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How Long Is the Window of Opportunity Between Adherence Failure and Virologic Failure on Efavirenz-Based HAART?

Robert Gross^{1,2,3}, Warren B. Bilker^{1,3}, Hao Wang¹, and Jennifer Chapman¹

¹Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

²Department of Medicine, Division of Infectious Diseases, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

³Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Abstract

Purpose—The time between onset of nonadherence and onset of virological failure is unknown. However, this information is critical to the design, implementation, and testing of interventions aiming to forestall treatment failure.

Method—We conducted an observational cohort study of 116 HIV-infected adults with virological suppression on efavirenz-based regimens. Patients were seen monthly and censored at virological failure (>1000 copies/mL) or 12 months, whichever came first. Adherence was measured using the Medication Event Monitoring System (MEMS). Percent of doses taken was summarized for 90-day periods. We assessed 4 adherence periods: immediately prior to censor, and then 30 days, 60 days, and 90 days prior to censor.

Results—Adherence was significantly lower for patients with virological failure ($n = 7$) than those without virological failure ($n = 99$) at all time points assessed. These differences were statistically significant even up to 90 days prior to the virologic failure date (failure group 57% vs. nonfailure group 95%; $p = .03$).

Conclusion—The window between the onset of nonadherence and virological failure can be as long as 90 days. This will allow substantial time for interventions to be implemented and to take effect.

Keywords

adherence; antiretroviral therapy; HIV; virologic failure

Sustained antiretroviral adherence is vital to HIV treatment success.^{1–4} Once virological failure occurs, it is often with resistant virus³ and increased adherence at that time may not result in virological suppression. Therefore, for adherence interventions to have the greatest

chance at virological success (e.g., maintained suppression), they should be instituted prior to regimen failure.

Clinicians may feel reassured and assume that patients with “undetectable” viral loads are adherent to treatment. However, in clinical care, substantial numbers of patients fail after initial suppression.⁵ These failures are likely due in part to nonadherence.⁶ The challenge for clinicians is to identify those adherence failures and intervene before virologic failure occurs, because many of these failures will occur with resistant virus and thereby reduce future treatment options. However, they must be identified with enough time for interventions to return adherence to optimal levels and prevent failure. Yet, the length of time between the onset of nonadherence and the eventual treatment failure is unknown. This time period is the potential window of opportunity for instituting adherence interventions. Therefore, we aimed to determine how long prior to virological failure nonadherence could be detected.

METHOD

We conducted an observational cohort study of individuals with undetectable viral loads on efavirenz-containing regimens for at least 3 months as previously described.⁷ Regimens had to include two or three nucleoside analog reverse transcriptase inhibitors (NRTIs) but no protease inhibitors. The study was approved by the PENN Institutional Review Board, and all participants provided written informed consent.

Assessments

Adherence was continuously monitored using a microelectronic processor and bottle (Medication Event Monitoring System [MEMS]; Aardex, Zug, Switzerland)⁸ for the efavirenz only. Blood was obtained and stored monthly and plasma viral loads were assayed every 3 months using the Quantiplex HIV-1 RNA 3.0 assay (Chiron Diagnostics, Emeryville, California, USA) until November 2002 and the Versant HIV-1 RNA 3.0 bDNA assay (Bayer Diagnostics, Berkeley, California, USA) thereafter. If a viral load was >75 copies/mL, stored samples from the prior visits were assayed to identify the earliest month with viremia. Patients were censored on the date their viral load was first found to be 1000 copies/mL or 12 months, whichever came first.

Data Analysis

Adherence was calculated for 90-day periods and was summarized as percent of prescribed doses taken. The first period included adherence for the 90 days prior to censor. Subsequent adherence periods were shifted back in time by 30-day increments up to a maximum of 90 days. That is, they included a time lag between the end of the adherence period and the event/censor date. The period for the 30-day time shift started at 120 days and ended at 30 days prior to censor, the period for the 60-day time shift started at 150 days and ended at 60 days prior to censor, and the 90-day period extended from 180 days to 90 days prior to censor as depicted in Figure 1.

Failure was defined as viral load 1000 copies/mL based on prior work questioning the clinical relevance of lower levels of viremia.^{9,10} Continuous variables were compared

between the failure and continually suppressed groups using the Wilcoxon rank sum test and dichotomous variables using the Fisher exact test. *P* values were two-sided except for adherence comparisons, because nonadherence was not plausibly associated with better outcomes.

We assessed for confounding using logistic regression in which we assessed whether potential confounders in a model changed the point estimate of the adherence-failure relation by 15%.

Sample Size

We targeted enrollment of 125 participants for 80% power to detect an 18% difference or greater in percent of doses taken between the always undetectable group and the failure group at an alpha level of 0.05 assuming a failure rate of 10% during a year of follow-up.

