A Prospective Study of Predictors of Adherence to Combination Antiretroviral Medication

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OBJECTIVE: **Adherence to complex antiretroviral therapy (ART) is critical for HIV treatment but difficult to achieve. The development of interventions to improve adherence requires detailed information regarding barriers to adherence. However, short follow-up and inadequate adherence measures have hampered such determinations. We sought to assess predictors of long-term (up to 1 year) adherence to newly initiated combination ART using an accurate, objective adherence measure.**

DESIGN: **A prospective cohort study of 140 HIV-infected patients at a county hospital HIV clinic during the year following initiation of a new highly active ART regimen.**

MEASURES AND MAIN RESULTS: **We measured adherence every 4 weeks, computing a composite score from electronic medication bottle caps, pill count and self-report. We evaluated patient demographic, biomedical, and psychosocial characteristics, features of the regimen, and relationship with one's HIV provider as predictors of adherence over 48 weeks. On average, subjects took 71% of prescribed doses with over 95% of patients achieving suboptimal (<95%) adherence. In multivariate analyses, African-American ethnicity, lower income and education, alcohol use, higher dose frequency, and fewer adherence aids (e.g., pillboxes, timers) were independently associated with worse adherence. After adjusting for demographic and clinical factors, those actively using drugs took 59% of doses versus 72% for nonusers, and those drinking alcohol took 66% of doses versus 74% for nondrinkers. Patients with more antiretroviral doses per day adhered less well. Participants using no adherence aids took 68% of doses versus 76% for those in the upper quartile of number of adherence aids used.**

CONCLUSIONS: **Nearly all patients' adherence levels were suboptimal, demonstrating the critical need for programs to assist patients with medication taking. Interventions that assess and treat substance abuse and incorporate adherence aids may be particularly helpful and warrant further study.**

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Available treatment for HIV can dramatically suppress viral load, enhance CD4 counts and decrease morbidity and mortality related to HIV infection.[1–6] If antiretroviral medications are not taken as prescribed, treatment failure may ensue.[7–21] Nonadherence is widely viewed as a risk factor for drug-resistant virus, which can be transmitted through unsafe sexual and drug use practices.[8] It appears that patients must ingest at least 90% to 95% of their prescribed doses consistently to maintain virologic success.[7,9] Although patients taking antiretrovirals generally achieve higher levels of adherence than do patients on other chronic medical therapies,[7,21] the regimens are complex and lifelong; not surprisingly, a large proportion of patients are unable to achieve the targeted levels of adherence.[13,21–25] Therefore, interventions to facilitate patients' adherence to antiretroviral medications are critical to optimal HIV care.

Development of successful interventions to improve adherence requires a detailed understanding of the numerous factors that influence patients' medication taking. Identified correlates of adherence are often grouped into several broad categories: characteristics of the patient,[26] features of the regimen,[27] aspects of the clinical interaction,[28] features of the illness, and socioenvironmental factors.[29] Studies that have assessed adherence to antiretroviral therapy (ART) have identified salient factors in each of these categories.[22,23,30–56] Unfortunately, many reports have been limited by a cross-sectional design, the use of self-report measures or both.[7,13,30–48] Several studies assessed only patients' self-reported reasons for nonadherence, rather than testing for associations between these factors and actual adherence.[36,37,45,47,48]

We designed a longitudinal, cohort study to address some of the unresolved questions related to the influence of various factors on adherence to ART. We prospectively measured hypothesized predictors of ART adherence and followed patients for a prolonged period of time (up to 48 weeks). Then we used a carefully constructed measure of adherence that has been shown to be significantly predictive of virologic outcomes.[21] We derived the following hypotheses from the existing literature and tested them in this study:

1. *Patient Factors:* We hypothesize that patients who have more-positive attitudes toward ART,[22,31,37,38,45] greater self-efficacy toward adherence,[44,38] and

higher literacy levels[42] will be more adherent with ART. We expect patients who are active substance abusers[22,31,33,38,46,49] or who report lower emotional well-being[7,33] to be less adherent.

