# Patterns and Predictors of Changes in Adherence to Highly Active Antiretroviral Therapy: Longitudinal Study of Men and Women

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***Background.*** Adherence to therapy is a dynamic behavior. However, few studies have identified factors associated with changes in adherence to highly active antiretroviral therapy (HAART) among men and women.

***Methods.*** From 1999 through 2004, self-reported adherence to HAART was recorded twice yearly as part of 2 prospective cohort studies. At each study visit, participants were categorized as being 100% adherent if they reported full adherence with their HAART regimen over the past 4 days (for men) and 3 days (for women). Repeated-measures logistic regression models were used to identify predictors for changes in adherence between consecutive visits.

***Results.*** Of the participants, 640 men and 1304 women contributed 2803 and 5972 visit-pairs, respectively. Among white men, the prevalence of 100% adherence decreased from 91% in 1998 to 80% in 2003. Among women and African American men, the prevalence of full adherence was lower (75% and 77% on average, respectively) and stable over time ($P > .6$). In both cohorts, the presence of clinical symptoms was independently associated with decreasing adherence (odds ratio [OR], 1.38 in men and 1.48 in women). Depression in men (OR, 1.44) and use of alcohol in women (OR, 1.81, 1.52, and 1.29, for binge drinking, moderate-to-heavy drinking, and low consumption, respectively) also predicted decreasing adherence. In addition, the use of drugs by men and women (OR, 0.61 and 0.58, respectively) and alcohol binging by women (OR, 0.41) were negatively associated with improving adherence.

***Conclusions.*** Adherence to antiretroviral treatment is a dynamic process; modifiable risk factors are associated with increasing and decreasing adherence, suggesting specific interventions. Moreover, the association of these risk factors with changes in adherence may differ by sex.

The effectiveness of HAART in reducing HIV-related mortality and morbidity has been consistently demonstrated [1–3]. However, high levels of adherence to therapy are necessary to achieve optimal responses to treatment [4–6]. Lack of adherence, because of its high prevalence [7], contribution to disease progression, and potential to increase the occurrence and propagation of drug-resistant virus [8], is of public health concern.

Adherence to HAART is a dynamic process [9–11], and several previously published studies have identified sociodemographic, behavioral, treatment-related, and health-related factors associated with low adherence [12–19]. However, to date, most studies have been cross-sectional and have examined predictors of adherence at a single time point; the few longitudinal studies have had relatively short follow-up and small sample sizes [9–11, 20].

In this study, we conducted a parallel evaluation of changes in adherence in 2 multicenter, long-term, prospective cohorts in the United States: the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS). The goals of this study were to determine the prevalence of 100% self-reported adherence over time and to identify sociodemographic, be-

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havioral, health-related, and treatment-related factors associated with changing adherence (i.e., decrease or increase) to HAART over a 5-year period.

## METHODS

***Study population.*** The MACS is an ongoing prospective study of the natural and treated histories of HIV-1 infection in men who have sex with men (MSM), which began in 1984 and enrolled 6973 MSM in 4 US cities: Baltimore, Maryland; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California [21]. The WIHS began in 1994 and enrolled 3768 women in 5 US cities: New York (2 sites); Chicago; Los Angeles; San Francisco, California; and Washington, DC [22]. The data centers of both studies are located in Baltimore. Institutional review boards approved all protocols, and informed consent forms were completed by study participants.

***Data collection.*** In both cohorts, participants were administered comprehensive questionnaires at 6-month intervals, to obtain information on the following: sociodemographic and behavioral characteristics, health care use, medical history, medication use, and HIV-related symptoms. In addition, blood samples were obtained for concomitant laboratory analysis and storage in both local and national repositories. Standardized flow cytometry techniques were used to quantify T cell subsets [23]. The HIV RNA level was measured in the MACS using an RT-PCR amplification technique (Roche Molecular Systems), which has a detection limit of 50 copies/mL. In the WIHS, an isothermal nucleic acid sequence–based amplification (NASBA/Nuclisens) method was used (bioMérieux), which has a detection limit of 80 copies/mL. The laboratories of both studies participated in the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID) Virology Quality Assurance Laboratory proficiency testing program. Lymphocyte subsets were quantified using standard flow cytometric methods in laboratories participating in the NIH/NIAID Flow Cytometry Quality Assessment Program [24]. The definition of HAART was taken from the 2005 guidelines of the Department of Health and Human Services [25].

