Taking Antiretroviral Therapy for HIV Infection

Learning from Patients' Stories

M. Barton Laws, PhD, Ira B. Wilson, MD, MSc, Diana M. Bowser, MPH, Sarah E. Kerr, MA

OBJECTIVE: To describe how people with HIV understand and experience the problem of adhering to antiretroviral medication regimens.

DESIGN: We performed a qualitative study based on interviews with HIV-infected patients, including 46 clients of AIDS service organizations, who were sampled according to age, ethnicity, and injection drug use history, and a convenience sample of 15 patients. Interviews were conducted in English or Spanish and were audiotaped and transcribed.

PARTICIPANTS: Of 52 respondents who had prescriptions for antiretroviral therapy, 25 were randomly selected for in-depth analysis. Of these, 5 reported having an AIDS diagnosis, 15 reported symptoms they attributed to HIV, and 5 reported having no symptoms of HIV disease.

MEASUREMENTS AND MAIN RESULTS: Investigators prepared structured abstracts of interviews to extract adherence-related data. One investigator compared the abstracts with the original transcripts to confirm the interpretations, and used the abstracts to organize and classify the findings. Most subjects (84%) reported recent nonadherent behavior, including ceasing treatment, medication "holidays," sleeping through doses, forgetting doses, skipping doses due to side effects, and following highly asymmetric schedules. Initially, most reported that they were not significantly nonadherent, and many did not consider their behavior nonadherent. Only a minority clearly understood the possible consequences of missing doses. Most said they had not discussed their nonadherence with their physicians.

CONCLUSIONS: Many people rationalize their difficulty in adhering to HIV treatment by deciding that the standard of adherence they can readily achieve is appropriate. Physicians should inquire about adherence-related behavior in specific detail, and ensure that patients understand the consequences of not meeting an appropriate standard.

KEY WORDS: antiretroviral therapy; adherence; HIV.
J GEN INTERN MED 2000;15:848-858.

Highly active antiretroviral therapy (HAART) has markedly reduced morbidity and mortality from HIV in the United States.¹ However, clinical stability requires long-term suppression of viral loads,^{2,3} which requires that patients take 10 to 20 pills every day for an indefinite period. Evidence is accumulating that missing only a few doses a week may impair virologic outcomes.⁴⁻⁶ Failure to completely suppress viral loads is associated with development of resistance to antiretroviral agents, which limits treatment options for individuals and creates risk of transmitting resistant virus to others.^{7,8} The level of adherence required to achieve long-term effectiveness is likely higher for HAART than for other chronic therapies.

Many empirical studies of adherence were done in the era of zidovudine (AZT) monotherapy.⁹⁻¹⁴ Recent reviews summarize our understanding of HIV medication adherence.¹⁵⁻¹⁸ Many abstracts relating to adherence have been presented at recent meetings, but understanding of adherence in the era of protease inhibitors is still in its early stages. Much current research focuses on quantifying patients' adherence,¹⁹ but adherence is a complex behavior. To achieve a more nuanced understanding of adherence, and learn about ways to improve it, we conducted a qualitative study to (1) describe patterns of patients' medication-taking behavior and factors related to nonadherent behavior, (2) describe how the adherence "story" emerges from in-depth interviews, and (3) assess patients' knowledge of viral resistance and the importance of not missing doses. Another goal of the study was to understand patients' decision-making processes regarding initiation and continuation of drug therapy.

METHODS

This study used qualitative research methods, which are appropriate to generate theoretical constructs and hypotheses that can be tested using quantitative methods.²⁰ Qualitative studies have been useful in understanding end-of-life care^{21,22} and health values²³ for patients with HIV. This study was approved by the Institutional Review Board of the Latino Health Institute.

Sampling

The study took place in Massachusetts. A selection strategy was used to recruit a diverse group of 46 respondents. Within each of five regions used by the Massachusetts Department of Public Health for planning purposes, we created targets for numbers of respondents according to gender, ethnicity, and injection drug use history, based on the proportion of people with these characteristics

Received from the Latino Health Institute Center for Research on Culture and Health and the Department of Family Medicine and Community Health, Tufts University School of Medicine, Boston, Mass (MBL); Department of Medicine, New England Medical Center and Tufts University School of Medicine, Boston, Mass (IBW); Harvard School of Public Health (DMB); and the Department of Anthropology, Case Western Reserve University, Cleveland, Ohio (SEK).

Address correspondence and reprint requests to Dr. Laws: Senior Investigator in Social Science and Policy, Center for Research on Culture and Health, Latino Health Institute, 95 Berkeley St., Boston, MA 02116 (e-mail bart@lhi.org).

among those reported to the Massachusetts AIDS Surveillance Program.²⁴

We asked AIDS service organizations (ASOs—providers of social services to people with HIV) from each region to assist in selecting clients from among those who fit a profile we needed to meet our sampling targets. In most cases, the ASO provided us with a list of client identification codes, which we placed in random order using a computer application. We then asked the ASO to attempt to recruit the first person on the list, and to move down the list in order if unsuccessful. Some ASOs made the selection by drawing slips of paper from a hat or similar means. Eligibility requirements included a diagnosis as HIV seropositive, aged 18 years or older, and ability to speak English or Spanish well enough to be interviewed. Those who were currently incarcerated were not eligible.

Whenever possible, we worked with organizations that were not providers of medical services. Of the 21 participating ASOs, however, two were community health centers, since these were the major providers of HIV/AIDS services in their cities. The social services departments, not the medical departments, made the contacts in these cases.

Fifteen additional interviews were conducted with a convenience sample recruited through flyers posted at two ASOs in Boston and through word of mouth by interviewees. This made it possible to interview people whose only association with an ASO was dropping in for lunch, information, or other purposes not requiring them to be enrolled as clients.

In this article, respondents are identified by a code indicating their gender, age in years, and ethnicity. When more than one respondent had the same demographic characteristics, they were identified by a parenthetical number.

