Gender Differences in Factors Associated with Adherence to Antiretroviral Therapy

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OBJECTIVE: To identify gender differences in social and behavioral factors associated with antiretroviral adherence.

DESIGN: Prospective cohort study.

SETTING: Methadone maintenance program.

PARTICIPANTS: One hundred thirteen HIV-seropositive current or former opioid users.

MEASUREMENTS AND MAIN RESULTS: Participants were surveyed at baseline about social and behavioral characteristics and at monthly research visits about drug and alcohol use and medication side effects. Electronic monitors (MEMS) were used to measure antiretroviral adherence. Median adherence among women was 27% lower than among men (46% vs. 73%; $P < .05$). In gender-stratified multivariate models, factors associated with worse adherence in men included not belonging to an HIV support group ($P < .0001$), crack/cocaine use ($P < .005$), and medication side effects ($P = .01$). Among women, alcohol use ($P = .005$), heroin use ($P < .05$), and significant medication side effects ($P < .005$) were independently associated with worse adherence. In a model including both men and women, worse adherence was associated with lack of long-term housing ($P < .005$), not belonging to any HIV support groups ($P < .0005$), crack or cocaine use ($P < .01$), and medication side effects ($P < .0005$). In addition, worse adherence was associated with the interaction between female gender and alcohol use ($P \leq .05$).

CONCLUSIONS: In this cohort of current and former opioid users, gender-stratified analysis demonstrated that different social and behavioral factors are associated with adherence in men and women. Among both men and women, worse adherence was associated with lack of long-term housing, not belonging to an HIV support group, crack/cocaine use, and medication side effects. Among women only, alcohol use was associated with worse adherence.

KEY WORDS: adherence; gender; alcohol; antiretroviral therapy; electronic monitors.

J GEN INTERN MED 2004;19:1111-1117.

In the past decade, advances in highly active antiretroviral therapy (HAART) have significantly decreased HIV-associated morbidity and mortality. However, to achieve

the clinical and survival benefits of HAART, patients must be highly adherent to complex medication regimens.¹⁻³ Though few factors have been consistently associated with adherence, interventions to improve antiretroviral adherence are already being implemented in clinical settings. Identifying correlates of suboptimal adherence is critical for appropriate clinical decision making and effective targeting of interventions.

In the growing literature on factors associated with antiretroviral adherence, a consistent relationship between gender and adherence has not been found. While several studies have failed to show a significant association between gender and antiretroviral adherence,⁴⁻¹³ four published studies¹⁴⁻¹⁷ and five preliminary studies¹⁸⁻²² have shown that women are less adherent than men. Most studies that found no association between gender and adherence were limited either by small numbers of women or by the use of self-report, which has been shown to overestimate adherence.⁶ Another possible explanation for inconsistency in the relationship between gender and adherence is that this relationship may have been confounded by unexamined social or behavioral factors.

Active drug and alcohol use has been found to be associated with worse adherence in several studies.^{5,7,10,11,23-29} However, it is unknown whether the active use of specific illicit drugs or alcohol affects antiretroviral adherence differently in men and women. Social factors have also been correlated with adherence in prior quantitative and qualitative studies,^{6,30-34} but whether differences in social characteristics between men and women explain the observed relationship between gender and antiretroviral adherence is also unknown.

We therefore sought to investigate whether social and behavioral factors, including active drug or alcohol use, are differentially associated with antiretroviral adherence in men and women in the same cohort. Using an objective measure of adherence and a study population that is almost half women, we examined the role of social and behavioral factors as potential confounders in the relationship between gender and adherence.

METHODS

Study Population

Participants were recruited from the HIV Epidemiologic Research on Outcomes (HERO) study, a longstanding cohort composed of current or former opioid users that began in 1985 at Montefiore Medical Center's Substance Abuse Treatment Program in the Bronx, New York. Subject recruitment and study design for the original cohort have

Received from the Division of Substance Abuse (KMB, MNG, JHA), Department of Psychiatry and Behavioral Sciences, Department of Medicine (KMB, AAH, EES, MNG, JHA), and AIDS Research Program (PAD, AAH, EES, MNG, JHA), Department of Epidemiology and Population Health, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

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been described elsewhere.³⁵ Eligibility criteria for this study included 1) having current prescriptions for HAART, and 2) being willing to use electronic monitors to measure adherence. Cognitive impairment or the use of alternative pill containers, such as pill boxes, rendered subjects ineligible.