2. *Regimen Factors:* We expect that patients receiving more complex antiretroviral regimens[22,27,31,49,52] and regimens that fit less well with the other daily activities[35,38,40,41,44,48,52,53] will be less adherent. We also expect that use of adherence aids (such as pillboxes, medication timers, etc.)[31] will be associated with better adherence.
3. *Features of the Clinical Interaction:* We expect patients with greater continuity of care, satisfaction with medical care, and trust in their provider to be more adherent,[57–65]
4. *Social/Environmental Factors*: We expect patients with more social support to be more adherent.[40,45,46,54,55]

METHODS

Subjects

All patients were enrolled in the ADEPT (Adherence and Efficacy to Protease inhibitor Therapy) study, a prospective observational investigation of medication adherence in HIV.[21] From February of 1998 through April of 1999, we enrolled HIV-infected patients attending a public hospital–affiliated HIV care clinic who spoke English or Spanish and who were newly initiating a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Participants were followed for 48 weeks after initiation of the new regimen. Sixty percent of eligible subjects enrolled in the trial. For this analysis, we examined all patients with adherence data available for at least 2 four-week periods.

Data Collection

Overview. Information was collected from patients at baseline and every 4 weeks for up to 48 weeks. A study nurse interviewed patients face-to-face at baseline, week 8, week 24, and study exit. During these interviews, a standardized questionnaire was administered to assess self-reported adherence, all current medications, barriers to adherence, and reasons for missed doses. In addition, chart review was conducted at baseline and at study exit using a standardized instrument to assess disease severity and to confirm information obtained from patients regarding their complete medication regimen.

Measurement of Adherence. Adherence was assessed by combining 3 measures of adherence: Medication Event Monitoring System (MEMS) cap data, pill count, and self-reported adherence. Adherence was computed as the actual number of doses taken divided by the number of doses prescribed over a 4-week period and expressed as a percentage.[21] Upon patient enrollment, the study nurse placed on the bottle of the patient's newly initiated PI medication a pill bottle cap containing a microchip that records each instance of bottle opening. If 2 PIs were started, each was fitted with a MEMS cap. For patients started on a non-PI or NNRTI-containing regimen, the most frequently dosed antiretroviral was measured. Every 4 weeks, at a follow-up visit, the study nurse downloaded information from the MEMS cap to a medication database and replaced the cap on the appropriate bottle. The study nurse also counted the patients' remaining ART pills. Self-reported adherence was assessed at baseline, week 8, week 24, and exit interview by asking patients: "Many people don't take their medication perfectly all the time. Over the past 7 days, how many times did you miss a dose of {Medication X}?" Responses were confirmed by a secondary question. Patients also were asked whether they had any medication changes since the last visit and whether they had used a pillbox. This information was used in the computation of a composite adherence score (CAS).[21]

The composite adherence score, described in detail elsewhere,[21] was based primarily on MEMS data, with the use of pill count and then interview data (each calibrated to the MEMS metric) when MEMS data were missing or inaccurate. To identify inaccuracies, all MEMS data were carefully reviewed along with other information collected from the patient (use of pillboxes, changes in medications, discontinuation of medication) and qualitative notes from study nurses about unusual use of the MEMS cap (such as regular use of "pocket doses," medication-sharing, use of liquid medication, and loss or damage of caps or bottles). The majority of CAS measures were based on MEMS data (61%). Where MEMS data were determined to be inaccurate or missing, calibrated pill count data were used (37%). In the 2% of cases in which neither accurate MEMS data nor pill counts were available, we based the CAS on calibrated self-report data. Of note, correlations between MEMS data and pill count were 0.46, between MEMS data and interview were 0.38, and between pill count and interview were 0.62. For this analysis, a patient's adherence was summed over all 48 weeks.

Measurement of Potential Determinants of Adherence and Covariates. At baseline, patients were interviewed to assess the following: 1) patient demographic, clinical, and psychosocial characteristics; 2) regimen characteristics; 3) features of the clinical interaction; and 4) socio-environmental factors.

