The Consistency of Adherence to Antiretroviral Therapy Predicts Biologic Outcomes for Human Immunodeficiency Virus–Infected Persons in Clinical Trials

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We prospectively studied long-term antiretroviral adherence patterns and their impact on biologic outcomes for human immunodeficiency virus (HIV)–infected participants in 2 randomized, multicenter clinical trials. For the period from baseline to month 12 of the study, participants who reported adherence levels of 100%, 80%–99%, and 0%–79% had plasma HIV RNA levels that decreased by 2.77, 2.33, and 0.67 $\log_{10}$ copies/mL, respectively ($P < .001$), whereas their CD4 counts increased by 179, 159, and 53 cells/mm^3, respectively ($P < .001$). Adherence predicted nondetectable HIV RNA levels (<50 copies/mL) at 12 months of follow-up ($P < .001$). The HIV RNA level was nondetectable in 72% of participants who reported 100% adherence at all 4 follow-up visits, compared with 66%, 41%, 35%, and 13% of participants who reported 100% adherence at 3, 2, 1, or 0 follow-up visits, respectively ($P < .001$). Nonwhite race was associated with poorer adherence ($P < .001$), and older age was associated with better adherence ($P < .001$).

Adherence to medication has become a major issue in the treatment of HIV-infected individuals and an important determinant of the outcome of highly active antiretroviral therapy (HAART). Adherence to antiretroviral medication is believed to be a crucial component in maintaining therapeutic drug levels, ensuring virologic suppression, and reducing the risk of drug resistance [1]. Several studies have demonstrated a significant correlation between adherence to medication and virologic suppression [2–8]. A study that used Medication Event Monitoring System (MEMS) caps (Aprex) to electronically measure medication adherence among initially antiretroviral-naive and antiretroviral-experienced patients found that (1) very high levels of adherence (>95% adherence) to protease inhibitors (PIs) were needed to achieve virologic suppression, and (2) small differences in levels of adherence (e.g., >95% adherence vs. 90%–95% adherence) were associated with substantial differences in virologic outcome ((78% virologic suppression at >95% adherence vs. 45% at 90%–95% adherence) [8]. Other investigators have confirmed these findings, using data obtained from pharmacy records of prescription refills [7] and self-reports [4] to assess adherence. Clinical trials of antiretroviral therapies that have incorporated measurements of adherence have found that variations in adherence explain therapeutic effects [3, 9]. Recent studies have also shown the sig-

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nificant impact of adherence on clinical end points, including AIDS progression, death, and hospitalization [10–12].

Although there is no "gold standard" for the measurement of medication adherence [13], different methods have been used with varying success. In general, direct methods, such as direct observation and therapeutic drug monitoring, are more objective and yield more-reliable assessments of adherence than are indirect methods, such as self-reporting, electronic monitoring, and pill counting [14]. Patient self-reporting is the most common method of assessing adherence, although inaccuracy may result from imprecise or inconsistent questioning, patient forgetfulness, or the patient's desire to provide socially desirable answers [15, 16]. Nevertheless, questioning that is carefully structured, nonjudgmental, and culturally appropriate may yield accurate information about adherence and has been shown to be the best indicator of nonadherence [17–19]. Although self-reports may overestimate the extent of patient adherence to medication [20, 21], a number of studies have demonstrated an association between self-reported adherence and HIV RNA, which suggests that self-reports may be a valid indicator of adherence [2–4, 22].

Current guidelines for the treatment of HIV-infected individuals recommend lifelong use of antiretroviral therapy. However, the majority of studies of adherence to antiretroviral therapy are cross-sectional or short-term in nature, and there is a lack of information on long-term adherence patterns and predictors of adherence over time in diverse populations that are infected with HIV.

We assessed medication adherence self-reports from participants in 2 clinical trials of antiretroviral therapy strategies, to determine the usefulness of a simple tool for self-reporting medication adherence, the impact of adherence on therapeutic outcome, and the predictors of adherence. Participants were followed prospectively, by use of repeated measures during the course of 1 year, to address the issue of durability of adherence as well as to examine the variability of predictors of adherence over time.

