ORIGINAL RESEARCH

Patterns of non-adherence to oral antiretroviral medication: frequencies of consecutively missed doses

Anna S Kaufman
Alan Morrison

ScribCo, Effort, PA, USA

Purpose: The therapeutic effect of a once-daily oral drug will be maintained if there are no occurrences of consecutively missed doses that exceed the duration of the drug's effect. The durations of effect of antiretroviral drugs are typically in the range of 1–4 days. Here, we report the observed frequencies of ≥ 2, ≥ 3, and ≥ 4 consecutively missed doses for patients taking a once-daily oral antiretroviral drug for HIV infection.

Patients and methods: Medication Event Monitoring System (MEMS) data were extracted from an electronic database of MEMS records, for a 30-day period for 555 patients taking once-daily oral HIV drug therapy. We recorded the number of days with missed doses and occurrences of ≥ 2, ≥ 3, or ≥ 4 consecutively missed doses. Distributions of the observed frequencies of ≥ 2, ≥ 3, and ≥ 4 consecutively missed doses as a proportion of number of missed doses were compared to calculated random distributions using the Wilcoxon signed-rank test.

Results: The frequencies of 0, 1, and ≥ 2 missed daily doses were 0.279, 0.312, and 0.409, respectively. The frequencies of ≥ 2, ≥ 3, and ≥ 4 consecutively missed doses were 0.184, 0.110, and 0.065, respectively. The probabilities that the observed frequencies of ≥ 2, ≥ 3, and ≥ 4 consecutively missed doses were as expected from random chance were $P=0.345$, $P<0.01$, and $P<0.01$, respectively.

Conclusion: Observed runs of ≥ 3 and ≥ 4 consecutively missed doses – and hence loss of therapeutic effect for drugs of duration of action of <3 and <4 days, respectively – occurred more frequently than expected if missed doses were randomly distributed.

Keywords: medication adherence, drug therapy/utilization, antiretroviral therapy, drug administration schedule

Summary

If a patient misses a number of doses of a drug, the therapeutic effect of the drug will be maintained if there are no occurrences of consecutively missed doses that exceed the duration of the drug's effect. Here, we report the observed frequencies of consecutively missed doses of once-daily oral antiretroviral drugs for HIV management, and we ask whether these distributions are purely random. Observed runs of ≥ 3 and ≥ 4 consecutively missed doses – and hence loss of therapeutic effect for drugs of duration of action of <3 and <4 days, respectively – occurred more frequently than expected from random chance.

Introduction

Patterns of non-adherence to medications should be understood in terms of their effect on the intended therapeutic effect of the drug.[1–3] It is not the number of missed

Correspondence: Anna S Kaufman
ScribCo, PO Box 580, Effort,
PA 18330, USA
Tel +1 414 801 8468
Email akaufman@uwalumni.com

389

doses per se but the distribution of these missed doses that determines whether the therapeutic effect is maintained.[4,5] Even if a patient misses a number of doses of a once-daily oral drug, the therapeutic effect will continue if there are no occurrences of consecutively missed doses that exceed the duration of the drug's effect.[6] Therefore, the therapeutic effect of a drug with a duration of action of, for example, 1.5 days is maintained if missed doses occur only on single days but lost if missed doses occur on ≥2 consecutive days.

In the case of oral antiretroviral drugs for the management of HIV infection, the therapeutic effect is the inhibition of viral replication, and the loss of the therapeutic effect results in viral rebound and disease progression.[7] Several once-daily oral antiretroviral drugs have terminal half-lives in the range 5–17 hours, and serum levels remain above the minimally effective concentration for durations of about 1 day (saquinavir), 1–2 days (emtricitabine), or 2–3 days (tenofovir, simeprevir).[8–11] Here, we report the observed frequencies of runs of consecutively missed doses of once-daily oral antiretroviral drugs for HIV management that are likely to result in the loss of the therapeutic effect, and we ask whether the distributions of these runs are purely random.

Patients and methods
Study design
This was a descriptive study of a pre-existing database of patients taking once daily oral antiretroviral therapy.

Data source
The data source was the iAdherence database (AARDEX Group), a depository of patients' medication-taking behavior recorded using a Medication Event Monitoring System (MEMS) during clinical trials of drugs in multiple classes.[12] This database contains de-identified MEMS records for 644 patients taking a once-daily oral antiretroviral drug for HIV infection. Each patient has a numeric identifier – a (non-sequential) number, from 384 to 68882, in series representing sets of patients from different clinical studies, conducted in 2000–2007. The data set records the date and time when each dose was taken (it is assumed in the following discussion that a MEMS-recorded event is equivalent to a dose taken). The iAdherence data set does not contain any demographic information about the patients, the identity of the drug, or whether the HIV therapy was for treatment or prevention. Analysis of the de-identified data contained within the database does not require approval by an institutional review board.