Interview

We conducted 61 interviews during April 1998 through June 1998. Forty-six interviews were in English and 15 in Spanish. Twenty-six interviews took place in respondents' homes, two in hospitals, four in residential substance abuse treatment programs, and 29 in our offices or offices of collaborating organizations. Interviews were audiotaped and transcribed. We paid respondents \$20.

In developing the interview guide, we held a focus group of eight people with HIV to discuss their experiences with making decisions about treatment and following treatment regimens. We consulted with staff of an HIV treatment education program and HIV case managers to learn about the issues they commonly see with their clients, and we consulted published literature on patient decision making and medication adherence. We developed the interview guide in English and Spanish, using standard back-translation methods. We field-tested the instrument with two individuals before beginning interviews. We made modifications in the instrument based on our experience with early interviews. It is standard practice in

qualitative research to add and modify items as early cases suggest new hypotheses and theoretical categories of interest, consistent with the inductive goal of qualitative inquiry.

The interview, which typically took from 1 to 2 hours, included closed-ended questions establishing sociodemographic background, health insurance coverage, and key parameters of self-reported medical history and current health status, including the date of HIV diagnosis, CD4⁺ cell count, and viral load. It also included the Control Preferences Scale,²⁵ consisting of 5 items, which respondents are asked to rank order using a series of 2-item comparisons: I prefer to make the final decision about which treatment I will receive; I prefer to make the final selection of my treatment after seriously considering my doctor's opinion; I prefer that my doctor and I share responsibility for deciding which treatment is best for me; I prefer that my doctor makes the final decision about which treatment will be used, but seriously considers my opinion; I prefer to leave all decisions regarding my treatment to my doctor. Respondents then picked the one item that best described the actual decision-making process in their cases.

Open-ended questions with probes and follow-ups and some closed-ended response check-offs queried current living situation, natural and formal support networks, and health, mental health, and substance abuse history. The instrument focused in most depth on the physician-patient relationship and communication, knowledge and beliefs about HIV and HIV treatments, and respondents' experiences with treatments, including nonallopathic remedies, the current prescribed regimen (if any), and past regimens.

Nonadherence is generally underreported,²⁶ perhaps in part because respondents tend not to report behavior they think may result in a negative judgment of them by the interviewer,²⁷ or because respondents might lack a clear definition of adherence or not recognize that certain behavior is nonadherent.²⁸ To overcome these problems, questions about respondents' regimens, side effects, and specific adherence behavior were asked several times, in a nonjudgmental fashion, and in different ways.

The full interview guide in English and Spanish is available on request from the first author. Interviewers were trained to use the guide flexibly; to create a comfortable, conversational feeling; and to pursue any unanticipated issues which seemed relevant.

ANALYSIS

To provide context, we will summarize findings on treatment decision making based on a descriptive analysis of the full set of 61 respondents; these findings are reported at length elsewhere.²⁹ The findings on adherence behavior are based on interviews with 25 respondents selected at random from among the 52 who had prescriptions for antiretroviral medications. All 61 respondents

received the same interview protocol. The selection was made after the interviews had been transcribed. We used a subset of 25 respondents to permit in-depth description and analysis. Fifteen had prescriptions for combination therapy including protease inhibitors; nine had prescriptions for reverse transcriptase inhibitors only. One had refused a prescription from his physician, but had a nonallopathic regimen prescribed by an "alternative practitioner."

We continued analyzing cases until we determined that we were not discovering new categories of adherence-related phenomena.³⁰ We reviewed the transcripts of cases that were not selected, and determined that they did not contain any broad categories not observed in the selected cases.

Two research assistants and two coauthors (DMB, SEK) prepared abstracts from the selected transcripts using a standard form to extract information with reference to page and line numbers. The form included sociodemographic background, addiction history, HIV disease history, treatment history, current prescribed medications, and references to adherence from throughout the interview. The abstracters summarized any reported changes in adherence over time, including adherence to previous regimens, changes made in regimens because of adherence problems, and the respondent's conceptualization of HIV disease and the activity of prescribed medications. Finally, the abstracters provided their interpretations of the respondent's medication-taking practice and reasons for adherent and nonadherent behavior.

The first author used these abstracts as the basis for organizing and classifying the findings, while checking all of the abstracts against the source material to confirm the abstracters' interpretations. The first author sorted the medication-taking practices and related beliefs into categories, which the coauthors reviewed. Only findings and interpretations that represent consensus among the authors are reported.

RESULTS

Participants

Table 1 summarizes the demographic characteristics of all 61 participants and the subsample. Compared with the best information on the demographics of the HIV epidemic in Massachusetts,³¹ both the sample and the subsample underrepresent African Americans and overrepresent Latinos. Latino overrepresentation is even greater in the subsample, in part because Latinos were more likely to have prescriptions for antiretroviral medications.

Of the 25 selected respondents, five reported that they had received an AIDS diagnosis, five that they did not know if they had been diagnosed with AIDS, and 15 that they did not have AIDS. Ten reported a history of opportunistic infections, including three who did not have a diagnosis of AIDS and two who did not know. Twelve others who did not have an AIDS diagnosis or did not know re-

ported other symptoms, such as wasting or fatigue, which they attributed to HIV. Three reported no symptoms they attributed to HIV.

Decision Making About Antiretroviral Therapy

All 61 respondents could identify a physician who was currently responsible for their HIV care. However, many reported that they had delayed consulting a physician for 2 months to 4 years after learning their diagnosis of HIV infection. (Our recruitment methods did not enable us to interview anyone who was currently in this phase.)

Fifty-two of the respondents had prescriptions for antiretroviral medications. Although most respondents said they had made or shared in the decision about what course of treatment to follow, many of those who had prescriptions had difficulty naming the medications they were taking, or identifying the class (e.g., protease inhibitor) to which they belonged. Most did not specify any known side effects of their medications, other than symptoms they had actually experienced and attributed to their medications. A notable exception is that many people who were taking protease inhibitors said they had been instructed to drink copious amounts of water to prevent kidney stones.

