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Predictive value of adherence in patients starting highly active antiretroviral treatment for HIV infection

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Summary

Strict adherence to the prescribed drug regimen is one of the most important predictors of success in the antiretroviral therapy of HIV infection. Ideally, patients should learn to optimise their drug adherence before they start antiviral therapy. This study evaluated the predictive role of adherence during the first four weeks of treatment for midterm treatment outcome. Adherence was evaluated using electronic dosing systems during the first 25 days of therapy in 66 drug-naïve patients starting a new antiretroviral therapy. Treatment outcome (HIV-RNA suppression) was evaluated at week 24 of treatment. Good adherence (>95% doses taken) was associated with better rates of viral suppression (77% vs. 44% Patients with HIV-RNA below 50 copies/ml). Specific education programmes targeted at the achievement of optimal adherence during the first few weeks of therapy might result in better treatment results.

Key words: HAART; HIV-therapy; adherence; medication event monitoring system; MEMS

Introduction

Approximately half of the patients starting highly active antiretroviral therapy (HAART) do not reach the desired treatment goal of complete viral suppression [1, 2]. Factors contributing to treatment failure are poor adherence, pharmacodynamic interactions and pre-existing drug resistance. An increasing number of studies identify drug adherence as the primary reason for failure [3–7]. The most critical phase for the development of drug resistant HIV variants is in the first few weeks of antiretroviral therapy [8].

Systematic evaluations of interventions to increase drug adherence are limited. This is in part due to the lack of a gold standard to measure drug adherence. According to Paterson et al, the medication event monitoring system (MEMS) is close to a gold standard [9]. MEMS, a tool monitoring each opening of the pill bottle, has been used successfully to monitor adherence in hypertension and other medical fields [10, 11]. Adherence measured with MEMS has been associated with treatment outcome in HIV treatment. As a step towards using MEMS as a training tool to optimise adherence prior to the initiation of HAART, this study investigated the predictive value of initial adherence measured with MEMS.

Methods

All drug naïve patients starting HAART in one of the three study sites (St. Gallen, Zurich, Basel, see author affiliations) were asked to participate. Adherence was measured during the first 25 days of HAART using the MEMS system (Aardex, Switzerland). Adherence was expressed as the ratio of number of doses taken per number of doses prescribed. In patients using more than one MEMS device due to complex dosing regimens (i.e. not all tablets taken at the same time), the average adherence value was used. Adherence values were then correlated with treatment outcome using HIV-RNA response (<50 copies/ml) as the primary outcome measure. At start of treatment, plasma HIV-RNA concentration and CD4 count were measured and patients received written instructions on the use of MEMS. At week 4 of treatment, patients were given a visual printout of the MEMS information with verbal backup. HIV-RNA was routinely measured at weeks 4, 12 and 24 by ultra sensitive HIV-RNA PCR (Amplicor) and blood CD4 counts were performed at baseline and at weeks 12 and 24.

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The predictive value of MEMS was calculated on an intention to treat (ITT) basis, i.e. patients who stopped the treatment or were lost to follow up were included in the primary analysis.

Results

Sixty-six patients used MEMS during the first 4 weeks of HAART. Of these, 62 completed the first 24 weeks of antiviral treatment. Two patients (4%) stopped treatment due to toxicity during the first 16 weeks and two patients were lost to follow up. Viral load set point (HIV-RNA) at baseline was above 10^5 copies/ml in 26 of the 66 patients (median HIV-RNA 4.85 $\log_{10}$ cp/ml). Mean CD4 value at baseline was 319/µl. Eight patients started with an NNRTI-based therapy, all the remaining patients started with a protease-inhibitor based treatment, 19 of which used a ritonvavir-boosted PI regimen.

Adherence during the first 25 days of HAART ranged from 0.25 to 1.0 (median 0.99, lower quartile 0.96). Forty-three patients (65% ITT; 69% OT) reached a plasma viral load below 50 copies/ml at week 24 of treatment. The likelihood of reaching a plasma viral load level below 50 copies/ml was significantly higher in patients with adherence levels above 0.95 during the first 4 weeks of therapy as compared to patients with lower adherence values (OR 3.31, 95% CI 1.03–10.6, p = 0.04, Chi-square) (Figure 1). Among all additional factors that were tested in univariate analysis (baseline viral load or CD4 count, centre, bid vs. tid dosing regimes) no additional association was found with treatment outcome (50 copies/ml at week 24) and in multivariate logistic regression analysis, adherence remained the only factor with a significant association (p = 0.04).