Study Design

For this prospective cohort study, subjects attended a baseline visit and then returned for 6 research visits at 4-week intervals for a total of 7 visits. Participation was voluntary and subjects were reimbursed \$20 for each follow-up visit. The study was approved by the Montefiore Medical Center Institutional Review Board; all participants gave written informed consent.

Assessment of Adherence

The main outcome variable was adherence, which was measured using electronic monitors (medication event monitoring systems [MEMS], Aprex Corporation, Menlo Park, Calif). MEMS caps record the date and time of each pill bottle opening as a presumptive dose. At the baseline visit, research assistants helped participants transfer all of their antiretroviral medications to pill bottles with MEMS caps, and demonstrated their correct use. Details concerning the use of MEMS caps for this cohort have been published previously.³⁶

For each subject, an adherence rate for each medication was calculated by dividing the number of actual MEMS cap openings by the number of prescribed doses during the study period. We then computed an overall average adherence rate for all of the medications in the antiretroviral regimen. This overall adherence rate has been shown to be highly correlated with HIV viral load.³⁶ Because it is unclear what level of adherence is necessary to achieve favorable clinical outcomes, we analyzed adherence as a continuous variable.³⁷

Assessment of Independent Variables

Independent variables included demographic characteristics, housing status, size and composition of social network, depression, active drug and alcohol use, duration of HIV infection, and medication side effects. Assessment was by interviewer-administered survey. Drug and alcohol use and medication side effects were assessed monthly, and all other characteristics were assessed at baseline.

Demographic Characteristics. Participants were asked to report their age, race/ethnicity, marital status, employment status, receipt of public benefits, and history of incarceration.

Housing Status. Housing assessment included type of residence, number of rooms, duration at current residence, and number of cohabitants. "Long-term housing" was defined based on median duration of current residence;

a participant was considered to have "long-term housing" if they had lived in their current residence for more than 3 years.

Social Network. Elements of each participant's social network were assessed using a 62-item scale that was adapted to include HIV-specific factors, such as disclosure of HIV status.³⁸ Social network was defined as the participant's spouse or main partner, parents, in-laws, close relatives, and close friends. The scale assessed number of individuals in the network, frequency of contact, disclosure of HIV status to network members, and membership in church or HIV support groups.

Depression. Depression was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), in which respondents rate how often during the past week they have experienced each of 20 distinct feelings on a 4-point scale, ranging from "less than 1 day" to "most or all days."³⁹ The CES-D has been used to identify depression in several populations,⁴⁰ including both drug users and HIV-infected patients.⁴¹⁻⁴⁵ The final score ranges from 0 to 60 and is derived by calculating the sum of the 20 individual items. The most commonly used cut-point for depression is a score of 16 or higher. However, because the somatic symptoms of depression commonly overlap with symptoms of HIV disease, we analyzed the CES-D after dropping 5 items that reflect somatic symptoms: poor appetite, lack of energy, restless sleep, fatigue, and difficulty concentrating. The CES-D has previously been altered in this way for use in HIV populations.^{41,44,45} For the modified CES-D, we maintained the cut-point for depression of greater than or equal to 16.

Drug and Alcohol Use. We defined "active heroin use" and "active crack or cocaine use" as the use of the drug by any route at any time during the 6-month study period. Our definition of problem alcohol use combined binge drinking with a measure of frequency, and included 1) drinking at least 5 drinks on one occasion, or 2) drinking frequently ("several days per week" or "every day") at any time during the study period.

Medication Side Effects. Participants reported whether they had experienced any medication side effects (including nausea, vomiting, stomach cramps, diarrhea, headaches, muscle aches, general fatigue, dizziness, insomnia, burning or numbness in hands or feet, memory problems, depression, fat redistribution, rashes, fevers, abnormal lab tests, kidney stones, pancreatitis, or hepatitis) in the past month. Because side effects were extremely common, we defined "significant" medication side effects as 2 or more side effects in our analysis.

Statistical Analysis

Rates of adherence are reported as median percentages with interquartile ranges (IQR). Bivariate analyses were

performed to investigate the association between adherence and other factors. Because adherence was not normally distributed and could not be transformed to normality, associations with adherence were measured using the Mann-Whitney U test for categorical variables and Spearman rank correlation coefficient for continuous variables.

We performed multivariate linear regression to examine the independent association of social and behavioral factors with antiretroviral adherence. First, potential interaction effects were identified by deriving separate regression models for men and women. Factors that were significant in these models were tested as interaction terms with gender in the final model, which included both men and women. Because of our relatively small sample size, in addition to gender, we included in the final model only variables that were significant at $P < .05$ or were of clinical interest, and were not highly correlated. Nonsignificant variables were then removed one by one until the best model was achieved. Because depression has been found to be strongly associated with adherence, we controlled for depression in all of our multivariate analyses. Data management and analyses were performed using the Statistical Package for Social Services version 10.1 (SPSS Inc., Chicago, Ill). All statistical tests were two-sided.