No one said that they had requested or believed they should be receiving any drug which their physician had not prescribed. No respondent reported that therapy was withheld because of a physician's belief that the respondent would not adhere to therapy. No one reported learning about a drug from some source other than their physician. Six respondents who were asymptomatic and had low or undetectable viral loads reported that their physicians recommended against antiretroviral therapy until they showed signs of disease progression. They accepted this judgment even when family members and associates did not.

In all, 56 of the 61 respondents stated that they intended to follow the course of therapy recommended by their physicians. There were five exceptions, all of whose physicians had recommended antiretroviral therapy.

Respondent M45AA, an active heroin user, had refused antiretroviral medications recommended by his physician in favor of herbal remedies and supplements prescribed by an "alternative practitioner," noting concerns about drug toxicity. However, his reasons for rejecting the physician's prescription centered on his feeling that she did not respect him. Respondent M48P, also an active heroin user, reported that he had refused an antiretroviral prescription because the physician dismissed his requests for help with his addiction and emotional problems. He had recently changed physicians. His new physician had referred him for substance abuse treatment and social work services, and he had agreed to begin an antiretroviral regimen shortly. Respondent M30L had chosen to cease pharmaceutical treatment and rely on Reiki therapy, citing disturbances of taste caused by

Table 1. Subject Characteristics

Characteristic	In Subsample (n = 25)	Not In Subsample (n = 36)	Total (n = 61)
Mean age, y $\pm$ SD	39.5 $\pm$ 6.7	39.2 $\pm$ 6.6	39.3 $\pm$ 6.6
Range	27–57	24–50	24–57
Mean years of school $\pm$ SD	11 $\pm$ 4	13 $\pm$ 3	12 $\pm$ 3
Range	1–20	7–20	1–20
Female, n (%)	8 (32)	7 (19)	15 (25)
Spanish speakers, n (%)	10 (40)	5 (14)	15 (25)
Ethnicity, n			
Euro-American*	9	15	24
African-American	3	4	7
Latina/o†	12	17	29
Portuguese	1	0	1
Region, n			
Western	6	2	8
Central	1	3	4
Northeast	4	4	8
Metro Boston	12	23	35
Southeast	2	4	6

* White, not Hispanic, U.S.-born.

† Includes those who gave their ethnicity as Puerto Rican, Indio (an indigenous person from Guatemala), and mestizo (Latinos of mixed European and indigenous American heritage).

his medications and the need to maintain balance and harmony in his life. In two cases, participants' doubts about their ability to adhere led them to decline to add protease inhibitors to their existing regimen of reverse transcriptase inhibitors.

Most English-speaking respondents reported that they made substantial efforts to inform themselves about HIV and HIV treatments from sources such as magazines, educational services of ASOs, conferences, the Internet, and literature provided at their physicians' offices. Spanish-speaking patients used these resources less often. Nevertheless, respondents' explanations of viral activity and drug mechanisms of action were usually different from accepted scientific explanations. Examples of nonscientific explanations were that the medication is "supposed to keep your immune system trapped or something . . . that keeps certain viruses trapped in one spot," (F30C) and that viral load is a measure of how many babies the mother virus is having (F48AA). F43C reported that she was taking AZT, not to suppress her viral load, but to combat anemia. Many complained about medical jargon. Said F48AA, "It's really frustrating to get . . . literature that's supposed to tell you what to look for, and you can't even understand the words."

Beliefs About Viral Resistance and Skipping Doses

The remaining findings are based on the subset of 25 respondents. At several points during the interview, respondents had the opportunity to express their understanding of the concept of drug resistance. Respondents commonly explained medication failure as the virus being intelligent and willful, and "learning" how to overcome the

medications. No respondent referred to Darwinian evolution, mutation, or natural selection in relation to the development of resistance. Indeed, few displayed accurate awareness of the possibility and consequences of resistance. Respondent F41C was aware that there was an issue of drug resistance associated with AZT monotherapy, but did not seem to know that the concept also applied to her current HAART regimen. Some who had heard the word had little idea what it might mean. For example, F43L, when asked if missing doses could cause resistance, said, "Yes, that changes your immunence [sic]. You know that it changes something there, I don't know."

M51C said that it "has been reported . . . that there is some resistance in some people to reduced dosages or to missed dosages." If this is true, he said, people ought to be reminded to take their medications. However, he was skeptical about it. Respondent M41L(2) had the idea that resistance is associated with the interaction of viral reproduction and pharmacokinetics, but could not explain how:

You know, the pills work for 8 hours. If you don't take—you know, if you take it every day, and if you took your next dose 2 hours later, your body is exposed, like you know, the reproduction of the—you know, to make—it makes—gives—gives open resistance to the effect of the pills. Makes you think, you know.

Most who used the term "resistance" seemed to view it as a change in their bodies, rather than the virus. M41L(2) later said:

[T]he body gets resistant . . . [T]he body is very intelligent . . . you know it gets to the time when the pills don't affect you any more. They don't do what they have to do

because the body knows how to . . . you know they detect itself, learning how to do, go around.

Respondent M37C(2), who reported good adherence, gave a clear statement of the consequences of drug resistance:

Well, if I took my antiretrovirals part of the time, there wouldn't be a constant minimum amount in my bloodstream to be able to defeat the virus, . . . and I would become drug-resistant to not only them, but a whole host of other antiretrovirals, and it would be a significant mark towards my death.

Respondent M36C, who also reported good adherence, offered an accurate explanation of drug resistance as a change in the viral protein structure. However, the other reportedly highly adherent subjects (M41AA and M57L) offered no concept of drug resistance at all.

Most respondents understood that adherence to their medication regimens was important so that the drugs will work effectively, but they did not necessarily remember being told why this is so. For example, respondent M34L(2) insisted that while his physicians told him he should not miss doses, they never explained to him what would happen if he did, but this did not disturb him. (He does not speak English, and his physicians do not speak Spanish.) Respondent F45AA also was told by her doctor that she needed to follow her medication schedule, but did not recall any explanation of why this was necessary.

