Relationship of Gender, Depression, and Health Care Delivery with Antiretroviral Adherence in HIV-infected Drug Users

Barbara J. Turner, MD, MSEd, Christine Laine, MD, MPH, Leon Cosler, PhD, RP, Walter W. Hauck, PhD

BACKGROUND: Antiretroviral adherence is worse in women than in men, and depression can influence medication adherence.

OBJECTIVE: To evaluate the relationship of gender, depression, medical care, and mental health care to adherence in HIV-infected drug users.

DESIGN: Retrospective cohort study.

SETTING: New York State Medicaid program.

PARTICIPANTS: One thousand eight hundred twenty-seven female and 3,246 male drug users on combination antiretroviral therapy for more than 2 months in 1997.

MAIN MEASURES: A pharmacy-based measure of adherence was defined as ≥95% days covered by at least 2 prescribed antiretroviral drugs. Independent variables were: depression, regular drug treatment (≥6 months), regular medical care (2+ and >35% of visits), HIV-focused care (2+ visits), psychiatric care (2+ visits), and antidepressant therapy.

RESULTS: Women were less adherent than men (18% vs 25%, respectively, $P < .001$) and more likely to be diagnosed with depression (34% vs 29%). In persons with depression, the adjusted odds ratio (AOR) for adherence was greater for those with psychiatric care alone (AOR 1.52; 95% confidence interval [95% CI], 1.03 to 2.26) or combined with antidepressants (AOR 1.49; 95% CI, 1.04 to 2.15). In separate models by gender in persons with depression, psychiatric care plus antidepressants had a slightly stronger association with adherence in women (AOR 1.92; 95% CI, 1.00 to 3.68) than men (AOR, 1.26; 95% CI, 0.81 to 1.98). In drug users without depression, antidepressants alone were associated with greater adherence (AOR, 1.23; 95% CI, 1.02 to 1.49) with no difference by gender. Regular drug treatment was positively associated with adherence only in men.

CONCLUSIONS: In this drug-using cohort, women had worse pharmacy-measured antiretroviral adherence than men. Mental health care was significantly associated with adherence in women, while regular drug treatment was positively associated with adherence in men.

Disturbing evidence documents inequities in the care of HIV-infected women and men. Women are less likely to receive care from an HIV specialty provider[1,2] or antiretroviral therapy.[3] Among persons treated with highly active antiretroviral therapy (HAART), women initiate this therapy later than men[4,5] and have a lower likelihood of achieving an undetectable level of HIV RNA.[6] Because failure to suppress viral load increases the risk of AIDS and death,[7,8] the consequences of poor response to treatment are grave. Virologic success from HAART depends on the level of adherence to this demanding regimen.[9,10]

Several preliminary studies have reported poorer adherence to antiretroviral therapy in women than men,[11–15] but differing socioeconomic status by gender may confound these findings. We conducted a population-based analysis of pharmacy-based adherence to antiretroviral therapy in Medicaid-enrolled drug users where men and women have a similar socioeconomic background. Depression is highly prevalent in drug users[16–19] but may be especially high in HIV-infected drug-using women.[20–21] Since depression has been linked to poor medication adherence in studies of general populations,[22] it is possible that it may be a contributing factor to women's poorer adherence. We also expected to find that mental health services would show a beneficial association with adherence in both women and men. We further hypothesized that regular drug treatment would be associated with improved adherence because active drug abuse has been associated with poor adherence to antiretroviral therapy.[23–24] If women had poorer access to or benefit from drug treatment, this might also contribute to gender inequities in adherence. Finally, HIV-focused care from providers under contract to New York State to deliver HIV care and supplementary services to Medicaid enrollees has been associated with improved adherence to antiretroviral therapy.[25] We hypothesized possible gender differences in receipt of this care might contribute to gender inequities in adherence.

METHODS

Study Population

We studied HIV-infected drug users enrolled in New York State (NYS) Medicaid in federal fiscal year 1997. Data were drawn from longitudinally linked Medicaid claims for outpatient physician, clinic, inpatient, and pharmacy

services in 1996–1997. We identified Medicaid claims associated with illicit drug use, HIV infection, and AIDS using previously tested algorithms developed by our group.[26–27] The algorithm to screen claims for evidence of drug use searches for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for heroin, cocaine, amphetamine, or unspecified illicit drug dependence or abuse; for Medicaid services (or rate codes) for methadone treatment or medically supervised substance abuse treatment; and for Diagnosis-Related Groups (DRGs) for inpatient illicit drug detoxification. From National Drug Codes on pharmacy claims, we identified all Food and Drug Administration–approved antiretroviral drugs.

Our study cohort was drawn from 59,104 individuals enrolled in New York State Medicaid for at least 10 months in 1997. Of this group, 11,427 (19%) met our HIV case finding algorithm. HIV-infected persons met at least one of the following criteria: 1) pharmacy claim for antiretroviral drug(s); 2) any inpatient stay with a diagnosis of an AIDS-defining condition or HIV-related DRG; or 3) at least 2 occurrences >30 days apart of a) an outpatient physician or clinic visit with an HIV-related or AIDS-defining diagnosis, b) an HIV outpatient care rate code, or c) inpatient stay for an HIV-related condition such as pneumonia.

