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

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Adherence over 48 weeks in an antiretroviral clinical trial: variable within patients, affected by toxicities and independently predictive of virological response


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Abstract

Objectives: To investigate adherence to antiretroviral therapy over 48 weeks, to investigate the association between adherence and treatment-related symptoms and to investigate the impact of adherence on virological response over 48 weeks among established predictors of treatment success.

Methods: One-hundred-and-sixty HIV-1 infected protease inhibitor- and stavudine-naive patients participating in a trial of ritonavir/saquinavir versus ritonavir/saquinavir/stavudine completed a adherence questionnaire and a symptom checklist at weeks 12, 24, 36 and 48. We calculated odds ratios between experienced symptoms and non-adherence. Regression models were used to determine predictors of HIV-1 RNA below 400 copies/ml at week 48, and of the area about the change from baseline over 48 weeks (ACFB) in serum HIV-1 RNA.

Results: The percentage of patients reporting skipping medication, deviation from time schedule and dietary prescriptions at separate time-points ranged from 12% to 15%, 32% to 35% and 17% to 22%, respectively. The percentage that changed their level of adherence during 48 weeks ranged from 29% for skipping medication to 48% for deviation from time-schedule. Experienced side effects were associated with an increased likelihood of non-adherence. Not skipping medication was an independent predictor of both having a serum HIV-1 RNA below 400 copies/ml at week 48 and the ACFB over 48 weeks in serum HIV-1 RNA.

Conclusions: Adherence was an independent predictor of virological response over 48 weeks. The level of adherence is variable within patients over time. This suggests the need for continued adherence monitoring in all patients as part of standard medical practice.
Introduction

Highly active antiretroviral therapy (HAART) for HIV-1 infection is able to suppress plasma HIV-1 RNA below detectable concentrations [1, 2]. Factors shown to affect virological response include baseline HIV-1 RNA, baseline CD4+ cell count, and previous antiretroviral therapy [3-5]. Additionally, suboptimal patient adherence proved to be related with failure to achieve or maintain viral suppression [6-8]. Only a few studies have investigated the relative contribution of adherence among established predictors of viral suppression and found that adherence was an independent predictor of virological response to HAART [9-11].

Adherence may be hampered by toxicities associated with HAART. However, studies investigating the relation between side-effects and adherence led to inconsistent results [10-13]. To date, studies of adherence to HAART have reported on a follow-up period of a maximum of 6 months. Therefore, it is not known whether patients change their level of adherence during a prolonged time period, as observed among other diseases requiring continuous therapy [14].

We investigated patient adherence over 48 weeks in a clinical trial comparing treatment with ritonavir/saquinavir versus ritonavir/saquinavir/stavudine [15]. We examined the association between adherence and disease- or treatment-related symptoms. Additionally, we investigated the impact of adherence on virological response over 48 weeks among established predictors of treatment success. We anticipated that patients who were non-adherent during the early part of the study might comprise a population at risk for treatment failure. Identification of this population might help target potential interventions to improve adherence for those patients most likely to benefit. Therefore, we also aimed to identify this potential population at risk.

Methods

Patients

Between January 1997 and January 1998, protease inhibitor (PI)- and stavudine (d4T)-naive HIV-1 infected patients were randomly assigned to either ritonavir (400 mg twice daily) plus saquinavir (400 mg twice daily) or ritonavir (400 mg twice daily) plus saquinavir (400 mg twice daily) plus stavudine (40 mg twice daily), on an open-label basis in 14 hospitals in The Netherlands and Belgium. In patients with a serum HIV-RNA above 400 copies/ml at week 12 and week 18, therapy was intensified with nucleoside reverse transcriptase inhibitors (NRTIs). Clinical results from this study were reported elsewhere [15]. Patient adherence was a secondary outcome. Patients were eligible for the adherence sub-study if they were able to complete a Dutch or English self-report questionnaire. The study
was approved by the Institutional Review Board of all centres. All patients gave written informed consent.