Patient Factors. Patients were asked about demographics (age, gender, race/ethnicity, acculturation level if Hispanic, education, income level, work status, number of children and relationship status), clinical characteristics (duration of antiretroviral treatment), physical and mental health,[66,67] source of infection, and current alcohol intake and drug use,[38] as well as psychosocial factors (therapy, self-efficacy, active coping style,[68] and literacy[69]). Acculturation was measured using a modification of the Marin Acculturation scale.[70] In addition, highest viral load and

lowest CD4 count were determined by chart review. To assess patients' beliefs about ART (perceived treatment utility, perceived susceptibility, and perceived medication efficacy), we adapted for HIV the health beliefs subscale of the Adherence Determinants Questionnaire.[71] Self-efficacy was assessed with a 1-item medication-specific question that used a visual analog scale: "On a scale of 0 to 10, where 0 = not at all sure and 10 = very sure, how sure are you that you will be able to take all of {medication X} exactly as directed over the next 30 days?"

Regimen Factors. Patients were asked how their ART regimens fit with their lifestyle: "How often will taking HIV medications fit into your daily activities in the next 30 days?" Regimen complexity was measured as: 1) the total number of antiretroviral and non-antiretroviral pills that the patient was prescribed to take each day; 2) the total number of antiretroviral medications the patient was prescribed to take each day; and 3) the number of daily doses of the most frequently dosed antiretroviral medication, referred to as "dose frequency." We identified whether patients received medication through a drug trial and whether they used any of 6 adherence aids (medication list, timer, calendar, pillbox, taking medications with meals, or other) to help them remember to take their antiretroviral medication.

Features of the Clinical Interaction. To assess features of the clinical interaction, we used 4 scales. Continuity of care was assessed by asking, "How often do you see the same doctor or nurse practitioner in this clinic?" with 5 response options ranging from none to all of the time. Our measure of satisfaction with health care in the clinic used the 0 to 10 global rating scale from the Consumer Assessment of Health Plans Study.[72] Trust in the provider was assessed using a previously published measure (Cronbach's α 0.86).[73,74] Provider adherence counseling behaviors were assessed using a 10-item scale that asked patients whether their provider had done each of 10 adherence counseling behaviors (Cronbach's α 0.68).

Socioenvironmental Factors. Access to medication was assessed using a 5-item scale that was adapted for medication use from an existing access to medical care measure for patients with HIV (Cronbach's α 0.74).[75] A 3-item social support scale was adapted from the Medical Outcomes Study (Cronbach's α 0.71).[76] We measured stress using 4 items adapted from a 14-item scale (Cronbach's α 0.65) and active coping style using 3 items adapted from an existing coping scale.[77]

Reasons for Missing Doses. At exit, among those patients who self-reported any history of nonadherence, we assessed reasons for nonadherence by asking whether they had ever missed any antiretroviral medication for each of 14 possible reasons listed (*see* Table 2). These reasons were selected because they were the most common causes for missed antiretroviral medication reported in a focus group of HIV-infected men conducted to help in designing the survey instrument.

Statistical Analyses

We first assessed each patient's mean adherence to the initiated PI or NNRTI over the course of the study. We used descriptive statistics to assess patients' demographic, clinical, psychosocial, regimen, provider interaction, and socioenvironmental characteristics. Missing data on predictors of adherence were imputed, grouped by age and gender, using the hot deck imputation procedure in STATA 6.0 (Stata Corp., College Station, Tex). Values were imputed for the following variables (number of missing values in parentheses): living with a partner with HIV (8), working (9), acculturation (5), duration of diagnosis (25), duration of time on an antiretroviral (19), alcohol use (2), drug use (3), fit with lifestyle (29), number of adherence aids used (15), antiretroviral attitude (PI is worth taking) (8), other attitudes (2), self-efficacy (22), continuity (14), provider adherence counseling behaviors (33), trust in the provider (3), satisfaction with medical care (5), access to care (35), social support (2), income (47), literacy (34), and active coping style (1). We then performed bivariate analyses of the associations of hypothesized predictor variables with adherence to PI or NNRTI using t test, χ^2, Wilcoxon rank sum, and analysis of variance as appropriate. On the basis of our a priori model and incorporating variables related to adherence in the bivariate analyses ($P < .15$), we used forward stepwise regression to help select variables for a multivariate model. We excluded acculturation from the final model because of its multicollinearity with ethnicity. The final model selected included only factors that were associated with adherence at $P < .10$ in the model. We used Predicted Residual Sum of Squares (PRESS), a method that combines model estimation and validation into a single step.[78] The final multivariate model had the lowest PRESS compared with 53 other plausible models (8 intermediate models from the forward stepwise regression, 9 models with 1 more predictor added to the final model, and 36 models with 2 more predictors added to the final model). Goodness of model fitting was evaluated using adjusted R^2. Adjusted means were computed for significant predictors of adherence. Holding other values in the model constant at their mean level, the final model was used to predict adherence levels for each category of the categorical predictors of adherence and for the upper and lower quartile of continuous predictors of adherence.

