the day after the baseline interview, and ending at 2:00 AM on the day of the sixth follow-up interview (or final interview if the subject withdrew). Data were combined for subjects who were given replacement caps for the same medication, and excluded for subjects who did not use MEMS caps for defined periods of time (e.g., while hospitalized or incarcerated).

An overall mean adherence rate for each study subject was calculated by averaging the adherence rate for each medication. The adherence rate for each medication was calculated by dividing the number of MEMS cap openings by the number of doses prescribed during the entire period of MEMS cap use. In addition, dose interval adherence was estimated by calculating the percent of days on which at least 1 dose was taken, the percent of days on which the correct number of doses was taken, and the percent of days on which all medication doses were taken within 25% of the correct dosing interval (e.g., within 9 to 15 hours of the previous dose for a twice-per-day medication).

For each of the adherence indices described above, adherence was analyzed as a continuous variable. HIV viral load determinations were performed at each visit and, because a significant minority (15%) of study subjects were antiretroviral naïve and experienced precipitous decreases in viral load during the study's first 2 months, mean HIV viral load (log-transformed) was calculated by excluding the first 2 viral load measurements and including the last 5. Associations between continuous variables were assessed by Spearman correlation coefficients, associations of drug use behaviors and other categorical variables with adherence were assessed using the Kruskal-Wallis test, and associations of categorical variables with viral suppression were assessed using Fisher's exact test. Multivariate linear regression analysis using a stepwise selection procedure was performed to determine the best predictive model for adherence, and stepwise logistic regression was used to determine the best predictive model for viral suppression; both regression procedures used a P value of .15 for model entry.

RESULTS

Between July 1998 and April 2000, 85 HERO cohort members were enrolled in the adherence study. Two hundred sixty-two MEMS caps were dispensed, and data were analyzed from 213 MEMS caps (81%). Reasons that MEMS cap data could not be analyzed included: cap malfunction (n = 11), improper use (n = 11), withdrawal before data downloaded (n = 17), medications discontinued before baseline (n = 4), and caps lost (n = 6). Eight subjects did not contribute any MEMS data because they did not

return (n = 5) or lost their MEMS caps (n = 3) after the first interview. The median length of follow-up was 157 days (interquartile range, 83 to 175 days), and 475 HIV viral load measurements were obtained.

Mean overall adherence was 53% (median, 51%; interquartile range, 25% to 87%). The mean percent of days on which at least 1 dose was taken was 64% (median, 73%; interquartile range, 31% to 94%), and the mean percent of days on which the correct number of doses was taken was 38% (median, 29%; interquartile range, 8% to 68%). The mean percent of days on which all medication doses were taken within 25% of the correct dosing interval was 23% (median, 14%; interquartile range, 1% to 37%). All of these adherence rates were highly correlated ($r \geq .9$; $P = .0001$); further analyses were therefore performed using only the mean overall adherence rate.

Sociodemographic, behavioral, and clinical characteristics are listed in Table 1. Forty percent of subjects reported active drug use (smoking, snorting, or injecting heroin or cocaine) during the study period. Among cocaine users, 83% (n = 20) used crack and 17% (n = 4) used only other forms of cocaine. Subjects were heavily antiretroviral experienced; only 15% were antiretroviral naïve, and the remainder had taken a mean of 2.7 (range, 1 to 10) antiretrovirals prior to their current regimen.