PATIENTS AND METHODS

Patients. Medication adherence was measured among HIV-infected persons who were participants in 2 clinical trials of antiretroviral therapy conducted by the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The CPCRA is a National Institutes of Health–sponsored national clinical trials group that conducts community-based HIV/AIDS research and seeks to enroll persons of color, women, and injection drug users in clinical trials. Data for this analysis were obtained from participants at 18 CPCRA sites throughout the United States. The 2 trials, CPCRA 057 and CPCRA 058, have evaluated antiretroviral therapy strategies among antiretroviral-experienced and -naive patients, respectively. CPCRA 057 was designed to compare salvage therapy strategies for persons for whom initial antiretroviral therapy regimens that contained a protease inhibitor (PI) had failed. CPCRA 058 was designed to compare 3 different antiretroviral therapy regimens for antiretroviral-naive patients: regimens that contain a PI, regimens that contain a nonnucleoside reverse-transcriptase inhibitor (NNRTI), and regimens that include both a PI and an NNRTI [23]. CPCRA 057 began in October 1998 and ended in June 2000, whereas CPCRA 058 began in January 1999 and is ongoing at the time of publication of this report (March 2002).

Data collection. Data was obtained from participants in both studies at baseline, at 1 and 4 months after treatment randomization, and then every 4 months for the duration of the studies. The data collected included information on participant demographics, HIV-transmission risk category, $CD4^+$ cell count, HIV RNA level (by use of reverse-transcription–PCR and ultrasensitive Roche Amplicor HIV assays), and history of AIDS-defining illnesses. Measurements of adherence were done after 1 and 4 months of follow-up and every 4 months thereafter for the duration of the studies.

Adherence was measured using the CPCRA Antiretroviral Medication Self-Report (Form 646 [24]). The questionnaire uses a global 7-day recall. For each medication prescribed, patients were asked to record whether they took "all," "most," "about half," "very few," or "none" of their pills during the preceding 7 days. The questionnaire also includes a checklist of 10 possible reasons why the antiretroviral doses were missed; these reasons include side effects, pill burden, forgetfulness, being away from home, concerns about confidentiality, difficulties with dietary requirements, and confusion. Study participants completed the questionnaire and submitted it in a sealed envelope directly to the CPCRA Statistical and Data Monitoring Center (Minneapolis, MN). Staff assistance with completion of the patient portion of the questionnaire was provided only when needed or requested by a study participant.

Data analysis. For the current analysis, we combined data from CPCRA 057 and CPCRA 058 participants who were enrolled in the studies between the time that the trials were opened (in October 1998 and January 1999, respectively) and May 2001. Data for all participants who had $\geq$1 month of follow-up as of May 2001 were included in the analysis, and up to 12 months of follow-up data on adherence were reviewed.

An adherence score was calculated on the basis of the mean of the combined total amount of each medication taken during the previous week, according to the scale: "all" (100%), "most" (80%), "about half" (50%), "few" (20%), or "none" (0%). χ^2 tests and Fisher's exact tests were used to compare categorical data. Analysis of variance was used to evaluate the relationship of the $CD4^+$ lymphocyte count and the HIV RNA level with adherence. Multiresponse logistic regression was used to evaluate

Table 1. Characteristics, at baseline, of 1095 participants in 2 large, randomized, multicenter clinical trials of antiretroviral agents.

Characteristic	Value
Age, mean years	39
Female sex	20
Race/ethnicity	
Black	53
Latino	16
White	28
Other	2
History of injection drug use	16
AIDS-defining illness	29
$CD4^+$ lymphocyte count, mean cells/mm^3	230
HIV RNA level, mean $\log_{10}$ copies/mL	4.95

NOTE. Data are % of participants, unless indicated otherwise.

predictors of adherence. In addition, a repeated-measures analysis was performed using the actual adherence score to examine predictors of adherence. Multivariate logistic regression was performed to assess the effects of adherence on virologic suppression (HIV RNA level, <50 copies/mL) at 12 months of follow-up, after adjustment for baseline CD4 count, baseline log HIV RNA level, and type of therapy (i.e., initial HAART regimen or salvage therapy). The adherence variable used in the analysis was whether or not 100% adherence was reported at all 4 follow-up visits during the 12-month period. Only patients who had been followed for ⩾12 months were included. Appropriate informed consent was obtained, and clinical research was conducted in accordance with guidelines for human experimentation, as specified by the US Department of Health and Human Services.