RESULTS

Sample Characteristics and Adherence Levels

Of the 140 patients enrolled in ADEPT, 117 had their adherence measured for at least 2 four-week periods. Data from a total of 1,030 four-week periods from these 117 patients were available for this analysis. Median follow-up

for patients in this sample was 40 weeks. Compared to the 23 without adherence data, the 117 patients in this study sample were somewhat older (37.7 vs 33.9 years; $P = .03$) and had more total daily ART doses (13.3 vs 9.8). All other demographic, clinical, and regimen features, including duration of time on ART and daily dose frequency, were not significantly different.

The mean age of the subjects was 38 years. Eighty percent of subjects were male, 47% were Hispanic, 26% African American, and 16% white. Subjects were largely poor (63% reported an annual income $\leq$\$10,000), with 35% having less than a high school education. On average, subjects had received an average of 24 months of ART (range, 1 to 120 months), and 40% had participated in a study that supplied HIV medication. The mean highest viral load was 422,429 copies/mL, and the mean CD4 count nadir was 148. Seventy-five percent of patients reported seeing the same provider most or all of the time. Additional sample characteristics are displayed in Table 1. On average, patients took 71.3% of their prescribed PI or NNRTI doses over the 48-week study period (SD, 18.1%; median 73.0%; range, 4.8% to 96.6%).

Patient Beliefs and Self-efficacy Regarding Antiretroviral Medications

At study baseline, about 80% of patients felt that protease inhibitors were definitely or probably worth taking and agreed that antiretroviral medications helped people to live longer. However, only 73% agreed that antiretroviral medications improved the quality of people's lives. Seventy-seven percent did not agree with the statement "you could fight off HIV without medication." Eighty-five percent of patients agreed that if they did not take antiretrovirals exactly as instructed, their HIV could become resistant. Patients' perceived self-efficacy to take their antiretroviral medication was 9.38 on a scale of 1 to 10 (SD, 1.42; median, 10; range, 1 to 10) (Table 1).

Self-reported Reasons for Missing Doses

Among the 71 patients who, at exit, reported having ever missed a dose of ART, being too busy or forgetting (62%), being away from home (59%), or having a change in their daily routine (42%) were the most commonly cited of 17 possible reasons for missing. Being asleep (38%) and running out of medication (20%) were also commonly reported reasons. Less frequently, patients reported that having too many pills (15%), or being confused about dosage instructions (8%) or drug toxicity (12%) lead them to miss doses (Table 2).

Bivariate Associations between Independent Variables and Adherence

In bivariate analyses of patient factors and adherence, patients who were younger, had lower income, and who had lower educational attainment were less likely to adhere. African-American patients had significantly lower levels of adherence compared with Hispanic patients (mean adherence 62.8% vs 71.6%; $P < .01$). Patients who drank no alcohol in the last 30 days took 74.6% of their doses compared with 65.5% for those who drank alcohol ($P = .008$). In addition, patients who received medications in a drug study missed fewer doses (76.1%) than those not enrolled in a drug study (68.0%; $P = .012$). Patient gender, whether they were in a committed relationship, whether they were working, number of children, literacy level, self-efficacy, other clinical characteristics and beliefs about antiretrovirals were not associated with adherence. (Table 1)

The total number of pills and the number of antiretroviral medications were not significantly associated with adherence. The fit of the regimen with the patient's lifestyle also was not related to adherence. However, a greater dose frequency was associated with lower adherence levels ($P = .006$). The number of adherence aids used by the patient was weakly related with adherence.