Thirty-one subjects (37%) maintained a mean viral load less than 500 copies/mL during the 6 months of the study. Mean viral load (log-transformed) was significantly correlated with overall adherence ($r = -.55$; $P = .0001$). As shown in Table 2, active cocaine use and the tendency to use alcohol or drugs to cope with stress were significantly associated with poorer mean overall adherence and with failure to achieve viral suppression. Female gender, being unmarried, and not receiving Social Security were also significantly associated with worse adherence. In multivariate analysis, the best predictive model for adherence included only active cocaine use ($\beta = -18.7$; $P = .02$) and an interaction term representing gender and depression ($\beta = -8.5$; $P = .05$). This interaction term indicated that women who screened positive for depression had poorer adherence than women with a negative depression screen, but the association between depression and adherence was

Table 2. Drug Use and Other Behavioral, Sociodemographic, and Clinical Factors Associated with Adherence and Viral Suppression

Variable	n*	Median adherence, %	P Value	With Viral Suppression, n (%)	P Value
Active cocaine use					
Yes	20	27	.005	3 (13)	.005
No	57	68		28 (46)	
Active heroin use					
Yes	20	40	.1	6 (29)	NS
No	57	62		25 (39)	
Alcohol use several times/wk or every day					
Yes	16	37	.09	4 (21)	.1
No	61	62		27 (41)	
Depressed (CESD ≥16)					
Yes	38	44	.09	13 (30)	NS
No	39	62		18 (43)	
Alcohol or drug coping style†					
Yes	22	28	.01	5 (19)	.03
No	55	68		26 (44)	
Marital status					
Unmarried	48	45	.05	17 (32)	NS
Married	28	72		14 (45)	
Receiving Social Security					
Yes	56	63	.01	24 (39)	NS
No	21	26		7 (29)	
Gender					
Female	32	41	.04	8 (24)	.07
Male	45	70		23 (45)	
Antiretroviral experience (past and current)					
>4 drugs	39	53	NS	15 (34)	NS
≤4 drugs	38	53		16 (39)	
CD4 count‡					
High	37	55	NS	17 (42)	NS
Low	38	52		13 (33)	

* n <85 due to incomplete Medication Event Monitoring Systems (MEMS) data.

† *Alcohol or drug coping style: When under stress or dealing with an upsetting problem, subject reported that "I use alcohol or drugs to help me get through it," or "I use alcohol or drugs to make myself feel better."*[8]

‡ *CD4 count dichotomized at the median for this analysis.*

NS, nonsignificant.

not observed in men. The best predictive model for achieving viral suppression included no active cocaine use (odds ratio [OR], 6.3; $P = .005$), male gender (OR, 3.4; $P = .04$), and less antiretroviral experience (OR, 0.7 for each additional medication; $P = .03$).

DISCUSSION

The strongest predictor of electronically monitored (MEMS) adherence in this population of HIV-infected current and former drug users was active cocaine use. Because previous studies of adherence to HAART have either failed to differentiate between active and former drug users,[9,10] or have not examined the relationship between adherence and ongoing use of specific illicit drugs,[6,7,11,12] ours is the first to quantify the impact of active cocaine use on adherence. Active cocaine use was associated with a 41% decline in median adherence, and was therefore also a strong predictor of failure to maintain viral suppression. Although median adherence was lower among active heroin users, this was not statistically significant. Less-frequent administration of heroin than cocaine, and its different behavioral sequelae, may account for the difference in impact of these drugs. Because other drug use, including methamphetamine use, was rare (<5%) in this study population, we were unable to examine its impact on adherence.

We further found that the tendency to use alcohol or drugs to cope with stress was associated with both poor adherence and detectable viral load. The questions we used to assess coping style (see footnote,Table 1) may be easily adopted in clinical practice, and provide the prescribing clinician with a means of both assessing and intervening with drug use behaviors. On the basis of our data, persons who report that they use alcohol or drugs to cope with stress are at particular risk for nonadherence, and should be counseled about alternative coping strategies.

Previous studies[13,14] have suggested that adherence is worse among HIV-infected women than men, although it remains unclear why this is so. In our study, this relationship appeared to be mediated by depression, with women who screened positive for depression being the least adherent. This was true despite a very high overall prevalence (51%) of depression, and supports other findings[15,16] that suggest that identifying and treating depression in HIV-infected women and drug users might substantially improve adherence.