**Measurements**

Adherence was assessed by a self-report questionnaire at weeks 12, 24, 36 and 48. Patients were asked during how many days: they had taken all antiretroviral medication, how many days they had taken it more than 2 h from time schedule, and how many days they had taken ritonavir/saquinavir together with food or after a meal. Questions were related to the preceding week and response categories comprised: all 7 days, 5-6 days, 3-4 days, 1-2 days and <1 day. In a subset of patients in whom plasma concentrations of ritonavir and saquinavir were assessed at completion of the questionnaire, good concordance was observed between self-reported adherence and plasma concentrations of ritonavir/saquinavir [16]. Additionally, patients completed a symptom-checklist referring to symptoms related to HIV infection or antiretroviral therapy [17]. Symptoms were scored on a four-point scale with the response categories 'not at all', 'a little', 'quite a bit', and 'very much' also referring to the past week. Completed questionnaires were returned in a sealed envelope.

In a subset of patients, the number of study medication dispensed at each study visit was recorded as well as the number of leftover pills that were brought to the outpatient clinic at the subsequent study visit.

Serum HIV-1 RNA concentrations were measured using a PCR based assay (Amplicor HIV Monitor Test, Roche Diagnostic Systems) with a lower quantification limit of 400 copies/ml, at the start of study medication and at weeks 12, 18, 24, 36, and 48.

**Statistical analysis**

We calculated the percentage of patients reporting skipping medication, deviation from time-schedule and dietary prescriptions during the preceding week, at weeks 12, 24, 36, and 48. For this analysis, patients were dichotomised into those reporting being adherent on all 7 days versus those reporting non-adherence on at least 1 day. Dichotomization was done because of a skewed distribution with the majority of patients reporting being adherent on all 7 days. Since the adherence questions specifically inquired about the study medication, patients were censored at the time study medication was discontinued. The percentage of patients that changed their level of adherence compared to the preceding measurement at weeks 24, 36 and 48, and the percentage who changed their level of adherence at least once was calculated. Improvement or deterioration in adherence was defined as a shift of at least one category upward or downward on the scale.

The following symptoms were considered for their effect on adherence: nausea, vomiting, lack of appetite, diarrhoea, abdominal pain, pain when swallowing, tingling feeling around the mouth or tongue, and taste disturbances. These predominantly gastrointestinal symptoms were selected because we hypothesised that they might affect adherence.
We calculated the average level of adherence for each of the three adherence questions. With respect to symptom experience, patients were dichotomised into those experiencing symptoms at least a little versus those who did not experience symptoms at all. The association between experienced symptoms and adherence was expressed in odds ratios and 95% confidence intervals. We additionally considered the association between adherence and baseline characteristics, such as, viral load, CD4 T-cell count, pretreatment status, treatment group, age, gender and CDC disease stage [18].

In the subset of patients in whom the numbers of pills dispensed and the number of leftover pills had been recorded, we separately calculated a pill count for ritonavir and saquinavir. For both medications, the pill count was defined as the number of pills dispensed minus the number of leftover pills brought to the outpatient clinic over the course of 48 weeks, divided by the total number of pills dispensed, and multiplied by 100. We compared the ritonavir and saquinavir pill count between patients reporting deviation from their regimen and those reporting adherence on all 7 days by Mann Whitney U test.

HIV-1 RNA concentrations were transformed to the \( \log_{10} \). We calculated the area about the change from baseline (ACFB) over 48 weeks in serum HIV-1 RNA using the trapezium rule, representing the averaged time-weighted change from baseline as measure of overall viral suppression [19, 20].

Univariate logistical regression analyses using the primary end-point of the Prometheus study, HIV-1 RNA below 400 copies/ml at week 48, as dependent variable, were performed to investigate the effect of the three adherence questions and baseline characteristics. Variables with P-values < 0.20 were subsequently entered in a multiple logistical regression analysis.

Additionally, the same procedure was repeated using the ACFB in serum HIV-1 RNA as dependent variable in separate- and multiple-linear regression analyses, controlling for baseline HIV-1 RNA.

We calculated the odds ratios between being non-adherent during the early part of the study, at week 12, on having serum HIV-1 RNA above 400 copies/ml at week 48. We additionally calculated the odds ratios between baseline characteristics on being non-adherent at week 12 in order to identify a population at risk for treatment failure. Two-sided P values < 0.05 were considered statistically significant. Data analysis was conducted using the SPSS software package (SPSS, Systat, Chicago, Illinois, USA).