Data extraction
The iAdherence data are displayed in a patient calendar plot, which shows the number of doses per day (0, 1, 2, etc.) for each calendar week (Monday through Sunday), where a "day" started and ended at midnight. Data were extracted for 30 days (4 weeks plus 2 days), beginning with the first Monday after the initiation of drug therapy.

Series of patients with fewer than 10 records, and series in which the first five records did not meet the following inclusion criteria, were omitted. Patients were excluded if they did not take at least one scheduled dose, if they consistently took two doses per day, or if they discontinued during the first 30 days (defined as a period of 28 or more consecutive days without a dose, beginning within the first 30 days of drug treatment). The following information was recorded: the date of initiating drug therapy, the total number of doses, the number of days with missed doses, and occurrences of consecutively missed doses.

Data analysis
The variable "m" represents the number of days with a missed daily dose. The following outcomes are reported: the average proportion of days with at least one dose; the mean m; the proportion of patients with missed doses (days without a dose), by value of m; the proportion of patients with instance(s) of consecutively missed doses, by value of m; and the average proportion of prescribed pills taken over 30 days (the mean number of pills taken per patient divided by 30). For each value of m, the observed proportion of patients with instances of ≥2, ≥3, and ≥4 consecutively missed days was computed and compared to the proportion arising by random chance ("calculated") using the Wilcoxon signed-rank test. The proportions of days with ≥2, ≥3, and ≥4 consecutively missed days of dosing arising by chance for any value of m over a 30-day period were calculated as a quotient, where for each value of m the denominator is the number of all possible combinations of m items in N elements, where N=30, and the numerator is the number of combinations of m items with ≥2, ≥3, and ≥4 consecutive instances.[6]

Results
Participants
The iAdherence database contained MEMS records for 644 patients taking a once-daily oral antiretroviral drug for HIV infection. Series 384–390 were omitted because it contained only four patients and series 51159–56006 because the first five patients did not meet the inclusion criteria.
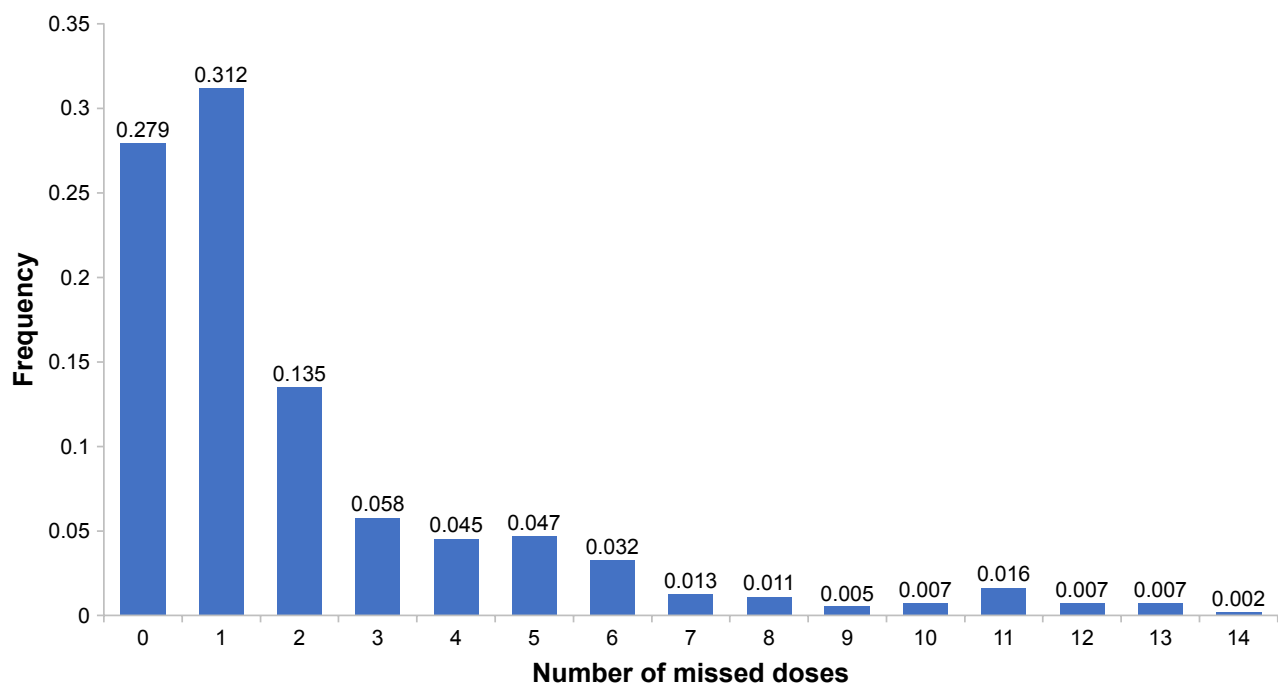
Table 1 Number of patients with missed doses

