Changes in adherence to highly active antiretroviral therapy medications in the Multicenter AIDS Cohort Study*

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Objectives: To characterize the determinants of changes in adherence to antiretroviral therapy and examine whether there are persistent lower adherers.

Design: A cohort study with repeated measurements.

Methods: Self-reported 100% adherence was defined as taking all doses and numbers of pills over a 4-day period as prescribed for current HIV medications. Independent predictors of changing adherence ($<100\%$ to 100% and 100% to $<100\%$) were determined by logistic regression, correcting for correlated repeated measures for 597 HIV-positive men reporting the use of highly active antiretroviral therapy (HAART) between October 1998 and October 2000.

Results: Of the 942 visit-pairs with initial 100% adherence, 106 (11.3%) reduced adherence to less than 100%, and 836 (88.7%) remained 100% adherent at the next 6-month visit. No recent outpatient visits, younger age, depression, less than college educated, and later in calendar time predicted decreasing adherence. Among 186 visit-pairs starting with less than 100% adherence, 133 (71.5%) improved adherence to 100% and 53 (28.5%) remained less than 100% adherent at the next visit. The determinants of improving adherence included not being African-American, not using recreational drugs, and having had more than three HAART regimens. Lower adherence was not a random event; it was significantly correlated across visits within the individual.

Conclusion: Characteristics associated with improving and lowering adherence differed and should be considered in developing interventions to enhance adherence and optimize effective therapies.

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Introduction

Highly active antiretroviral therapy (HAART) has led to significant reductions in AIDS-associated morbidity and mortality [1–4]. Many factors, including complicated therapeutic regimens, depression, alcohol and drug use, and changes in daily routines, may impact a patient's ability to adhere to these medications [5,6], which may then compromise the effectiveness of HAART [3,7,8].

The possible lifetime use of HAART necessitates a clear understanding of the barriers to continued adherence over time. Long-standing cohort studies, such as the Multicenter AIDS Cohort Study (MACS), provide an arena for obtaining this longitudinal information. On the basis of the adherence data captured at one visit, we previously found that being African-American, not having had recent outpatient visits, the concurrent use of more than three antiretroviral medications, having a lower income and being depressed significantly predicted lower adherence [6]. Using longitudinal adherence assessments, our current goals were to examine the predictors of improving and reducing adherence, and to examine whether there exists a cluster of men who are persistently non-adherent or if non-adherence is a random event.

Methods

Population and data collection

The MACS is an ongoing prospective study of HIV infection among 5622 homosexual men in the United States [9–11]. The men were followed every 6 months, with interviews, physical examinations, quality-of-life assessments, neuropsychological testing, and blood sample collections to measure laboratory markers. The institutional review boards of each center approved the study protocols, and informed consent was obtained from each participant.

The self-reported use of antiretroviral medications at each visit was summarized to define whether participants were using HAART [12]. A questionnaire to ascertain the adherence to current antiretroviral medications was incorporated into the protocol as of October 1998 (visit 30) [6]. Most responses were limited to the last 4 days. Questions (as previously provided [6]) were either drug-specific or related to the overall use of antiretroviral therapy. Self-reported adherence was dichotomized as 100% adherence or less than 100% adherence based on a defined algorithm [6].

Statistical analysis

Four visits within a 2-year period were used to examine changes in adherence over time. Consecutive visit-pairs were studied such that the change in adherence from Visit i (V_i) to Visit i+1 (V_{i+1}) was the outcome, and characteristics at V_i were assessed as determinants. Interaction terms were used to see whether these determinants changed over time. Multivariate logistic regression, correcting for correlated repeated measures, was used to identify significant ($P < 0.05$) predictors of adherence change. Variables were included on the basis of their significance ($P < 0.05$) univariately. As consecutive visit-pairs were the units of analysis, the maximum number of visit-pairs per individual was three. We evaluated the reduction in adherence for men with 100% adherence at V_i. At V_{i+1}, they either decreased to less than 100% adherence or remained 100% adherent. To identify the predictors of improved adherence, the population was men with less than 100% adherence at V_i. The outcome at V_{i+1} was either an increase in adherence to 100% or remaining less than 100% adherent.

