Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection

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Background: **Combination antiretroviral therapy with protease inhibitors has transformed HIV infection from a terminal condition into one that is manageable. However, the complexity of regimens makes adherence to therapy difficult.**

Objective: **To assess the effects of different levels of adherence to therapy on virologic, immunologic, and clinical outcome; to determine modifiable conditions associated with suboptimal adherence; and to determine how well clinicians predict patient adherence.**

Design: **Prospective, observational study.**

Setting: **HIV clinics in a Veterans Affairs medical center and a university medical center.**

Patients: **99 HIV-infected patients who were prescribed a protease inhibitor and who neither used a medication organizer nor received their medications in an observed setting (such as a jail or nursing home).**

Measurements: **Adherence was measured by using a microelectronic monitoring system. The adherence rate was calculated as the number of doses taken divided by the number prescribed. Patients were followed for a median of 6 months (range, 3 to 15 months).**

Results: **During the study period, 45 397 doses of protease inhibitor were monitored in 81 evaluable patients. Adherence was significantly associated with successful virologic outcome ($P < 0.001$) and increase in CD4 lymphocyte count ($P = 0.006$). Virologic failure was documented in 22% of patients with adherence of 95% or greater, 61% of those with 80% to 94.9% adherence, and 80% of those with less than 80% adherence. Patients with adherence of 95% or greater had fewer days in the hospital (2.6 days per 1000 days of follow-up) than those with less than 95% adherence (12.9 days per 1000 days of follow-up; $P = 0.001$). No opportunistic infections or deaths occurred in patients with 95% or greater adherence. Active psychiatric illness was an independent risk factor for adherence less than 95% ($P = 0.04$). Physicians predicted adherence incorrectly for 41% of patients, and clinic nurses predicted it incorrectly for 30% of patients.**

Conclusions: **Adherence to protease inhibitor therapy of 95% or greater optimized virologic outcome for patients with HIV infection. Diagnosis and treatment of psychiatric illness should be further investigated as a means to improve adherence to therapy.**

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Improved therapeutic strategies, including the introduction of protease inhibitors, have led to a striking decrease in HIV-related morbidity and mortality (1, 2). It is widely believed that adherence to an antiretroviral regimen is central to the likelihood that a patient will derive sustained benefit from therapy (3, 4).

Conventional wisdom holds that two groups of patients are currently experiencing clinical and virologic failure. The first group consists of patients who have received multiple different antiretroviral drugs over a prolonged period of time and who may be infected predominantly with HIV strains that are resistant to multiple drugs. The second group comprises patients who adhere poorly to their antiretroviral regimen. The two groups are not mutually exclusive: Patients with suboptimal adherence may be more likely to have antiretroviral drug–resistant HIV infection.

The potential public health importance of adherence to therapy in prevention of transmission of drug-resistant virus has also been emphasized (5). Patients with suboptimal adherence to antiretroviral therapy and poor adherence to use of safer-sex practices, such as use of condoms, may infect others with their own antiretroviral drug–resistant virus. Anecdotal experience suggests that physicians may be unwilling to prescribe combination antiretroviral therapy to patients whom they perceive to be at high risk for poor adherence (6).

Given the critical importance of adherence to therapy to patient outcome, secondary prevention of HIV infection, and willingness of providers to prescribe therapy, we prospectively investigated the association between protease inhibitor adherence and patient outcome, factors related to adherence, and the accuracy of physicians' prediction of patient adherence. We used a microelectronic monitoring system to assess adherence to antiretroviral therapy.

Methods

Study Sample

The study was conducted at the HIV clinics of the Veterans Affairs Medical Center, Pittsburgh, Pennsylvania, and University of Nebraska Medical Center, Omaha, Nebraska. The HIV physicians at these clinics were primary care providers for the study patients. Each site also had a dedicated HIV nurse coordinator. From August 1997 to March 1999, we enrolled consecutive patients with HIV infection who were already receiving a protease inhibitor ("experienced" patients) or who were to begin taking a protease inhibitor ("naive" patients). Exclusion criteria were inability to give informed written consent; expectation of continued use of a medication organizer to include protease inhibitors; and residence in a nursing home, jail, or hospice, where medications were dispensed at least daily.

Collection of Baseline Data

At baseline, a study investigator used medical chart review to complete a 52-item questionnaire for each patient. The questionnaire covered demographic information (age, sex, ethnicity, risk factors for HIV infection, educational and employment status, income), medical history (years known to be HIV infected; opportunistic infections; history of schizophrenia, depression, or bipolar affective disorder), and medication use (name, dose, and frequency of all antiretroviral agents, other antimicrobials, and other prescription therapies). The enrolling physician assessed use of illegal drugs and nonprescription therapies (including herbal or alternative therapies) by interview. Alcohol abuse was assessed by using the CAGE questionnaire (*cutting* down, *annoyance* with criticism, *guilty* feelings, and use of *eye*-opener drinks) (7). Information about use of adherence aids (such as personal reminders by significant others or timers, alarms, or other devices) was specifically sought. The investigator asked study patients if they felt that their current symptoms were attributable to HIV infection, the antiretroviral medications, or both. In addition, patients were asked whether they agreed with such health beliefs as "Do you think your antiretroviral therapy will make you live longer?" At baseline, each patient completed the Beck Depression Inventory and the General Health Questionnaire (8, 9), well-validated measures of psychiatric morbidity that have been widely used in patients with HIV infection (9–11). Patients completed the inventories as a written task without the assistance of a physician or clinic nurse.