The number of provider adherence counseling behaviors as reported by the patient was not associated with adherence. Although patients' satisfaction with their health care and continuity of care were not associated with adherence, trust in the provider was directly related to subsequent adherence ($P = .03$).

No socioenvironmental factor was found to be statistically significantly related to adherence, although there was a weak correlation between self-reported access to antiretroviral medication and adherence levels ($P = .10$).

Multivariate Results

In the final multivariate model, African-American ethnicity, lower income, lower education, greater alcohol use and active drug use, higher dose frequency, and the use of more medication reminders were independently associated with adherence (Table 3). Patient age and whether the patient had received HIV medication in a clinical trial were not significant predictors of adherence in this model. When we added use of medication reminders at 6 months to the final model, this variable was not associated with adherence and did not change the other parameter estimates in the model, so this was not included in the final model. Using the final model, we predicted adherence levels for each category of the significant categorical predictors of adherence and for the upper and lower quartile of continuous predictors of adherence while holding other values in the model constant at their mean level. Accordingly, those actively using drugs were predicted to take 59% of doses versus 72% for nonusers. Alcohol users were predicted to take 66% of ART doses, compared to 74% for nondrinkers. Patients with dosing regimens in the top quartile of frequency took 67% of prescribed pills versus 72% adherence for those with less-frequent dosing. Those using no adherence aids were predicted to take 67.5% of doses versus 76% adherence among the top quartile of adherence aid users.

Table 1. Sample Characteristics and Their Bivariate Associations with ART Adherence over the 12 Months Following Initiation of a HAART Regimen

Variable	Study Sample *N* = 117	% or μ for Study Sample	Range for Study Sample	Bivariate Association with Adherence
Patient demographics				
Gender, %				
Male	94	80%		0.717
Female	27	20%		0.696 (*P* = .61)
Race, %				
African American	31	27%		*0.628
Hispanic	55	47%		*0.701
White	19	16%		*0.761
Other	12	10%		*0.731 (*P* = .01)
Education, %				
Less than high school graduate	41	35%		0.659
High school graduate	56	48%		0.739
College graduate	20	17%		0.750 (*P* = .06)
Income/y, %				
≤$10,000	74	63%		0.686
>$10,000	43	37%		0.759 (*P* = .06)
In a committed relationship, %				
No	73	62%		0.719
Yes	44	38%		0.703 (*P* = .64)
Lives with HIV+ partner, %				
No	102	87%		0.671
Yes	15	13%		0.719 (*P* = .34)
Working, %				
Yes	35	30%		0.722
No	82	70%		0.709 (*P* = .71)
Age, μ		37.7	23 to 67	**r* = .19 (*P* = .04)
Children, *n*, μ		1.11	0 to 8	*r* = .14 (*P* = .12)
Acculturation, 5-point scale		3.6	1.0 to 5.0	**r* = −.21 (*P* = .03)
Literacy, 36-point scale		30.0	10 to 36	*r* = −.01 (*P* = .88)
Patient clinical				
Duration of diagnosis, mo		24	1 to 120	*r* = −.09 (*P* = .32)
Duration on ART, mo		14.4	0 to 98	*r* = −.11 (*P* = .90)
Highest VL, copies/cc		422,429	1 to 7,750,000	*r* = −.01 (*P* = .90)
CD4 count nadir, cells/cc		148.5	0 to 1130	*r* = −.09 (*P* = .32)
Physical health, 1- to 3-point scale		2.56	1.0 to 3.0	*r* = .08 (*P* = .40)
Emotional health, 0- to 5-point scale		2.08	0.57 to 3.57	*r* = −.07 (*P* = .48)
EtOH use in the last 30 d				
No	74	63%		*0.746
Yes	43	37%		*0.655 (*P* = .008)
IVDU as source of infection				
Yes	20	17%		0.686
No	97	83%		0.718 (*P* = .46)
Ever used illicit drugs?				
Yes	53	45%		0.689
No	64	55%		0.733 (*P* = .19)
Drug use in last 30 d?				
Yes	6	95%		*0.562
No	111	5%		*0.721 (*P* = .03)
Currently in drug study?				
Yes	47	40%		*0.761
No	70	60%		*0.680 (*P* = .017)
Regimen factors				
Total of antiretroviral doses per d, *n*		13.38	0 to 34	*r* = .07 (*P* = .45)
Dose frequency/d		2.80	2 to 5	**r* = −.25 (*P* = .006)
Total of antiretrovirals in regimen, *n*		3.67	3.0 to 8.0	*r* = .03 (*P* = .78)
Fit with lifestyle				
Some/a little/none	19	16%		0.685
Most/all	98	84%		0.703 (*P* = .74)
Use of adherence aids (% of total of 6 aids)		0.265	0 to 0.67	*r* = .157 (*P* = .09)