**Results**

The Prometheus study enrolled 208 patients. Twenty-three were unable to complete a Dutch or English self-report questionnaire. Others never started allocated treatment \((n = 6)\), discontinued treatment before week 12 \((n = 12)\), did not complete a questionnaire at
week 12 and discontinued treatment thereafter (n = 5), or refused participation (n = 2). Thus, 160 patients entered the adherence study. Of those, 84 (51.3%) were allocated to ritonavir/saquinavir, 93 (58.1%) were antiretroviral naive, 145 (90.6%) were males, 120 (75%) were men-having-sex-with-men, and 72 (45%) were CDC stage A. Their mean age was 38.6 (SD 9.3) years. The median baseline HIV-1 RNA log_{10} copies/ml and median baseline CD4 count were 4.47 [interquartile range (iqr), 3.93-4.97] and 255 (iqr, 111-415), respectively.

All eligible patients completed a questionnaire at week 12. The proportion of patients that did not complete a questionnaire at weeks 24, 36 and 48 were 7%, 13% and 12%, respectively. These proportions were statistically significantly higher compared to week 12 (X^2, P=0.003, P=0.001 and P=0.001, respectively). No other statistically significant differences in response rates between time points were observed. At week 24, the proportion of patients that did not complete a questionnaire was higher in the ritonavir/saquinavir group compared to the ritonavir/saquinavir/stavudine group (12 versus 3%, X^2 test, P=0.016). No other differences in response rates between the treatment groups were observed.

In 89 out of 160 patients participating in the adherence study, a pill count had been performed. Patients reporting that they had not ingested all medications in the past 7 days had a significantly lower saquinavir pill count compared to patients reporting to have ingested all medications (Mann Whitney U test, P=0.032). A tendency toward the same pattern was found for the ritonavir pill count (Mann Whitney U test, P=0.091).

Table 1 shows the percentages of patients reporting skipping medication, being off time schedule, not taking ritonavir/saquinavir with food at each measurement, and the percentage of patients that changed their level of adherence. The non-adherence rates generally remained relatively stable over time with a maximum of 5% difference between

<table>
<thead>
<tr>
<th>Table 1. Patient reported adherence during 48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 12</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>On-treatment (n)</td>
</tr>
<tr>
<td>Completed questionnaire (n)</td>
</tr>
<tr>
<td>Skipping medication (%)</td>
</tr>
<tr>
<td>Being off time schedule (%)</td>
</tr>
<tr>
<td>Not taking RTV/SQV with food (%)</td>
</tr>
<tr>
<td>Changed adherence*</td>
</tr>
<tr>
<td>skipping medication (%)</td>
</tr>
<tr>
<td>being off time schedule (%)</td>
</tr>
<tr>
<td>not taking RTV/SQV with food (%)</td>
</tr>
<tr>
<td>Ever changed*</td>
</tr>
</tbody>
</table>

* Compared to preceding measurement. † Level of adherence changed at least once during follow-up. RTV, ritonavir; SQV, saquinavir; NA, not applicable.
the highest and lowest percentages. Within the individual patient there was greater variability in adherence over time. At each measurement, 13% to 32% of the patients had changed their level of adherence compared to the preceding measurement and the percentage that changed their level of adherence during 48 weeks ranged from 29% for skipping medication to 48% for deviation from time-schedule.

Patients who were antiretroviral-naïve showed higher levels of adherence compared with patients who were pre-treated (Table 2). No difference in adherence was observed between the treatment groups. Patients who experienced treatment- and/or at least some disease-related symptoms, were more likely to report deviation from their regimen compared to patients who did not experience symptoms.

A total of 134 patients (84%) had a serum HIV-1 RNA below 400 copies/ml at week 48. Having HIV-1 RNA below 400 copies/ml was associated with not skipping medication (P=0.016) and being antiretroviral naïve (P= 0.030) in univariate logistic regression analysis. In the multivariate logistic regression analysis it remained significantly associated with not skipping medication (P=0.048). A trend was found for being antiretroviral naïve (P=0.095).

