Highly active antiretroviral therapy for HIV-1 infection: patients' quality of life and treatment adherence

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Chapter 8

Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis

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Abstract

**Background:** Adherence to highly active antiretroviral therapy (HAART) for HIV-1 infection is essential for plasma HIV-1 RNA suppression. Self-report is the most frequently used measure of adherence to HAART, but its validity is controversial. Studies on the relation between self-reported adherence and virologic treatment response have shown inconsistent results. We investigated whether this variability between studies about the effect of self-reported adherence on virologic treatment response could be attributed to study design features.

**Methods:** We searched for studies reporting on adult nonpregnant patients prescribed antiretroviral therapy for chronic HIV-1 infection using a self-report adherence measure and providing information about the relation between adherence and plasma HIV-1 RNA concentrations. Meta-analysis with random-effects modeling was used to pool data and to investigate sources of heterogeneity.

**Results:** Sixty-five studies fulfilled inclusion criteria, containing data from 15,351 patients. The pooled odds ratio (95% confidence interval) of detectable plasma viral load in non-adherent patients was 2.31 (1.99-2.68). There was significant heterogeneity among studies ($P<0.001$). Not ascertaining confidentiality of responses, use of actual viral load measurements, an adherence threshold lower than 95%, higher percentages of patients on their initial antiretroviral regimen, and higher percentages of patients with a history of intravenous drug-use within a study were associated with higher point estimates.

**Conclusions:** Overall, we observed that self-reported adherence measures can distinguish between clinically meaningful patterns of medication taking behavior. Distinct study characteristics were significantly associated with the relation between adherence and virologic response. These characteristics should be taken into consideration when interpreting results from studies on self-reported adherence.
Introduction

To date, self-report is the most frequently used measure of adherence to highly active antiretroviral therapy (HAART) because it offers low costs and ease of administration and is applicable in a variety of clinical and research settings. More quantitative adherence measures exist, such as electronic monitoring devices, pill counts, and pharmacy prescription refill monitoring. However, use of these more quantitative methods is limited by high costs, labor intensity, and other issues, however. Consequently, it is expected that self-report will remain an important tool for measuring adherence to HAART [1].

The use of self-reported measures of adherence to HAART is controversial, because the validity of such data may be hampered by social desirability and recall bias [2]. Support for the validity of a self-reported adherence measurement is provided if an association is found between higher levels of adherence and lower plasma HIV-1 RNA concentrations. Such an association is biologically plausible, and has been demonstrated using more objective measures of adherence [3]. Factors other than adherence may influence plasma viral load as well, including viral resistance, whether patients are on their initial regimen or not, potency of the regimen, drug absorption and metabolism, and HIV disease stage [4]. Studies on the relation between self-reported adherence to HAART and plasma viral load have shown inconsistent results, with some studies finding fairly strong associations and others finding no association at all [5, 6]. The reason for this inconsistency in results is unclear. Our objective was to investigate through meta-analysis whether this variability between studies about the effect of self-reported adherence on virologic treatment response could be attributed to characteristics of the adherence measurement, study design, or study population.

Methods

We searched in PubMed and EMBASE from 1996 through September 2003, using combinations of the terms adherence or compliance with HIV, HAART or antiretroviral therapy. We included articles published in peer-reviewed English-language journals reporting on adult non-pregnant patients prescribed antiretroviral therapy for chronic HIV-1 infection, and using a self-reported measure of adherence. We included studies that related self-reported adherence to absolute plasma viral load concentrations, such as detectable or undetectable concentrations, thereby excluding studies relating adherence to change in viral load. Because we anticipated that insignificant associations between adherence and viral load might not have been reported, we contacted corresponding authors of 33 articles that did not report such a relation and asked if this association had been investigated (26 authors responded).
From each paper, we extracted characteristics that were previously presumed or shown to be related with the association between self-reported adherence and virologic response (Figure 1). We had no a priori hypotheses regarding which characteristics would be related to high correlations. We recorded whether or not articles specifically noted that respondents were told that their responses to questions about adherence would be kept confidential by mentioning 1 of the following methods: questionnaires being collected in sealed envelopes, assessments being confidential or anonymous, responses not being passed on to health care providers, interviews being conducted by a person not directly involved in the patient's care, or providers being blinded to patient responses.

We retrieved or calculated odds ratios (ORs) and associated standard errors of detectable plasma viral load concentrations in non-adherent patients relative to adherent patients [7]. Data were independently extracted by both authors. ORs were transformed to their natural logarithm before analyses. To detect the presence of publication bias, we plotted ORs by sample size [8]. Heterogeneity between studies was assessed using a X^2 test. We estimated the pooled OR and 95% confidence intervals (CIs) in a random effect model. We performed uni- and multivariate meta-regression analyses to investigate the effects of study characteristics on the ORs. We expressed the effects of study characteristics on the ORs as standardized regression coefficients with 95% CIs to enable comparison of the effects of different study characteristics.

**Results**

By September 2003, we found 129 potentially eligible studies, from which we excluded 64 studies that did not meet inclusion criteria. The final sample thus included 65 studies, containing data from a total of 15,351 patients. A list of all studies is available from the first author.

Visual inspection of plotting ORs by sample size did not suggest publication bias, because the plot was symmetric and funnel shaped. There was significant heterogeneity in point estimates between studies (P <0.001). The pooled OR (95% CI) from the random effect model was 2.31 (1.99-2.68).