The potential predictors of adherence change included race and education, obtained at study entry. Other potential determinants included sociodemographics (age, employment, income), behavioral characteristics (alcohol use, recreational drug use, smoking), health-care utilization (medical insurance coverage, outpatient medical care), psychological covariates (depression, cognitive decline, quality of life), and HIV disease stage [clinical symptoms, AIDS-defining illnesses [13], HIV-1 plasma RNA level (ultrasensitive polymerase chain reaction assay, 50 copies/ml detection limit; Roche Molecular Systems, Branchburg, NJ, USA) and number of CD4 cells/μl [14,15]] from V_i, before outcome. The total number of antiretroviral medications taken concurrently and the number of different HAART regimens taken previously were examined to assess their influence on adherence.

We used a beta binomial model to examine the persistence of non-adherence. This model quantified the correlation of non-adherent visits for each individual, and determined whether race, age, education or year of HAART initiation characterized this clustering. For each individual, the outcome was the proportion of visits that were less than 100% adherent. All visits in the 2-year period were used, i.e. this modeling was not restricted to consecutive visits. This model was applied to the overall population of HAART users and was also restricted to men with one or more non-adherent visit. For the latter analysis describing the probability of remaining less adherent, the first non-adherent visit was considered the index visit, and only those visits after the index visit were used.

Results

Of 605 men reporting HAART use at visits 30–33,

597 provided adherence data, but 111 either missed the next consecutive visit or did not remain on HAART. The 486 HAART users with adherence data contributed 1128 consecutive visit-pairs. Self-reported adherence was similar across the four visits, with 78–85% of participants reporting perfect adherence at each visit.

Determinants for changing adherence

Of the 942 visit-pairs with 100% adherence at V_i, 106 (11.3%) had lower adherence and 836 (88.7%) remained 100% adherent at V_{i+1}. The univariate results are shown in Table 1 and Table 2. The independent predictors of lowering adherence, using multivariate regression, were no outpatient visits within the period 6–12 months before the visit [odds ratio (OR) = 2.8; $P = 0.004$), being younger than 40 years (OR = 1.8; $P = 0.03$), having a Centers for Epidemiologic Studies Depression Scale (CES-D) score greater than 16 (OR = 1.8; $P = 0.03$), having less than a college education (OR = 1.5; $P = 0.03$) and later calendar time (OR = 1.3; $P = 0.05$). The length of time on HAART was not significant.

Of the 186 visit-pairs at which adherence was less than 100% at V_i, 133 (71.5%) reported 100% adherence and 53 (28.5%) remained less than 100% adherent at V_{i+1}. The univariate association (Table 1) between having anal sex and not improving adherence did not persist when adjusting for other significant variables (OR = 0.98, $P = 0.97$). From the multivariate analysis, not being African-American (OR = 3.6; $P < 0.001$), not using recreational drugs (OR = 3.2; $P = 0.005$) and having a history of more than three different HAART regimens (OR = 3.3; $P = 0.006$) independently predicted improving adherence. Men with AIDS were also likely to improve adherence, but few men with AIDS had less than three HAART regimens to assess their independent contributions accurately.

Persistence of non-adherence over time

Most of the 597 men on HAART (90.1%) were seen three to four times in the 2-year period. Of those seen once, 19.7% were less than 100% adherent. The proportion with one or more non-adherent visits increased to 32.3, 41.4 and 38.8% for those with two, three and four visits, respectively. To examine whether non-adherers were likely to persist as non-adherers, we restricted the population to the 214 men with one or more non-adherent visit and subsequent follow-up. The proportions reporting less than 100% adherence at subsequent visits were higher than observed in the overall cohort. Of the 54 men with only one subsequent visit

Table 1. Results from univariate examinations of HIV-1-associated markers, symptoms, and therapy use with change in adherence.