M41L was given a rationale by his physician which does not correspond to any medical model, but did make an impression:

[The doctor] explained it to me . . . that medication are [sic] like the soldiers, okay? There are 100 soldiers, fighting the enemy, no? The enemy is the virus. . . . Then of those 100 soldiers, well, the virus is going, the enemy is going to kill [some] of them, so there are going to be fewer. . . . well then one has to keep the medication . . . constantly there so that it will be in the battle. Because if not, well, the virus, well, it's going to take advantage of that and it's going to, the virus is like intelligent.

Some respondents reported their physicians told them they should not be overly concerned about occasional missed doses. F43L said her doctor told her that if she misses a dose, she should just take the medication the next day and that "I'm not going to die because I don't take them one day." M43L had decided that worrying too much about adherence was more likely to make him sick than was missing doses, although his physician had tried to convince him otherwise. He declined the doctor's offer of assistive devices such as alarms and pill boxes.

How the Adherence "Story" Emerges

Only four respondents reported being fully adherent to their prescribed regimen and made no statement indicating that they were substantially nonadherent or had been recently. Many others asserted that they were adherent, but reported behavior that would normally be

classified as nonadherent. Most described their adherence as good when first asked. Table 2 shows examples of the first assertion about current adherence made by respondents, followed by a summary of their behavior as revealed by subsequent dialogue. A complete table of this information is available from the corresponding author.

Typically, people's first description of their pattern of adherence included a qualifier that indicated they missed doses to a degree which was infrequent or inconsequential. Later, this might turn out to be several times a week or for days at a time.

Patterns of Nonadherence

Failure to Initiate Treatment. Respondent F43L(2) had received a prescription for Combivir 3 months previously, shortly after being released from jail, but had not filled the prescription because she could not afford it. However, she repeatedly referred to her anxiety about side effects, particularly diarrhea. She had not discussed these fears with her HIV specialist physician who could have enrolled her in a state program to pay for her medications.

Respondent F32L was diagnosed with HIV in Puerto Rico while pregnant. She said doctors urged her to take medication (presumably AZT) during her pregnancy, but that she did not, because she and her husband were afraid people would see her at the clinic and word would get back to her family that she was HIV infected.

Stopping Treatment. F32L immediately accepted antiretroviral treatment for her perinatally infected newborn, but did not seek treatment for herself until several months later after the family had moved to Massachusetts. She soon stopped because, "I decided 'I don't want any more,' because I grew tired, and 'I don't want to know anything more about medicines.'" Her physician discovered that her viral load had soared, and she admitted upon inquiry that she had discontinued the medications. She said he then told her, "If you had followed to the letter, your medicines are working in your body [sic]." So, "Now I follow to the letter and you can see [the result]." She reported her adherence has been good recently, although not 100%.

Respondent M37C stopped taking his medications 2 weeks before the interview because he had been instructed to stay out of the sun while taking Indinavir, which was incompatible with his work as a roofer. He maintained that he had asked his physician's secretary to inform the physician that he had stopped taking his medications and that he needed an appointment immediately to discuss the problem, but the physician refused to see him. Respondent F41C reported stopping treatment for 4 weeks because she did not find time to get to the pharmacy to pick up a refill.

Drug Holidays. Respondent M39C said that "sometimes I do holidays" of 3 to 4 days from the medication, because "I like to get myself free from all drugs." He did not tell his

Table 2. Selected First References to Adherence and Subsequent Self-reports, Selected Subjects

ID code	First Assertion about Adherence	Pattern as Described Later
F46L	"No, I don't have problems, sometimes I forget but not so much."	Sometimes forgets because she is busy; because at the scheduled time she is in the car or does not have water, and then forgets to take medication later; has failed to refill her prescription on time; sometimes misses a few days at a time.
F41C	"I've never really missed a lot of this. This combination I'm on." "I've never missed, you know, a day."	Sometimes misses nighttime dose due to falling asleep. "Sometimes it can be at least once a week. Sometimes it can be more." Also late on midday dose if at a meeting.
M39C	Switched to Combivir from a more complex regimen because he is sometimes forgetful. He has been offered a phone reminder service, but "I am not going to try it because I got . . . I basically remember 2 times a day."	Takes 3 to 4 day holidays. Sometimes forgets to take medication with him. Seems not to consider holidays to constitute nonadherence.
M33C	Asked, "Do you ever miss a dose?" Responds, "I have. Fell asleep."	Released from jail about 6 months prior to interview. Missed doses while in shelters, but cannot remember how often. Prescriptions had run out day of interview, claimed he intended to fill them but had already missed morning dose. Admits that has happened before. Later in interview, claims he never misses a dose.
M34L(2)	"I'm getting better little by little, thank the Lord. Or it's because I've followed the rules of the treatment."	Forgets once or twice a month when visiting mother; forgets when drinking beer with the family. Has had pills left over 3 days after they should have run out. (Note: was dropped by his previous physician for missing too many appointments.)
F45AA	Says her health is good because "I've been taking my medicine the right way."	Does not take when she misses meals. Does not take when out of house and does not trust the water. Sometimes forgets. Admits to missing doses 1 to 2 times a week. Takes Nevirapine on her own asymmetrical schedule (6:00 AM, 3:00 PM).
M43L	"Well, it isn't hard for me. Really I have no problem. The only thing I have is that often I leave here in a hurry and I forget to take it."	Sometimes forgets his morning dose—indeed, has forgotten the morning of the interview. When interviewer urges him to take it now, suggests he does not really want to. Says he has run out and not filled his prescription on time 2 or 3 times in last year. Says he also just forgets once or twice a week, then says maybe 3 times a week. Finally says it is more important not to worry than it is to be adherent.

physician about this practice. Respondent F43L said she sometimes stopped for 2 or 3 days "when I get angry." Respondent M51C said he had taken 6-week drug holidays. His viral load "shot up" on those occasions, but he did not believe the practice was harmful. He was convinced that almost every HIV patient takes holidays. A variation on the holiday is the practice of M43L who fasted as often as a few times a week, during which he did not take medications. He believed this was beneficial to his health, as fasting caused the body to cleanse itself, and that it brings him closer to God.