Figure 1 shows the association between distinct study characteristics and ORs as determined in the univariate meta-regression analyses. Articles that did not specifically note that respondents were told that their responses would be kept confidential had significantly higher ORs than articles that did specifically note this. Studies using an adherence threshold lower than 95% had significantly higher point estimates than studies using a threshold of 95% or higher (Figure 2). Studies with actual viral load measurements had significantly higher ORs than studies using self-reported viral loads. Studies including a higher percentage of patients on their initial antiretroviral regimen had significantly higher ORs than studies including a lower percentage of patients on their initial regimen (Figure
Figure 1: Association between study characteristics and odds ratio's of detectable viral load in non-adherent patients

- not confidential versus confidential
- self-versus interviewer administered
- time frame 7 days versus >7 days
- adherence threshold <95% versus 95%
- >1 versus 1 adherence measurement
- subsequent versus concurrent viral load measurement
- actual versus self-reported viral load
- lower detection limit 50-80 copies/ml versus 400-500 copies/ml
- % of patients within study on their initial regimen
- % of patients within study on PI regimen
- % of females within study
- % of patients within study with history of IVD-use
- % of patients within study with <200 CD4 cells/mm$^3$

Figure 2: Adherence thresholds and adherence - virologic response relationship
3). This percentage could be derived for 32 of 65 studies only, however. Studies including a higher percentage of patients with a history of intravenous drug (IVD) use had significantly higher point estimates than studies including a lower percentage of patients with such history. Because of the amount of missing data, we could not include the percentages of patients on their initial regimen and percentages with a history of IVD use as predictors in the multivariate analysis. The effect of not ascertaining confidentiality of responses and use of actual viral load measurements both remained significantly associated with higher point estimates in the multivariate analysis.

**Discussion**

Our pooled analysis containing data from 15,351 patients showed a significant effect of self-reported adherence to HAART on virologic response. This indicates an overall ability of self-reported adherence measures to distinguish between clinically meaningful patterns of medication-taking behavior. Moreover, we found that there are study design factors that are associated with the relationship between self-reported adherence and virologic treatment response. The percentage of patients on their initial antiretroviral regimen within a study had the strongest association with the adherence- virologic response relationship. It is well established that with increasing antiretroviral experience, the likelihood of reaching
undetectable plasma viral load decreases [3]. Our results suggest that the ability to predict patients' virologic response on the basis of adherence is affected by prior treatment experience. Another possible explanation is that patients early in their experience to HAART are more inclined to complete self-reports carefully. With time, patients may become accustomed to the self-report instruments and may learn that there are advantages to reporting higher adherence (ie, making completing forms easier and perhaps sparing time that may go to counseling about adherence based on their responses).

Studies using an adherence threshold lower than 95% yielded higher ORs than studies using a threshold higher than 95%. The interpretation of this finding depends upon whether thresholds had been determined a priori or not, which we could generally not infer from the original articles. If thresholds had been determined a priori, it would suggest that choosing a threshold below 95% would be more appropriate. Because studies that did not report a threshold yielded lower ORs, it seems that choice of threshold was not unrelated with outcome. Therefore, our finding may reflect that the ability of self-report to distinguish between adherent and non-adherent patients decreases when patients uniformly report high levels of adherence.

An unexpected finding was that papers not specifically mentioning that respondents were told that their responses would be kept confidential yielded higher ORs than articles that did specifically mention this. It is generally recommended that patients' responses to questions about adherence be kept confidential. This is supposed to minimize social desirability bias. Our findings suggest an opposite effect, however. It is possible that telling a patient that responses to questions about adherence are handled with confidentiality increases the patients' awareness that non-adherence is undesirable behavior, thereby increasing his or her reluctance to disclose non-adherence. Another explanation might be that centers cautious about confidentiality might be those in which clinicians are more judgmental and reports are therefore less valid.

Previously, it has been suggested that patients with a history of IVD are less adherent than patients without such a history. We anticipated that this could influence the adherence-virologic response relationship, which was indeed found to be true. It is possible that patients with a history of IVD use admit non-adherence sooner than patients without such a history. Also, a larger variation in reported levels of adherence among studies, including a higher percentage of patients with a history of IVD-use, could explain the stronger relationship between adherence and virologic response.

Our study has several limitations. Inclusion of English language articles only may have introduced selection bias. Because studies were the unit of measurement in our analysis, characteristics of the study population comprising a summary measure of individual patients' data may be subject to ecologic fallacy (ie, summary data for a group misrepresent the individual patients) [9]. We allowed inclusion of studies with variable measures and definitions of adherence, because it is recommended to use broad inclusion criteria and then to perform analyses relating design features to outcome [10]. As a result of this
heterogeneity between studies, we considered random effect modeling most appropriate, because this method incorporates an estimate of between-study variation into the estimation of the common effect.

Based on our results, we suggest that future researchers on self-reported adherence take the following precautions. Collect information about whether or not patients are on their initial regimen. Our results suggest that the reporting about antiretroviral experience of patients in self-reported adherence studies could be improved. Our results further suggest that researchers use actual viral load measurements instead of self-reported measurements. The effect of conveying to patients that their responses will be kept confidential clearly deserves further investigation. Another area of future research is examining strategies to reinforce accurate reporting.

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References