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Electronic Compliance Assessment of Antifungal Prophylaxis for Human Immunodeficiency Virus-Infected Women

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Several prophylactic medications for opportunistic or recurrent infections are used in human immunodeficiency virus-infected individuals. Essential to the efficacy evaluation of these agents is the accurate reporting of medication compliance. We hypothesized that poor patient compliance with thrice-weekly fluconazole prophylaxis would correlate with the occurrence of clinical events. Fluconazole compliance was monitored electronically by using the Medication Event Monitoring Systems with 19 women receiving fluconazole at 50 mg thrice weekly for prophylaxis of recurrent mucocutaneous candidiasis. During 202 patient-months of follow-up, eight breakthrough episodes of mucocutaneous candidiasis developed in four women; compliance data were available for seven of these episodes. At 6 months of therapy, more women with greater than or equal to 80% compliance were disease free compared with women with less than 80% compliance ($P < 0.05$; the Fisher exact test). These data suggest that documentation of medication compliance is essential in studies of chronic prophylaxis in human immunodeficiency virus-infected patients to properly evaluate drug efficacy and to avoid erroneous conclusions concerning drug failure.

Noncompliance with drug therapy may lead to the increased use of health care resources and reduced quality of life. It has been reported that 11 to 28% of emergency room visits or hospital admissions are due to medication noncompliance (4, 7, 13). One meta-analysis estimated that the annual cost of medication noncompliance is approximately $8.5 billion (17). Several methods for the assessment of medication compliance have been used in clinical settings as well as in clinical trials. These methods include monitoring of the level of the drug in the patient's blood, measurement of drug excretion in urine, pill counts, patient questionnaires, observation of therapeutic outcome, and the presence of side effects (5). All of these methods have certain important limitations. For example, pill counts may be altered by patients and monitoring of drug levels in blood and urinary excretion studies are inconvenient, nonquantitative, and expensive. Single measurements of drug concentrations in serum are subject to the need for accurate dosing histories and assumptions concerning steady-state conditions; hence, these measures are not precise assessments of drug compliance patterns, particularly compliance with drugs with long half-lives. The Medication Event Monitoring Systems (MEMS) are normal-appearing prescription vials with caps containing microprocessors which record the date and time of vial opening. Studies have shown that MEMS can assess patient compliance with certain medications (3, 14). The advantage of MEMS compared with other forms of compliance monitoring is the ability to quantitatively assess compliance over prolonged periods of treatment. Other methods, such as determination of drug levels in serum, only measure compliance since the preceding dosing interval or the last few days prior to testing of the drug level in serum. MEMS have the additional advantage of reporting the length of time between scheduled doses (14). With the increasing rise in the number of women with human immunodeficiency virus (HIV) infection, an understanding of the unique health care needs of women and their obstacles to the provision of health care is essential, including assessment of medication compliance. Furthermore, medication noncompliance can obfuscate the assessment of the efficacy of a prophylactic medication. The purpose of the study described here was to electronically monitor thrice-weekly fluconazole dosing events during a clinical trial with HIV-infected women in order to assess the influence of compliance on clinical events.

MATERIALS AND METHODS

Trial design. A multicenter, randomized, cross-over study was conducted with HIV-infected women with $CD4^+$ counts of less than 500 cells per mm^3 to determine if fluconazole prophylaxis is effective for the prevention of vaginal, oropharyngeal, and esophageal candidiases; the preliminary results have been reported elsewhere (6). HIV-infected women with $CD4^+$ counts of less than 500 cells per mm^3, over 18 years of age, without a history of systemic fungal disease, without current mucosal fungal infection, and with transaminase levels less than five times the upper limit of normal qualified for randomization. Informed consent was obtained from the patients, and the guidelines for human experimentation of the U.S. Department of Health and Human Services and The Miriam Hospital and Rhode Island Hospital, Providence, R.I., were followed in the conduct of the study. Women were randomized to receive either fluconazole at 50 mg on a Monday, Wednesday, and Friday or to receive no treatment but to undergo regular observation. A history was taken and a symptom-oriented physical examination was performed every 3 months for all women enrolled in the study. If women were symptomatic for mucocutaneous candidiasis, a potassium hydroxide preparation of the potentially infected site was completed. If a breakthrough episode developed while a woman was noncompliant with fluconazole, the patient was treated with topical antifungal agents; if a breakthrough episode developed while a women was compliant with thrice-weekly fluconazole, the patient was treated with a higher daily dose of fluconazole.