In the separate linear regression analyses using the time-weighed change from baseline in serum HIV-1 RNA as dependent variable, greater decline in HIV-1 RNA was associated with

**Table 2. Odds ratios (95% confidence intervals) on non-adherence by pre-treatment characteristics and treatment- and disease related symptoms**

<table>
<thead>
<tr>
<th>Pre-treatment characteristics</th>
<th>Skipping medication</th>
<th>Being off time schedule</th>
<th>Not taking RTV/SQV with food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral pretreated (versus naive)</td>
<td>2.5 (1.2-5.1)*</td>
<td>2.1 (1.1-4.0)*</td>
<td>1.3 (0.7-2.4)</td>
</tr>
<tr>
<td>Baseline CD4+ T-cells/ml &lt; 200 (versus ≥200)</td>
<td>1.3 (0.6-1.6)</td>
<td>1.4 (0.7-2.7)</td>
<td>1.7 (0.9-3.3)</td>
</tr>
<tr>
<td>CDC class A (versus B and C)</td>
<td>0.7 (0.4-1.5)</td>
<td>0.8 (0.4-1.5)</td>
<td>2.1 (1.1-4.1)*</td>
</tr>
<tr>
<td>Baseline serum HIV-1 RNA log10 copies/ml ≥ 5.0 (versus &lt; 5.0)</td>
<td>0.7 (0.3-1.7)</td>
<td>0.7 (0.3-1.4)</td>
<td>0.8 (0.4-1.6)</td>
</tr>
<tr>
<td>RTV/SQV/d4T (versus RTV/SQV)</td>
<td>1.0 (0.6-2.3)</td>
<td>1.5 (0.8-2.7)</td>
<td>1.2 (0.6-2.3)</td>
</tr>
<tr>
<td>Gender (male versus female)</td>
<td>1.4 (0.5-4.4)</td>
<td>0.9 (0.3-2.5)</td>
<td>0.5 (0.2-1.7)</td>
</tr>
<tr>
<td>Age (≤ 35 years versus &gt; 35 years)</td>
<td>2.2 (1.1-4.4)*</td>
<td>1.4 (0.7-2.6)</td>
<td>1.4 (0.7-2.7)</td>
</tr>
</tbody>
</table>

**Disease- or treatment-related symptoms†**

| Vomiting | 9.3 (1.8-48.2)* | 0.7 (0.2-3.1) | 2.6 (0.6-11.4) |
| Abdominal pain | 5.0 (1.1-21.9)* | 0.7 (0.2-3.1) | 2.6 (0.6-11.4) |
| Taste disturbances | 2.4 (1.1-5.4)* | 1.1 (0.5-2.3) | 2.5 (1.1-5.6)* |
| Tingling feeling mouth/tongue | 2.3 (1.1-4.6)* | 1.0 (0.5-2.0) | 1.5 (0.8-2.8) |
| Nausea | 2.1 (1.1-4.3)* | 1.4 (0.8-2.6) | 1.5 (0.8-2.9) |
| Pain when swallowing | 2.9 (0.7-12.1) | 0.7 (0.2-3.1) | 4.9 (0.9-24.8) |
| Lack of appetite | 2.0 (0.8-5.3) | 0.6 (0.2-1.5) | 4.2 (1.5-11.6)* |
| Diarrhoea | 0.8 (0.4-1.7) | 1.2 (0.6-2.4) | 0.8 (0.4-1.6) |

* Statistically significant effect. † Experiencing some symptoms versus not at all. RTV, ritonavir; SQV, saquinavir; d4T, stavudine.
higher baseline CD4 count (P=0.16), not skipping medication (P=0.001), taking ritonavir/saquinavir with food (P=0.067), allocation to ritonavir/saquinavir/stavudine (P=0.003), being antiretroviral naive (P=0.039) and CDC class A (P=0.052). Entered in the multiple regression analysis, allocation to ritonavir/saquinavir/stavudine (P=0.004) and not skipping medication (P=0.014) were independently associated with a greater decline in serum HIV-1 RNA. When both not skipping medication and being antiretroviral naive were entered in the analyses, not skipping medication was associated with viral suppression (P=0.003) but not being antiretroviral naive (P=0.135).