At baseline, we used the following question to elicit a prediction of adherence to protease inhibitor therapy from the patient's primary HIV physician and clinic nurse: "Do you think that the patient is compliant with antiretroviral therapy, that is, taking greater than 80% of the prescribed doses of antiretroviral medications?" This prediction was made after collection of the baseline information but before actual measurement of adherence using the microelectronic monitoring system had begun.

Collection of Follow-up Data

Every 3 months for the duration of the study, the study participants were asked whether any of the following had changed since their previous visit: employment, use of alcohol or illegal drugs, residence, attribution of symptoms to the antiretroviral therapy or HIV infection, and changes in medications. Patients completed a new Beck Depression Inventory and General Health Questionnaire. The primary HIV physician determined whether the patient had developed an opportunistic infection in the past 3 months.

Laboratory Testing

At baseline and every 3 months for the duration of the study, HIV RNA levels were measured by using the Roche Amplicor System (Roche Diagnostics, Nutley, New Jersey) and CD4 lymphocyte subpopulation assays were performed.

Assessment of Adherence

Adherence was measured by using the Medication Events Monitoring System ("MEMS") (Aprex, Union City, California). The MEMS TrackCap system consists of standard medication bottles that have a pressure-activated microprocessor in the cap (12). The microprocessor records each opening and lists the date, time, and duration of opening. The information on medication dosing is retrieved by scanning the cap over a purpose-built communicator module. The information is then stored in a database provided by Aprex. Although the MEMS TrackCap system cannot prove consumption of the drug by the patient, prolonged deception by patients has been shown to be unlikely (13).

Patients were provided with a MEMS TrackCap bottle for each prescribed protease inhibitor (including refriger-

Table 1. **Baseline Characteristics of the 81 Study Patients**

Characteristic	Data
Demographic	
Median age (range), *y*	40 (21–62)
Ethnicity, *n*	
White	62
African-American	19
Risk factors for HIV, *n**	
Man who had sex with a man	52
Man who had sex with a woman	37
Injection of illicit drugs	13
Receipt of blood products	10
Woman who had sex with a man	7
Possible work-related exposure	7
Highest education level, *n*	
High school	31
Technical school	8
College	38
Graduate school	4
Monthly income, *n*	
$0–$500	11
$501–$1000	36
$1001–$1500	10
>$1500	22
Did not reveal	2
Type of housing, *n*	
Rents home	53
Owns home	28
History of drug and alcohol use	
Alcoholism, *n*†	11
Active use of illegal drugs, *n*	
Marijuana	5
Crack cocaine	1
Psychiatric history	
Previous psychiatric diagnosis, *n*	
Depression	21
Bipolar affective disorder	3
Schizophrenia	1
Anxiety	2
Beck Depression Inventory	
Mean score ± SE	11.1 ± 5.2
Patients with score >14, *n*	20
General Health Questionnaire	
Mean score ± SE	5.9 ± 0.66
Patients with score >6, *n*	24
HIV-related variables	
HIV RNA level, *n*	
<400 copies/mL	24
400–999 copies/mL	11
1000–9999 copies/mL	17
10 000–99 999 copies/mL	20
>100 000 copies/mL	9
CD4 lymphocyte count, *n*	
<50 cells/mm^3	11
50–99 cells/mm^3	5
100–199 cells/mm^3	14
200–500 cells/mm^3	29
>500 cells/mm^3	22
History of opportunistic infection, *n*	32
Attributes current symptoms to HIV infection, *n*	31
Attributes current symptoms to antiretroviral drugs, *n*	38
Mean pills taken per week ± SE, *n*	119 ± 4.5
Uses herbal or alternative therapies, *n*	22
Naive to all antiretroviral drugs, *n*	8
Was prescribed the following protease inhibitors at baseline, *n*	
Indinavir	23
Nelfinavir	33
Ritonavir	3
Saquinavir‡	3
Ritonavir and saquinavir‡	17
Amprenavir	2
Other variables possibly significant to adherence, *n*	
Uses timer or alarm as aid to adherence	13
Relies on significant other for adherence	14
Believes antiretroviral therapy will extend lifespan	76
Believes antiretroviral therapy will improve HIV RNA level	73
Believes antiretroviral therapy will decrease the risk for opportunistic infection	69

* Some patients had >1 risk factor.
† Defined as ≥2 positive responses on the CAGE questionnaire.
‡ Of 20 patients who received saquinavir, 8 received the soft-gel preparation and 12 received the hard-gel preparation.

