Patterns of adherence to antiretroviral medications: the value of electronic monitoring

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Objective: To investigate the patterns of intra-subject (between medication) adherence to antiretroviral therapy.

Design: A prospective, observational, 3-month study of adherence to antiretroviral therapy at an inner-city clinic in 40 HIV-infected subjects.

Methods: Adherence was monitored monthly by the use of medication event monitoring system (Aprex) caps placed on each antiretroviral drug in a subject's regimen. Agreement between different drug classes and dosing schedules, for each subject, was quantified by estimating the mean difference in adherence, with 95% limits of agreement. An analysis of variance model was used to estimate the variance of the differences. Individual dosing calendars were examined for each subject.

Results: The dosing schedule was a strong predictor of intra-subject adherence. Regardless of the subject's overall adherence rate, high or low, when subjects missed a dose of one medication, they missed a dose of both medications taken at that dosing time. Conversely, when medications were scheduled to be taken together, regardless of the drug class, the medications were taken at the same times. The majority of the subjects took medications at obviously incorrect times. Problematical adherence was related to thrice-daily dosing and food restrictions.

Conclusion: This is the first report objectively to quantify intra-subject adherence to antiretroviral therapy and report the findings in detail. We observed clear patterns of drug-taking behavior among the subjects in our study. To the extent that medication scheduling is a controllable factor, our report provides an insight into specific patterns of behavior that may be targets for adherence counseling.

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Introduction

In the past few years, highly active antiretroviral therapy (HAART) has significantly decreased the morbidity and mortality caused by AIDS [1]. Although combination therapy is highly efficacious, suboptimal adherence is a major contributor to virological failure in clinical practice [2]. Studies in the HIV-infected population have demonstrated that adherence is significantly related to virological outcome, and that a high degree of adherence is necessary for virological suppression [3]. More recently, adherence studies have begun to define the relationship between adherence, virological suppression and the development of drug resistance [4,5]. Such studies have not addressed the issue of intra-subject adherence. Although it is commonly assumed that adherence to one HAART medication predicts adherence to the other medications in the regimen, no objective measures have been reported in the literature to support this assumption.

We recently conducted a study of adherence to HAART, which assessed the relationship between adherence rates and virological outcome. To address the issue of between-medication adherence, medication event monitoring system (MEMS; Aprex) caps were placed on each medication in the subject's regimen. Electronic monitoring with MEMS is the only currently available method that provides a separate analysis of each individual HAART medication dosing time. Because the medications must be taken at specific times with defined food requirements, information about an individual's pattern of drug-taking behavior is essential for a complete evaluation of adherence to HAART. The objective of this report was to describe the patterns of HAART drug-taking behavior as evaluated by MEMS.

Methods

Adherence study

Between February 1999 and August 1999, we conducted a prospective, open-label, observational study of adherence to HAART in an inner-city, HIV-infected, minority population. The methods and major findings are reported elsewhere [6]. Briefly, over 3 months, we monitored adherence to HAART in 40 treatment-experienced individuals using MEMS, self-report and pill counts. MEMS caps were placed on the medication vials for all antiretroviral drugs, for as many as three drugs per subject. The subjects included 30 men and 10 women who were 75% Hispanic, 23% African American and 68% injection drug users.

Data analysis

The agreement between adherence to different drug classes and different dosing schedules was quantified using methods suggested by Altman and Bland [7] and Bland and Altman [8]. Specifically, the mean difference in adherence between pairs of drug classes or dosing schedules was estimated and the 95% limits of agreement were computed based on the normal distribution. An analysis of variance model, which was adjusted for a random subject effect and a fixed month effect, was used to estimate the variance of the differences. Confidence intervals for the limits of agreement were also calculated. Data are presented as the mean plus or minus standard deviation. In addition, we examined, by visual inspection, the MEMS dosing calendars, including the date and time of each medication dose, for all subjects.