Sleep Patterns. Ten respondents reported chronic fatigue and sleepiness, which they attributed variously to HIV, comorbid conditions, or medication side effects. Some said they tended to fall asleep in the afternoon and miss

the midday dose, some fell asleep too early at night and missed the evening dose, others overslept and were late with or missed morning doses.

Patient Follows Own Schedule. M41C defined adherence as "3 times a day. I don't take them every 8 hours . . . I take them whenever I eat. Sometimes 2 hours apart." He said he ate breakfast at 10:00 AM, when he took his protease inhibitors and Lamivudine; lunch at 1:00 PM, when he took another dose of protease inhibitors; and he took his final dose of both medications with dinner at approximately 6:00 PM:

[T]hey're not spaced like they're supposed to, but I know enough about the medication where I know that they still overlap . . . These medications don't flush out of your system in 8 hours like they make . . . people believe.

Respondent F45AA put herself on a twice-a-day schedule for Nelfinavir, because she did not eat at midday. Her doctor had told her that twice-a-day dosing was acceptable, but did not review how to divide the doses. She decided to take her morning and afternoon doses together in the morning (6 pills) and her evening dose (3 pills) at night.

Forgetting Doses. Many respondents reported memory deficits, attributed, as with chronic fatigue, to various causes. F29C was a mentor in a program to promote adherence, but nevertheless reported difficulties due to forgetfulness and excessive sleeping. She was often surprised to find she had pills left when it was time for refills. M34L(2) was seldom aware of having missed doses, but he also found he had pills left over. Forgetfulness may be triggered by emotional stress. M34L(3) said that when his brothers did not write to him, he forgot about everything, including his medications.

Respondent M41L(2) lived in a residential substance abuse treatment facility. The program holds residents' medications at the front desk, and requires that residents take the initiative to pick up one dose at a time. He often could not remember whether he had taken a dose. He described going to pick up his medications, getting into a conversation with the attendant, forgetting why he was there, and leaving without the medications.

Skipping Doses Due to Side Effects. Respondent M34L skipped doses when he experienced symptoms (headache and vomiting) he attributed to his medication. He did not consider this nonadherence, and he did not tell his physician about it. Respondent F37L intensely disliked her current physician, who she accused of giving her unnecessary treatments and vaccinations which made her sick. She complained of unanticipated side effects of her antiretroviral medication: "I didn't know [it] make your ass skinny and your arms skinny. If I knew that I wouldn't take that medication in the first place." Although she said she was still taking the medication, she was unable to produce the bottles from her single-room occupancy unit and admitted to missing doses, although she would not say how often.

Disruption of Routine, or Circumstantial Barriers. F45AA was told that if she took her medication without food, it would make her sick. So when she skipped a meal, she also skipped her medication. Sometimes she also forgot to take medication with her when she left the house. If she was in a house where the housekeeping was not up to her standards, she would not take her medications because she did not want to drink the water. Respondent M41L said that the only reason he ever misses a dose is because he leaves the house in a hurry and forgets to take his medications with him. M34L(2) sometimes missed doses when visiting his mother or drinking beer with family members. F41C, a member of the consumer advisory board of an ASO, reported she sometimes missed doses because there was no water available during board meetings.

Heroin and Cocaine Addiction. M45AA reported that his active heroin addiction interfered with adherence to his non-allopathic regimen. Subject M39C, a cocaine user, had difficulty with adherence, but would say only that this was for "personal, private reasons."

Respondents M33C, M34L(3), F29C, F43L, and M41L(2) reported having had prescriptions for antiretroviral medications during previous periods of active heroine and/or cocaine abuse. All reported poor adherence during these periods, and all but F43L specifically attributed poor adherence to their drug abuse. M34L(3) and F29C said that it was their single-minded focus on obtaining and using heroine that caused them not to take medications. M41L(2) said that when he was an active cocaine addict, he "forgot most of the time to take them . . . I didn't want anything to interfere with my high. I didn't want to think about HIV when I was high."

Cultural and Language Issues

There were distinct differences between Spanish- and English-speaking subjects in their approach to treatment decision making. Using the Control Preferences Scale, we found that most respondents reported that they prefer to share responsibility for treatment decision making with their physicians or to make the final decision themselves. However, there was a strong tendency for Spanish-speaking people to want to cede a larger share of the decision to their doctor. Indeed, 3 of 15 persons interviewed in Spanish said they preferred to leave the decision entirely up to their physicians, while none of the 46 English-speaking respondents said this.

Like M34L(2), many Spanish-speaking respondents expressed little need for information or explanation. F43L said she actively rejected information and cut her doctor off when he tried to give her any.

Differences in adherence-related behavior were less clear. While Spanish-speaking subjects did not report holidays as such, we noted the case of the man who stopped taking medications when he fasted, and two individuals who stopped for a day or more when they became emotionally upset. While all Spanish-speaking subjects made an effort to follow their prescribed regimens, they were no more likely than English-speaking subjects to be so diligent that they did not miss doses due to forgetfulness, sleeping, or disruption of routine. While the language barrier limited the ability of some to communicate with their physicians about medication-taking practices and problems, such communication was often limited even in the absence of a language barrier.

DISCUSSION

The first important observation to emerge from these interviews is that few (4 of 25) of our interviewees reported being fully adherent with their medications. A recent report using Medication Event Monitoring Systems (MEMS;

APREX, Union City, Calif) verifies that “perfect” adherence is uncommon.³² Physicians should assume that most patients will have at least some difficulties taking their medications.