The sensitivity and specificity of these approaches for identifying drug users and HIV-infected persons have been evaluated in a chart review validation study at Montefiore Medical Center that has been reported previously.[26–27] The drug user algorithm had a sensitivity of 0.86 and a specificity of 0.87 for identifying drug abuse. When misclassification in charts due to drug users receiving drug treatment services from other locations was taken into account, these characteristics rose to 0.87 and 0.97, respectively. The sensitivity and specificity were 0.96 and 1.0, respectively, for detecting HIV infection.

From the HIV-infected group ($N = 11,427$), we excluded 3,424 persons with no antiretroviral therapy claims in 1996 and 1997, 163 pregnant or peripartum women, on the basis of diagnoses and services received in 1997 because of changes in care, and 12 persons without demographic data. Of the remaining 7,840 subjects, we excluded 1,315 persons with fewer than 60 days of combination antiretroviral therapy, 821 persons with fewer than 180 days from initiation of combination therapy until last prescription(s) in 1997, and 601 persons whose antiretroviral therapy was started in the last 90 days of 1997. These criteria allow sufficient time to evaluate adherence to combination antiretroviral therapy using the pharmacy-based measure.[28] Our final study population totaled 5,103 persons.

Pharmacy-based Measurement of Adherence

To assess adherence, we employed an approach that we used in several other similar studies.[25,29] After identifying antiretroviral drugs from National Drug Codes, we examined adherence among persons prescribed at least 2 drugs concurrently for at least 60 days of 180 days or more on therapy. Adherent subjects needed to have a sufficient amount of prescribed antiretroviral drug(s) to cover at least 95% of days from the first filled prescriptions for combination therapy in 1997 until the end of the last filled prescription(s) in that year. We ascertained the number of days covered by prescribed drug from the "days supply" field on the claim. In other analyses, we found that the calculated number of days covered based on counting the number of pills and the dose provided differed by only a mean of 2.1 days (SD 13.5) from the "days supply" field on the claim.[25] To avoid counting erroneous claims, we considered only 1 claim when duplicate claims appeared from 1 pharmacy for the same amount of a drug on the same day (<1% of antiretroviral claims). After a patient had received at least 2 weeks of outpatient antiretroviral therapy, we counted inpatient days as continuing this initiated therapy because we lacked inpatient pharmacy data. When a new drug was prescribed, we gave credit for days potentially covered by the discontinued antiretroviral drug, because a patient might take it until it was finished. Persons prescribed more than 2 drugs concurrently needed to demonstrate adherence to at least 2. The denominator in the calculation of adherent days excluded short gaps in Medicaid eligibility in 1997. The average duration from first to last prescribed antiretroviral therapy in 1997 for the study population was 321 days (SD 55) and the average duration of combination therapy was 241 days (SD 84).

Classification of Outpatient Patterns of Care

Regular drug treatment was defined as care from a single methadone or medically supervised, drug free (Title 1035) clinic for at least 6 contiguous months of non-hospitalized days in 1997 as recommended for effective treatment.[30,31] At least 3 weekly drug treatment claims per month were required to indicate ongoing care, allowing for 1-week lapses. In infrequent instances in which providers submitted daily drug treatment claims, 15 or more such claims from the same provider in a 30-day interval indicated care for that month. Office physician care was not considered because only a small fraction of office physicians dispense methadone.

A regular source of medical care for a study subject was defined as a clinic or physician visited at least twice as an outpatient during 1997 and delivering >35% of all outpatient encounters with primary care, obstetrics-gynecologists, or medical subspecialties in that year.[2] These providers could be clinics, group practices, or individual physicians. For ties, a previously developed hierarchy of specialties was used to select 1 provider (i.e., primary care, followed by HIV-related specialties [i.e., infectious diseases, hematology/oncology, allergy/immunology], obstetrics-gynecology, and other medical subspecialties).[2] We also examined the receipt of at least 2 outpatient encounters in 1997 with clinics or private

physicians with an agreement with the State to offer HIV-related services and expertise (HIV enhanced rate care) in exchange for higher Medicaid payment rates, or with a provider in infectious diseases.[32,33] We specified at least 2 visits for such care to be able to potentially influence adherence. Finally, we created a variable for at least 2 visits in 1997 to a psychiatric clinic or a private psychiatrist. As with HIV enhanced rate care, 2 or more visits for psychiatric care were viewed as a minimum to affect adherence.

To identify persons prescribed antidepressant therapy, we searched for the appropriate National Drug Codes from the NYS Medicaid Management Information System (5-digit) therapeutic codes and/or the FirstDataBank–Medispan formulary therapeutic classification system. We created an indicator for at least 1 filled prescription for antidepressant therapy. We did not require multiple claims for therapy even though more than 1 month of antidepressant treatment is necessary for effective treatment,[34] because this served as another measure of adherence to pharmacologic therapy and was highly correlated with adherence to antiretroviral therapy.

