A Prospective Study of Predictors of Adherence to Combination Antiretroviral Medication

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

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

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

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

KEY WORDS: adherence; antiretroviral; medication compliance; HIV.


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

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

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

1. Patient Factors: We hypothesize that patients who have more-positive attitudes toward ART,22,31,37,38,45 greater self-efficacy toward adherence,44,38 and
higher literacy levels\textsuperscript{42} will be more adherent with ART. We expect patients who are active substance abusers\textsuperscript{22,31,33,38,46,49} or who report lower emotional well-being\textsuperscript{7,33} to be less adherent.

2. \textit{Regimen Factors:} We expect that patients receiving more complex antiretroviral regimens\textsuperscript{22,27,31,49,52} and regimens that fit less well with the other daily activities\textsuperscript{35,38,40,41,44,48,52,53} will be less adherent. We also expect that use of adherence aids (such as pillboxes, medication timers, etc.)\textsuperscript{31} will be associated with better adherence.

3. \textit{Features of the Clinical Interaction:} We expect patients with greater continuity of care, satisfaction with medical care, and trust in their provider to be more adherent.\textsuperscript{57-65}

4. \textit{Social/Environmental Factors:} We expect patients with more social support to be more adherent.\textsuperscript{40,45,46,54,55}

\section*{METHODS}

\subsection*{Subjects}

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

\subsection*{Data Collection}

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

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

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

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

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