***Measurement of adherence.*** Adherence questionnaires recording self-reported adherence to all current antiretroviral drugs in the past 4 days in the MACS and in the past 3 days in the WIHS were introduced in both protocols starting in October 1998 and were based on the Adult AIDS Clinical Trials Group adherence measurement form [14]. For this study, self-reported adherence to antiretroviral therapy was dichotomized as 100% or <100% on the basis of a previously published algorithm [13]. One hundred percent adherence was defined as taking all doses and numbers of pills as prescribed for current medications. In contrast, inclusion in the <100% adherence group resulted when either the participant reported taking any current medications fewer times than prescribed or the participant reported taking all current medications at the times prescribed in the past 3 or 4 days (WIHS or MACS, respectively), although this was not a typical pattern.

***Definition and measurement of potential predictors.*** Race/ethnicity and education were recorded at study entry. Racial/ethnic categories used were white, African American, Hispanic/Latino, and "other" (American Indian, Alaskan native, Asian, Pacific Islander, or other). Education was categorized as less than high school, high school, and more than high school. Another potential predictor examined and recorded at the visit prior to the outcome was self-reported annual income, collapsed into categories to represent low, medium, and high income; given slight differences in the data collection between men and women cohorts, these categories were ≤$18,000, $18,001–$36,000, and >$36,000 among women, whereas for men these categories were ≤$20,000, $20,001–$50,000, and >$50,000. Among men, employment was categorized as unemployed, retired, disabled, and employed if either full-time or part-time; among women, employment was characterized as full-time or part-time employed and unemployed. Self-reported smoking status in the past 6 months was used to define smoking (yes vs. no). Low alcohol consumption was defined as drinking ≤2 drinks per day among men and 0 or 1 drink per day for women; moderate-to-heavy consumption was defined as drinking 3–4 drinks at least 3 times per month or >5 drinks at a time but less frequently than once a month; binge drinking was defined as drinking >5 and >4 drinks at least once per month for men and women, respectively. Drug use was examined among men as any self-reported use of marijuana, "poppers," crack cocaine and/or cocaine, crystal or other methamphetamines, "speedballs," heroin, or ecstasy; among women, drug use consisted of self-reported use of marijuana, crack/cocaine, heroin, and methamphetamine.

Symptoms of depression were measured using the Center for Epidemiologic Studies depression scale [26]; for our analysis, a Center for Epidemiologic Studies depression score of ≥16 was considered suggestive of clinical depression. Self-reported sexually transmitted infection included syphilis, any form of gonorrhea, nonspecific urethritis (for men), pelvic inflammatory disease (for women), and genital or anal warts, *Chlamydia* infection, herpes, *Trichomonas* infection, and other parasitic infections (including worms, shigellosis, salmonellosis, amebiasis, or giardiasis) since the previous visit.

History of AIDS was defined as an opportunistic illness or malignancy and identified by the 1993 Centers for Disease Control and Prevention clinical definition [27]; length of time since first diagnosis of AIDS was assessed as a potential determinant of change in adherence. The presence of the following clinical symptoms or signs for at least 3 consecutive days was investigated: vomiting, fatigue, fever (temperature, >37.8°C), diarrhea, drenching sweats, vivid nightmares or dreams, neuropathies, or

weight loss of >10 lbs (>4.5 kg). Other treatment-associated factors were also investigated as determinants for changing adherence. Number of medications was calculated as the sum of reported nonnucleoside reverse-transcriptase inhibitor (NNRTIs), protease inhibitors (PIs), and nucleoside reverse-transcriptase inhibitors (NRTIs). Combination pills were counted as single drugs for this calculation. Type of HAART regimen was categorized as PI-based (no NNRTIs), NNRTI-based only (no PIs), both PIs and NNRTIs, and PIs and NNRTIs spared (e.g., HAART defined by the presence of abacavir-tenofovir). CD4 T cell counts and HIV RNA levels recorded at the last visit were also assessed as potential determinants. For health care use, we included self-reported number of hospitalizations and outpatient and emergency visits reported at the index visit ($V_i$).