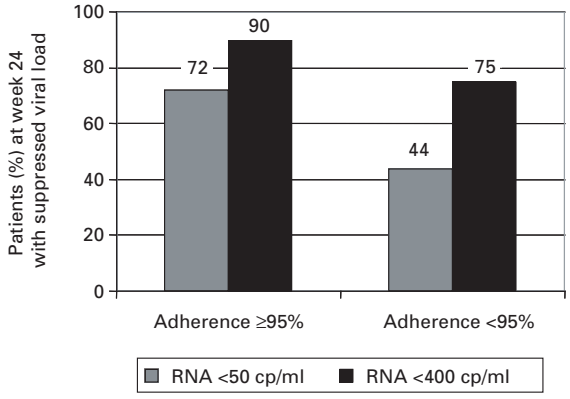

Figure 1

HIV-RNA suppression rates (<50 copies and <400 copies/ml) after 24 weeks of therapy in patients with taking adherence < and ≥95%).

Among the 43 patients with an undetectable viral load at week 24, 41 (95%) had an adherence value better than 0.95. In contrast only 15 patients (65%) among the 23 with a detectable HIV viral load (or lost to follow up) had an adherence value better or equal than 95% (p = 0,001, Chi-square, ITT). The mean adherence level for patients with undetectable viral load was 0.97 and for patients with a detectable viral load 0.91. Adherence measures had no significant effect on CD4 increase at week 24, on HIV-RNA drop at week 4 and no difference in adherence among centres was detectable (Chi-square). Adherence in the first 4 weeks did not predict the likelihood of a patient remaining on treatment at week 24. Among patients who were still on treatment at week 24, the fraction with adherence >0.95 during the first 4 weeks of therapy was significantly higher than in the four patients who stopped treatment prior to week 24 or were lost of follow up (Fisher's exact test, p = 0.01). Drug adherence appears to be a substitute for adherence behaviour related to motivational factors and other recommendations. For example, Glass et al. found a direct association between adherence to safer sex recommendations and HIV treatment outcome in the Swiss HIV Cohort Study [12].

Discussion

This study was planned to determine the prospective role of MEMS adherence estimates during the first 25 days of treatment for the outcome of HAART at 24 weeks. Despite the small sample size chosen in this study, we found a significant association between early adherence measurements and treatment outcome. Several recent studies have shown that an adherence rate >95% is necessary to achieve undetectable viral load in 80% of treated patients [7, 8]. In accordance with studies investigating the association of long term adherence with treatment outcome, the present study demonstrates that short term measurement of initial adherence to HAART predicts treatment outcome.

An adherence rate above 0.95 in the first 4 weeks of therapy resulted in a significantly higher suppression rate after 6 months, as compared to patients with lower adherence rates. Thus, adherence during the first month of therapy appears to play an important role. In our study, only one patient with a four week adherence of less than 80% had a suppressed viral load at week 24 of therapy, and this patient reported an increase in taking compliance after the first MEMS readout.

A failure to reach the predefined goal of HAART at week 24 in patients with good compliance during the first four weeks of therapy was usually associated with temporal or continued treat-

ment interruption at later time points. In contrast, patients with low adherence at treatment initiation were significantly less likely to reach the predefined treatment goal.

The high predictive value of adherence in this small study is remarkable. Previous studies have highlighted the importance of consistency in adherence to HAART [7, 13]. This seems to be particularly relevant at the start of HAART. Fraser et al. have emphasized the importance of a high adherence level during the first few weeks of HAART [8]. However, this was based on their mathematical model of viral replication and development of drug resistance and not proven by clinical studies. Adherence levels usually decrease in the later stages of antiviral therapy [14]. The maintenance of good viral suppression despite a gradual decrease of drug adherence suggests that HAART might be more lenient in the later stages of treatment.

The findings of this study indirectly support the exceptional importance of adherence during the first few weeks of therapy. Therefore, strong efforts to assure optimal treatment should precede any new regimen of HAART. Further studies are needed to evaluate whether a special adherence training prior to the start of HAART improves outcome.

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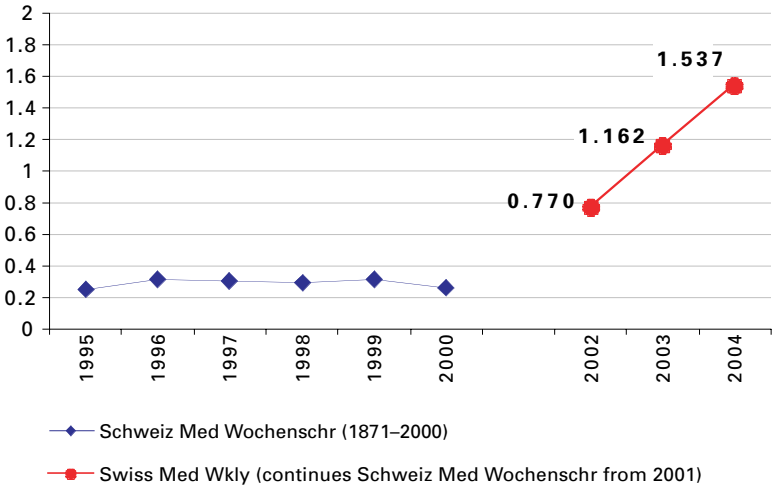

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