Measures	Number of patients (N=555)	Proportion of patients[a]
Patients with m missed days[b]		
0	155	0.279
1	173	0.312
≥2	227	0.409
Patients with consecutively missed days[c]		
≥2	102	0.184
≥3	61	0.110
≥4	36	0.065

Notes: [a]Proportion of 555 patients. [b]Number and proportion of 555 patients with m consecutively or non-consecutively missed days, for values of m of 0, 1, and ≥2 missed daily doses during the 30-day analysis. [c]Number and proportion of 555 patients with consecutively missed days, for values of ≥2, ≥3, and ≥4 consecutively missed days during the 30-day analysis. m, number of missed daily doses.

Of the remaining 610 patients, 55 did not meet the inclusion criteria, leaving 555 patients in the analysis.

Main results

The average number of doses taken over the 30-day period was 28.5. The average number of missed days (average value of m) was 2.5, and the average number of days with treatment was 27.5. The numbers and frequencies of patients with missed days of dosing are presented in Table 1.

The frequencies of 0, 1, and ≥2 missed daily doses were 0.279, 0.312, and 0.409, respectively (Table 1 and Figure 1). The frequencies of ≥2, ≥3, and ≥4 consecutively missed doses were 0.184, 0.110, and 0.065, respectively (Table 1). The observed and calculated frequencies of these consecutively missed doses for each value of m are shown in Figure 2. The observed frequencies typically exceeded the calculated frequencies, and probabilities that the observed frequencies of ≥2, ≥3, and ≥4 consecutively missed doses were as expected from a random distribution of missed doses were $P=0.345$, $P<0.01$, and $P<0.01$, respectively.