Other Study Variables

Medicaid eligibility files offered age, gender, and NYS region of residence. Residence was classified from ZIP codes as rural, small city, upstate urban, New York City suburb, or New York City. NYS Medicaid files do not contain reliable data on ethnicity. Data on comorbid conditions were also obtained from ICD-9-CM codes on inpatient and outpatient claims files in 1997. We created an indicator for depression based on an approach used by Sambamoorthi et. al.[35] in an analysis of health care utilization of HIV-infected persons that searches for the following diagnoses: major depressive disorder; depressive-type psychosis; neurotic depression; depressive reaction (brief or prolonged); and depression not otherwise specified. To identify persons with advanced HIV infection, we created a flag for patients who had been diagnosed with an AIDS-defining condition. An indicator was also created for chronic diseases other than HIV (i.e., diabetes, hypertension, asthma, sickle cell anemia) that are prevalent in this population. We also created an indicator for acute infections including: septicemia, pneumonia, chronic cutaneous ulcers, endocarditis, osteomyelitis, meningitis, pyelonephritis, and pelvic inflammatory disease.

We also identified specific types of illicit drug and alcohol abuse or dependence. Illicit drug abuse was classified as: drug dependence of unspecified type; heroin or cocaine abuse or dependence; or other drug abuse or dependence (i.e., amphetamine, hallucinogens, marijuana, barbiturates). Acute drug-related events included: drug-related psychosis; overdose; staphylococcal abscess, myocarditis or sepsis; cellulitis; chest pain or acute myocardial infarction; stroke; intracranial/intraspinal abscess; seizures; nephritis; or rhabdomyolysis. This set of conditions was identified by an expert panel and review of the literature on drug-related complications. Alcohol abuse or dependence was identified by a separate indicator from diagnosis codes (Table 1).

Analyses

Analyses were performed using Statistical Analysis Software, version 8.0 (SAS, Inc., Cary, NC). We first examined bivariate associations between all covariates and adherence in 1997 for men and women separately. We also conducted bivariate comparisons of the use of the health services of interest by gender. We were also interested in examining differences by depression status, so we examined bivariate associations of all covariates by gender among those with and without depression diagnosed in 1997. Because the effects of health care delivery variables differed by diagnosed depression status, we estimated separate multivariate models for persons with and without depression and within each of these groups by gender. All multivariate models included demographic, clinical, and health care covariates regardless of the significance of their bivariate associations with adherence.

A significant interaction ($P < .05$) was observed between regular medical care and regular drug treatment and HIV-focused care, respectively. However, neither interaction changed the finding that regular medical care and HIV-focused care did not have significant independent effects on adherence and, therefore, are not reported. An interaction of borderline significance ($P = .06$) between psychiatric therapy and antidepressant use did show different effects by gender and depression status and is reported using 4-part dummy variables

The P value for the Hosmer-Lemeshow statistic for the full model was .90 and for the separate models was .43 (women with depression), .98 (women without depression), .73 (men with depression), and .11 (men without depression). These statistics indicate generally very good fit. Although the fit for the model of men without depression is less adequate, we found effects similar to those in the model for women without depression, making us less concerned about the poorer fit.

RESULTS

Our pharmacy-based measure indicated that 22% of the study population was adherent to combination antiretroviral therapy at a 95% level. Less than one fifth of women were adherent compared with one quarter of men ($P < .001$) (Table 1). More women were diagnosed with depression than men (34% vs 29%, respectively; $P < .001$). Surprisingly, adherence was greater in persons of both genders who were diagnosed with depression. In women, adherence was significantly poorer for those with heroin or cocaine abuse. In men, adherence was greater for those residing in New York City and worse for those who developed acute infections such as pneumonia.

Table 1. Demographic and Clinical Characteristics and Unadjusted Associations* with Adherence† to Combination
Antiretroviral Therapy for Female and Male HIV-infected Drug Users Enrolled in New York State Medicaid

Characteristic	Women Adherent, n, (%) (N = 1,857, 18%)	P Value	Men Adherent, n (%) (N = 3,246, 25%)	P Value
Age, y		.95		.44
<30	95 (20)		95 (22)	
30–39	847 (18)		1,091 (23)	
40–49	793 (18)		1,678 (25)	
50+	122 (19)		382 (27)	
Residence		.16		<.0001
New York City	1,596 (19)		2,811 (26)	
Outside New York City	261 (15)		435 (17)	
Depression		.03		.003
Yes	625 (21)		948 (28)	
No	1,232 (17)		2,298 (23)	
AIDS		.18		.06
Yes	561 (16)		932 (22)	
No	1,296 (19)		2,314 (25)	
Acute HIV-associated infection		.12		.02
Yes	616 (16)		960 (22)	
No	1,241 (19)		2,286 (26)	
Chronic non-HIV medical condition(s)		.77		.94
Yes	752 (18)		1,144 (24)	
No	1,105 (18)		2,102 (24)	
Heroin or cocaine abuse/dependence		.02		.54
Yes	912 (16)		1,531 (24)	
No	945 (20)		1,715 (24)	
Unspecified drug dependence		.40		.13
Yes	213 (16)		380 (28)	
No	1,644 (18)		2,866 (24)	
Other drug abuse/dependence		.16		.96
Yes	95 (13)		191 (25)	
No	1,762 (18)		3,055 (25)	
Acute drug-related complication		.08		.26
Yes	607 (16)		1,013 (23)	
No	1,250 (19)		2,233 (25)	
Alcohol dependence/abuse		.10		.15
Yes	333 (15)		593 (23)	
No	1,396 (19)		2,333 (25)	