A second theme is that patients rely heavily on their physician’s advice when deciding about antiretroviral therapy, but often do not have a good understanding of information relevant to decision making. Many had difficulty in understanding medical jargon. Of particular concern is that patients usually had a limited understanding of the concepts of viral resistance and the importance of adherence. Although we do not know what actually transpired between patients and physicians, it is clear that physicians’ efforts to explain the concept and cause of viral drug resistance, or to specify standards of adherence were often unsuccessful, or misdirected. In a study conducted in Massachusetts and Rhode Island using focus groups, Stone et al.³³ found a higher level of understanding of resistance and standards of adherence among people with HIV. The difference in results with our study could result from different methods of selecting subjects (recruitment through clinical settings vs social service settings) and/or from the different methods of collecting data (focus groups vs in-depth interviews). A disadvantage of focus groups is that a confident and knowledgeable participant can cue others to information or ideas, making the method less suitable for learning about subjects’ knowledge and understanding.

A third theme is that patients who initially reported no problems taking their medications as prescribed usually revealed problems on further questioning. We do not believe that this is simply that subjects at first report what they believe the interviewer wants to hear. Rather, it appears that patients often do not recognize that the ways in which they have “customized” their regimens, or the frequency with which they unintentionally miss doses, may jeopardize treatment efficacy. These modifications often appear to be efforts to make combination therapy fit into patients’ complex lives, or to make compromises with what seems possible or worthwhile.

Similar observations have been made regarding adherence to antiseizure regimens.³⁴ Conrad found, based on semistructured interviews with patients, that patient-provider interactions are not as salient in understanding people’s medication taking behavior as are the “meanings of medication in people’s everyday lives.” He calls deviation from prescribed practices “self-regulation,” rather than “noncompliance.” As in our study, instances include “reducing the dose, stopping for a time, or regularly skipping or taking extra doses . . . depending on various circumstances.”

Our respondents generally did not report important details of their medication-taking practices to their physicians. While this may represent an aversion to being judged as “nonadherent,” another explanation is that patients simply do not appreciate that their physician needs to know this level of detail, and do not believe that their

medication-taking behavior is problematic. Observations based on analysis of actual medical encounters with people taking antihypertensive medication found that physicians may inquire about adherence indirectly or without seeking sufficient specific information for accurate assessment.³⁵

A final set of themes relate to patterns of nonadherence. While there are many patterns of taking medications, we believe that the basic categories of nonadherent (or self-regulating) behavior that we observed are a useful framework for communicating with patients about this topic. Physicians may do well to inquire specifically about drug holidays, sleep patterns, timing of meals, forgetfulness, perceived side effects, recurring disruptions of routine, and drug and alcohol use. Other work supports the importance of these factors.^{36–38}

Another way to think about these observations is in terms of the classic social-psychological models for behaviors affecting health. The health beliefs model³⁹ postulates that people’s health-related behaviors are determined by a “rational” cost-benefit analysis based on their perception of the likelihood and costs of an adverse health event (such as progression of HIV disease), and the health-related costs and benefits of adopting a protective behavior (such as taking anti-retroviral medications). This is similar to the way physicians think in making clinical decisions, and indeed, our subjects derive important health beliefs—that their prescribed medications will combat HIV disease and prolong their lives—largely from their physicians. The developers of the model³⁹ contend that unsatisfactory relationships with physicians, including the perception that physicians have not provided sufficient medical information, can be related to nonadherence, but we found this to be clearly evident in only three cases (M41C, F37L, M45AA). In other cases, physicians may indeed have failed to provide all the important relevant information, but respondents did not report perceiving this to be the case.

In the more complex social cognition theory,⁴⁰ beliefs about health risks and benefits are included among the personal factors that shape behavior. Environmental influences—social, institutional, and physical—are also included, as are people’s skills and “self-efficacy”: their perception of whether they are able to carry out a behavior, and that their own actions determine their fate.⁴¹ We hypothesize that our subjects frequently reconciled dissonance between their health belief that adherence to their medication regimen would save their lives and their limited or compromised ability to actually follow the regimen, by conforming their health beliefs to their behavior. That is, people come to believe that whatever standard of adherence they are able to achieve is good enough, as in the case of respondent M41C who “knows” that compressing his doses into a 10-hour period is just as good as taking them every 8 hours.

Our respondents face 3 categories of difficulties in adherence to their medication. The first is knowledge: not

understanding the importance of strict adherence or believing that some pattern of dosing is adherent when in fact it is not. This category is consistent with the health beliefs model. The second category is the patient's ability to carry out his or her intentions regarding medications, which may be compromised by external barriers, such as not having access to one's physician to solve problems or answer questions, or by intrinsic conditions, such as disabilities or comorbidity (falling asleep, forgetting, addiction, drug toxicity). The third category is social and psychological—not wishing for others to know that one is HIV-infected, not wishing to confront the fact oneself, and self-efficacy, which is a prerequisite for making a serious effort. This is essentially the explanation for holidays: they are a time during which someone not only can be free of the burdens of taking medications, but can consider oneself free of HIV. The latter 2 categories are consistent with Social Cognition Theory, but cannot be accommodated as easily to the health beliefs model.

Another widely used framework for thinking about health-related behavioral change is the so-called transtheoretical, or stages of change model,⁴² which posits five stages: (1) precontemplation, when the person is not considering changing the behavior; (2) contemplation, when the person is thinking about changing the behavior but has not made a commitment to do so; (3) preparation, when there is a firm intention to change soon; (4) action, while the change is implemented; and (5) maintenance, during which the individual works to avoid relapse. This idea is called the transtheoretical model because it is consistent with the leading cognitive models of behavior cited earlier. While health beliefs are usually necessary to motivate people to move through the stages of change, the model does not assume they are sufficient. The model also incorporates self-efficacy. It suggests that to promote adherence and support patients in achieving it, physicians or other counselors must assess the individual's current stage and provide the appropriate information and support to facilitate movement to the next one. In most cases, our subjects were in an action phase in that they were trying to be adherent to their regimens, but the situation was sometimes ambiguous. What they were trying to do may not have been consistent with what their physicians wished for them to do, but they were not aware of this.