We found that electronically monitored adherence in drug users is low (median, 51%), but that adherence among drug users who are not actively using cocaine (median, 68%) is similar to that found in previous MEMS adherence studies conducted in diverse populations.[17,18] The lower adherence rates we obtained using MEMS are consistent with studies that have compared electronic monitoring to other measures of adherence in both HIV infection[17,19,20] and other disease states, and are particularly robust because they represent adherence with all antiretrovirals. The sensitivity of the MEMS device for detecting nonadherence allowed us to identify patient-specific characteristics, including active cocaine use, depression, and the tendency to use drugs or alcohol to cope with stress, that may be amenable to adherence-enhancing interventions.

This study was funded by the National Institute on Drug Abuse (R01-DA11869, R01-DA104347), and by a Robert Wood Johnson Generalist Physician Faculty Scholar Award to Dr. Arnsten.

REFERENCES

1. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report 2000;12(2).
2. Celentano DD, Galai N, Sethi AK, et al. Time to initiating antiretroviral therapy among HIV-infected drug users. AIDS. 2001;15:1707–15.
3. Shapiro MF, Morton SC, McCaffrey DF, et al. Variations in the care of HIV-infected adults in the United States: results from the HIV cost and services utilization study. JAMA. 1999;281: 2305–15.
4. Strathdee SA, Palepu A, Cornelisse PG, et al. Barriers to use of free antiretroviral therapy in injection drug users. JAMA. 1998;280: 547–9.
5. Lucas GM, Cheever LW, Chaisson RE, Moore RD. Detrimental effects of continued illicit drug use on the treatment of HIV infection. J Acquir Immune Defic Syndr. 2001;27:251–9.
6. Haubrich RH, Little S, Currier JS, Forthal DN, Kemper C. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. AIDS. 1999;13: 1099–107.
7. Gifford AL, Bormann JE, Shively MJ, Wright BC, Richman DD, Bozzette SA. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. J Acquir Immune Defic Syndr. 2000;23:386–95.
8. Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: A theoretically based approach. J Pers Soc Psychchol. 1989;56: 267–83.
9. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. Clin Infect Dis. 1999;29:824–30.
10. Gordillo V, del Amo J, Soriano V, Gonzalez-Lahoz H. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. AIDS. 1999;13:1763–9.
11. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. AIDS Care. 2000;12:255–66.
12. Stein MD, Rich JD, Maksad J, et al. Adherence to antiretroviral therapy among HIV-infected methadone patients: effect of ongoing illicit drug use. Am J Drug Alcohol Abuse. 2000;26:195–205.
13. Johnston Roberts K, Mann T. Barriers to antiretroviral medication adherence in HIV-infected women. AIDS Care. 2000;12: 377–86.
14. Turner BJ, Newschaffer CJ, Zhang D, Cosler L, Hauck WW. Antiretroviral use and pharmacy-based measurement of adherence in postpartum HIV-infected women. Med Care. 2000;38: 911–25.
15. Moore J, Schuman P, Schoenbaum EE, Boland B, Solomon L, Smith DK. Severe adverse life events and depressive symptoms among women with, or at risk for, HIV infection in four cities in the United States of America. AIDS. 1999;13:2459–68.
16. Avants SK, Margolin A, Warburton LA, Hawkins KA, Shi J. Predictors of nonadherence to HIV-related medication regimens during methadone stabilization. Am J Addict. 2001;10:69–78.

17. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS. 2000;14:357–66.
18. Kastrissios H, Suarez JR, Katzenstein D, Girard P, Sheiner LB, Blaschke TF. Characterizing patterns of drug-taking behavior with a multiple drug regimen in an AIDS clinical trial. AIDS. 1998;12: 2295–303.
19. Liu H, Golin C, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med. 2001;134:968–77.
20. McNabb J, Ross JW, Abriola K, Turley C, Nightingale CH, Nicolau DP. Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city HIV clinic. Clin Infect Dis. 2001; 33:700–5.