Results

Of the 40 evaluable subjects, three subjects were receiving Combivir alone and were not evaluated for intra-subject adherence. Seventeen subjects were prescribed twice-daily regimens that included two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor, 15 subjects were prescribed regimens that included a thrice-daily PI, and five subjects were prescribed dual NRTI. PI included indinavir, saquinavir or nelfinavir; the non-nucleoside reverse transcriptase inhibitor was nevirapine. Our first analysis included comparisons of various dosing schedules for all 37 subjects (data not shown). However, because the twice-daily regimens are the most relevant dosing schedules for contemporary prescribing practices, we performed separate analyses of subjects prescribed twice-daily versus thrice-daily regimens, excluding the subjects on dual NRTI. Fig. 1 illustrates the intra-subject adherence for the 17 subjects prescribed twice-daily regimens. The mean difference between adherence to one of the NRTI and adherence to the third drug, either a PI or nevirapine (NRTI adherence − third drug adherence), was $2 \pm 9\%$ with Bland-Altman limits of agreement −14% to 19%. With 45 observations from 17 subjects, we were able to exclude expected differences in adherence larger than 23% and smaller than −18%, based on confidence intervals for the limits of agreement. The mean difference in adherence between the two NRTI in this patient group was $2 \pm 8\%$, similar to the difference between the NRTI and the third drug. In contrast, for the 15 subjects prescribed a PI on a thrice-daily regimen, the difference in adherence rates between the NRTI and the PI (twice-daily − thrice-daily adherence) was $14 \pm 15\%$, Bland-Altman limits of agreement, −16% to 43%. With 64 observations from 15 subjects, we were able to exclude expected differences in adherence larger

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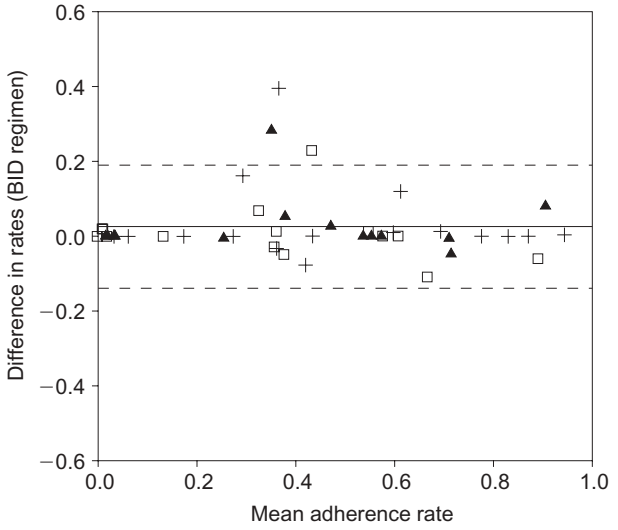

Fig. 1. Agreement between adherence rates to antiretroviral drugs prescribed on a twice-daily dosing schedule (n = 17). The horizontal axis displays the subjects' mean adherence rates during the study. The vertical axis displays the difference in adherence rates between one of the nucleoside reverse transcriptase inhibitors (NRTI) and the third drug, either the protease inhibitor or non-nucleoside reverse transcriptase inhibitor (calculated as NRTI adherence − third drug adherence). The dashed lines are the limits of agreement (95% confidence intervals for the difference). Each observation is indicated according to the month of follow-up. BID, Twice-daily. ▲ Month 3; □ month 2; + month 1.

than 49% and smaller than −22%, based on confidence intervals for the limits of agreement.

These data demonstrate that adherence between antiretroviral drug classes does differ in the same subject, but that this occurs, for the most part, when the drugs are prescribed on different dosing schedules. For the subjects prescribed twice-daily regimens, between-medication adherence was practically identical. Regardless of the drug class, adherence to one antiretroviral medication did, in fact, predict adherence to the other antiretroviral drugs. Because the adherence rates in this population were relatively low, approximately 54%, it was not possible to determine the effect of the dosing schedule on virological suppression.

Evaluation of individual dosing patterns

Dosing schedule

An examination of individual dosing calendars revealed an additional source of problematical adherence, dose timing related to food restrictions. Fig. 2 illustrates the dosing pattern of a subject who had difficulty taking didanosine correctly in relation to the food restrictions. Although all of the antiretroviral drugs in his regimen were prescribed twice daily; in actuality, the subject had to take medication four times a day to separate the didanosine (empty stomach) and nelfinavir (with food).

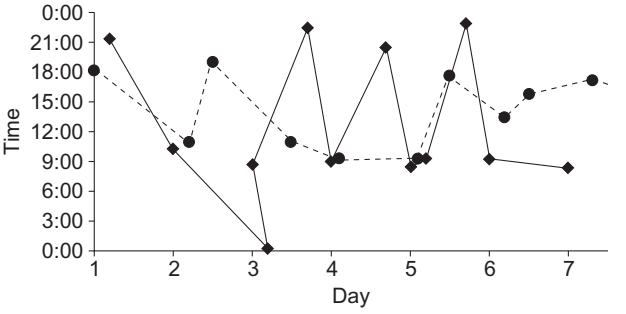

Fig. 2. Individual subject's dosing times for one week of the regimen, stavudine twice a day, didanosine twice a day and nelfinavir twice a day. —–◆—– Didanosine; – –●– – stavudine plus nelfinavir. Each mark represents one dose.