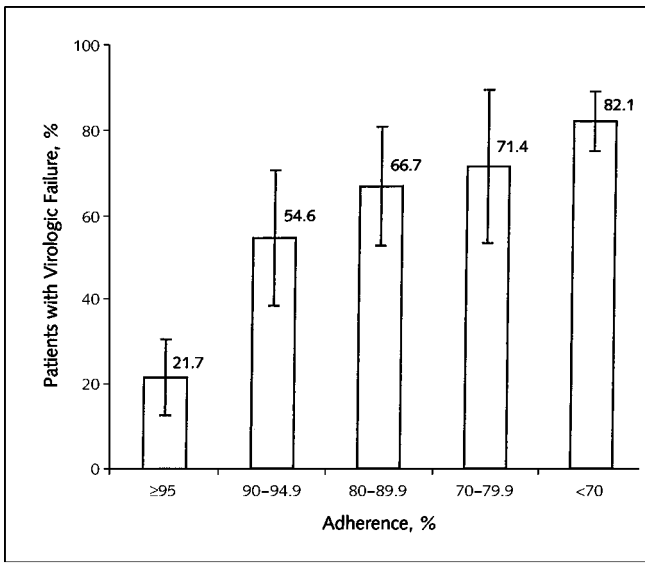
ated ritonavir capsules). Use of the MEMS TrackCaps system was not possible for patients who were prescribed ritonavir from August 1998 onward because ritonavir capsules were no longer available. The patients could use their regular medication organizer for all other medications. The caps were scanned each time the patient presented to the HIV clinic. Patients were specifically instructed not to take extra doses out at any time (for example, not to take out an extra dose in the morning for consumption at lunchtime). Patients were offered small pill bottles that could be easily carried in a coat pocket.

Adherence rates were defined as the number of doses recorded by the MEMS TrackCap divided by the total number of doses prescribed during the monitoring period. To evaluate the effect of dosing frequency on adherence, dosing interval errors were defined as medication doses taken at a time other than that prescribed (that is, <9 hours or >15 hours after the previous dose of a medication prescribed every 12 hours or <5 hours or >11 hours after the previous dose of a medication prescribed every 8 hours) (12).

Definitions of Virologic and Clinical Outcomes

Virologic failure was defined as an HIV RNA level greater than 400 copies/mL at the last study visit. Changes in CD4 lymphocyte counts were calculated as the difference between the count at the baseline visit and the count

Figure 1. **Adherence to antiretroviral therapy and virologic failure.**



The degree of adherence was significantly associated with risk for virologic failure ($P < 0.001$). Adherence of 95% or greater was associated with the lowest incidence of virologic failure.

at the final study visit. Opportunistic infections were defined according to Centers for Disease Control and Prevention criteria (14). Hospitalization for all causes was recorded as the number of nights spent in any acute-care hospital; nursing homes and drug or alcohol rehabilitation facilities were excluded. Mortality was defined as all-cause mortality at any time during the study period.

Statistical Analysis

All data was entered into a computerized database, PROPHET Statistics Version 6.0 (AB Tech Corp., Charlottesville, Virginia). The chi-square or Fisher test was used to compare categorical variables. Continuous variables were examined by using the *t*-test or the Mann–Whitney test. Baseline and follow-up values were compared by using the paired *t*-test or the Wilcoxon signed-rank test. To examine the relation between two continuous measures, a best-fit line was obtained. The slope of this line was then tested against the null hypothesis of a slope of zero. The Pearson correlation coefficient was also calculated. Cox proportional hazards regression was used to evaluate the relation between adherence and time to virologic failure. In the Cox model, predictor variables found to be significant ($P < 0.1$) in univariate analysis were added to the model. Logistic regression models were used to assess the effects of multiple variables on adherence. Factors were entered into the regression model if they were found by univariate analysis to be significantly associated ($P < 0.1$). To analyze time to return of detectable HIV RNA for patients with an undetectable viral load at baseline, Kaplan–Meier survival curves were computed for less than 95% adherence and 95% or greater adherence and were compared by using the Mantel–Cox test. The McNemar test was used to compare the predictions of the clinical nurses and physicians.

Ethical Considerations

The study was approved by the institutional review boards of the two study centers. Patients were fully informed that their adherence to protease inhibitor therapy was being measured by using the MEMS TrackCap system.

Results

Patient Characteristics

Of 99 patients enrolled in the study, 6 withdrew before follow-up data were collected (4 wished to use a medication organizer for their protease inhibitors and 2 did not give a reason). An additional 12 patients did not return their MEMS TrackCap system for data collection. Therefore, our study sample comprised 81 patients for whom data on adherence were collected by using the MEMS TrackCap and in whom HIV RNA levels were measured at least 3 months after the baseline visit. The demographic, clinical, and HIV-related characteristics of these patients are shown in **Table 1**. In total, 45 397 doses of protease inhibitors were observed in the 81 evaluable patients; 33 894 of these doses were taken (overall adherence for the study sample, 74.7%).

The median duration of follow-up for the study patients was 6 months (range, 3 to 15 months). The duration of follow-up was 15 months in 6% (5 of 81) of the patients, 12 months in 21% (17 of 81), 9 months in 16% (13 of 81), 6 months in 23% (19 of 81), and 3 months in 33% (27 of 81).