RESULTS

Participant characteristics. Adherence was evaluated among all CPCRA 057 and CPCRA 058 participants who had completed 1 month of follow-up and the 1-month adherence self-report as of May 2001. Self-reported adherence data were available for 1095 (96%) of the 1141 participants who had completed 1 month of follow-up. The numbers of participants who had completed 4, 8, and 12 months of follow-up as of May 2001 were 946, 718, and 540 participants, respectively; the smaller numbers of participants seen at later time points reflect different dates of participant enrollment. Approximately 33% of the participants requested assistance in completing the questionnaire about adherence. Table 1 summarizes the characteristics of the 1095 participants at baseline.

Adherence scores. Among the participants who reported adherence, 100% adherence was reported by 74% of the 1095 participants at 1 month of follow-up, 68% of 946 participants at 4 months, 65% of 718 participants at 8 months, and 67% of 540 participants at 12 months (figure 1). A similar pattern was seen among the cohort of participants who completed 12 months of follow-up, with 100% adherence being reported by 76% of the cohort at 1 month, 66% at 4 months, 66% at 8 months, and 67% at 12 months. There was a significant difference ($P < .001$) in adherence scores noted between follow-up of at 1 and 4 months. Mean adherence scores were 89% at 1 month of follow-up, 86% at 4 months, 85% at 8 months, and 85% at 12 months.

Virologic and immunologic outcomes. Self-reported antiretroviral adherence predicted therapeutic outcome as measured by HIV RNA level and $CD4^+$ cell count (table 2). At 12 months of follow-up, the decrease in the HIV RNA level (from baseline) was 2.77 $\log_{10}$ copies/mL among participants who reported 100% adherence, 2.33 $\log_{10}$ copies/mL among those who reported 80%–99% adherence, and 0.67 $\log_{10}$ copies/mL among those who reported 0%–79% adherence ($P < .001$). Similarly, the percentage of subjects with nondetectable HIV RNA levels (<50 copies/mL) at 12 months was 66%, 47%, and 17% among the groups with 100%, 80%–99%, and 0%–79% adherence, respectively ($P < .001$). The $CD4^+$ cell count increased by 179, 159, and 53 cells/mm^3 among the groups with 100%, 80%–99%, and 0%–79% adherence, respectively ($P < .001$). In addition, multivariate analysis found adherence to be a strong independent predictor of virologic suppression (OR, 3.41; 95% CI, 2.29–5.06; $P < .001$).

Consistently high levels of adherence were also an important determinant of virologic and immunologic outcome. Among participants who completed 12 months of follow-up, the frequency of follow-up visits during which participants reported 100% adherence was significantly associated with virologic out-

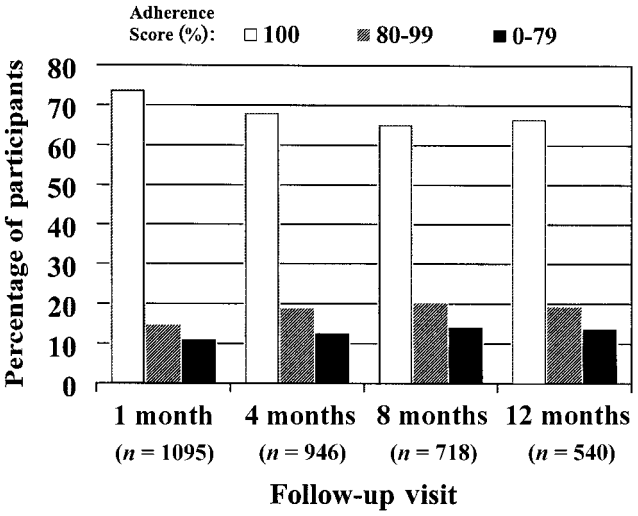

Figure 1. Distribution of self-reported adherence scores over time for participants in 2 large, randomized, multicenter clinical trials of antiretroviral therapy.