* P *value from* χ^2 *statistic.*
† *Adherence defined as >95% of days covered by at least 2 antiretroviral drugs from initiation of combination therapy in 1997 until the end of the year.*

Women and men did not differ significantly in receipt of mental health care, regular drug treatment, or regular medical care. However, women were slightly more likely to receive HIV-focused care (77% vs 74%, respectively; P = .006). We examined the association of depression and receipt of these health care services with adherence further among drug users in the cohort who were diagnosed with depression (Table 2). Most women (84%) and men (81%) in this subset received either psychiatric care or antidepressant therapy. In these groups, adherence was not significantly associated with any of the health care services, with the exception of a positive association of greater adherence for men with depression in regular drug treatment.

Table 3 shows the distribution of these health care services and association with adherence among persons without a depression-related diagnosis. Of note, one third of this group received mental health treatment. We observed that, in both genders, psychiatric care and/or antidepressants were not associated with significantly higher proportions of adherent patients. Similar to the group with depression, the only significant association in this subset was a higher proportion of adherence in men who received regular drug treatment.

After adjustment for patient demographic, substance abuse, clinical, and health care factors, an overall model of the entire study cohort showed that women had significantly lower adjusted odds of adherence than men (odds ratio [OR], 0.67; 95% confidence interval [95% CI], 0.58 to 0.78). In a model of only persons diagnosed with depression, the adjusted odds of adherence were significantly increased for those with regular drug treatment or who received psychiatric care with or without antidepressant therapy, compared to those with neither (Table 4). In

Table 2. Health Care Delivery to Female and Male HIV-infected Drug Users With Diagnosed Depression and Unadjusted Associations* with Adherence[†] to Combination Antiretroviral Therapy

Characteristic	Women Adherent, n (%) (N = 625, 21%)	P Value	Men Adherent, n (%) (N = 948, 28%)	P Value
Psychiatric care (2+ visits) and antidepressant medication		.38		.62
Both	245 (24)		364 (28)	
Psychiatric care only	166 (20)		222 (30)	
Antidepressant medication only	111 (19)		181 (29)	
Neither	103 (17)		181 (24)	
Regular drug treatment		.34		<.0001
Yes	275 (23)		416 (35)	
No	350 (19)		532 (23)	
Regular medical care		.65		.92
Yes	335 (22)		464 (28)	
No	290 (20)		484 (28)	
HIV-focused care (2+ visits)		.85		.08
Yes	506 (21)		740 (29)	
No	119 (20)		208 (23)	

* P *value from* χ^2 *statistic.*
[†] *Adherence defined as >95% of days covered by at least 2 antiretroviral drugs from initiation of combination therapy in 1997 until the end of the year.*

separate models by gender among persons diagnosed with depression, the effect of regular drug treatment was significant only in the men. On the other hand, the adjusted odds of adherence were 90% greater among those women with depression who received both psychiatric care and antidepressant therapy, compared with those receiving neither type of care but only 26% greater in men. This association was weaker in the model including only men with depression, but the confidence interval substantially overlaps that from the model for women with depression. The favorable effect of psychiatric care alone was similar in women and men but did not achieve

statistical significance in separate models by gender. A smaller favorable association was observed for antidepressant therapy alone but was also not statistically significant.

Among persons without the diagnosis of depression, longitudinal drug treatment showed a significant positive association again only for men (Table 5). After adjustment, antidepressant therapy had a small but significant positive association that was similar by gender. Psychiatric care had a somewhat stronger favorable association with adherence for women without diagnosed depression than for men in this subgroup. We created an 8-part dummy variable for the interaction of gender (2 levels) and

Table 3. Health Care Delivery to Female and Male HIV-infected Drug Users Without Diagnosed Depression and Unadjusted Associations* with Adherence[†] to Combination Antiretroviral Therapy

Characteristic	Women Adherent, n (%) (N = 1,232, 17%)	P Value	Men Adherent, n (%) (N = 2,298, 23%)	P Value
Psychiatric care (2+ visits) and antidepressant medication		.65		.28
Both	64 (16)		85 (26)	
Psychiatric care only	59 (17)		103 (19)	
Antidepressant medication only	358 (19)		626 (25)	
Neither	751 (16)		1,484 (22)	
Regular drug treatment		.90		.001
Yes	662 (17)		1,182 (26)	
No	570 (17)		1,116 (20)	
Regular medical care		.86		.35
Yes	632 (17)		1,114 (22)	
No	600 (17)		1,158 (24)	
HIV-focused care (2+ visits)		.78		.44
Yes	928 (17)		1,655 (23)	
No	304 (16)		643 (22)	

* P *value from* χ^2 *statistic.*
[†] *Adherence defined as >95% of days covered by at least 2 antiretroviral drugs from initiation of combination therapy in 1997 until the end of the year.*

Table 4. Adjusted* Associations of Health Care Delivery Variables and Adherence[†] to Combination Antiretroviral Therapy for HIV-infected Female and Male Drug Users With Diagnosed Depression