Patients who had not ingested all medications in the past week at week 12, were more likely to have serum HIV-1 RNA above 400 copies/ml at week 48 compared to patients who reported to have ingested all medications (40 versus 15%, $X^2$ test, P=0.036). A tendency toward the same pattern was found for deviation from time-schedule. Patients reporting deviation from time schedule were more likely to have a viral load above 400 copies/ml at week 48 than patients reporting to have taken medications on time (26 versus 12%, $X^2$ test, P=0.059).

Patients who did not ingest all medications in the past week at week 12, were younger compared to patients who did ingest all medications (mean age 32 years versus 39 years, Student t-test, P=0.002) and were more likely to be antiretroviral pre-treated (73 versus 27%, $X^2$ test, P=0.019). No association was found with treatment group, gender, HIV-1 disease stage, baseline HIV-1 RNA and baseline CD4 T cell-count.

**Conclusions**

Although adherence rates generally remained relatively stable over a 48-week period, a substantial percentage of patients changed their level of adherence during 48 weeks. This suggests that adherence or non-adherence is not a stable patient characteristic but rather a dynamic phenomenon. This implies that any patient at any point in time may encounter difficulties in adhering to their antiretroviral regimen [21]. Our finding supports the current recommendation that adherence should be regularly monitored and reinforced in all patients on HAART as part of routine clinical practice [22].

We found that patients who experienced disease- or treatment related symptoms were more likely to report deviation from their regimen compared to patients who did not experience these symptoms. This suggests that managing toxicities might facilitate patient adherence.
Patient adherence was an independent predictor of virological response over 48 weeks. This finding is consistent with three other studies that examined adherence among other established predictive factors of viral suppression [9-11]. Skipping medication was the most infrequently reported form of non-adherence, followed by deviation from dietary prescriptions and from time-schedule. Only skipping medication was independently related with virological response. Since the consequences of low adherence will depend upon characteristics of the particular drugs, such as the plasma elimination half-life and the degree to which drug exposure is dependent upon food intake, this may not be generalised to other regimens.

We found that being antiretroviral pre-treated, as compared with being antiretroviral naive, was both associated with lower levels of adherence and with a poorer virological response. The association between pre-treatment and virological response was no longer statistically significant when adherence was taken into account in the multivariate analyses. A poorer virological response among pre-treated patients as compared with naive patients has also been observed by others [4]. The present study suggests this may, in part, be explained by lower levels of adherence in this group of patients. Clearly, our observation needs to be confirmed by future studies.

We found that during the early part of the study, patients who were younger and who were antiretroviral pre-treated showed lower levels of adherence compared to patients who were older and were antiretroviral-naive. The association between younger age and lower adherence has also been established by others [10,25]. The association between pre-treatment and lower levels of adherence might be explained by the longer duration of antiretroviral therapy. From the literature on adherence, it is known that adherence generally tends to decline over time [16]. Our results suggest that younger patients and/or those who have received antiretroviral therapy for prolonged time might benefit from potential interventions to improve adherence.

Seventeen patients who discontinued treatment before week 12 or shortly thereafter, due to toxicity (n = 7), patient decision (n = 4) or adverse events (n = 6) were excluded from the adherence-study. These patients' level of adherence could have differed from the level of adherence of patients who entered the adherence-study. Therefore, our results only apply to patients who stayed on study medication for at least 12 weeks. Additionally, patients who participated in the adherence study needed to have sufficient language skills to complete a Dutch or English self-report questionnaire. Our results may therefore not be generalised to patients with insufficient literacy in Dutch or English.

Prometheus was an open-label study; however, we feel it is not likely this has affected the adherence results and the assessment of symptoms. Adherence is most critical to PIs and
the PIs were identical between both treatment groups. The only difference between the regimens was the prescription of stavudine, which can be taken together with the other medications and has no specific dietary prescriptions. The symptoms we considered for their effect on adherence were associated with the use of ritonavir/saquinavir and these were prescribed in both treatment groups.

In conclusion, adherence was an independent predictor of virological response over 48 weeks. Prior antiretroviral therapy and higher levels of experienced symptoms were associated with lower levels of adherence. A substantial number of patients changed their level of adherence during 48 weeks, suggesting that most patients may encounter difficulties with adherence at any time during antiretroviral therapy. This suggests the need for assisting and monitoring adherence in all patients as standard clinical practice.

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