***Study sample and statistical methods.*** This analysis was restricted to MACS and WIHS participants who reported use of a HAART regimen for whom adherence data were available (figure 1). To study changes in adherence to HAART, we used consecutive visit-pairs as the unit of analysis ($V_i$ and $V_{i+1}$). From 1999 through 2004, each participant could participate for up to 5 years and thus provide 10 visit-pairs. All visit-pairs that had complete information on adherence were included. Each visit-pair was categorized as follows: (1) perfect adherence with no change (100% adherence at both $V_i$ and $V_{i+1}$), (2) decreases in adherence (100% adherence at $V_i$ and <100% adherence at $V_{i+1}$), (3) poor adherence with no change (<100% adherence at both $V_i$ and $V_{i+1}$), and (4) improving adherence (<100% adherence at $V_i$ and 100% adherence at $V_{i+1}$). Separate models were used to identify determinants for decreasing and improving adherence. Visit-pairs starting with the same level of adherence but with no change served as the reference group. For example, visit-pairs in which adherence decreased were compared with those with 100% adherence with no change.

In addition to sex, the cohorts differed in other sociodemographic characteristics; thus, we calculated ORs separately for men and women. To account for correlation in outcomes from repeated observations from each individual, we used generalized estimating equation [28] methods with a logit link function, binomial variance structure, robust (Huber) estimates of the parameter SEs, and a working independence correlation structure. We included in the multivariate model predictors that were significantly associated with changing adherence in either of the cohorts, with $P$ values of ≤.10 in the univariate analysis. Anything with a $P$ value >.05 but <.01 was considered to be "marginally significant."

## RESULTS

***Participant characteristics.*** Subjects in this study included 640 MACS participants and 1304 WIHS participants. Men and women were on average 44 and 39 years of age, respectively; among men, 73% were white, and the proportion of white women was 15%. Twenty percent of these men and 40% of these women had AIDS (table 1). During the 5-year period, 552 men contributed 2054 visit-pairs at which they reported complete (100%) adherence at both visits. There were 284 visit-pairs, contributed by 222 men, during which adherence decreased (i.e., 100% to <100%). In contrast, 224 men contributed 284 visit-pairs during which adherence improved (i.e., <100% at $V_i$ to 100% at $V_{i+1}$). There were 181 visit-pairs in which 94 men remained at lower adherence (<100% at $V_i$ and at $V_{i+1}$). Among WIHS participants, 1046 women contributed 3850 visit-pairs with complete adherence at both visits $V_i$ and $V_{i+1}$. There were 760 visit-pairs, contributed by 576 women, in which adherence decreased. In contrast, 590 women contributed 770 visit-pairs during which adherence improved, and 296 women contributed 592 visit-pairs in which low adherence was recorded at both visits.

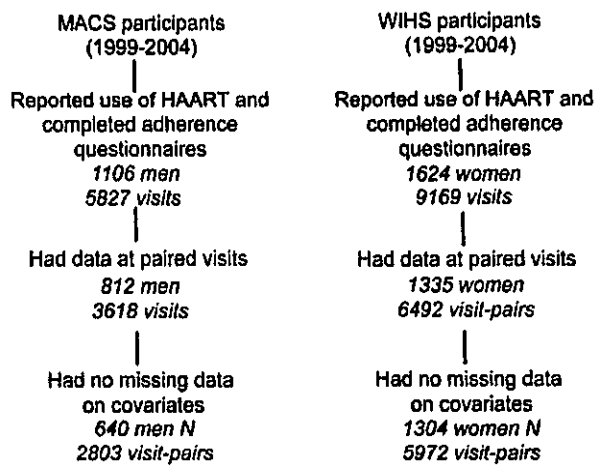


**Figure 1.** Women's Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS) participants in HAART adherence study.

***Prevalence of self-reported 100% adherence to HAART.*** The prevalence of self-reported 100% adherence among white men decreased across calendar year of visit from 91% in 1999 to 80% in 2003 ($P = .02$). Among African American men, a significant temporal trend was not observed and was, on average, 75% (range, 67%–85%; $P = .66$). Among women, a total of 1304 HAART users contributed 5972 visit-pairs. The prevalence of self-reported 100% adherence was similar across time and races, with an average of 77% (range, 76%–80%; $P = .69$) (figure 2).