	Adjusted Odds of Adherence (95% CI)		
Characteristic	Overall	Women	Men
Psychiatric care (2+ visits) and antidepressant medication			
Both	1.49 (1.04 to 2.15)	1.92 (1.00 to 3.68)	1.26 (0.81 to 1.98)
Psychiatric care only	1.52 (1.03 to 2.26)	1.58 (0.78 to 3.17)	1.53 (0.94 to 2.49)
Antidepressant medication only	1.30 (0.86 to 1.97)	1.46 (0.69 to 3.09)	1.21 (0.73 to 2.03)
Neither	1.00	1.00	1.00
Regular drug treatment			
Yes	1.44 (1.12 to 1.87)	1.16 (0.75 to 1.79)	1.65 (1.19 to 2.28)
No	1.00	1.00	1.00
Regular medical care			
Yes	1.04 (0.81 to 1.34)	1.05 (0.69 to 1.61)	1.03 (0.75 to 1.42)
No	1.00	1.00	1.00
HIV-focused care (2+ visits)			
Yes	1.19 (0.86 to 1.63)	1.04 (0.61 to 1.79)	1.28 (0.85 to 1.92)
No	1.00	1.00	1.00

* *Also adjusted for: gender (in overall model); age; residence; chronic non-HIV medical condition; acute infection, AIDS; acute illicit drug–related complication; drug dependence; heroin or cocaine abuse/dependence; other drug abuse/dependence; alcohol abuse/dependence.*
[†] *Adherence defined as >95% of days covered by at least two antiretroviral drugs from initiation of combination therapy in 1997 until the end of the year.*
CI, confidence interval.

psychiatric care and antidepressant medication (4 levels) and set the reference as men without diagnosed depression and without mental health care to evaluate whether women without diagnosed depression and without mental health care had lower adjusted odds of adherence. In this model (not shown), women without mental health care had significantly lower adjusted odds of adherence (OR, 0.65; 95% CI, 0.51 to 0.82), while the adjusted odds ratios for the groups of women with psychiatric care and/or antidepres-

sant therapy did not differ significantly. We suggest that a substantial fraction of women in the group without diagnosed or treated depression might have mood disorders affecting adherence.

DISCUSSION

HIV-infected women appear to be particularly vulnerable to experiencing depressive symptoms.[36] Persistent

Table 5. Adjusted* Associations of Health Care Delivery Variables and Adherence[†] to Combination Antiretroviral Therapy for HIV-infected Female and Male Drug Users Without Diagnosed Depression

	Adjusted Odds of Adherence (95% CI)		
Characteristic	Overall	Women	Men
Psychiatric care (2+ visits) and antidepressant medication			
Both	1.15 (0.73 to 1.80)	1.25 (0.60 to 2.62)	1.08 (0.59 to 1.86)
Psychiatric care only	0.88 (0.56 to 1.39)	1.26 (0.60 to 2.65)	0.72 (0.39 to 1.26)
Antidepressant medication only	1.23 (1.02 to 1.49)	1.28 (0.90 to 1.82)	1.21 (0.96 to 1.53)
Neither	1.00	1.00	1.00
Regular drug treatment			
Yes	1.17 (0.98 to 1.40)	1.02 (0.73 to 1.41)	1.26 (1.02 to 1.56)
No	1.00	1.00	1.00
Regular medical care			
Yes	0.95 (0.80 to 1.12)	0.96 (0.70 to 1.31)	0.94 (0.76 to 1.17)
No	1.00	1.00	1.00
HIV-focused care (2+ visits)			
Yes	1.03 (0.84 to 1.26)	1.06 (0.73 to 1.55)	1.00 (0.80 to 1.28)
No	1.00	1.00	1.00

* *Also adjusted for: gender (in overall model); age; residence; chronic non-HIV medical condition; acute infection, AIDS or chronic HIV-related complication; acute illicit drug–related complication; drug dependence; heroin or cocaine abuse/dependence; other drug abuse/dependence; alcohol abuse/dependence or acute alcohol-related complication.*
[†] *Adherence defined as >95% of days covered by at least 2 antiretroviral drugs from initiation of combination therapy in 1997 until the end of the year.*
CI, confidence interval.

depression in women has been associated with significantly poorer survival[37] that may reflect deficiencies in adherence to antiretroviral therapy among depressed women. In this study, we examined the effect of gender, depression, and health care services on adherence in a population-based cohort of Medicaid-enrolled drug users who were at increased risk of deficiencies in adherence.[23–24] Indeed, the overall adherence rate in this cohort was a dismal 22% over an average of 8 months, according to a pharmacy-based measure using a 95% cut point. As expected, we found that women had adjusted odds of adherence to antiretroviral therapy that were one third lower than that of men. This finding is unlikely to be confounded by socioeconomic differences present in the other large U.S.-based studies of gender differences in antiretroviral adherence.[11,12] Our Medicaid-enrolled population included persons who met New York State requirements for eligibility, which are relatively generous compared to the rest of the nation but still not much above federal poverty level. Thus, all of our study population was indigent.