On days 4 and 5, he took didanosine at the same time as nelfinavir, incorrectly in relation to the food restrictions. Fig. 2 also illustrates an observation that is consistent among all the subjects in this study. Regardless of the subject's overall adherence rate, when subjects missed a dose of one medication, they missed a dose of both medications taken at that dosing time. Conversely, when medications were scheduled to be taken together, regardless of the drug class, the medications were taken at the same times. In this particular subject, very often he missed one of the four dosing times on any given day, either a dose of didanosine or doses of stavudine plus nelfinavir. Although he had an undetectable viral load during the study, his viral load had risen to greater than 2500 copies/ml by 6 months follow-up.

Dosing times

Only three out of 37 subjects took medications at exactly the right times. The adherence rates of all three subjects were greater than 90%. The majority of the subjects in our study took medications at obviously incorrect times. Twice-daily regimens were taken 8 or 15 h apart and thrice-daily medications were often taken at the same time as the twice-daily medications.

Pocket doses

Some subjects removed a noon medication dose from the MEMS vial to take away from home during the day, without our approval. Even though the subject took the 'pocket dose' appropriately, the MEMS cap would not record a noon opening of the vial. This particular pattern has been well documented in the REACH cohort, a prospective study of HIV-positive homeless and marginally housed individuals in San Francisco [9]. Our subjects did not report pocket doses; however, we suspected this behavior in six subjects with decreased adherence to the third medication in their drug regimen. For three subjects, pill counts confirmed that the subjects were not taking the noon dose of the PI, e.g. these were not pocket doses. On the basis of a pattern of decreasing adherence over time

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and detectable viral loads, two subjects appeared to 'dump' their medications before monthly pill counts. Only one subject appeared genuinely to pocket the noon doses of PI. Although this subject's MEMS adherence to the PI was less than 70%, his viral load was undetectable during the study and at one year of follow-up.

Discussion

There are numerous adherence studies of HAART in the literature. To our knowledge, however, this is the first report to quantify intra-subject adherence to HAART objectively and report the findings in detail. We observed clear patterns of drug-taking behavior among the subjects in our study. To the extent that medication scheduling is a controllable factor, our report provides insight into specific patterns of behavior that may be targets for adherence counseling.

There is no 'gold standard' for measuring adherence to HAART. The most reliable method for research purposes, although not practical in a clinical setting, may be a combination approach that includes pill counts, patient self-report, and electronic monitoring [10]. A particular limitation of pill counts and self-report is that these methods can only measure an average adherence rate, not the timing of doses or the pattern of drug-taking behavior. Electronic monitoring is an important adjunct to these methods.

Our report confirms and broadens the findings of other investigators. A number of previous reports have shown that the complexity of the HAART regimen influences adherence. As the pill burden, dosing frequency or dietary restrictions increase, adherence declines [11–16]. Also, the pill burden has been shown to correlate negatively with viral load [17]. Our results are consistent with a previous report, which evaluated between-medication adherence by self-report. Wilson and colleagues [18] asked patients to report adherence to antiretroviral drugs within the previous week and found that patients skipped or were off schedule with all medications taken at the same dosing time. In a study similar to ours in which MEMS caps were placed on all antiretroviral drugs, Arnsten and colleagues [19] reported no difference in adherence between medications taken twice versus those taken three times a day. Although these findings appear to be in contrast to our results, the disparity is probably caused by differences in both the patient population (96% in methadone maintenance and an apparent high number of pocket doses) and the methodology. Mean adherence rates by drug class and schedule will obscure any real differences in intra-subject adherence.

Our study was conducted before the advent of pharmacokinetically enhanced HAART regimens. It will be important to repeat objective adherence studies to determine the impact of these regimens on adherence and on the relationship between adherence and virological suppression. Nevertheless, these results are relevant to current treatment, regardless of the specific regimen, because knowledge of a patient's pattern of drug-taking behavior is the key to effective intervention strategies. By understanding a particular patient's adherence pattern, the reasons for missed doses can be addressed individually.

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