Discussion

The analysis presented here is based on days with/without treatment rather than the proportion of doses taken, which is how medication adherence is typically defined.[13] The validity of the analysis depends on the assumption that MEMS events represent the actual consumption of doses, rather than merely opening of pill bottles. There are also certain limitations to measuring missed days using MEMS calendar plots. The calendar plots simply record doses taken on a day but do not show the time. Variations in the hour of day when a patient takes a dose could affect whether or not a time interval between doses exceeding 24 hours is recorded as a
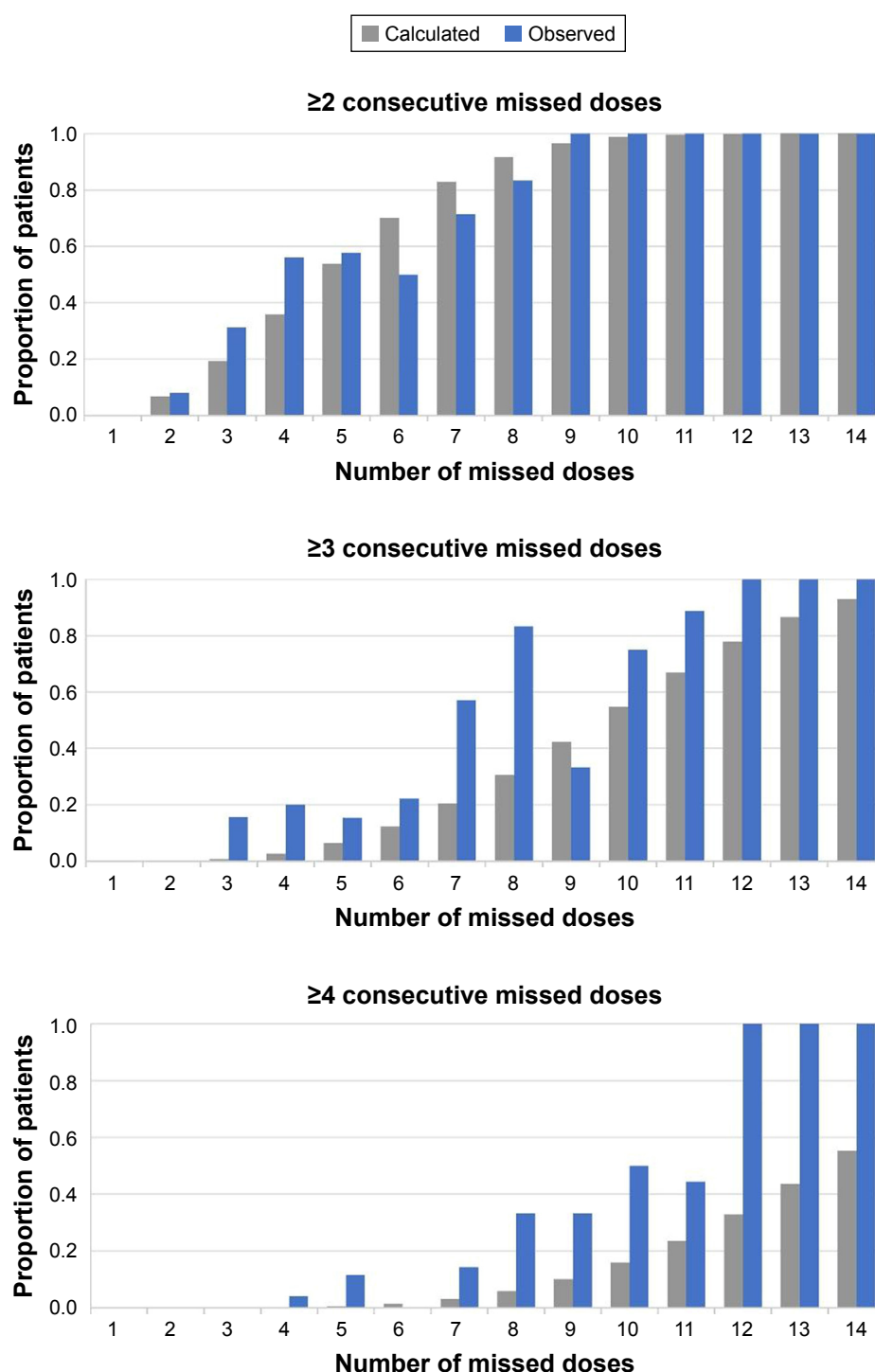

Figure 1 Frequency of missed doses by number of missed doses.
Note: Frequency, number of patients with m missed doses (in total) divided by total patient N (555), is graphed against the number of missed doses, m, for the 30-day period.

Figure 2 Proportion of patients with ≥2, ≥3, or ≥4 consecutively missed doses by number of missed doses.
Notes: Shown are the observed frequencies ("observed") of ≥2, ≥3, and ≥4 consecutively missed doses (upper, middle, and lower panels) in patients with missed doses. The distributions of observed frequencies ("observed") and theoretical random distribution ("calculated") patterns are compared. The "observed" data represent the 555 HIV patients during the 30-day observation period. The "calculated" data assume that the missed doses were distributed randomly during the 30-day period and were computed as described.[6] The denominator is the number of patients with m missed doses, and the numerator is number of patients with ≥2, ≥3, or ≥4 consecutively missed doses for each value of m. *P*-values for comparison of observed and calculated distributions of ≥2, ≥3, and ≥4 consecutively missed doses, 0.345, <0.01, and <0.01, respectively.

missed day. A different approach would be to use the MEMS chronology plots, which record the precise hour and minute of each dose, and to measure the actual time interval in hours between doses. Neither approach accounts for occurrences of multiple doses on 1 day, which might extend the duration of therapeutic effect on the days following. In effect, the proportion of missed days of dosing obtained from the calendar plot is a surrogate for the higher-resolution measure

of the percentage of time in hours that serum drug levels fall below the therapeutic range. The total time serum drug levels fall below the minimally effective concentration can be calculated from MEMS data by pharmacokinetic modeling, which is an alternative and more sophisticated approach.[1–3,14]

The current analysis was based on a period of 30 days, which is a standard period for drug dosing. The 30-day period was taken at the beginning of the course of treatment lasting up to about 10 months, and it is possible that the results may differ during 30-day periods taken later in the course of treatment. However, in a report of the Uganda AIDS Rural Treatment Outcomes Study, Haberer et al[15] found that the number of interruptions of ≥48 hours in antiretroviral treatment of HIV per month was stable over a median follow-up period of 25 months.