RESULTS

From July 1998 to September 2001, we recruited 113 participants. The median length of follow-up was 180 days (IQR 150 to 180). Seventy-four percent of subjects completed 6 months of follow-up. The overall median adherence rate with all antiretrovirals was 62% for the 6-month period (IQR 26% to 87%).

Baseline Characteristics

Social and Demographic Characteristics. The majority of the study population was male, Hispanic, and between the ages of 30 and 50 (Table 1). These demographic characteristics are similar to those of the population of persons living with AIDS in the Bronx.⁴⁶ By several criteria, this opioid-dependent population was stable. Almost half the population was married or living with a spouse. Secure housing was common; the majority of participants (81%) lived in their own apartments, and 45% had lived at their current residence for longer than 3 years. Temporary housing was very rare (4%) and few participants had been in prison or jail in the prior 6 months (9%). However, despite these measures of stability, the vast majority was unemployed (86%) and received some form of public assistance (97%). In addition, of the 61 participants with minor children, only 21 (34%) had any of their minor children living with them.

Social Network. The median total network size, defined as spouse or main partner plus the number of living parents,

Table 1. Social and Behavioral Characteristics of the Study Population (N = 113)

	n (%)
Gender	
Women	49 (43)
Men	64 (57)
Mean age, y	44 ± 7
Race	
Hispanic	74 (66)
African American	25 (22)
White	13 (12)
Marital status	
Married/living with spouse	49 (43)
Separated/divorced	13 (12)
Widowed	16 (14)
Single	33 (29)
Housing status	
Living in own apartment	91 (81)
Living in other apartment	15 (14)
Temporary housing*	4 (4)
Drug use	
Ever used injection drugs	93 (82)
Partner ever used injection drugs	27 (24)
Current crack or cocaine use	31 (27)
Current heroin use	27 (24)
Problem alcohol use	34 (30)
CD4 count, cells/mm ³	
<50	9 (8)
50 to 199	26 (23)
200 to 500	46 (40)
>500	30 (26)
Baseline viral load, copies/ml	
≤50	40 (35)
51 to 400	23 (20)
401 to 20,000	31 (27)
>20,000	17 (15)

* Temporary housing defined as living in a hotel, motel, shelter, temporarily with someone, or being without shelter.

in-laws, close relatives, and close friends, was 5 (IQR 4 to 9). Eighty-two percent of network members were identified as frequent contacts ("see or talk to on the phone at least once every 2 weeks"), and participants reported disclosing their HIV status to 88% of friends and 83% of relatives. Twenty-seven percent belonged to an HIV support group, and 33% belonged to a church group.

Depression. A substantial minority of the population (35%) was depressed at the baseline evaluation using the modified CES-D.

Drug and Alcohol Use. Rates of crack or cocaine use (27%) and heroin use (24%) were similar. Problem alcohol use was reported by 30%.

HIV Duration and Medication Side Effects. The median duration of HIV disease was 8 years (IQR 4 to 10). Sixty-three percent of participants had experienced significant medication side effects during the study period.

Gender Differences. Women were less adherent to HAART than men, with a median adherence rate of 46% (IQR 18% to 77%) compared to 73% (IQR 30% to 93%) ($P = .04$). Fewer women than men reported working more than 20 hours per week (4% vs. 22%; $P = .007$). Though women and men reported similar rates of active heroin and crack or cocaine use, fewer women had ever used injection drugs (71% vs. 92%; $P = .008$). While women tended to have fewer close friends than men (median 1 vs. 3; $P = \text{NS}$), women disclosed their HIV status to their friends more often than men (97% vs. 81%; $P = .003$). There were no gender differences in the total number of children, number of minor children, or number of children living in the household. The prevalence of depression was not significantly different in men and women.

Associations with Adherence

Bivariate Analysis of Combined Population. In addition to male gender, better antiretroviral adherence was associated with long-term housing (75% vs. 42%; $P = .003$), living with a partner (73% vs. 46%; $P = .04$), and belonging to an HIV support group (84% vs. 54%; $P = .006$).

Worse adherence was associated with having experienced 2 or more HIV medication side effects (45% vs. 81%; $P = .009$), active crack or cocaine use (29% vs. 72%; $P = .005$), and active heroin use (40% vs. 70%; $P = .04$). Participants with problem alcohol use had a median adherence 29% lower than those without problem alcohol use (40% vs. 69%). However, this bivariate association with problem alcohol use was not statistically significant ($P = .07$).