However, contrary to our prior hypotheses, we found that the diagnosis of depression, based on administrative data, was associated with improved adherence in this cohort. However, most of the persons who were diagnosed with depression in this cohort also received mental health services. Mental health services had favorable associations with adherence that were stronger in women than in men. Women with a diagnosis of depression who received psychiatric care in combination with antidepressant therapy had nearly 2-fold greater adjusted odds of adherence than depressed women without either form of care. A synergistic effect of psychotherapy with pharmacotherapy has been described in general populations.[38]

Although receipt of regular drug treatment did not differ by gender, men in this cohort had significantly higher adjusted odds of adherence when they received regular drug treatment regardless of depression status. We predicted that regular drug treatment would have a favorable effect on adherence because ongoing substance abuse is strongly associated with poorer adherence.[39] It is possible that men also take more advantage of mental health services available through some drug treatment programs than do women.[40]

In both women and men with depression, psychiatric care alone was associated with approximately 50% greater adjusted odds of adherence, whereas antidepressant therapy alone showed positive but nonsignificant effects. In a study of over 1,000 depressed patients, the majority of both women and men preferred counseling over antidepressant therapy, but that study did not examine response to therapy.[41] In a small study of antidepressant therapy in depressed HIV-infected women, Ferrando et al. reported that women often refused participation because they preferred counseling and, of those enrolled, only 60% completed the 8-week study, in part because of frequent

side effects.[42] Similar problems with acceptance, persistence, and side effects were observed in a randomized trial of antidepressant therapy in primarily non-drug-abusing HIV-infected men with depression.[43] Therefore, is possible that our cohort did not persist with treatment for depression long enough to demonstrate a benefit in regard to improved adherence.

Another potential reason that persons diagnosed with depression in this cohort had better adherence may be the presence of undiagnosed and untreated depression in the group without a depression-related diagnosis. Although approximately one third of our study cohort had a diagnosis compatible with depression or dysthymia, the prevalence of depression was likely even higher. Brienza et al. reported that 54% of persons in a needle exchange program and 42% of those in a methadone maintenance treatment program met criteria for major depression using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.[16] Moore et al. reported that over 65% of HIV-infected women with recent injection drug use or cocaine abuse in a 4-city study screened positive for depressive symptoms on the Center for Epidemiologic Studies Depression Scale.[21] In support of the possibility that some patients in the group without diagnosed depression were actually depressed, we observed a small but significant benefit of antidepressant therapy on adherence in this subset. Although it is possible that these patients were taking these drugs for other indications, such as using imipramine for neuropathy, this type of alternative indication is likely to be infrequent. It is likely that patients or providers may be loath to give a patient the diagnosis of depression, given the stigma associated with this condition.[44]

We were surprised to find that neither having regular medical care nor having HIV-focused medical care was associated with improved adherence. We previously reported that more intensive antiretroviral therapy, including HAART, was more likely in drug users treated by providers delivering HIV-focused care.[27] In a cohort of postpartum HIV-infected women, adherence was significantly greater in those who received HIV specialty care.[25] Similarly, adherence was improved in HIV-infected persons in Canada who received care from a more experienced provider.[13] It is possible that drug users have a greater need of adjunctive services such as psychiatric and drug treatment to improve adherence.

This study uses a pharmacy-based measure of adherence as in several earlier analyses conducted by our group.[25,29] This pharmacy-based methodology has the distinct advantage of permitting population-based research[45] and has been applied, for example, in studies of large populations using lipid-lowering medications.[46] For this analysis, we studied only subjects who had been prescribed combination antiretroviral therapy for more than 2 months, as recommended by experts in pharmacy-based measures of adherence.[28] This type of

pharmacy-based measure is based on the straightforward premise that when an individual does not receive timely refills of a drug from the pharmacy, she or he is either not taking medication between refills or missing doses such that a given prescription lasts longer than it should. Additional strengths of this approach are that it is not susceptible to reporting bias or tampering.[47]

Admittedly, this measure does not take into account the daily timing of taking pills. However, a similar approach to determining adherence that was applied to 266 HIV-infected persons treated with HAART that found that 36% were adherent and that the adherent group had significant reductions in HIV RNA level.[48] A Canadian study of nearly 900 HIV-infected persons applied a pharmacy-based measure and found a linear association between increasing levels of adherence and viral load suppression.[49]

A pharmacy claims–based approach to measuring adherence is possible only in settings in which all medications are covered by a single payer as in Medicaid, the Veterans Administration, or a universal health care system, as in Canada. We could not evaluate our approach to measuring adherence because of strict confidentiality agreements that permit analysis of Medicaid claims data. We were only able to conduct a validation study of our case finding methodology through a special agreement with one location at the start of this study.

In this study, we required a high level of adherence of at least 95% of days simultaneously covered by 2 or more prescribed antiretroviral agents in those prescribed combination therapy for at least 2 months. Using a similar pharmacy-based measure, Low-Beer et al. reported that viral load suppression to <500 copies/mL was achieved in 85% of persons who were adherent at a 95% to 100% level, compared with only 64% of persons adherent at a 90% to 95% level.[49] Unfortunately, less than one fourth of the drug users in this cohort were adherent at the 95% level over an 8-month period. Few other studies have used as long a time frame to assess adherence for comparison. However, Arnsten et al. reported a mean of 38% adherence using electronic monitors over a 6-month study period in a cohort of drug users.[24]

To identify persons with depression, we employed a methodology that was previously used by Sambamoorthi et al. to a study health care service utilization of HIV-infected persons in New Jersey.[35] In their analysis of 5,559 HIV-infected Medicaid enrollees in New Jersey, these authors found that women and drug users were more likely to be diagnosed with depression on claims. The face validity of this approach is supported by their observation that persons treated for depression were more likely to receive appropriate services. However, as noted previously, the specificity of this approach is high but the sensitivity is likely limited in a cohort of drug users with a high prevalence of depression.