Numbers of ≥2, ≥3, and ≥4 consecutively missed doses are relevant to the durations of action of many antiretroviral drugs. HIV viral replication is expected to proceed once the concentration of antiretroviral drugs in tissues falls below the minimally effective concentration. Investigators have reported that the odds of detecting circulating HIV RNA increased linearly after ≥2 consecutively missed days of dosing, where patients were taking various regimens, including nevirapine and efavirenz.[15,16] Knobel et al[17] reported that antiretroviral drug treatment interruptions of >3 days were associated with treatment failure (defined as a viral load of >500 HIV RNA copies per mL). The actual time before viral rebound depends on the duration of the therapeutic effect of the specific drug. The serum concentration of saquinavir falls below the minimally effective concentration at medians of 23 and 29 hours after doses of 1,600 and 2,000 mg, respectively.[8] Serum levels of emtricitabine are predicted to fall below the 50% inhibitory concentration at about 24–42 hours after cessation of once daily doses of 25–300 mg.[18] Plasma concentrations of efavirenz are predicted to fall below the minimally effective concentration at a median of 7 days (IQR 4.7–9.2 days) after the last 600 mg dose.[19] (The identities of the drugs that patients received in the iAdherence data set are not recorded.)

We found that observed frequencies of runs of ≥3 and ≥4 consecutively missed doses were significantly greater than expected from random chance. In a similar approach, Harris et al[20] compared the observed and calculated distributions of ≥3 consecutively missed doses of an antiretroviral drug regimen. (Figure 1 in the study by Harris et al,[20] comparing the observed and theoretical distributions of ≥3 consecutively missed doses in 185 patients over a period of 90 days, is the formal equivalent of Figure 2, middle panel in the present work.) In the study by Harris et al, the observed frequencies

of ≥3 consecutively missed doses were statistically significantly higher than the calculated random probabilities at levels of average adherence of 0.85–0.97, corresponding to between 1 and 4–5 missed doses in a 30-day period, whereas there was no statistically significant difference between the observed and calculated frequencies at levels of average adherence of 0.40 to <0.85, corresponding to 4–5 to 18 missed doses in a 30-day period. The two analyses differ in several respects. The absolute values of the proportions of consecutively missed doses reported by Harris et al are higher than those in the present study, which we attribute to the longer observation period of 90 days. In addition, Harris et al calculated the chance probabilities of consecutively missed doses using an approximating formula (Feller's formula), whereas we determined the exact probability using a computer program, which generated all possible combinations of missed doses for each value of m misses and counted those with one or more instances of ≥2, ≥3, and ≥4 consecutively missed doses. In addition, the independent variable in Harris et al was expressed as an adherence rate (the proportion of prescribed doses taken – in effect the converse of the number of missed doses in the present work). The analysis presented here is based on the number of days with or without doses, and the two approaches give somewhat different results. Here, the average proportion of doses taken (0.947) exceeded the average proportion of days with treatment (0.917), because some patients took more than one dose on one or more days during the 30-day period of analysis.

Whether the findings, that observed frequencies of ≥3 and ≥4 consecutively missed doses are higher than expected by random chance, are generalizable and apply beyond the treatment of HIV infection with antiretroviral drugs is an open question. It is possible that the results are a characteristic of specific populations, and the absence of information about the patients in this analysis is a limitation. However, we found similar results in an analysis of MEMS dosing patterns of patients taking once-daily hypercholesterolemia medications (Supplementary material, Figure S1). In both analyses, ie, for antiretroviral and cholesterol-lowering drugs, observed runs of consecutively missed doses occurred statistically significantly more frequently than expected if missed doses were randomly distributed for ≥3 and ≥4 (but not ≥2) consecutively missed doses.

Conclusion

In this study, we defined non-adherence on the basis of missed days of dosing, rather than in terms of a proportion of pills taken. We determined the frequencies of runs of consecutively missed days of dosing likely to cause loss of

therapeutic effect of an antiretroviral drug and found that runs of ≥3 and ≥4 consecutively missed doses occurred more frequently than expected by random chance. Whether this non-random pattern of consecutively missed days of dosing is generalizable to other therapeutic areas is a hypothesis to be tested.

Data sharing statement

At the time of the study (2016–2017), the data were freely available from the iAdherence database. Restrictions now apply to the availability of these data. A transcript of the raw data extracted for this study is presented as a Supplementary material (Table S1).

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Disclosure

The authors report no conflicts of interest in this work.

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