	Negative change			Positive change		
	Visit-pairs with 100% adherence	% Negative change	*P* value	Visit-pairs with < 100% adherence	% Positive change	*P* value
AIDS						
No	705	11		142	66	
Yes	237	12	0.76	44	89	0.02
HIV-1 symptoms						
No	519	10		99	67	
Yes	422	12	0.37	87	73	0.12
CD4 cells/mm^3						
Greater than 350	575	12		110	67	
350 or less	252	10	0.64	54	78	0.24
HIV-1-RNA copies/ml						
50 or more	338	12		82	71	
Less than 50	446	11	0.82	67	72	0.91
Increase in HIV RNA						
No	525	10		102	74	
Yes	223	14	0.15	40	63	0.23
Depression						
No	656	10		110	66	
Yes	180	17	0.01	50	78	0.13
More than three HAART regimens						
No	654	11		119	63	
Yes	287	11	0.94	66	86	0.006
Time on HAART						
< 4 years	878	11		178	72	
> 4 years	64	16	0.26	8	63	0.57

HAART, Highly active antiretroviral therapy.

Table 2. Results from univariate examinations of demographics and behavioral characteristics with change in adherence.

	Negative change			Positive change		
	Visit-pairs with 100% adherence	% Negative change	*P* value	Visit-pairs with < 100% adherence	% Positive change	*P* value
Age (years)						
Older than 40	762	10		143	73	
40 or younger	180	16	0.03	43	67	0.54
Race						
Non-African-American	878	11		156	77	
African-American	64	16	0.26	30	43	< 0.001
Education						
College or more	562	9		101	69	
Less than college	372	14	0.03	85	74	0.51
Income (US$)						
50K or more	359	10		43	74	
Less than 50K	581	12	0.20	143	71	0.61
Medical insurance						
Yes	889	11		175	71	
No	50	14	0.53	11	73	0.92
Outpatient visit						
Yes	873	10		171	72	
No	66	23	0.004	15	67	0.66
Smoking						
No	743	11		131	72	
Yes	196	14	0.23	55	71	0.91
Recreational drug use						
No	435	12		83	83	
Yes	504	11	0.63	103	62	0.005
Anal sex						
No	377	11		77	79	
Yes	506	12	0.64	100	66	0.05
Average drinks/week						
< 14	910	11		174	72	
⩾ 14	31	19	0.17	12	67	0.55

after a non-adherent visit, 27.8% remained less than 100% adherent; 20.1% of the 43 men with two visits after a non-adherent visit reported being less than 100% adherent on one or more other occasion, and 46.3% of the 67 men with three subsequent visits reported one or more additional less than 100% adherent visit. Although the intraclass correlation was relatively small (0.194), it was significant, demonstrating that lower adherence was not a random event ($P < 0.01$). Once an individual was less than 100% adherent, he was likely to be less than 100% adherent subsequently.

From the beta binomial model, being African-American (OR = 2.57, $P = <0.001$) and younger than 40 years (OR = 1.45, $P = 0.011$) were associated with lower adherence in the overall population. In the restricted population, being African-American (OR = 2.23, $P = 0.009$) was the only predictor of lower adherence. We did not observe heterogeneity in the persistence of less than 100% adherence by race, age, education or time of HAART initiation. That is, the clustering was similar within subgroups defined by these characteristics.

Discussion

Hindrances to adherence to HAART include substance abuse, mental illness, limited financial resources and other barriers to care, special instructions for taking medications, side-effects, changes in daily routine, and the ability to attend regular clinic visits [6,16–20]. Few studies have looked at changes in adherence over prolonged periods.