This observational study cannot prove causation. Persons who are sufficiently organized to receive psychi-atric care or see a physician to be diagnosed with depression might also be more organized in taking medications. After adjustment, we found that women without diagnosed depression or any mental health treatment had significantly poorer adjusted odds of adherence then men without diagnosed depression or mental health treatment. This group of women might have had a high prevalence of depression but been unwilling to receive treatment or even to recognize that they had a problem with depression. We cannot be sure how our results would change if we could include women who had depression that was not diagnosed with the women who were diagnosed with depression. Another limitation of our study is our use of data from the later 1990s. Since that time, both providers and patients have gained more experience with combination antiretroviral therapy and regimens have been simplified somewhat. Current levels of adherence may be better than we observed.

In focus groups, HIV-infected substance-abusing women readily acknowledge the detrimental effects of their own depression and others' negativism and as well as "drinking and drugging" on antiretroviral adherence.[49] In their review of HIV infection in women, Hader et al. emphasized the need to address mental health issues to improve outcomes of HIV-infected women.[36] Our study supports the benefit of mental health care to adherence to antiretroviral therapy by drug-using women who are diagnosed with depression according to administrative data. In addition, we observed an important benefit of regular drug treatment to antiretroviral adherence in drug-abusing men. Given the critical role that adherence plays in successful treatment of HIV, these findings have important clinical and policy implications for the treatment of one of the most challenging HIV-infected populations.

REFERENCES

1. Anonymous. Women and minorities less likely than men to receive specialty care. AIDS Alert. 1998;13:87–9.
2. Turner BJ, McKee L, Fanning T, Markson LE. AIDS specialist versus generalist ambulatory care for advanced HIV infection and impact on hospital use. Med Care. 1994;32:902–16.
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. Mocroft A, Gill MJ, Davidson W, Phillips AN. Women initiate highly active antiretroviral therapy later than men. J Acquir Immune Defic Syndr. 2000;24:475–82.
5. Andersen R, Bozzette S, Shapiro M, et al. Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS Consortium. HIV Cost and Services Utilization Study. Health Serv Res. 2000;35:389–416.

6. Valdez H, Lederman MM, Woolley I, et al. Human immunodeficiency virus 1 protease inhibitors in clinical practice: predictors of virological outcome. Arch Intern Med. 1999;159:1771–76.

7. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. Lancet. 1999;353:863–68.

8. Hogg R, Yip B, Chan K, O'Shaughnessy M, Montaner J. Non-adherence to triple combination therapy is predictive of AIDS progression and death in HIV-positive men and women. In: Program and Abstracts of the XIII International Conference on AIDS, Durban, South Africa, July 9–14, 2000. Abstract no. TuOrB419.

9. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV. Ann Intern Med. 2000;133:21–30.

10. Garcia de Olalla P, Knobel H, Carmona A, Guelar A, Lopez-Colomes JL, Cayla JA. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. J Acquir Immune Defic Syndr. 2002;30:105–10.

11. Wenger N, Gifford A, Liu H, et al. Patient characteristics and attitudes associated with antiretroviral (AR) adherence. In: Program and Abstracts of the 6th Conference on Retroviruses and Opportunistic Infections, Chicago, Ill, January 31–February 4, 1999. Abstract no. 98.

12. Gebo KA, Moore RD. Correlation of social stressors, illicit drug use, and health beliefs with adherence to antiretroviral regimens. RWJ Clinical Scholars Program, Ft. Lauderdale, November 2000.

13. Montaner J, Hogg R, Yip B, et al. Predictors of compliance with triple combination therapy among HIV-positive men and women in British Columbia. In: Program and Abstracts of the XIII International Conference on AIDS, Durban, South Africa, July 9–14, 2000. Abstract no. TuPpD1200.

14. Abriola K, McNabb JC, Ross J, et al. Adherence to HAART by MEMS predicts virologic outcome in minority/IVDU clinic population. In: Program and Abstracts of the XIII International Conference on AIDS, Durban, South Africa, July 9–14, 2000. Abstract no. TuOrB416.

15. Arabe J, Rubini NP, Rodrigues AC, et al. Factors which influence adherence to the use of protease inhibitors. In: Program and Abstracts of the XII International Conference on AIDS, Geneva, Switzerland, June 28–July 3, 1998. Abstract no. 32404.

16. Brienza RS, Stein MD, Chen M, et al. Depression among needle exchange program and methadone maintenance clients. J Subst Abuse Treat. 2000;18:331–37.

17. Darke S, Ross J. Polydrug dependence and psychiatric comorbidity among heroin injectors. Drug Alcohol Depend. 1997; 48:135–41.