Compliance monitoring. MEMS-3 (Aprex Corporation, Fremont, Calif.) was used to monitor patient compliance. At the time of entry into the trial, patients randomized to receive fluconazole were dispensed a 3-month supply of fluconazole in a MEMS vial. The patients were informed that the cap contained a computer chip for the purpose of recording the timing of dosing, but it was

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TABLE 1. Demographic data for 15 women without and 4 women with resulting episodes during fluconazole prophylaxis[a]

Characteristic	Value	
	15 women without breakthroughs	4 women with breakthroughs
Age		
Median	30	37.5
Range	24–45	28–40
Race (no. [%])		
Caucasian	12 (80)	2 (50)
Hispanic	3 (20)	2 (50)
Transmission risk group (no. [%])		
IVDU or heterosexual contact	7 (47)	2 (50)
IVDU (no. [%])	5 (33)	2 (50)
Heterosexual contact (no. [%])	2 (13)	0 (0)
IVDU or contact with blood products (no. [%])	1 (7)	0 (0)
Duration of HIV seropositivity (yr)		
Median	3	3
Range	1–6	3–6
Diagnosis of AIDS (no. [%])	1 (7)	1 (25)
Prophylactic antibiotic use (co-trimoxazole or dapsone) (no. [%])	3 (20)	2 (50)
Antiretroviral therapy (no. [%])	14 (93)	4 (100)
Prior episodes of candidiasis (no. [%])	11 (73)	4 (100)

[a] No difference between groups by Fisher's exact test.

stressed that dosing readings would not threaten their status in the study. Patients were instructed to keep the fluconazole in the MEMS vial and not to remove the drug and put it in another container. At every 3-month follow-up visit, a clinical pharmacist transferred the information from the MEMS cap to a laptop computer using the appropriate software, and an additional 3-month supply of fluconazole was dispensed in the same MEMS vial.

Data analysis. Medication events were quantitatively calculated per week, with 100% compliance considered three vial openings per week. Qualitative compliance (i.e., doses taken on Monday, Wednesday, and Friday, as prescribed) was similar to the quantitative compliance and was not incorporated into the present analysis. A quantitative value of greater than 80% compliance was classified as good compliance, as previously defined by others (1, 15). Failure of therapy was concluded when a patient either developed a documented episode of mucocutaneous candidiasis or dropped out of the study. Treatment failure after 6 months of therapy was compared in women with greater than 80% compliance versus those with less than 80% compliance by Kaplan-Meier analysis and the Fisher exact test (9, 11, 16, 17).

RESULTS

Electronic compliance data were available for 19 patients monitored for 202 patient-months. Table 1 provides the characteristics of the patients. Most women were Caucasian and identified intravenous drug use (IVDU) as one risk factor for HIV transmission. A minority of women were diagnosed with AIDS. The reasons for patient attrition from the study included IVDU, pregnancy, lack of desire to take another medication, medication side effects, breakthrough infections, or death.

Eight episodes of mucocutaneous candidiasis occurred in four patients during the period of monitoring with MEMS, with compliance information available for seven of these episodes. Figure 1 displays the biweekly compliance by the 15 women without breakthrough episodes and each of the 4 women who developed breakthrough episodes.

Patient 1. Two episodes of documented vaginal candidiasis occurred in weeks 20 and 24 in patient 1. In both episodes, a period of significant noncompliance was observed prior to or at the time of breakthrough.

Patient 2. Patient 2 experienced a symptomatic, KOH-positive episode of vaginal candidiasis after 6 weeks of fluconazole prophylaxis. The patient appeared to be compliant with the regimen by MEMS recordings. Despite poor compliance after this single episode, no further episodes of vaginal candidiasis occurred in this patient. This patient's $CD4^+$ count remained at between 100 and 200 cells per mm^3 during the study period.

Patient 3. Esophageal candidiasis developed in patient 3 after 23 months of fluconazole prophylaxis. The pattern of fluconazole use in this patient over the preceding 3 months showed erratic drug administration. Furthermore, this patient's most recent $CD4^+$ count 10 months before the candidal infection was 70 cells per mm^3.

Patient 4. Three episodes of mucocutaneous candidiasis occurred in patient 4 during prophylaxis. Two breakthrough episodes appeared to be related to noncompliance. The third episode in this patient occurred while the patient was compliant, but her $CD4^+$ count had recently dropped below 50 cells per mm^3.