Adherence and Outcome

Figure 1 shows the relation between the degree of adherence and risk for virologic failure. In univariate analysis, other significant predictors of virologic failure were baseline viral load of 400 copies/mL or greater (relative risk, 2.4 [95% CI, 1.3 to 4.6]; $P < 0.001$), use of ritonavir (relative risk, 1.6 [CI, 1.1 to 2.2]; $P = 0.022$) or saquinavir

Table 2. **Factors Associated with Virologic Outcome**

Variable	Virologic Failure (n = 47)	Virologic Improvement (n = 34)	Univariate Analysis		Cox Model	
			Relative Risk (95% CI)	*P* Value	Relative Risk (95% CI)	*P* Value
Mean age ± SE, *y*	40.7 ± 1.3	41.3 ± 1.7	–	>0.2	–	–
Mean baseline CD4 lymphocyte count ± SE, *cells/mm*^{3}	264.9 ± 34	385.9 ± 37	–	0.011	0.99 (0.99–1.0)	>0.2
Mean (median) degree of adherence, %	58.7 (74.0)	87.0 (95.3)	–	<0.001	0.97 (0.96–0.98)	<0.001
Patients with ≥95% adherence, %	13	53	0.35 (0.17–0.70)	<0.001	–	–
Baseline viral load ± SE, *HIV RNA copies/mL**	18 241 ± 30 000	3247 ± 1428	–	<0.001	1.15 (1.01–1.31)	0.031
Patients with baseline viral load ≥400 HIV RNA copies/mL, %	85	50	2.4 (1.3–4.6)	<0.001	–	–
Nonwhite ethnicity, %	34	9	1.7 (1.2–2.2)	0.008	0.8 (0.60–1.6)	>0.2
Received ritonavir, %	34	12	1.6 (1.1–2.2)	0.022	2.4 (0.8–7.1)	0.12
Received saquinavir, %	34	15	1.4 (1.0–2.0)	0.03	0.76 (0.2–2.2)	>0.2
Has depression, %†	33	15	1.4 (1.0–2.1)	0.07	1.3 (0.67–2.7)	>0.02
Abuses alcohol, %‡	19	6	1.5 (1.0–2.1)	0.11	–	–

* Log transformation was done before analysis.
† Defined as Beck Depression Inventory score >14.
‡ Defined as a positive response to ≥2 items on the CAGE questionnaire.

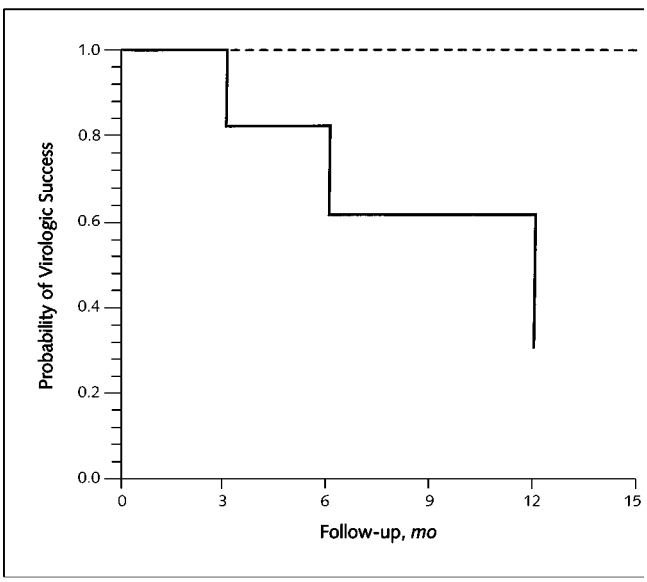
(relative risk, 1.4 [CI, 1.0 to 2.0]; $P = 0.03$), and nonwhite ethnicity (relative risk, 1.7 [CI, 1.2 to 2.2]; $P = 0.008$) (**Table 2**). Borderline nonsignificant associations were found between virologic failure and active depression (relative risk, 1.4 [CI, 1.0 to 2.1]; $P = 0.07$) and active alcoholism (relative risk, 1.5 [CI, 1.0 to 2.1]; $P = 0.11$). When these variables were subjected to Cox proportional hazard survival regression analysis, only degree of adherence (relative risk, 0.97 [CI, 0.96 to 0.98]; $P = 0.001$) and baseline viral load (relative risk, 1.1 [CI, 1.0 to 1.3]; $P = 0.031$) were independent predictors of virologic failure (**Table 2**).

Only 5 of 23 (22%) patients with adherence of 95% or greater throughout the study period had virologic failure. In contrast, compared with patients with adherence of 95% or greater, the risk for virologic failure was 61% in patients with adherence of 80% to 94.9% (odds ratio, 5.6 [CI, 1.3 to 25.7]) and 80% in patients with less than 80% adherence (odds ratio, 14.4 [CI, 3.4 to 66.6]).

Among patients with baseline HIV RNA levels less than 400 copies/mL, 0 of 7 with adherence of 95% or greater had detectable HIV RNA at the final study visit compared with 41% (7 of 17) of patients with less than 95% adherence (**Figure 2**). Among patients with baseline HIV RNA levels of 400 copies/mL or greater, 31% (5 of 16) of those with adherence of 95% or greater had detectable HIV RNA at the final study visit compared with 85% (35 of 41) of those with adherence less than 95%.