Table 2. Virologic and immunologic outcomes, according to adherence level self-reported by participants in 2 large, randomized, multicenter clinical trials of antiretroviral agents.

Outcome assessed, month of follow-up[a]	Outcome value, by self-reported patient adherence level		
	100%	80%–99%	0%–79%
Change in HIV RNA level,[b] $\log_{10}$ copies/mL			
1 (n = 1074)	−2.23[c]	−2.04	−0.94
4 (n = 922)	−2.73[c]	−2.52	−0.80
8 (n = 699)	−2.74[c]	−2.23	−1.02
12 (n = 525)	−2.77[c]	−2.33	−0.67
HIV RNA level <50 copies/mL, % of participants			
1 (n = 1074)	10.7	11.9	10.9
4 (n = 922)	50.7[c]	39.0	10.9
8 (n = 699)	61.6[c]	45.7	18.4
12 (n = 525)	65.6[c]	47.1	16.7
Change in $CD4^+$ lymphocyte count,[b] cells/mm^3			
1 (n = 1074)	74.0	73.0	46.8
4 (n = 940)	104.9[c]	120.7	22.8
8 (n = 709)	146.6[c]	131.1	50.0
12 (n = 531)	178.9[c]	159.4	53.0

[a] The n values denote the number of study participants who provided self-reported adherence data at follow-up visits made during the months indicated.
[b] From baseline level.
[c] $P < .001$ for 3-way comparison outcomes, by adherence level.

come. For participants who reported 100% adherence, the decrease in the HIV RNA level between baseline and 12 months of follow-up was 3.02, 2.59, 2.10, 1.62, and 0.91 $\log_{10}$ copies/mL at 4, 3, 2, 1, or 0 of the 4 possible follow-up visits, respectively ($P < .001$). Among participants who reported 100% adherence at all 4 follow-up visits, 72% achieved nondetectable HIV RNA levels. In contrast, 66%, 41%, 35%, and 13% of participants who reported 100% adherence at 3, 2, 1, or 0 follow-up visits, respectively, achieved nondetectable HIV RNA levels ($P < .001$, figure 2). A similar relationship was noted for immunologic outcome, with $CD4^+$ count increases of 178, 188, 145, 106, and 92 cells/mm^3noted for participants who reported 100% adherence at 4, 3, 2, 1, or 0 of 4 possible follow-up visits, respectively ($P < .001$).

Correlates of adherence. The longitudinal nature of the current study revealed some variability in the relationship between patient-related factors and adherence. Nonwhite race was the only factor consistently associated with adherence, with nonwhite participants having lower levels of adherence, compared with white participants, at all 4 follow-up points ($P < .03$). In addition, age, history of injection drug use, and baseline HIV RNA level were significantly associated with adherence at ⩾1 time point. Higher baseline HIV RNA levels predicted better adherence at 1 month ($P < .02$), increased age predicted better adherence at 4 and 12 months ($P < .01$), and history of injection drug use predicted poorer adherence at 8 and 12 months ($P = .01$). According to repeated-measures analysis, nonwhite race was associated with poorer adherence ($P < .001$), and older age was associated with better adherence ($P < .001$). Sex, baseline $CD4^+$ cell count, and previous diagnoses of AIDS were not predictive of adherence.

In terms of factors related to participants' antiretroviral medication regimens, drug class was significantly related to level of adherence at 2 of the 4 follow-up visits (table 3). At months 4 and 8 of follow-up, patients who received regimens that contained an NNRTI were significantly more likely to report 100% adherence than were those who received regimens that contained a PI. A similar trend was also noted after 1 month of follow-up. Adherence was not associated with the total daily pill burden. Whether participants had previously received antiretroviral therapy was also associated with adherence. Adherence levels were higher for antiretroviral-naive participants who were receiving their first antiretroviral regimen, compared with antiretroviral-experienced participants who were receiving salvage therapy after their first PI regimen had failed (figure 3).