Analysis of compliance. Compliance over the entire study period was analyzed by grouping the women according to whether or not they were greater than or equal to 80% compliant. Figure 2 shows that the time to treatment failure was significantly shorter for women with less than 80% compliance compared with that for women with greater than or equal to 80% compliance. The median time to the first breakthrough infection was 19 weeks. At 6 months of treatment, significantly more women with less than 80% compliance had failed treatment than women with greater than 80% compliance ($P < 0.05$; the Fisher exact test).

DISCUSSION

In the present study of 19 women receiving fluconazole prophylaxis, eight breakthrough episodes of mucocutaneous candidiasis occurred in four women. Because of the low number of breakthrough episodes, we cannot definitely associate noncompliance with breakthrough episodes. In some study patients (e.g., patient 2), there were no breakthrough episodes during prolonged periods of noncompliance. While noncompliance immediately preceding a breakthrough event did not occur in every instance, it does appear that women with an overall higher level of compliance (greater than 80%) experienced a longer disease-free period than women with an overall lower level of compliance (less than 80%). Advanced immunosuppression, as suggested by markedly decreased $CD4^+$ counts, may have predisposed even a compliant patient to a breakthrough infection. Although medication resistance could have contributed to the breakthrough episodes in some of these women, this hypothesis cannot be confirmed since the organisms isolated were not tested for their susceptibilities to fluconazole.

Assurance of medication compliance and the degree of medication compliance are crucial for the proper assessment of the efficacies of new treatment approaches. In studies of oral trimethoprim-sulfamethoxazole in the prevention of infection in neutropenic patients, good medication compliance was associated with a significant reduction in the incidence of fever or infection compared with the incidence in placebo-treated patients (12). When both compliant and noncompliant patients were combined, there was no significant difference in infection rates between placebo and trimethoprim-sulfamethoxazole-