***Predictors of decreasing adherence.*** Among men, the predictors univariately associated with decreasing adherence between consecutive visits included the following: (1) sociodemographic characteristics (younger age, African American race, a yearly income of <$20,000, and unemployment), (2) clinical indicators (presence of ≥2 symptoms, symptoms of depression,

**Table 1. Characteristics of the 640 men (Multicenter AIDS Cohort Study participants) and 1304 women (Women's Interagency HIV Study participants) at the first visit.**

| Characteristic | Men ($n$ = 640) | Women ($n$ = 1304) | $P$ |
|---|---|---|---|
| Age, mean years ± SD | 44.1 ± 7.5 | 38.8 ± 8.2 | <.01 |
| Race/ethnicity | | | |
| White | 469 (73) | 195 (15) | <.01 |
| African American | 123 (19) | 681 (52) | |
| Hispanic/Latino | 42 (7) | 396 (30) | |
| Other | 6 (1) | 32 (2) | |
| Education less than high school | 21 (3) | 487 (37) | <.01 |
| Low income[a] | 186 (29) | 892 (68) | <.01 |
| Employed | 398 (62) | 402 (31) | <.01 |
| Health care insurance | 615 (97) | 1170 (90) | <.01 |
| Alcohol consumption | | | |
| Binging behavior | 39 (7) | 56 (4) | <.01 |
| Heavy | 99 (15) | 106 (8) | |
| Low | 355 (55) | 369 (28) | |
| Use of ≥2 recreational drugs | 167 (27) | 115 (9) | <.01 |
| Symptoms of depression | 243 (38) | 477 (37) | .5 |
| AIDS | 125 (20) | 523 (40) | <.01 |
| Clinical symptoms | 339 (53) | 575 (44) | <.01 |
| Hospitalizations | 53 (8) | 220 (17) | <.01 |
| Antiretroviral regimen | | | |
| >3 antiretrovirals | 163 (25) | 191 (15) | <.01 |
| PI-based regimen | 332 (52) | 614 (47) | <.01 |
| Both PI and NNRTI | 118 (18) | 154 (12) | |
| PI and NNRTI spared | 19 (3) | 110 (8) | |
| Undetectable viral load | 368 (57) | 596 (46) | <.01 |
| CD4 cell count >350 cells/mm$^3$ | 144 (23) | 290 (22) | .8 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] Low income was defined as <$18,000 per year for women and <$20,000 per year for men.

and prior hospitalization), (3) treatment-related factors (PI-based or PI/NNRTI-based HAART regimen versus NNRTI-only regimen and HAART duration of ≥5 years), and (4) biological markers (HIV RNA level >100,000 copies/mL and CD4 T cell count <200 cells/mm$^3$) (table 2).

Among women, the factors associated with decreasing adherence included the following: (1) behavioral characteristics (low-to-moderate or moderate-to-heavy alcohol consumption, binge drinking, drug use, and smoking, (2) clinical indicators (history of AIDS, ≥2 clinical symptoms, and presence of a sexually transmitted infection), (3) treatment-related factors (PI-based regimen, receipt of ≥4 antiretroviral drugs, and increase in the number of antiretroviral drugs), and (4) biological markers (HIV RNA level >100,000 copies/mL at $V_i$ and CD4 T cell count <200 cells/mm$^3$) (table 2).

Table 3 shows stratified multivariate models for decreasing adherence including common variables for both cohorts. Among men who initially reported 100% adherence, older age and fewer antiretroviral drugs in the regimen were associated with continued 100% adherence. In contrast, the presence of symptoms of depression and history of hospitalization in the past 6 months were associated with decreasing adherence. For women, a dose-response relationship between alcohol use and decreasing adherence was found: those with low-to-moderate, moderate-to-heavy, and binge consumption had 29%, 52%, and 81% higher odds of decreasing adherence, respectively; the use of ≥4 antiretroviral drugs also predicted such decreases. The use of a PI-only regimen and the presence of ≥2 HIV-related symptoms predicted decreasing adherence in both men and women.

***Predictors of improving adherence.*** Behavioral characteristics, such as drug use among men and women and alcohol use (low and binging) among women, were negatively associated with improving adherence. Among men, the predictors univariately associated with improving adherence included older age, increase in the number of antiretroviral drugs, and CD4 T cell count of 350–500 cells/mm$^3$. Among women, having had ≥4 outpatient visits was associated with such improvement (table 2). In the multivariate analyses, among men with initially low adherence, increasing age was independently associated with improving adherence. In women, alcohol binging and heavy and low consumption of alcohol hindered improving adherence. The use of drugs precluded improving adherence in both men and women (table 3).