The most frequently stated reason for missing doses at all follow-up time points was "I forget to take the pills." Other common reasons included being away from home, experiencing side effects, and having problems taking pills at specified times. The frequency of the reasons reported was stable during the 12-month period. At 4 and 12 months of follow-up, nonwhite individuals were more likely than white individuals to report confidentiality concerns ($P < .04$ and $P < .02$) and side effects ($P < .04$) as reasons why they missed doses. At the same time points, white participants reported forgetfulness more often than did nonwhite participants ($P < .02$ and $P < .01$).

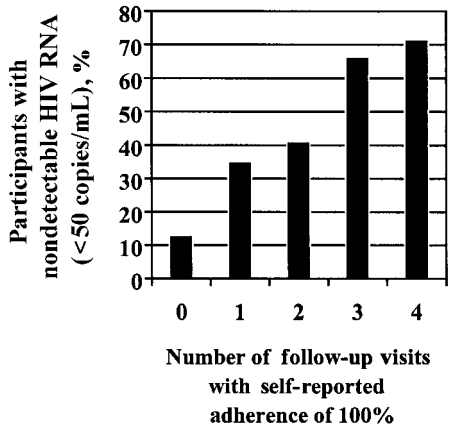

Figure 2. Association between consistency of 100% antiretroviral adherence and virologic outcome among 540 participants who completed 12 months of follow-up in 2 large, randomized, multicenter clinical trials of antiretroviral agents.

Table 3. Proportion of participants who reported 100% adherence, by antiretroviral drug class.

Month of follow-up	Total no. of participants receiving designated therapy (% reporting 100% adherence)			*P* value[a]
	PI	NNRTI	NRTI	
1	722 (74.1)	725 (77.9)	942 (78.1)	.088
4	612 (67.3)	623 (73.8)	808 (70.4)	.012
8	446 (65.5)	482 (71.6)	601 (68.2)	.045
12	331 (68.0)	352 (72.7)	422 (70.1)	.174

NOTE. NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] PI vs. NNRTI.

DISCUSSION

The CPCRA 7-day recall adherence questionnaire produced adherence data that clearly and significantly predicted biologic outcomes—that is, virus load and $CD4^+$ cell levels. Adherence, as measured by this instrument, was associated with nondetectable HIV RNA levels, a change in HIV RNA levels, and a change in $CD4^+$ cell counts during a 12-month period. Although 100% adherence was required to achieve the best virologic outcomes, similar increases in $CD4^+$ cell counts were seen among participants who reported 100% adherence and those who reported 80%–99% adherence, a finding that suggests that $CD4^+$ cell count response may be a less sensitive marker of adherence levels than virus load.

The current study confirms what other studies have found: self-reported medication adherence is a strong and independent predictor of virologic outcome. Other methods of measuring adherence, such as the use of MEMS caps, may allow for greater precision in measurement; however, these methods also have many drawbacks, including greater cost, inconvenience, patient dissatisfaction, and confidentiality concerns [19, 25, 26]. Self-reporting offers the advantages of low cost and ease of administration, in addition to revealing the reasons why doses were missed. In the current study, the important aspect of the collection of self-reported data was that the instrument was nonjudgmental and was administered in a confidential manner by someone not directly involved in the patient's care, thereby reducing potential bias in the responses.

The longitudinal data revealed additional findings of interest. Adherence changed over time, with the proportion of participants who reported 100% adherence decreasing significantly between 1 month and subsequent months of taking the study medications. The consistency of the adherence behavior over time was also shown to be predictive of virologic and immunologic outcomes. Participants who consistently reported 100% adherence at all study visits were significantly more likely to achieve suppression of the virus to a level below the level of detection, compared with those who less frequently reported 100% adherence. It is noteworthy that only 72% of those who reported 100% adherence at all follow-up visits achieved nondetectable HIV RNA levels. Potential explanations for this include the possibility of self-reporting resulting in overestimation of the actual adherence level, as well as other reasons for virologic failure, including resistance and pharmacologic factors. Few studies have examined pooled adherence data over time [4, 8], and only 1 published study has demonstrated the importance of maintaining uniformly high levels of adherence over time [27]. This may have important implications for interventions to promote adherence. Our study suggests the need to focus efforts on promoting adherence during the first 4 months that individuals are taking a new therapy as well as the need to encourage consistently high levels of adherence over time.