Adherence was not associated with depression or with the following demographic and social characteristics: age, race/ethnicity, employment, receipt of public benefits, history of incarceration, or marital status.

Gender-stratified Multivariate Analysis. Table 2 shows the results of gender-stratified multivariate models. Factors

Table 2. Multivariate Adjusted Analysis: Factors Associated with Antiretroviral Adherence

Factor	Beta	(95% CI)	P Value
Men			
HIV support group	38.4	(20.2 to 56.5)	<.0005
Active crack or cocaine use	-29.1	(-47.1 to -11.1)	.002
Significant medication side effects	-20.5	(-36.7 to -4.3)	.014
Depression	13.6	(-3.8 to 31.1)	.12
Women			
Problem alcohol use	-27.3	(-44.7 to -9.8)	.003
Active heroin use	-18.2	(-35 to -1.3)	.04
Significant medication side effects	-28.6	(-46.4 to -10.9)	.002
Depression	1.2	(-14.3 to 16.8)	.16

All variables coded as yes = 1, no = 0.
CI, confidence interval.

Table 3. Multivariate Adjusted Analysis: Factors Associated with Antiretroviral Adherence in Men and Women

Factor	Beta	(95% CI)	P Value
Long-term housing*	16	(5.3 to 26.7)	.004
HIV support group*	25.2	(12.3 to 38.2)	<.0005
Active crack or cocaine use*	-18.3	(-31.2 to -5.4)	.006
Significant medication side effects*	-22.5	(-34.2 to -10.9)	<.0005
Gender $\times$ problem alcohol use	-23.9	(-47.3 to -0.5)	.046
Problem alcohol use*	0.50	(7.8 to 0.01)	.95
Gender (M = 0, F = 1)	-1.47	(6.45 to -0.023)	.82
Depression*	4.05	(5.82 to 0.06)	.49

* Variables coded as yes = 1, no = 0.

CI, confidence interval.

independently associated with worse adherence in men included not belonging to an HIV support group, active crack or cocaine use, and significant medication side effects. For women, factors independently associated with worse adherence included problem alcohol use, active heroin use, and significant medication side effects.

Multivariate Analysis of Combined Population. The best model for adherence for the entire study population is shown in Table 3. Factors associated with worse adherence included lack of long-term housing, not belonging to an HIV support group, active crack or cocaine use, and significant medication side effects. In addition, the interaction between female gender and problem alcohol use was significantly associated with worse adherence. The interaction term indicates that the association between problem alcohol use and adherence is different for men and women. Because multivariate linear regression is based on mean differences, in Figure 1 mean adherence is used to illustrate this relationship graphically. As shown, problem alcohol use had no impact on adherence for men (mean adherence 61% for both groups), but a significant negative impact on adherence for women (mean adherence 57% for women without problem drinking vs. 25% for women with problem drinking; $P = .003$).

DISCUSSION

In this population of current and former opioid users, different social and behavioral factors were associated with antiretroviral adherence in men and women. Our gender-stratified multivariate analysis demonstrates that worse adherence for women was associated with problem alcohol use and active heroin use. In contrast, for men, not belonging to an HIV support group and active crack or cocaine use were associated with worse adherence. In both men and women, there was an independent association between significant medication side effects and worse adherence. The disparity in these models suggests that the complex

FIGURE 1. Interaction between Gender and Problem Alcohol Use.

behavioral processes that determine adherence and drug use in women may be different than that in men. Importantly, potential gender differences may be obscured by combined analysis. Our results indicate that future adherence research would be informed and strengthened by gender-stratified analysis. If consistent gender differences are found in future studies, it will suggest that adherence-improving interventions should be gender specific.

In the best multivariate model for the combined population, worse antiretroviral adherence was associated with a lack of long-term housing, not belonging to an HIV support group, active crack or cocaine use, and significant medication side effects. Among women only, problem alcohol use was associated with worse adherence. Female gender was not independently associated with worse adherence in the best final multivariate model. This finding is consistent with several other studies that also found a bivariate, but not multivariate, association between gender and adherence. A new finding from this study is that women with problem alcohol use are less adherent than men with problem alcohol use.