(*Continued*)

Table 1. (Continued)

Variable	Study Sample *N* = 117	% or μ for Study Sample	Range for Study Sample	Bivariate Association with Adherence
Patient beliefs				
PIs are worth taking, %				
Definitely not	1	1%		0.803
Probably not	0	0%		NA
Neutral	20	17%		0.682
Probably worth	31	26.5%		0.699
Definitely worth	65	55.5%		0.727 (*P* = .71)
May develop resistance if ART not taken as directed, %				
Strongly agree	41	35%		0.686
Agree	59	50%		0.735
Neutral	14	12%		0.713
Disagree	2	2%		0.714
Strongly disagree	1	1%		0.507 (*P* = .54)
ART helps you to live longer, %				
Strongly agree	53	45%		0.733
Agree	42	36%		0.697
Neutral	21	18%		0.698
Disagree	1	1%		0.600
Strongly disagree	0	0%		NA (*P* = .67)
ART improves quality of life, %				
Strongly agree	33	28%		0.734
Agree	52	44%		0.722
Neutral	30	26%		0.692
Disagree	1	1%		0.297
Strongly disagree	1	1%		0.600 (*P* = .15)
You can fight HIV without ART, %				
Strongly agree	4	3%		0.771
Agree	6	5%		0.748
Neutral	17	15%		0.657
Disagree	51	44%		0.681
Strongly Disagree	39	33%		0.768 (*P* = .11)
Self-efficacy, 0 to 10 scale		9.38	1 to 10	*r* = .05 (*P* = .59)
Provider factors				
Continuity				
All of the time		42%		0.730
Most/some		52%		0.709
Little/none		6%		0.627 (*P* = .37)
Provider adherence counseling behaviors, % of 10 behaviors		0.78	0.30 to 1.00	*r* = −.02 (*P* = .80)
Trust, 5-point scale		4.5	2.0 to 5.0	**r* = .20 (*P* = .03)
Satisfaction, on an 11-point scale		9.14	5.0 to 11.0	*r* = .02 (*P* = .87)
Socioenvironmental factors				
Access to ART, 5-point scale		3.89	1.4 to 5.0	*r* = .15 (*P* = .10)
Social support, 5-point scale		3.47	1.0 to 5.0	*r* = −.11 (*P* = .22)
Stress, 5-point scale				*r* = −.05 (*P* = .59)
Active coping, 5-point scale		3.60	1.0 to 5.0	*r* = .10 (*P* = .27)

* *Indicates result is significant at* P < .05.

ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; IVDU, intravenous drug use; NA, not applicable; VL, viral load.

DISCUSSION

We conducted a prospective cohort study among patients initiating a new highly active ART regimen to assess their objectively measured antiretroviral adherence during the 48 weeks following initiation of therapy. This study goes beyond prior work by evaluating adherence prospectively over a long time period among patients at the time of initiation of a new combination antiretroviral regimen. On average, patients attending this public hospital–affiliated clinic took about 71% of their prescribed doses. This is consistent with other studies showing that patients on combination ART miss fewer pills than do most patients on other chronic medical therapies.[7] However, this adherence level is lower than that required to prevent treatment failure.[7] In fact, 96% of patients in this sample took less than the 95% of prescribed doses probably necessary for long-term success.[7,21] These data underscore

Table 2. Patient-reported Reasons for Missing Doses (*N* = 71)

Ever missed a dose because...?	Yes at exit, %
You were away from home	59
You were busy or forgot	62
You had too many pills	15
The medication made you feel sick	30
You didn't want others to notice	14
You were confused about dosage directions	8
The drug reminded you of your HIV	8
You didn't think the drug was improving your health	11
There was a change in your daily routine	42
You felt the drug was too toxic	12
You took a drug holiday	18
You felt depressed or overwhelmed	17
You wanted to make the medication last longer	5
You ran out of medication	20
You were using alcohol or drugs	12
You were asleep when a dose was due	38
You used an alternative therapy	5

the extraordinary need that exists for interventions to facilitate patient adherence to antiretrovirals.