The current study provides interesting information about predictors of adherence. First, the longitudinal nature of the study revealed that factors predictive of adherence varied at different time points. Therefore, a cross-sectional analysis could have missed some significant predictors, which possibly explains the disparate findings regarding predictors of adherence in many studies, most of which have been cross-sectional in nature. Although some factors, such as active substance use, mental illness, and lack of trust in a health care provider, have been found to predict poorer adherence consistently across studies [4, 6, 8, 28–30], there has been more variability in the correlation between adherence and demographic factors, such as age, race, and sex. The current study identified a race-

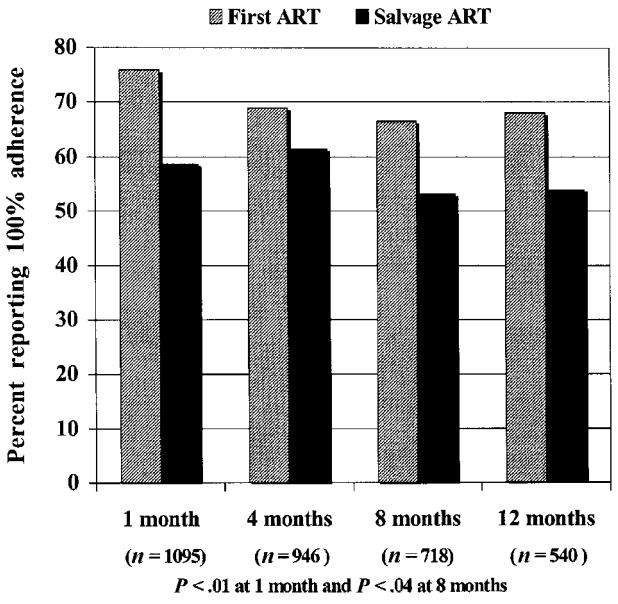

Figure 3. Changes in self-reports of 100% adherence over time among participants in clinical trials of antiretroviral agents who were receiving their first antiretroviral therapy (ART) regimen, compared with those who were receiving salvage therapy.

associated difference in adherence: nonwhite individuals were less likely to report high levels of adherence than were white individuals. The association between nonwhite race and nonadherence has been described elsewhere [6, 31–37] and has been shown to be independent of age, history of injection drug use, education, employment, income, and medical regimen followed [34, 35]. It has been suggested that nonwhite race may be a marker for other factors, such as dissatisfaction with social support, unhealthy coping mechanisms, and a lower level of literacy [34, 38, 39]. In comparison with white individuals, black individuals also have been found to have greater perceived barriers to taking medications [33], greater misconceptions about HIV disease and its treatments, and greater mistrust of health care authorities [40, 41]. The reason for the association noted in our study remains unclear; examination of the reasons why doses were missed in terms of differences between nonwhite and white individuals did not provide much insight. In the current study, adherence was also associated with the antiretroviral medication class (i.e., nucleoside, nonnucleoside, or protease inhibitor), with lover levels of adherence noted among patients who were receiving a regimen that contained a PI. This may be related to the pill burden, side effects, toxicities, dosing frequency, and complexity associated with these regimens in comparison with regimens that contained an NNRTI. However, pill burden alone was not predictive of adherence. Lower levels of adherence were also seen among persons who received antiretroviral salvage therapy, a finding that suggests the need for additional support for such patients.

The limitations of the present study are associated with the measurement of adherence, the duration of follow-up, and the end points of the clinical trials. Self-reporting was the only means of measuring adherence that was used. In addition, the CPCRA self-report consisted of a global 7-day recall rather than a day-by-day 3- or 4-day recall, as used in many other studies [42]. In the calculation of adherence scores by use of data from the CPCRA questionnaire, the percentages used as estimates of corresponding categorical responses may have over- or underestimated the intentions of the participants. The self-report form also offered only a limited number of reasons why antiretroviral doses were missed. This may explain the lack of a consistent explanation for the racial difference in adherence. Although the duration of the present study was longer than that of most studies of adherence, participants were followed during a relatively short period of antiretroviral use, considering the current recommendations for lifelong therapy. Because the end points of the antiretroviral trials were virologic and not clinical, the impact of adherence on the clinical outcomes of these participants is unknown.