The high adherence to medications is not surprising considering that those in this analysis have participated in the MACS for over 10 years, indicating a possible high compliance profile. The use of an interviewer-administered survey, although also used in most studies, may yield overestimates. However, as these data were not collected by primary physicians or in a monitored clinical trial setting, the over-reporting of adherence was less likely. Despite these high levels of adherence, we identified significant determinants of changes in adherence. Importantly, the characteristics associated with lowering and improving adherence differed. No recent outpatient visit, younger age, depression and

lower educational levels were all independent determinants of decreasing adherence. Although increasing calendar time (1998–2000) was associated with declining adherence, this may have subsequently changed with the increasing availability of combination pills.

Our results extend those of others [21,22] by demonstrating that among adherers to HAART medication, depression may result in a loss of adherence, which is not surprising as self-neglect and forgetfulness are depressive behaviors. This relationship with depression is distinct from that dealing with quality of life. The lack of association between the eight quality-of-life domains and adherence change is consistent with previous findings [6,23].

Identifying individuals who are likely to lower their adherence provides a basis for interventions aimed at maintaining adherence, and thereby optimizing the benefit of effective therapies. Healthcare providers need to be alert for conditions that may lead to a decrease in adherence, such as skipping outpatient visits and symptoms of depression. Also, younger and less educated individuals may need more stress put on the importance of continued high levels of adherence.

We found different characteristics related to improving adherence. Among those with lower adherence, African-Americans, recreational drug users, and those having had less than three different HAART regimens were less likely to improve adherence. The lower adherence overall by African-Americans has been observed previously [6,23–26]. Therefore, not only were African-Americans more likely to report lower adherence, but they were also less likely to improve their adherence subsequently. However, African-Americans who reported being 100% adherent did not lower their adherence any more than non-African-American men, suggesting that if adherence is optimal, education efforts do not need to focus on race to maintain that level. Similarly, substance abusers have been consistently identified as lower adherers [19,27–29]. Like race, recreational drug use did not predict lowering adherence among those starting out adherent, but if suboptimally adherent, recreational drug users did not improve their adherence.

We also found that non-adherence to HAART medications was not a random event in the MACS. Participants reporting non-adherence were more likely to continue to be non-adherent, consistent with the findings of Murri *et al.* [30], in which previous non-adherence predicted non-adherence at the next visit.

Current guidelines now suggest initiating HAART at later stages of infection [16], which should allow physicians more time to assess the potential barriers to adherence before prescribing HAART. Besides education, providers should assess and treat depression to enhance continued adherence to optimize the effectiveness of HAART.

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Appendix

The Multicenter AIDS Cohort Study (MACS) includes the following:

Baltimore: The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (Principal Investigator), Haroutune Armenian, Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Shenghan Lai, Justin McArthur. Chicago: Howard Brown Health Center and Northwestern University Medical School: John P. Phair (Principal Investigator), Joan S. Chmiel, Bruce Cohen, Maurice O'Gorman, Frank Pallela, Daina Variakojis, Steven M. Wolinsky. Los Angeles: University of California, UCLA Schools of Public Health and Medicine: Roger Detels and Beth Jamieson (Principal Investigators), Barbara R. Visscher (Co-Principal Investigator), Anthony Butch, John Fahey, Otoniel Martínez-Maza, Eric N. Miller, John Oishi, Paul Satz, Elyse Singer, Harry Vinters, Otto Yang, Stephen Young. Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence Kingsley (Co-Principal Investigator), James T. Becker, Phalguni Gupta, John Mellors, Sharon Riddler, Anthony Silvestre. Data Coordinating Center: The Johns Hopkins University Bloomberg School of Public Health: Alvaro Muñoz (Principal Investigator), Lisa P. Jacobson (Co-Principal Investigator), Linda Ahdieh Grant, Stephen Cole, Stephen Gange, Cynthia Kleeberger, Eric Seaberg, Janet Schollenberger, Michael Silverberg, Sol Su. National Institutes of Health: National Institute of Allergy and Infectious Diseases: Carolyn Williams. National Cancer Institute: Sandra Melnick. Website located at http://www.statepi.jhsph.edu/macs/macs.html.