## DISCUSSION

In these 2 long-standing and well-characterized populations of men and women in the United States, we found that the majority of the HAART-using population reported 100% adherence. Among white men, the prevalence of 100% adherence decreased from 91% in 1999 to 80% in 2003. In contrast, among African American men and among women of all races, no temporal relationship was found, and on average, the prevalence of 100% adherence was lower among these subjects than among their white counterparts.

Despite high levels of adherence in these cohorts, we were able to identify predictors of changing adherence in men and women. Some of the factors associated with improving adherence differed from the determinants of decreasing adherence. Among men and women with lower adherence, use of drugs hindered improvement of adherence. Nevertheless, if men and women had high adherence, drug use was not associated with decreasing adherence after adjustment for other predictors. This finding extends the prior work by Kleeberger et al. [10] in the MACS, in which not using drugs was associated with improving adherence (OR, 3.2; $P$ = .005), and agrees with cross-sectional studies that suggest that drug use is associated with poor adherence.

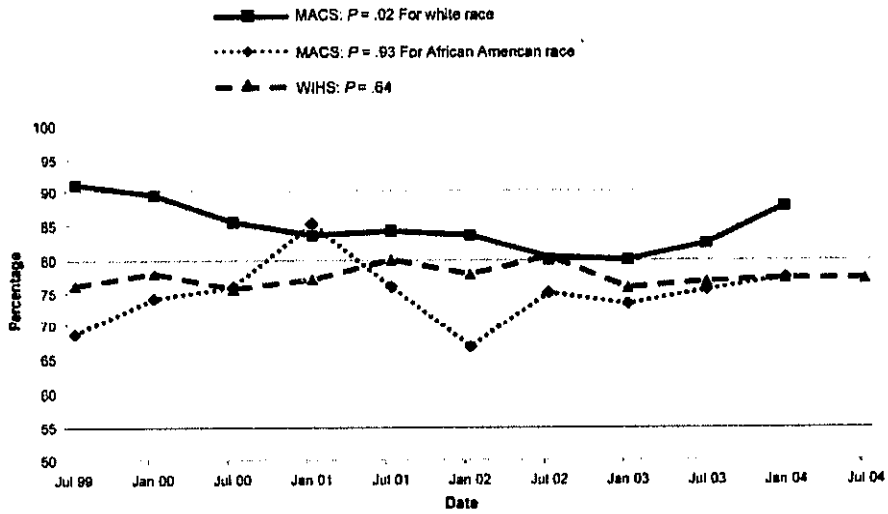


**Figure 2.** Prevalence of 100% adherence to HAART. MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study. *P* values were determined by the test for trend.

The longitudinal nature of this study allowed us to characterize the predictors prior to the outcome, removing to some extent the temporal ambiguity between certain risk factors and the outcome. In the association of presence of symptoms and hospitalization with decreasing adherence, we determined adherence to HAART in the last 4 days before the visit ($V_{i+1}$) and assessed occurrence of hospitalization(s) in the last 6 months before the index visit ($V_i$). We hypothesize that sicker patients may believe that their medications are ineffective and, therefore, that continuing their 100% adherence is not important. Alternatively, during hospitalization, interruptions of HAART may represent structured treatment interruptions. Studies conducted at clinical care may be better suited than our interval cohort design [29] to examine attitudes among hospitalized HIV-infected patients and current medical practices.

The association of PI-based HAART with subsequent decreases in adherence was consistent for men and women. Prior cross-sectional studies have shown lower adherence to this type of regimen than to NNRTI-based regimens [30–33]. Similarly, Mannheimer et al. [34] demonstrated a decrease in the prevalence of 100% adherence among those taking PI-based regimens from 74% to 68% over 12 months, with significantly lower adherence levels at 4 and 8 months of follow-up than among those taking NNRTI-based regimens. Characteristics of PI-based regimens, including the number of daily doses and pills, complicated dosing schedules, dietary instructions, and secondary effects, could potentially explain the differences in the durability and tolerability of those HAART regimens.