In summary, the current study confirms that self-reporting is a useful method of measuring adherence and that self-reported adherence is a strong predictor of virologic and immunologic outcomes. The changes in levels of adherence and its predictors over time illustrate that adherence is a complex and dynamic behavioral process with subtle and important nuances that must be identified and followed over time, not solely at a single time point. The importance of constancy in adherence needs to be emphasized in interventions for enhancing adherence.

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References

1. Altice FL, Friedland GH. The era of adherence in antiretroviral therapy. Ann Intern Med **1998**; 129:503–5.
2. Hecht FM, Colfax G, Swanson M, Chesney MA. Adherence and effectiveness of protease inhibitors in clinical practice [abstract 151]. In: Program and abstracts of the 5th Conference on Retrovirus and Opportunistic Infections (Chicago). Alexandria, VA: Foundation for Retrovirology and Human Health, **1998**:107.
3. Montaner JSG, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients. The INCAS Trial. JAMA **1998**; 279: 930–7.
4. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. AIDS **1999**; 13:1099–107.
5. Bangsberg DR, Hecht FM, Charlobois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS **2000**; 14:357–66.
6. Gifford AL, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. J Acquir Immune Defic Syndr **2000**; 23:386–95.
7. Montessori V, Wood E, Low Beer S, et al. Virologic success rates drop off sharply with decreasing levels of adherence to antiretroviral therapy [abstract MoPpD1056]. In: Program and abstracts of the XIIIth International AIDS Conference (Durban, South Africa). **2000**.
8. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med **2000**; 133:21–30.
9. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. JAMA **2000**; 283:205–11.
10. Carmona A, Knobel H, Guelar A, et al. Factors influencing survival in HIV infected patients treated with HAART [abstract TuOrB417]. In: Program and abstracts of the XIIIth International AIDS Conference (Durban, South Africa). **2000**.
11. Hogg R, Yip B, Chan K, O'Shaughnessy M, Montaner J. Non-adherence to triple combination therapy is predictive of AIDS progression and death in HIV-positive men and women [abstract TuOrB419]. In: Program and abstracts of the XIIIth International AIDS Conference (Durban, South Africa). **2000**.
12. Knobel H, Carmona A Guelar A, et al. Adherence in patients treated with HAART: influence in hospital admissions [abstract MoPeD2556]. In: Program and abstracts of the XIIIth International AIDS Conference (Durban, South Africa). **2000**.
13. Melkinow J, Kiefe C. Patient compliance and medical research: issues in methodology. J Gen Intern Med **1994**; 9:96–104.
14. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. Am J Hosp Pharm **1991**; 48:1978–88.