Good adherence may or may not require that the patient have an understanding of viral replication, mechanisms of drug action, and viral drug resistance which corresponds to the biomedical model. For some people, these modes of thinking are congenial and persuasive, but for others, metaphors such as "enemy soldiers" or viral intelligence are more acceptable. Of course, it is ethically essential that patients recognize these explanations as metaphors, not literal truths.

Regardless of the terms of explanation, many of our respondents simply had not been told clearly and memorably what they must do in order to be adequately adherent, nor did they understand the consequences of partial

adherence. Some subjects had been told by their physicians that they should not be overly concerned about occasional missed doses. While this may be perfectly good advice in the abstract, "occasional" may be redefined by patients to correspond to whatever they can readily achieve.

Our study has several strengths. Qualitative methods of research and analysis were used that provide an in-depth understanding of adherence behaviors related to the complex, but life-prolonging treatment regimens for a prevalent condition, HIV infection. Accepted methods of qualitative research were used, including grounded theory³⁰ in which categories are derived from the data rather than assumed a priori, that enhance the validity of our findings with respect to the population studied. Our participants were diverse in terms of their sites of care, geographic location within Massachusetts, gender, ethnicity, and proficiency in English. The overrepresentation of Spanish speakers enabled us to examine language and cultural issues.

Several limitations should be considered in interpreting the results of this study. Our study population is not representative of all HIV-infected patients or of all those prescribed antiretroviral therapy. It does not include people who have no contact with AIDS service organizations. The sample may overrepresent people with substantial psychosocial problems. African Americans are underrepresented, possibly because they have limited involvement with ASOs. Finally, Massachusetts is unusual among the states in the substantial public investment it has made to ensure that people with HIV have access to medical treatment and prescription drugs. In other states, financial barriers may be more important.

Because this was a qualitative study, we cannot make assertions about the percentage of people taking antiretroviral medications to whom any of our observations apply. However, we can reasonably expect that most of the phenomena we have identified are not rare, as we found repeated instances of most of them in a small sample.

The study is based on self-reports. In addition to the known unreliability of self-reports of adherence, repeated questioning could give respondents cues about the nature of nonadherent behavior, leading to response bias. However, respondents tended to report more nonadherent behavior as the interview went on. Repeated questioning and in-depth discussion provide a test of reliability lacking in typical closed-ended interviews.

Although we asked people to describe the complete history of their HIV treatments and adherence-related behavior, this is a cross-sectional study which suffers from the unreliability of recall. A longitudinal study that followed patients' adherence behavior from the inception of treatment would give information about how changing circumstances, knowledge, and beliefs; interventions by physicians and others; and patients' experience of illness affect adherence over time.

A further limitation of this study is that it is based on deficit, rather than success, modeling. So few of our

respondents reported exemplary adherence that from our data, we are reluctant to put forward a theory of what makes for success in following these regimens.

Finally, we do not have the physicians' side of the story. We do not know what physicians actually told respondents, or what efforts physicians made to assess and encourage patient adherence. We can only observe the results. A study including interviews with physicians as well as patients and/or recorded encounters would be of great interest.

Nevertheless, this study adds to our understanding of medication adherence, particularly to these exceptionally demanding regimens. Most studies model adherence as a 1-dimensional scale, essentially the percentage of doses taken on schedule. Our open-ended discussions with patients revealed many complex patterns of behavior which are not captured by simple numerical measures and explanations for why these occur. By exploring patients' understanding of the medical issues related to adherence, and the practical and psychological factors affecting medication-taking practice, the findings are a basis for designing better methods to educate and support patients in the challenging task of taking antiretroviral medications.

Further qualitative studies, particularly those focusing on highly adherent subjects and on subpopulations of interest, may lead to additional insights into the adherence behavior of HIV-infected patients. Studies of inception cohorts would improve our understanding of initial and sequential treatment decisions and adherence behavior. Trials of interventions to improve physician-patient communication about medication taking, and to support adherence by patients who are on complex, demanding treatment regimens, are important next steps for research in this field.

This work was supported by a contract with the Massachusetts Department of Public Health.

The authors gratefully acknowledge the contributions of interviewers Mariam Missaghian and Raphael Pol, transcriptionist Marta Rodriguez, and research assistants Julie Whitman and Marie Angeline Cabiya.