Changes in CD4 lymphocyte count throughout the study were significantly associated with degree of adherence ($P = 0.006$; $R = 0.31$). Changes in CD4 lymphocyte counts differed significantly between patients with 95% or greater adherence (mean increase, 83 cells/mm^3) and those with less than 95% adherence (mean increase, 6 cells/mm^3)

Figure 2. **Kaplan–Meier plot of patients with HIV RNA levels less than 400 copies/mL at baseline, stratified by degree of adherence.**



The probability of having detectable HIV RNA levels at follow-up was significantly greater in patients with less than 95% adherence (*solid line*; $n = 7$) than in patients with 95% or greater adherence (*dotted line*; $n = 17$) ($P = 0.02$, Mantel–Cox test).

($P = 0.045$). This relation was significant even when we controlled for length of follow-up.

During the study, three new AIDS-defining opportunistic infections were observed (cryptosporidiosis, *Pneumocystis carinii* pneumonia, and cytomegalovirus); all occurred in patients with less than 95% adherence (**Table 3**).

Only two patients died during the study period. One was a patient with 25% adherence who developed intractable cryptosporidial diarrhea. The other patient was enrolled in the study but never had adherence recorded; he died of cardiac toxicity caused by cocaine abuse.

Degree of adherence and duration of acute-care hospital stay during the study period were also significantly associated ($P = 0.001$) (**Table 3**).

Predictors of 95% or Greater Adherence

According to univariate analysis, patients with 95% or greater adherence were more likely to be older ($P = 0.035$), to be white ($P = 0.0017$), to have a higher monthly income ($P = 0.058$), and to have lower psychiatric morbidity as measured by the General Health Questionnaire ($P = 0.0014$) (**Table 4**). Compared with patients with less than 95% adherence, patients with 95% or greater adherence had been infected with HIV for a longer time (median duration of infection, 8 compared with 6 years; $P = 0.12$). Only 1 of 23 (4%) patients with 95% or greater adherence had alcohol abuse problems compared with 10 of 58 (17%) patients with less than 95% adherence ($P = 0.127$). Sex, risk factors for HIV, employment, accommodation status, attribution of symptoms to HIV infection or to antiretroviral therapy, or use of a timer or alarm as a reminder to take therapy was not associated with 95% or greater adherence ($P > 0.2$ for all comparisons).

Multivariate analysis of the variables that were significantly associated with 95% or greater adherence on univariate analysis showed that lower psychiatric morbidity (odds ratio, 1.7 [CI, 1.0 to 3.0]; $P = 0.04$) and older age (odds ratio, 1.1 [CI, 1.0 to 1.2]; $P = 0.01$) were significantly associated with 95% or greater adherence. White ethnicity (odds ratio, 8.4 [CI, 0.9 to 71.8]; $P = 0.11$), absence of alcoholism (odds ratio, 5.8 [CI, 0.6 to 57.8]; $P = 0.13$), and higher income (odds ratio, 1.5 [CI, 0.1 to 1.8]; $P > 0.2$) were not independently associated with 95% or greater adherence.

Effect of Drug and Dosing Frequency on Adherence

By using the definition of adherence rate as the number of total doses recorded by the MEMS TrackCap system divided by the total number of doses prescribed during the monitoring period, twice-daily administration of protease inhibitors was associated with a nonsignificant improvement in adherence compared with three-times-daily administration (median adherence, 89.2% compared with 85.7%; $P = 0.09$). No protease inhibitor was associated with significantly better adherence.

When adherence rate was defined as the number of doses taken at the correct time divided by the total number of doses prescribed during the monitoring period, twice-daily administration of therapy was associated with significant improvement in adherence compared with three-times-daily administration (median adherence, 63% and 45%; $P = 0.04$).

Prediction of Adherence by Health Care Professionals

Physicians misjudged the degree of adherence in 41% of their patients. Fifty-one percent of patients in whom physicians predicted that adherence would be less than 80% actually had greater than 80% adherence (among these patients, 21% had >95% adherence). Clinic nurses misjudged the degree of adherence in 30% of their patients, but the superiority of clinic nurses over physicians in predicting adherence was not statistically significant (odds ratio, 1.8 [CI, 0.8 to 4.0]; $P = 0.12$).