To help inform such interventions, we tested an a priori conceptual model of hypothesized determinants of adherence to identify factors affecting ART adherence. In multivariate analyses, African-American ethnicity, lower income and education, alcohol use, active drug use, greater dose frequency, and the use of no adherence aids were independently associated with worse adherence.

The relationship between substance abuse and adherence appears to be complex. Patients who drank alcohol were significantly less adherent. Current active drug use was also associated with suboptimal adherence. At the same time, there was no association between adherence and a history of prior drug use. Some studies have shown that any history of intravenous drug use is associated with worse adherence,[31,46] while others have found that recovered intravenous drug users demonstrate increased adherence to ART.[33,49] Our results are consistent with studies showing that active substance abuse is the important predictor of ART adherence.[22,31,33,38,46,49] These findings underscore the need for ongoing assessment of substance abuse and concurrent alcohol and drug counseling for patients on antiretroviral therapy. Use of alcohol and drugs needs to be talked about as a part of in-depth discussions about antiretroviral medication taking.

Patients who used more adherence aids were more adherent. This finding is interesting, and to our knowledge, this relationship has been noted in only 1 prior study.[31] We cannot assume a causal relationship between aids such as pillboxes and calendars and adherence, yet such reminder systems may represent important intervention options. Preliminary reports of the impact of reminders on adherence have had mixed results. In a pilot study of 55 patients, only those who received monetary reinforcement in addition to reminders and MEMS feedback were more adherent than controls.[79] In contrast, in preliminary data from another randomized trial of an on-line paging system, patients receiving paged medication reminders improved their adherence significantly more than controls over 4 weeks.[80] In qualitative studies, HIV-positive patients reported the usefulness of technological adherence aids, but many patients were unaware that such aids existed.[56] The incorporation of these aids into clinical practice may be warranted, given their association with adherence in this prospective study. Including standardized patient education about adherence aids during ART initiation is a practical way to introduce patients to these potentially valuable interventions. Further studies are needed to assess the long-term effects of medication reminder systems and to compare the efficacy of different types of reminders to improve ART adherence. Of note, because the use of MEMS

Table 3. Independent Predictors of Adherence to a PI or NNRTI

Variable	Parameter Estimate	Standard Error	*P* Value	Category	Predicted Adherence, %*
Ethnicity	−0.105	0.033	.002	African American	63.5
				Other	74.0
High school education	0.058	0.029	.05	High school	74.0
				Other	68.5
Income level	0.066	0.030	.03	<$10,000/y	68.8
				>$10,000/y	75.5
Alcohol use	−0.078	0.031	.01	None	74.2
				Any	66.3
Current active drug use	−0.129	0.066	.05	Some	59.0
				None	71.9
Dose frequency	−0.047	0.021	.02	25th percentile	75.1
				75th percentile	67.1
Number of reminders	0.033	0.014	.01	25th percentile	67.5
				75th percentile	76.3

* *Predicted adherence levels based upon multivariate model for an average patient for the upper and lower values of each of the significant predictor variables.*

Model included age and receipt of ART in a study, both of which were not predictive of adherence at $P < .05$. *PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.*

precludes pillbox use, the relationship between pillbox use and adherence could be confounded by the measurement technique used. To determine whether this is the case requires more intensive study with a trial focused on types of adherence adjuncts. If such studies show that pillboxes are associated with better adherence than MEMS, then for both ethical and clinical reasons, clinical trials should not preclude pillbox use in favor of MEMS.