Some of the factors associated with changing adherence differed slightly by sex, such as symptoms of depression and use of alcohol, which affected men and women, respectively. It was previously shown in the WIHS cohort [35] that women with high levels of depressive symptoms are significantly less likely to be taking HAART regimens and more likely to discontinue HAART. Thus, it is possible that depressed women may not have been represented in the current analysis because of the requirement of HAART use at both visits. Given that discontinuation of HAART had been systematically studied in the MACS and WIHS before [35–39], we a priori limited our study to changes in adherence among HAART users.

A limitation of the study was the use of self-reported adherence, which can be subject to desirability bias and recall bias. Self-reported data may overestimate adherence; thus, the differences presented in this study may be conservative. Nevertheless, self-reported adherence using the AIDS Clinical Trials Group questionnaire is simple and inexpensive and has been the most widely used method in clinical settings [40, 41].

Another important limitation of this study was defining adherence as 100% adherence versus <100% adherence. Published literature has indicated the need for 100% adherence to achieve virus suppression, potentially protecting against mutation to treatment-resistant strains. Accordingly, the majority of studies using self-reported measures of antiretroviral adherence have chosen the cutoff of 100% [40, 41]. Some recent studies have suggested that, with some antiretrovirals, the need for 100% adherence may not be entirely true and have suggested using lower levels of adherence as cutoff for optimal virus suppression. For example, Bangsberg [42] showed that <100% adherence to NNRTI regimens may still yield good virus suppression. Future studies are needed to determine the consequences of decreasing adherence to specific antiretroviral therapies and the clinically relevant changes in adherence, also antiretroviral-spe-