Table 3. **Association between Adherence to Antiretroviral Therapy and Virologic, Immunologic, and Clinical Outcomes**

Outcome	Adherence ≥95% ($n = 23$)	Adherence <95% ($n = 58$)	Relative Risk (95% CI)	*P* Value
Patients with virologic failure, % (*n*/*n*)	22 (5/23)	72 (42/58)	0.3 (0.14–0.66)	<0.001
Patients with decrease in CD4 lymphocyte count, % (*n*/*n*)	17 (4/23)	33 (19/58)	0.35 (0.2–1.4)	>0.2
Mean change (increase) in CD4 lymphocyte count ± SE, *cells/mm*^{3}	83 ± 23	6 ± 20		0.045
Mean days hospitalized per 1000 days of follow-up (range), *n*	2.6 (1.5–4.3)	12.9 (10.8–15.9)	4.9 (2.9–9.1)	<0.001
Patients with new opportunistic infections, % *(n/n)*	0 (0/23)	5 (3/58)		>0.2
Deaths, % *(n/n)*	0 (0/23)	2 (1/58)		>0.2

Table 4. **Variables Associated with Degree of Adherence**

Variable	Patients with ≥95% Adherence (n = 23)	Patients with <95% Adherence (n = 58)	Relative Risk (95% CI)	P Value
Demographic characteristics				
Mean age ± SE, *y*	44.4 ± 2.1	39.6 ± 1.1		0.035
Sex, %				
Female	4	4	0.48 (0.1–3.0)	>0.2
Male	96	90		
Ethnicity, %			Noncalculable	
White	100	67		0.0017
African-American	0	33		
Risk factors for HIV				
Man who had sex with a man, %*	82	65	1.9 (0.7–4.9)	0.17
Injected illicit drugs, %	17	12	1.3 (0.6–3.2)	>0.2
Highest education level, %				
High school	22	45		0.005
Technical school	9	10		
College	52	45		
Graduate school	17	0		
Currently employed, %	48	41	1.2 (0.6–2.4)	>0.2
Monthly income, %†				
$0–$500	22	45		
$501–$1000	9	10		
$1001–$1500	52	45		
>$1500	17	0		
Housing situation, %				
Owns home	43	4	1.4 (0.7–2.9)	>0.2
Rents home	57	69		
Lives alone	35	30	1.4 (0.7–2.9)	>0.2
History of drug or alcohol abuse, %				
Any current illicit drug use	9	7	1.1 (0.4–3.9)	>0.2
Alcoholism	4	17	0.28 (0.04–1.9)	0.127
Psychiatric history				
Previous psychiatric diagnoses, %	30	34	0.87 (0.4–1.9)	>0.2
Mean Beck Depression Inventory score ± SE	8.5 ± 1.1	12.2 ± 1.6		0.05
Mean General Health Questionnaire score ± SE	3.5 ± 0.8	6.0 ± 0.5		0.12
HIV-related variables				
Median time known to be HIV infected ± SE, *y*	8.0 ± 0.8	6.0 ± 0.5		0.12
Median baseline CD4 count ± SE, *cells/mm^3*	336 ± 55	243 ± 30		0.136
Mean baseline viral load ± SE, *HIV RNA copies/mL*	844 ± 3800	332 ± 25 000		0.121‡
Naive to antiretroviral therapy, %	9	10	0.86 (0.2–3.0)	>0.2
Median pills prescribed to be taken per week ± SE, *n*	108 ± 9	112 ± 5		>0.2
Uses alternative therapies, %	30	26	1.2 (0.2–3.0)	>0.2
Attributes symptoms to current antiretroviral therapy, %	52	48	1.2 (0.7–2.3)	>0.2
Attributes symptoms to HIV infection, %	35	40	0.8 (0.4–1.8)	>0.2
Uses the services of ≥2 physicians for HIV care, %	13	9	1.4 (0.5–3.6)	>0.2
Sees same physician >80% of the time, %	87	79.5	1.5 (0.5–4.4)	>0.2
Believes that use of antiretroviral drugs will prolong life, %	100	91	Noncalculable	>0.2
Believes that use of antiretroviral drugs will decrease risk for opportunistic infection, %	87.5	84	1.1 (0.4–3.3)	>0.2
Believes that use of antiretroviral drugs will improve HIV RNA level, %	96	88	2.4 (0.4–15.6)	>0.2
Uses timer or alarm to enhance adherence, %	9	19	0.5 (0.1–1.9)	>0.2
Relies on a significant other for reminders to take pills, %	13	19	0.7 (0.2–2.1)	>0.2

* Six female patients were excluded from this analysis.
† Two patients with <95% adherence declined to state their monthly income.
‡ Log transformation was performed before comparison.

Discussion

By convention, an acceptable level of adherence to therapy in chronic illness is consumption of more than 80% of the prescribed doses. This breakpoint has been widely used in studies of antihypertensive agents and orally administered oncologic therapy and in earlier studies of adherence to therapy in HIV-infected patients (15–18). However, we show that patients with 95% or greater adherence had a superior virologic outcome, a greater increase in CD4 lymphocyte count, and a lower hospitaliza-

tion rate than did patients with lower levels of adherence. Of much practical importance is the finding that asking about missed doses in the past 1 or 2 days, as is widely recommended (19), may not be sensitive enough to determine whether a patient has 95% or greater adherence.

Although unmeasured confounders, such as psychological state or physical comorbid conditions, may have influenced the relation between adherence and the outcomes in our study, such a scenario is unlikely. Our relatively short follow-up (mean, 7.3 months [range, 3 to 15 months]) made it less likely that changes in psychological state or physical comorbid conditions would be dramatic enough to affect virologic or clinic outcome. In support of this idea, only three opportunistic infections occurred during follow-up.