Dose frequency was related to adherence, although the total number of pills and the total number of antiretrovirals prescribed was not. This supports prior studies demonstrating the importance of the number of times per day medications must be taken, although not all of these studies also assessed the number of medications taken.[22,27] More frequent dosing may lead to missing doses because patients have difficulty with the middle of the day dose.[56] The impact of dosing complexity on adherence can guide clinicians in selecting medication regimens and delineates a role for adherence aids to help to remind patients of midday doses. In addition, the fact that dose frequency is the only aspect of regimen complexity that affected adherence may have important implications for the development of combination pills, particularly if these medications are taken more frequently and/or are more expensive.

Lower educational achievement and lower income each were independently associated with having lower adherence. The relationship of lower socioeconomic status with ART adherence has been identified in other studies[34,44,50] but not consistently. This strong association does not appear to be mediated by access to care or literacy, neither of which were related to adherence in this study. Literacy, found to be related to adherence in other studies,[42] may have been compromised in this evaluation because of the large number of imputed values. The finding that lower education level is associated with worse adherence is consistent with the fact that understanding of treatment recommendations is necessary for adherence.

The finding that after controlling for other sociodemographic features, African-American patients were less adherent than others has also been noted in some studies[34,44,50] but not others.[22,41,42] Attempts to understand the mediators of the association between African-American ethnicity and nonadherence were unsuccessful in this study. We evaluated patients' beliefs about antiretrovirals, their trust in the provider, and their access to care. Post-hoc analyses indicate that there was no correlation between African-American ethnicity and beliefs about the medication. Further, there was no association between ethnicity and trust in the provider or access to care. It may be that because we measured trust in the physician only and access to medications specifically, we did not assess the exact beliefs that might explain these differences. Further studies to understand the mediators of nonadherence in relation to ethnicity are needed.

Several factors hypothesized to be associated with antiretroviral adherence were not. Patients who reported that their provider performed more adherence counseling and those with more-positive beliefs about the medications and more social support were no more adherent than other patients. However, adherence counseling was measured by patient report and may not accurately reflect provider behavior. At the same time, the trend toward greater adherence among patients with more trust in their provider and who were in a drug study suggests that the contact and rapport with the medical provider may play a role in influencing adherence. The vast majority of patients had positive beliefs about their medication, including high self-efficacy to take the medications. The minimal variation in responses to these questions may explain the lack of association between beliefs and adherence. Alternatively, some of the nonsignificant associations between predictors and the adherence measure could be due to limitations of the measures.

It is interesting that the reasons that patients gave for missing doses differed from those identified in comparative analyses. Although patients reported that factors related to fitting the regimen into their lifestyle (such as being busy, having a change in routine, being asleep) were important reasons for missing doses, perceptions of the medication fit with their routine was not associated with objectively measured adherence. This is in contrast to studies of self-reported adherence.[44] Hence, patients' perceptions of how well the regimen fits into their lifestyle may be more related to perceived adherence than to actual adherence.

The findings of this study must be interpreted in light of its limitations. Because it was conducted at a single site, the findings may not be generalizable to dissimilar clinical settings. In addition, this is an observational study, and the associations found cannot be assumed to be causal. However, the prospective design does reduce temporal ambiguity, and our multivariate analyses reduce confounding bias. Although the method we used to measure adherence allowed us to exclude MEMS data that were likely to be invalid (such as with the use of pillboxes), we may have missed some episodes in which patients took more than 1 dose out of their bottle at a time. Missing such episodes would result in a slight underestimate of adherence, but failure to adjust for these errors is extremely unlikely to change the findings of the study. Further, we did not assess predictors of different patterns of adherence, which may also be related to virologic outcomes. Finally, our sample size may have prevented us from detecting some relationships.

In summary, consistent with other studies, the vast majority of patients in this longitudinal study need interventions to improve adherence. Interventions are needed that attend to the needs of low-income, low-education patients. We also confirm other studies that underscore the need for ongoing assessment and treatment of substance abuse in concert with antiretroviral therapy. In addition, data reported here suggest a new finding: interventions that include technological aids and other reminders to help patients take their doses may be particularly useful and warrant further study. Finally, more forgiving,

less-frequently dosed medications are needed to help patients on ART adhere and maintain virologic success.

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