**Table 2. Univariate predictors of changes in adherence among men and women.**

| Predictor | OR (95% CI) | | | |
|---|---|---|---|---|
| | Decreasing adherence | | Increasing adherence | |
| | Men | Women | Men | Women |
| Sociodemographic characteristics | | | | |
| Age (each 10 years) | **0.80 (0.65–0.99)**[a] | 0.95 (0.85–1.05) | **1.41 (1.03–1.92)**[a] | 1.13 (0.94–1.36) |
| Race (referent: white) | | | | |
| African American | **1.58 (1.03–2.44)**[a] | 1.17 (0.92–1.5) | 0.64 (0.36–1.12) | 0.71 (0.45–1.12) |
| Hispanic | 1.02 (0.58–1.79) | 1.14 (0.88–1.49) | 1.16 (0.47–2.80) | 0.88 (0.54–1.44) |
| Low income[b] | **1.75 (1.20–2.55)**[a] | 1.11 (0.85–1.45) | 1.10 (0.67–1.81) | 0.84 (0.53–1.34) |
| Employment status (referent: employed) | | | | |
| Unemployed | **2.08 (1.30–3.33)**[a] | 0.98 (0.82–1.17) | 1.01 (0.53–1.9) | 1.05 (0.80–1.38) |
| Retired | 0.97 (0.60–1.67) | ... | 1.50 (0.72–3.13) | ... |
| Disabled | 1.05 (0.72–1.53) | ... | 1.49 (0.90–2.46) | ... |
| Behavioral characteristics | | | | |
| Current smoker (referent: no) | 1.23 (0.89–1.69) | **1.19 (1.00–1.42)**[a] | 0.93 (0.56–1.53) | 0.87 (0.66–1.14) |
| Drinking | | | | |
| Binging behavior | 1.14 (0.59–2.2) | **1.75 (1.17–2.64)**[a] | 0.78 (0.31–1.94) | **0.38 (0.21–0.72)**[a] |
| Moderate to heavy | 1.06 (0.69–1.61) | **1.47 (1.08–1.99)**[a] | 1.03 (0.54–1.98) | 0.79 (0.50–1.27) |
| Low | 0.77 (0.55–1.07) | **1.28 (1.05–1.54)**[a] | 0.95 ( 0.55–1.64) | **0.74 (0.57–0.97)**[a] |
| Drug use | 1.17 (0.88–1.55) | **1.27 (1.03–1.56)**[a] | **0.53 (0.34–0.83)**[a] | **0.68 (0.51–0.91)**[a] |
| Clinical indicators | | | | |
| History of AIDS diagnosis | 1.08 (0.75–1.56) | **1.24 (1.04–1.48)**[a] | 1.54 (0.87–2.72) | 0.95 (0.72–1.25) |
| More than 2 clinical symptoms | **1.60 (1.20–2.14)**[c] | **1.42 (1.15–1.76)**[c] | 1.08 (0.71–1.65) | 1.02 (0.76–1.39) |
| Hospitalization (≥1) | **1.77 (1.16–2.70)**[a] | 1.20 (0.95–1.50) | 1.90 (0.83–4.40) | 1.11 (0.80–1.53) |
| Outpatient visit (≥1) | 1.26 (0.66–2.40) | 1.23 (0.82–1.84) | 0.59 (0.26–1.35) | 1.21 (0.95–1.53) |
| Emergency department visit (≥1) | 1.24 (0.87–1.77) | 1.18 (0.95–1.45) | 1.08 (0.57–2.06) | 1.07 (0.8–1.42) |
| Symptoms of depression | **1.55 (1.17–2.05)**[a] | 1.02 (0.86–1.21) | 0.88 (0.59–1.29) | 0.90 (0.70–1.16) |
| Sexually transmitted infection | 1.12 (0.70–1.78) | **1.37 (1.02–1.86)**[a] | 0.73 (0.33–1.61) | 1.05 (0.65–1.69) |
| Treatment-related variables | | | | |
| Type of regimen (referent: NNRTI-based treatment) | | | | |
| PI based | **1.59 (1.12–2.25)**[a] | **1.34 (1.11–1.62)**[a] | 0.84 (0.49–1.43) | 0.82 (0.60–1.11) |
| Both PIs and NNRTIs | **1.85 (1.24–2.76)**[a] | 1.18 (0.90–1.56) | 1.15 (0.58–2.27) | 0.77 (0.50–1.2) |
| PIs and NNRTIs spared | **2.76 (1.26–6.02)**[a] | 1.10 (0.80–1.51) | 0.78 (0.24–2.57) | 0.64 (0.35–1.15) |
| ≥4 antiretrovirals[d] | 1.20 (0.90–1.59) | **1.26 (1.01–1.56)**[a] | 0.82 (0.51–1.32) | 1.06 (0.76–1.48) |
| Increase in no. of antiretrovirals[e] | 1.05 (0.70–1.57) | **1.29 (1.01–1.67)**[a] | **2.10 (1.10–4.10)**[a] | 1.25 (0.87–1.79) |
| Decrease in no. of antiretrovirals[e] | 0.81 (0.53–1.25) | 0.90 (0.67–1.20) | 1.80 (0.90–3.64) | 1.12 (0.78–1.59) |
| Biological indicators | | | | |
| Detectable[f] HIV RNA level | | | | |
| Last visit | 1.27 (0.96–1.67) | **1.23 (1.04–1.45)**[a] | 1.11 (0.72–1.72) | 0.87 (0.68–1.10) |
| Current level | **1.36 (1.04–1.79)**[a] | **1.36 (1.16–1.61)**[c] | 0.97 (0.62–1.52) | 0.80 (0.63–1.02)[a] |
| CD4 cell count (referent: >500 cells/mm$^3$) | | | | |
| <200 cells/mm$^3$ | 1.61 (0.99–2.60)[a] | **1.34 (1.05–1.71)**[a] | 1.05 (0.53–2.11) | 1.13 (0.76–1.69) |
| 200–350 cells/mm$^3$ | 1.06 (0.73–1.52) | 1.13 (0.91–1.40) | 1.00 (0.58–1.73) | 1.13 (0.80–1.59) |
| 350–500 cells/mm$^3$ | 1.06 (0.76–1.49) | 1.1 (0.89–1.36) | **1.72 (1.01–2.94)**[a] | 1.00 (0.73–1.36) |

**NOTE.** Boldface type indicates statistical significance. NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] $P \leq .05$.

[b] Low income was defined as <$18,000 per year for women and <$20,000 per year for men; referent was >$36,000 per year for women and >$50,000 per year for men.

[c] $P \leq .001$.

[d] Combination pills were counted as a single ART medication.

[e] Since last visit.

[f] HIV RNA level, >50 copies/mL.

cific, that need to occur to induce virus rebound and/or viral resistance.