18. Knowlton AR, Latkin CA, Schroeder JR, Hoover DR, Ensminger M, Celentano DD. Longitudinal predictors of depressive symptoms among low income injection drug users. AIDS Care. 2001;13:549–59.

19. Coelho R, Rangel R, Ramos E, Martins A, Prata J, Barros H. Depression and the severity of substance abuse. Psychopathology. 2000;33:103–9.

20. Powell-Cope GM, White J, Henkelman EJ, Turner BJ. Qualitative and quantitative assessments of HAART adherence of substance abusing women. AIDS Care. In press.

21. Moore J, Schuman P, Schoenbaum E, Boland B, Solomon L, Smith D. 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.

22. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160:2101–7.

23. Lucas GM, Gebo KA, Chaisson RE, Moore RD. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. AIDS. 2002;16:767–74.

24. Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. J Gen Intern Med. 2002;17:377–81.

25. Turner BJ, Newschaffer CJ, Zhang D, Cosler L, Hauck WW. Antiretroviral use and pharmacy-based measurement of adherence in post-partum HIV-infected women. Med Care. 2000;38:911–25.

26. Laine C, Hauck WW, Gourevitch MN, Rothman J, Cohen A, Turner BJ. Regular outpatient medical and drug abuse care and subsequent hospitalization of persons who use illicit drugs. JAMA. 2001;285:2355–62.

27. Laine C, Hauck WW, Turner BJ. Outpatient pattern of care and longitudinal intensity of antiretroviral therapy for HIV-infected drug users. Med Care. 2002;40:976–95.

28. Christiansen DB, Williams B, Goldberg HI, Martin DP, Engelberg R, LoGerfo JP. Assessing compliance to antihypertensive medications using computer-based pharmacy records. Med Care. 1997;35:1164–70.

29. Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. Obstet Gynecol. 2000;95:167–73.

30. Ball JC, Ross A. The Effectiveness of Methadone Maintenance Treatment. New York: Springer-Verlag; 1991.

31. Rawson RA, Shoptaw SJ, Obert JL, et al. An intensive outpatient approach for cocaine abuse treatment. J Subst Abuse Treat. 1995; 12:117–27.

32. Anonymous. Designated care programs for patients with AIDS and HIV-related illnesses in designated care centers. N Y State J Med. 1989;89:542–3.

33. Anonymous. State of New York Department of Health Memorandum. Health Facilities Series: H-23, D&TC-17, HMO-16. New York State Department of Health; 1993:93–6.

34. Williams JW Jr., Mulrow CD, Chiquette E, Noel PH, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann Intern Med. 2000;132:743–56.

35. Sambamoorthi U, Walkup J, Olfson M, Crystal S. Antidepressant treatment and health services utilization among HIV-infected Medicaid patients diagnosed with depression. J Gen Intern Med. 2000;15:311–20.

36. Hader SL, Smith DK, Moore JS, Holmberg SD. HIV infection in women in the United States: status at the millennium. JAMA. 2001;285:1186–92.

37. Ickovics JR, Hamburger ME, Vlahov D, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. JAMA. 2001;285:1466–74.

38. Thase ME, Greenhouse JB, Frank E, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Arch Gen Psychiatry. 1997;54:1009–15.

39. Lucas GM, Cheever LW, Chaisson RE, Moore RD. Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection. J Acquir Immune Defic Syndr. 2001;27:251–59.

40. Laine CL, Newschaffer C, Zhang D, Rothman J, Hauck WW, Turner BJ. Models of care in New York State Medicaid substance abuse clinics: range of services and linkages to medical care. J Subst Abuse. 2000;12:271–85.

41. Dwight-Johnson M, Sherbourne CD, Liao D, Wells KB. Treatment preferences among depressed primary care patients. J Gen Intern Med. 2000;15:527–34.

42. Ferrando SJ, Rabkin JG, de Moore GM, Rabkin R. Antidepressant treatment of depression in HIV-seropositive women. J Clin Psychiatry. 1999;60:741–46.

43. Rabkin JG, Wagner GJ, Rabkin R. Fluoxetine treatment for depression in patients with HIV and AIDS: a randomized, placebo-controlled trial. Am J Psychiatry. 1999;156:101–7.

44. Sirey JA, Bruce ML, Alexopoulos GS, Perlick DA, Friedman SJ, Meyers BS. Stigma as a barrier to recovery: perceived stigma and patient-rated severity of illness as predictors of antidepressant drug adherence. Psychiatr Serv. 2001;52: 1615–20.

45. Paes AH, Bakker A, Soe-Agnie CJ. Measurement of patient compliance. Pharm World Sci. 1998;20:73–7.

46. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. JAMA. 1998;279: 1458–62.

47. Turner BJ, Hecht FM. Improving on a coin toss to predict patient adherence to medications. [Editorial]. Ann Intern Med. 2001;134: 1004–6.

48. Maher K, Klimas N, Fletcher MA, et al. Disease progression, adherence, and response to protease inhibitor therapy for HIV infection in an urban Veterans Affairs Medical Center. J Acquir Immune Defic Syndr. 1999;22:358–63.

49. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. J Acquir Immune Defic Syndr. 2000;23:360–61.

◆