In multivariate analysis, 95% or greater adherence was independently associated with lower psychiatric morbidity and older age. Given that psychological history was not associated with adherence, it is possible that poor outcome due to poor adherence leads to psychological illness. Our data, however, support the temporal sequence of psychological illness leading to poor adherence. Nonadherence may lead to psychological illness, predominantly (if not exclusively) by the association of poor adherence with poor physical health. However, objective data obtained during follow-up do not suggest that physical morbidity was sufficient to affect patients' mental health. Numerous studies, both of HIV infection and other illnesses, have associated the presence of psychiatric illness with decreased adherence to therapy (20–24). Clearly, interventions to effectively diagnose and treat active psychiatric illness should be examined as a potential strategy to improve adherence.

Our data documented no association between illegal drug use and poor adherence. A weakness of our study is that only 7% of patients were active users of illegal drugs; of these, 5 were marijuana users. Therefore, the size of the β error precludes determination of whether active illegal drug use is associated with suboptimal adherence to antiretroviral therapy.

In the era of zidovudine monotherapy, negative beliefs about the efficacy of zidovudine were associated with suboptimal adherence (22, 25). Our study sample had generally positive attitudes about use of protease inhibitors. Ninety-two percent of the patients felt that their antiretroviral regimen would improve their longevity. Positive beliefs that the antiretroviral regimen would prolong life or improve HIV RNA levels were nonsignificantly associated with improved adherence. Of note, patients were able to maintain high levels of adherence to antiretroviral therapy even in the presence of symptoms that were ascribed to antiretroviral therapy: Fifty-two percent of patients with 95% or greater adherence had symptoms that they believed were therapy-related. Physicians are more likely than their HIV-infected patients to believe that therapy-related symptoms are a major barrier to continued adherence (26). It is possible that patients with HIV tolerate side effects better than patients with "less severe" chronic diseases, such as hypertension and diabetes mellitus (27), because they are more aware of adverse outcomes associated with poor adherence.

An advantage of the MEMS TrackCap system is that timing of doses can be ascertained. Protease inhibitors are increasingly prescribed on an every-12-hours basis if their pharmacokinetics allow such administration. We noted a nonsignificant trend toward improved adherence with less frequent dosing of protease inhibitors (for example, every 12 hours), as has been seen outside of the HIV setting (27–32). Previous studies in HIV-infected patients and other patients with chronic illnesses have shown that as the complexity of a regimen increases, adherence to it decreases (32). The a higher rate of virologic failure seen with ritonavir or saquinavir could be due to the fact that these drugs were used primarily in combination as salvage therapy.

We found that clinicians are poor predictors of their patients' adherence to therapy. Physicians miscategorized adherence for 41% of their patients. Underestimation of a patient's adherence is of particular concern because physicians may be reluctant to prescribe active therapy for many patients. Overestimation of adherence (based on a cutoff value of 80%) occurred in 28% of cases; such overestimation may lead to therapeutic changes based on perceived failure of therapy. In fact, therapy may be failing simply because the patient has not adhered to the antiretroviral regimen. Perhaps accurate measures of adherence (electronic monitoring or well-validated self-reported measures) should be used whenever physicians consider changing a therapeutic regimen.

In summary, we found a significant association between poor adherence to antiretroviral therapy and virologic failure. Adherence with protease inhibitors of 95% or greater is necessary to optimize virologic outcome. Improved efforts to diagnose and treat psychiatric comorbid conditions should be further investigated as a means to

improve adherence to therapy and, perhaps, outcome in patients with HIV infection.