The levels of adherence reported by participants of 2 long-standing cohorts may be higher than those of the general population. However, we believe that our results are generalizable to 2 of the most vulnerable groups for HIV infection in the United States—women and MSM—who are frequently excluded or underrepresented in other studies [41]. The demo-

**Table 3. Independent predictors of changes in adherence among men and women.**

| Predictor | OR (95% CI) | | | |
|---|---|---|---|---|
| | Decreasing adherence | | Increasing adherence | |
| | Men | Women | Men | Women |
| Sociodemographic characteristics | | | | |
| Age (each 10 years) | 0.80 (0.64–1.00) | 0.92 (0.83–1.02) | **1.46 (1.07–1.99)** | 1.19 (0.99–1.43) |
| Race (referent: white) | | | | |
| African American | 1.54 (0.96–2.45) | 1.27 (0.98–1.64) | 0.68 (0.39–1.20) | 0.64 (0.40–1.01) |
| Hispanic | 0.92 (0.51–1.64) | 1.22 (0.93–1.61) | 1.06 (0.40–2.81) | 0.80 (0.49–1.33) |
| Employment status (referent: employed) | | | | |
| Unemployed | 1.59 (0.97–2.59)[a] | 0.93 (0.77–1.12)[a] | ... | ... |
| Retired | 1.02 (0.62–1.67) | ... | ... | ... |
| Disabled | 0.74 (0.49–1.11) | ... | ... | ... |
| Behavioral characteristics | | | | |
| Drinking (referent: none) | | | | |
| Binging behavior | 1.04 (0.68–1.59) | **1.81 (1.20–2.72)** | 0.99 (0.38–2.57) | **0.41 (0.21–0.78)** |
| Moderate to heavy | 0.84 (0.59–1.18)[a] | **1.52 (1.11–2.07)**[a] | 1.31 (0.67–2.56) | 0.84 (0.51–1.39) |
| Low | 1.22 (0.62–2.41) | **1.29 (1.06–1.57)** | 0.91 ( 0.54–1.54) | **0.73 (0.57–0.95)** |
| Drug use | ... | ... | **0.61 (0.40–0.93)** | **0.58 (0.37–0.92)** |
| Clinical indicators | | | | |
| More than 2 clinical symptoms | **1.38 (1.0–1.92)** | **1.48 (1.18–1.85)** | ... | ... |
| Hospitalization (≥1) | **1.71 (1.11–2.65)** | 1.13 (0.89–1.43) | ... | ... |
| Symptoms of depression | **1.44 (1.06–1.95)**[a] | 0.97 (0.81–1.15)[a] | ... | ... |
| Treatment-related factors | | | | |
| Type of regimen (referent: NNRTI based) | | | | |
| PI based | **1.94 (1.34–2.80)** | **1.35 (1.11–1.64)** | ... | ... |
| Both PIs and NNRTIs | **2.34 (1.45–3.80)**[a] | 1.14 (0.82–1.57)[a] | ... | ... |
| PI and NNRTI spared | **2.41 (1.03–5.61)** | 1.02 (0.74–1.40) | ... | ... |
| ≥4 antiretrovirals[b] | 1.11 (0.76–1.60) | **1.35 (1.03–1.77)** | ... | ... |
| Increase in no. of antiretrovirals[c] | 0.94 (0.61–1.43) | 1.24 (0.96–1.59) | **2.16 (1.09–4.29)**[a] | 1.22 (0.85–1.76)[a] |
| Decrease in no. of antiretrovirals[c] | **0.60 (0.36–0.99)** | **0.71 (0.51–0.99)** | 1.62 (0.77–3.40) | 1.12 (0.79–1.58) |

**NOTE.** Boldface type indicates statistical significance. NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] $P \leq .05$ for heterogeneity.

[b] Combination pills were counted as a single antiretroviral medication.

[c] Since last visit.

graphic characteristics and factors related to adherence in other parts of the world are different and frequently far more resource-limited, which further limits the generalizability of these results to HIV-infected men and women in other countries.

To our knowledge, this is the largest and longest study of patterns and predictors of changes in adherence to HAART among men and women. Our study identifies modifiable determinants of decreasing adherence (health-related factors and treatment factors) that may be slightly different from those hindering improvement in adherence (behavioral factors), and thus our findings underline the need to consider more specific interventions in an effort to enhance or maintain very high levels of adherence.

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***MACS study centers (and principal investigators).*** Johns Hopkins Bloomberg School of Public Health (Joseph Margolick); Howard Brown Health Center and Northwestern University Medical School (John Phair); University of California, Los Angeles (Roger Detels); University of Pittsburgh (Charles Rinaldo); and Data Analysis Center (Lisa Jacobson).

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