REFERENCES

1. Palella FJJ, Delaney KM, Moorman AC, 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.
2. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society-USA Panel. *JAMA*. 1998;280:78-86.
3. Feinberg MB, Carpenter C, Fauci AS, et al. Report of the NIH Panel to Define Principles of Therapy of HIV Infection and guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. *Ann Intern Med*. 1998;128:1057-110.
4. Paterson D, Seindels S, Mohr J, et al. How much adherence is enough? A prospective study of adherence to protease inhibitor therapy using MEMS Caps. Presented at the 6th Conference on Retroviruses and Opportunistic Infections; Jan 31-Feb 4, 1999. Washington, DC.
5. Bangsberg DR, Hecht FM, Charlebois EC, et al. Spontaneous adherence (ADH) audits (SAA) predict viral suppression in the REACH Cohort. Presented at the 6th Conference on Retroviruses and Opportunistic Infections; Jan 31-Feb 4, 1999. Washington, DC.
6. Demasi R, Tolson J, Pham S, et al. Self-reported adherence to HAART and correlation with HIV RNA: initial results with the Patient Medication Adherence Questionnaire. Presented at the 6th Conference on Retroviruses and Opportunistic Infections; Jan 31-Feb 4, 1999. Washington, DC.
7. Hecht FM, Grant RM, Petropoulos CJ, et al. Sexual Transmission of an HIV-1 variant resistant to multiple reverse-transcriptase and protease inhibitors. *N Engl J Med*. 1998;339:307-11.
8. Hirsch MS, Conway B, D'Aquila RT, et al. Antiretroviral drug resistance testing in adults with HIV infection: implications for clinical management. International AIDS Society-USA Panel. *JAMA*. 1998;279:1984-91.
9. Samet JH, Libman H, Steger KA, 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.
10. Broers B, Morabia A, Hirschel B. A cohort study of drug users' compliance with zidovudine treatment. *Arch Intern Med*. 1994;154:1121-7.
11. Morse EV, Simon PM, Coburn M, Hyslop N, Greenspan D, Balson PM. Determinants of subject compliance within an experimental anti-HIV drug protocol. *Soc Sci Med*. 1991;32:1161-7.
12. Ferrando SJ, Wall TL, Bakti SL, Sorenson JL. Psychiatric morbidity, illicit drug use and adherence to zidovudine (AZT) among injection drug users with HIV disease. *Am J Drug Alcohol Abuse*. 1996;22:475-87.
13. Eldred LH, 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.
14. Stall R, Hoff C, Coates TJ, et al. Decisions to get HIV tested and to accept antiretroviral therapies among gay/bisexual men: implications for secondary prevention efforts. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;11:151-60.
15. Lerner BH, Gulick RM, Dubler NN. Rethinking nonadherence: historical perspectives on triple-drug therapy for HIV disease. *Ann Intern Med*. 1999;14:53.
16. Bangsberg D, Tuskys JP, Hecht FM, Moss AR. Protease inhibitors in the homeless. *JAMA*. 1997;278:63-5.
17. Altice FL, Friedland GH. The era of adherence to HIV therapy. *Ann Intern Med*. 1998;129:503-5. Editorial.
18. Wainberg MA, Friedland G. Public health implications of antiretroviral therapy and HIV drug resistance. *JAMA*. 1998;279:1977-83.
19. Rand CS, Weeks K. Measuring adherence with medication regimens in clinical care and research. In: Shumaker SA, Schron EB, Ockene JK, McBee WL, eds. *The Handbook of Health Behavior Change*. 2nd ed. New York: Springer Publishing Company, Inc.; 1998: 114-32.
20. Miles MB, Huberman MA. *Qualitative Data Analysis: A Sourcebook of New Methods*. Newbury Park, Calif: Sage Publications; 1984: 15.
21. Curtis JR, Patrick DL. Barriers to communication about end of life care in AIDS patients. *J Gen Intern Med*. 1997;12:736-41.
22. Wilson IB. End-of-life care and HIV disease: let's talk. *J Gen Intern Med*. 1997;12:784-6.
23. Tsevat J, Sherman SN, McElwee JA, et al. The will to live among HIV-infected patients. *Ann Intern Med*. 1999;131:194-8.
24. Massachusetts AIDS Surveillance Program. Metropolitan area statistical data. Massachusetts Department of Public Health. January 1998.
25. Degner LF, Sloan JF. Decision making during serious illness: what role do patients really want to play? *J Clin Epidemiol*. 1992;45:944-50.
26. Caron HS. Compliance: the case for objective measurement. *J Hypertens Suppl*. 1985;3:S11-7.

27. Bradburn NM. Response effects. In: Rossi D, Wright JD, Anderson AB, eds. *Handbook of Survey Research*. San Diego, Calif: Academic Press; 1983.
28. Johnson SB. Methodological issues in diabetes research. Measuring adherence. *Diabetes Care*. 1992;15:1658-67.
29. Laws MB. *Choice or Chance: Treatment Decision Making by People with HIV in Massachusetts*. Boston: Latino Health Institute; 1999.
30. Glaser B, Strauss AL. *The Discovery of Grounded Theory: Strategies for Qualitative Research*. Chicago: Aldine; 1967.
31. Massachusetts Department of Public Health. *Massachusetts AIDS Surveillance Monthly Update*. April 1999.
32. Mar-Tang M, Noonan C, Ballard C, et al. Early adherence pattern and virologic outcomes after initiation or change of antiretroviral therapy. *J Gen Intern Med*. 1999;14:53. Abstract.
33. Stone VE, Clarke J, Lovell J, et al. HIV/AIDS patients' perspectives on adhering to regimens containing protease inhibitors. *J Gen Intern Med*. 1998;13:586-93.
34. Conrad P. The meaning of medications: another look at compliance. *Soc Sci Med*. 1985;20:29-37.
35. Steele DJ, Jackson TC, Gutmann MC. Have you been taking your pills? The adherence-monitoring sequence in the medical interview. *J Fam Pract*. 1990;30:294-9.
36. Golin C, Kaplan A, Liu HH, et al. Patient factors associated with and self-reported reasons for nonadherence to antiretroviral therapy. *J Gen Intern Med*. 1999;14:32. Abstract.
37. Gifford AL, Bormann JE, Shively MJ, Wright BC, Richman DD, Bozzette SA. The influence of social, psychological and clinical factors on antiretroviral medication adherence and plasma HIV levels. *J Gen Intern Med*. 1994;14:32. Abstract.
38. Wenger N, Gifford A, Liu H, et al. Patient characteristics and attitudes associated with antiretroviral (AR) adherence. Presented at the 6th Conference on Retroviruses and Opportunistic Infections; Jan 31-Feb 4, 1999. Washington, DC.
39. Becker M, Maiman L. Sociobehavioral determinants of compliance with health and medical care recommendations. *Med Care*. 1975;13:10-24.
40. Bandura A. *Social Foundations of Thought and Action*. Englewood Cliffs, NJ: Prentice-Hall; 1986.
41. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;94:191-215.
42. Prochaska JO, DiClemente CC. Stage of change in the modification of problem behaviors. In: Hersen M, Eysler RM, Miller PM, eds. *Progress in Behavior Modification*. Newbury Park, Calif: Sage; 1992.

ANNOUNCEMENT

SGIM Website

Please visit the Society of General Internal
Medicine on their World-Wide Website.
SGIM is located at

<http://www.sgim.org>