15. Windsor R, et al. Evaluation of health promotion and education programs. Palo Alto, CA: Mayfield Publishing, **1984**.
16. Ley P. Communicating with patients: improving communication, satisfaction and compliance. New York: Routledge Chapman and Hall, **1988**.
17. Fletcher SW, Pappius EM, Harper SJ. Measurement of medication compliance in a clinical setting. Arch Intern Med **1979**; 139:635–8.
18. Orr PR, Blackhurst DW, Hawkins BS. Patient and clinic factors predictive of missed visits and inactive status in a multicenter clinical trial. Control Clin Trials **1992**; 13:40–9.
19. Office of AIDS Research, Forum for Collaborative HIV Research, National Minority AIDS Council. Proceedings of Adherence to New HIV Therapies: A Research Conference (Washington, DC). **1997**.
20. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA **1989**; 261:3273–7.
21. Waterhouse DM, Calzone KA, Mele C, Brenner DE. Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol **1993**; 11:1189–97.
22. Berge J, Braun S, Becker A, et al. Relationship between demographic and clinical disease characteristics and medication adherence among patients in CHORUS [abstract I-212]. In: Program and abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Diego, CA). Washington, DC: American Society for Microbiology, **1998**.
23. MacArthur RD, Chen L, Mayers DL, et al. The rationale and design of the CPCRA (Terry Beirn Community Programs for Clinical Research on AIDS) 058 FIRST (Flexible Initial Retrovirus Suppressive Therapies) Trial. Controlled Clinical Trials **2001**; 22:176–90.
24. Terry Beirn Community Programs for Clinical Research on AIDS. Form 646: antiretroviral medication self-report. Available at http://sdmc.cpcra.org/CRFormsIndex.html#module. Accessed 15 February 2002.
25. Matsui D, Hermann C, Klein J, Berkovitch M, Olivieri N, Koren G. Critical comparison of novel and existing methods of compliance assessment during a clinical trial of an oral chelator. J Clin Pharmacol **1994**; 34:944–9.
26. Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. Epilepsia **1995**; 36:1111–7.
27. Tuldra A, Fumaz CR, Ferrer MJ, et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. J Acquir Immune Defic Syndr **2000**; 25:221–8.
28. Altice FL, Mostashari F, Thompson AS, Friedland GH. Perceptions, acceptance and adherence to antiretrovirals among prisoners. In: Program and abstracts of the 4th Conference on Retroviruses and Opportunistic Infections (Washington, DC). Alexandria, VA: Foundation for Retrovirology and Human Health, **1997**.
29. Wilson T, Barren Y, Cohen, et al. Prevalence and predictors of adherence to antiretroviral therapy (ART) among HIV+ women [abstract TuPpD1199]. In: Program and abstracts of the XIIIth International AIDS Conference (Durban, South Africa). **2000**.
30. Mannheimer S, Schmitz K, Holson N, et al. Substance use predicts antiretroviral nonadherence in Harlem [abstract TuOrB421]. In: Program and abstracts of the XIIIth International AIDS Conference (Durban, South Africa). **2000**.
31. Besch CL, Collins G, Morse E, Simon P. Cofactors associated with participant compliance in two CPCRA trials [abstract Pu B7040]. In: Program and abstracts of the International Conference on AIDS. **1992**.
32. Moore RD, Stanton D, Gopalan R, Chaisson RE. Racial differences in the use of drug therapy for HIV disease in an urban community. N Engl J Med **1994**; 330:763–8.
33. Muma RD, Ross MW, Parcel GS, Pollard RB. Zidovudine adherence among individuals with HIV infection. AIDS Care **1995**; 7:439–47.
34. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus–infected patients to antiretroviral therapy. Clin Infect Dis **1999**; 29:824–30.
35. Singh N, Squier C, Sivek C, Wagener M, Nguyen MH, Yu VL. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. AIDS Care **1996**; 8:261–9.
36. Wenger N, Gifford A, Liu H, et al. Patient characteristics and attitudes associated with antiretroviral adherence [abstract 98]. In: Program and abstracts of the 6th Conference on Retroviruses and Opportunistic Infections (Chicago). Alexandria, VA: Foundation for Retrovirology and Human Health, **1999**:85.
37. Kleeberger C, Jacobson LP, Strathdee S, et al. Determinants of heterogeneous adherence to antiretroviral therapies (ART) in the multicenter AIDS cohort study (MACS) [abstract ThPeB4984]. In: Program and abstracts of the XIIIth International AIDS Conference (Durban, South Africa). **2000**.
38. Cross JT, Davis TC, Arnold C, Green K. The role of literacy, socioeconomic status, and race in compliance to HIV medication regimens [abstract 38]. In: Program and abstracts of the 36th Annual Infectious Disease Society of America Meeting (Denver). **1998**.
39. Sipler AM, Cross JT, Lane DR, et al. The relationship between literacy, race, and adherence to potent anti-retroviral therapies [abstract 108]. In: Programs and abstracts of the 6th Conference on Retrovirus and Opportunistic Infections (Chicago). Alexandria, VA: Foundation for Retrovirology and Human Health, **1999**:87.
40. Guinan ME. Black communities' belief in "AIDS as genocide": a barrier to overcome for HIV prevention. Ann Epidemiol **1993**; 193–5.
41. Mannheimer SB, Minnifield C, Hunt J, Scimeca M, El-Sadr W. The use and the fear of antiretroviral therapy in HIV-infected individuals in Harlem (abstract). In: Program and abstracts of the XIth International Conference on AIDS (Vancouver). **1996**.
42. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: The AACTG Adherence Instruments. AIDS Care **2000**; 12:255–66.