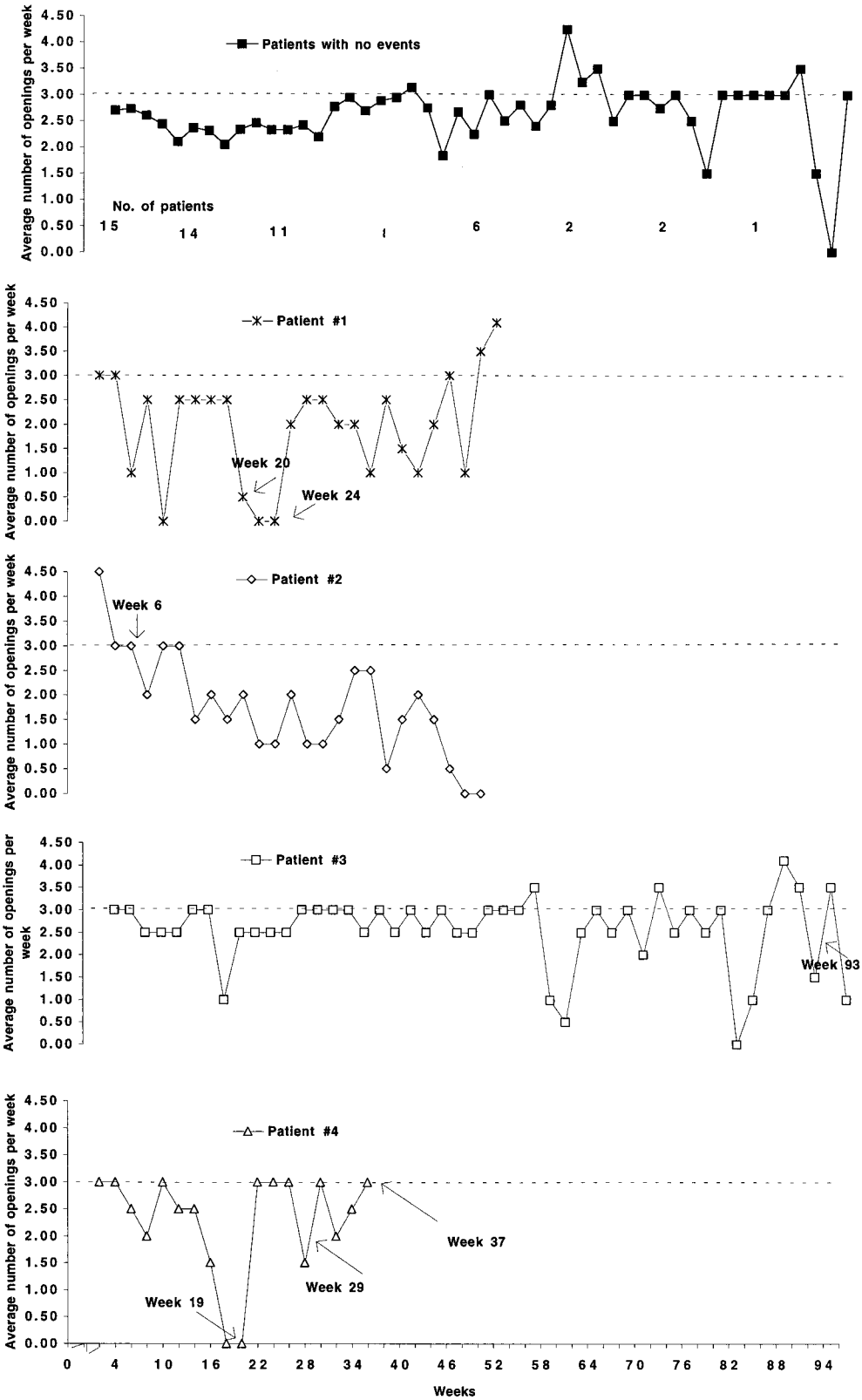

FIG. 1. Average number of openings in a 2-week period recorded by MEMS for study patients on thrice-weekly fluconazole therapy. Arrows indicate when breakthrough events occurred. Dashed lines indicate 100% compliance (three recorded openings per week).

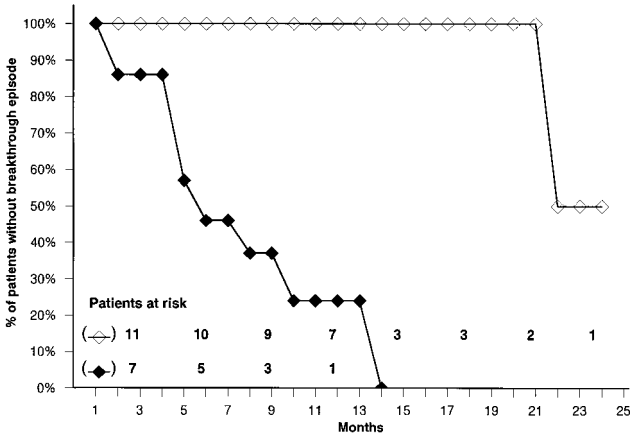

FIG. 2. Kaplan-Meier analysis according to average compliance with thrice-weekly fluconazole therapy ($P < 0.001$, log-rank test). ◇, patients with ≥80% compliance; ◆, patients with <80% compliance.

treated patients. For prophylactic medications taken for a prolonged period of time, consistent therapy correlates with a favorable outcome. In patients receiving isoniazid prophylaxis for the prevention of tuberculosis reactivation, compliance tends to decrease over time, with the duration of prophylaxis associated with medication benefit (2). Compared with placebo, isoniazid prophylaxis for 12 weeks caused only a slight reduction in reactivation, whereas compliance for 24 weeks was associated with a 65% reduction in reactivation. A full year of treatment resulted in a 75% reduction in reactivation. In the four women developing mucocutaneous candidal infections that we describe, erratic fluconazole dosing was displayed over time in each patient.

Several logistic and technical problems occurred during the study that we report here. MEMS data were not available for a few patients because the patient lost the vial or broke the cap when she accidentally dropped it. Spurious noncompliance readings occurred for a few women who reported removal of several medication doses from the vial all at once for travel purposes.

The use of MEMS in the present study required coordination between the study nurses and the clinical pharmacist. Good communication was necessary, as was flexibility in dealing with women who would show up for a refill without a scheduled appointment and with women who would not show up for scheduled appointments.

Most women were very enthusiastic about seeing the computer display of compliance. Patients often wanted to know their medication compliance rates over the previous 3-month period, and many were encouraged when they saw that they had been compliant. In addition, during refill appointments with MEMS readings, the patients would often explain why the medication dosages were missed on certain days, which was helpful in gathering accurate dosing histories.

We believe that the present study emphasizes the importance of tracking individual patient compliance during a clinical trial, specifically with a medication not dosed every day. Because breakthrough episodes of mucocutaneous candidiasis have been attributed to medication failure or resistance development, it is essential to confirm patient compliance in these situations (10). In addition to erroneously assuming drug failure, noncompliance during clinical trials can lead to overestimation of the optimal dose of a medication (8). In the present study, electronic compliance monitoring provided data on both overall compliance and the specific patterns of drug use, which were necessary to determine an association with breakthrough infections. Implementation of strategies to enhance medication compliance may improve patient outcomes as a result of the use of prophylaxis in this population and reduce the cost of care for these patients.

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