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References

1. **Hogg RS, Health KV, Yip B, Craib KJ, O'Shaugnessy MV, Schechter MT, et al.** Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA. 1998;279:450-4.
2. **Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al.** Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338:853-60.
3. **Montaner JS, Hogg R, Raboud J, Harrigan R, O'Shaughnessy M.** Antiretroviral treatment in 1998. Lancet. 1998;352:1919-22.
4. **Deeks S, Loftus R, Cohen P, Chin S, Grant R.** Incidence and predictors of virologic failure to indinavir (IDV) and/or ritonavir (RTV) in an urban health clinic [Abstract]. In: 37th International Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, 1997. Washington, DC: American Soc for Microbiology; 1997:.
5. **Wainberg MA, Friedland G.** Public health implications of antiretroviral therapy and HIV drug resistance. JAMA. 1998;279:1977-83.
6. **Bangsberg DR, Hecht FM, Charlebois EC, Zolopa AR, Holodniy M, Sheiner L, et al.** Spontaneous adherence (ADH) audits (SAA) predict viral suppression in the REACH cohort [Abstract]. In: Program and Abstracts of the 6th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, 31 January-4 February 1999. Alexandria, VA: Foundation for Retrovirology and Human Health; 1999:84.
7. **Buchsbaum DG, Buchanan RG, Welsh J, Centor RM, Schnoll SH.** Screening for drinking disorders in the elderly using the CAGE questionnaire. J Am Geriatr Soc. 1992;40:662-5.
8. **Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J.** An inventory for measuring depression. Arch Gen Psychiatry. 1961;6:561-71.
9. **Lyketsos CG, Hutton H, Fishman M, Schwartz J, Treisman GJ.** Psychiatric morbidity on entry to an HIV primary care clinic. AIDS. 1996; 10:1033-9.
10. **Zich J, Temoshok L.** Perceptions of social support in men with AIDS and ARC: relationships with distress and hardiness. Journal of Applied and Social Psychology. 1987;17:193-215.
11. **Singh N, Squier C, Sivek C, Wagener M, Nguyen MH, Yu VL.** Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. AIDS Care. 1996;8:261-9.
12. **Waterhouse DM, Calzone KA, Mele C, Brenner DE.** Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol. 1993;11:1189-97.
13. **Kastrissios H, Suarez JR, Katzenstein D, Girard P, Sheiner LB, Blaschke T.** Characterization patterns of drug-taking behavior with a multiple drug regimen in an AIDS clinical trial. AIDS. 1998;12:2295-303.
14. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep. 1992;41:1-19.
15. **Eldred LJ, Wu AW, Chaisson RE, Moore RD.** Adherence to antiretroviral and pneumocystis prophylaxis in HIV disease. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18:117-25.
16. **Besch CL, Morse E, Simon P, Hodges J, Franchino B.** Preliminary results of a compliance study within CPCRA 007 Combination Nucleoside Study (NuCombo). For the Terry Beirn Community Programs for Clinical Research on AIDS [Abstract]. In: Program and Abstracts of the 4th National Conference on Retroviruses and Opportunistic Infections, 22–26 January 1997, Washington, D.C. Alexandria, VA: Infectious Diseases Soc of America for the Foundation for Retrovirology and Human Health; 1997:111.
17. **Lopez-Suarez A, Fernandez-Gutierrez del Alam C, Perez-Guzman E, Giron-Gonalez JA.** Adherence to the antiretroviral treatment in asymptomatic HIV-infected patients [Letter]. AIDS. 1998;12:685-6.
18. **Rodriguez-Rosado R, Jimenez-Nacher I, Soriano V, Anton P,**

Gonzalez-Lahoz J. Virological failure and adherence to antiretroviral therapy in HIV-infected patients [Letter]. AIDS. 1998;12:1112-3.
19. **Hecht FM.** Measuring HIV treatment adherence in clinical practice. AIDS Clinical Care. 1998;10:57-9.
20. **Young JL, Zonana HV, Shepler L.** Medication noncompliance in schizophrenia: codification and update. Bull Am Acad Psychiatry Law. 1986; 14:105-22.
21. **Coons SJ, Sheahan SL, Martin SS, Hendricks J, Robbins CA, Johnson JA.** Predictors of medication noncompliance in a sample of older adults. Clin Ther. 1994;16:110-7.
22. **Draine J, Solomon P.** Explaining attitudes toward medication compliance among a seriously mentally ill population. J Nerv Ment Dis. 1994;182: 50-4.
23. **Carney R, Freedland K, Eisen S, Rich J, Jaffe A.** Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol. 1995;14:88-90.
24. **Pugh R.** An association between hostility and poor adherence to treatment in patients suffering from depression. Br J Med Psychol. 1983;56(Pt 2):205-8.
25. **Fernandez F, Ruiz P.** Psychiatric aspects of HIV disease. South Med J. 1989;82:999-1004.
26. **Gallant JE, Block DS.** Adherence to antiretroviral regimens in HIV-infected patients: result of a survey among physicians and patients. Journal of the International Association of Physicians in AIDS Care. 1998;May:32-5.
27. **Mehta S, Moore RD, Graham NM.** Potential factors affecting adherence with HIV therapy. AIDS. 1997;11:1665-70.
28. **Anderson RJ, Kirk LM.** Methods of improving patient compliance in chronic disease states. Arch Intern Med. 1982;142:1673-5.
29. **Gatley MS.** To be taken as directed. J R Coll Gen Pract. 1968;16:39-44.
30. **Malahey B.** The effect of instructions and labeling in the number of medication errors made by patients at home. American Journal of Hospital Pharmacology. 1966;23:283-92.
31. **Porter AM.** Drug defaulting in general practice. BMJ. 1969;1:218-22.
32. **Samet JH, Libman H, Steger KA, Dhawan RK, Chen J, Shevitz AH, et al.** Compliance with zidovudine therapy in patients infected with human immunodeficiency virus, type I: a cross-sectional study in a municipal hospital clinic. Am J Med. 1992;92:495-502.

When the pneumonia hit, everything changed.

Mrs. Dutta had been ill before, but those illnesses had been different. Even in bed she'd been at the center of the household with Reba coming to find out what should be cooked, Sagar's father bringing her shirts with missing buttons, her mother-in-law, now old and tamed, complaining that the cook didn't brew her tea strong enough, and Sagar running in crying because he'd had a fight with the neighbor boy. But now she had no one to ask her querulously, Just how long do you plan to remain sick? No one waited in impatient exasperation for her to take on her duties again. No one's life was inconvenienced the least bit by her illness.

Therefore she had no reason to get well.

Chitra Divakaruni
"Mrs. Dutta Writes a Letter"
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Submitted by:
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