Prior research, including two studies in women only,^{23,31} supports the inverse association between alcohol use and adherence.^{5,10,12,26,28,47-49} Research on gender differences in alcohol use disorders has suggested that the physical, psychological, and social effects of alcohol are different in women and men.⁵⁰⁻⁵⁵ Our results suggest that alcohol use may disproportionately impact antiretroviral adherence in women. This may be because women with problem alcohol use have greater psychiatric comorbidity than men, because the social consequences of alcohol use are more profound for women than for men, or because women who drink alcohol experience more social stigma and a greater need for secrecy. Because alcohol use in women is underdiagnosed, in part because of the lower sensitivity in women of common screening tools such as the CAGE questions,^{56,57} the potential impact of alcohol use on adherence may be underappreciated.

For men, active crack or cocaine use was strongly associated with poor adherence. In the majority of the literature

on drug use and antiretroviral adherence, drug use is defined as the use of any illicit drug. Our results are consistent with the few studies that have examined drugs of abuse separately.^{47,58} Adherence-improving interventions should place particular emphasis on addressing crack and cocaine use. Additionally, in contrast to previous studies, we found that active heroin use among women only was associated with worse adherence. Prior studies of methadone-maintained patients have found gender differences in reasons for initial heroin use and social context of ongoing use.⁵⁹⁻⁶¹ Further examination of gender differences in patterns and context of heroin use may be helpful in better understanding our finding that heroin use has a greater effect on adherence in women than it does in men.

In the final model including both men and women, better adherence was associated with long-term housing, defined as having lived in the current residence for more than 3 years. Considerable research has found that temporary housing and homelessness have a negative impact on treatment adherence, but less is known about the impact of long-term housing stability.^{9,16,29,62} While half of our participants had long-term, stable housing, many current and former drug users struggle with temporary housing and homelessness. In New York City, the Division of AIDS Services and Income Support, which is part of the Department of Welfare, provides housing in single-room occupancy (SRO) hotels for all homeless persons with AIDS. Although long-term placements are possible, the majority of hotel placements are 28 days. Ours is one of the few studies to demonstrate an adherence benefit of long-term housing. Further research on the impact of short-term versus long-term placements in SRO hotels is needed to inform policy changes that could potentially improve health outcomes among HIV-infected homeless persons.

We found the association between adherence and membership in an HIV support group to be strong, particularly in men. However, this association may represent confounding rather than causation; an unmeasured variable may be motivating patients to both attend HIV groups and adhere to their antiretroviral regimens. Nonetheless, as HIV support groups are a relatively simple intervention to implement, prospective research is needed to evaluate the adherence impact of participating in such groups. Consistent with many other studies, we also found that the experience of medication side effects is associated with worse adherence.^{8,63-65} Lastly, the finding that depression was not significantly associated with worse adherence is unusual and was most likely due to limited statistical power.

There are several limitations to our study. First, our definition of problem alcohol use was the same for men and women. If using a single definition combined men with less severe alcohol problems and women with more severe alcohol problems, then differential misclassification may have contributed to the observed difference in antiretroviral adherence seen between men and women. Because the overall adherence rate in this cohort is comparable to or

lower than those reported in other cohorts that also use electronic monitors to measure antiretroviral adherence, we do not feel that there was significant selection bias toward more adherent subjects. Last, these results may not be generalizable to a nonopioid-dependent HIV-infected population.

Despite these limitations, our study is strengthened by the high proportion of women in our sample, and by our use of electronic monitors, which are considered the most objective measure of adherence. Last, adjusting for potentially confounding variables, including depression, reduces bias and supports our results.

In this cohort of current and former drug users, gender-stratified multivariate models demonstrated that different drug use and social characteristics are associated with adherence in men and women. Our results suggest that in future studies, investigators should examine drugs of abuse individually. Furthermore, adherence research would be informed by gender-stratified analysis. Alcohol use among women may have a particularly harmful impact on adherence and should be screened for and addressed. Last, interventions to improve adherence should focus on managing medication side effects, helping to secure long-term housing, providing HIV support groups, decreasing active crack or cocaine use, and among women, addressing problem alcohol use.

This study was supported by NIH R01 DA11869 (NIDA, PI: J. Arnsten). Dr. Berg was funded by NIH R25 DA14551 (NIDA, PI: J. Arnsten). Dr. Arnsten was also supported by a Robert Wood Johnson Generalist Physician Faculty Scholar Award.

We would like to thank Megha Ramaswamy for her generous assistance with the manuscript. The authors would also like to thank Richard Grant, MD, MPH, Donna Buono, MS, Randy Teeter, Yungtai Lo, PhD, Megha Ramaswamy, MPH, and the faculty and staff of the Clinical Research Training Program at the Albert Einstein College of Medicine.

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