RESULTS

Enrollment began in May 2000 and follow-up ended in August 2004. Of the original 125 individuals enrolled, 116 (93%) were available for analysis. Those not analyzed included one lost to follow-up, one who moved away from the area, four who had their efavirenz stopped prior to virological failure, two who lost their MEMS cap, and one who had a defective MEMS cap that precluded analysis. Participants who were not analyzed were more likely to be female (6 not analyzed [67%] compared with 22 analyzed [19%], $p = .004$), but other characteristics including race, history of injection drug use, employment, and use of three nucleoside analogs in the regimen were similar between those included and excluded. Table 1 displays the demographics of the cohort included in the analysis. They were predominantly male and African American with most on two NRTIs in the regimen. A variety of NRTIs were used including 46 (40%) on zidovudine and lamivudine; 19 (16%) on lamivudine and stavudine; 9 (8%) on didanosine and stavudine; 8 (7%) on zidovudine, lamivudine, and abacavir; 7 (6%) on lamivudine and abacavir; and 5 (4%) on abacavir and stavudine. Twelve other combinations were used with 4 participants each.

Seven participants experienced failure with a median viral load of 10,029 (range 2,268–59,570 copies/mL) occurring a median of 6 months (range 1–11 months) into follow-up.

Adherence was substantially lower for the failure group for each 90-day period assessed (Table 2). Although the difference was greatest at the time closest to failure, the relation was present even 90 days prior to failure. The differences were all statistically significant except for the 30-day point that did not achieve traditional significance level despite the 33% difference in percent adherence between the failure and continual suppression groups. No other patient characteristics were associated with failure. There were no confounders of the adherence-failure relation.

DISCUSSION

Nonadherence associated with failure was detectable up to 90 days prior to virological failure. This study provides insight into the length of time HIV requires to achieve

significant viremia with incomplete adherence to an efavirenz-based regimen. Further, it provides a potential time window during which adherence interventions might forestall failure. Of course, determining whom to target for such interventions will require direct adherence measurement. In addition, our study shows the danger of simply encouraging patients with undetectable viral loads to “keep doing what you’re doing.” That strategy might reinforce occult nonadherence that has not yet resulted in virologic failure. Rather, clinicians should monitor their patients’ adherence directly either performing self-reports or assessing pharmacy refills¹¹ or both with every clinic visit despite an undetectable viral load.

Our study had several limitations including a low failure rate and therefore the inability to determine a clinically relevant threshold of nonadherence or a threshold for how long before failure nonadherence might have been detected. Further, we only studied efavirenz-based regimens, and the time window between nonadherence and virological failure may differ for different antiretrovirals such as protease inhibitors. Further, we measured adherence using MEMS, likely the most accurate measure,⁸ but, like all adherence measures, it can be inaccurate.¹² Also, we did not assess adherence to the nucleoside analogs in the regimen. However, the presence of the association between adherence and failure suggests that substantial misclassification due to errors in MEMS or differential adherence between the efavirenz and NRTIs¹³ is unlikely. Although women were more likely to be excluded from the analysis, we retained 93% of the cohort. Further, because the biological relation between adherence and virological failure has not been shown to differ by sex, we do not believe this difference affects the conclusions of the study.¹⁴

Recent intervention study results have been encouraging, but they are most likely to be cost-effective when targeted to the patients needing them the most.¹⁵ The substantial window period between the onset of nonadherence and frank treatment failure should encourage clinicians to continue to monitor adherence despite suppressed viral loads. Our results suggest that sufficient time may be present to forestall treatment failure if interventions are able to improve adherence during this time window. However, further observational studies with larger sample sizes, diverse regimens, and monitoring adherence to all medications in the regimen, and/or intervention studies implemented prior to virological breakthrough are needed to define the magnitude of adherence needed to maintain suppression and the duration of the window of opportunity to prevent virological failure.

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R.G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The sponsors of this study had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. Bristol-Myers Squibb was provided with a copy of the article prior to submission and provided comments for consideration.

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Figure 1.

Adherence intervals consisting of contiguous 90-day periods were constructed. These included an adherence period from 90 days prior to the event/censor date to the event/censor date (noted as adherence period without time shift). Adherence periods were also assessed with time shifts of 30 days, 60 days, and 90 days (noted as adherence period with time shift). For example, the adherence period with 30-day time shift extended from 120 days prior to event/censor date to 30 days prior to the event/censor date.

Table 1

Comparison of participants with and without virological failure

Characteristic	No failure (<i>n</i> = 109)	Failure with viral load 1000 copies/mL (<i>n</i> = 7)	<i>p</i>
Median age, years (range)	44 (28–65)	42 (33–50)	.48
Male sex, <i>n</i> (%)	88 (81%)	6 (86%)	>.5
African American race, <i>n</i> (%)	72 (66%)	4 (57%)	>.5
History of IDU, <i>n</i> (%)	30 (28%)	2 (29%)	>.5
Men who have sex with men, <i>n</i> (%)	46 (43%)	3 (43%)	>.5
Prior AIDS diagnosis, <i>n</i> (%)	93 (85%)	6 (86%)	>.5
Duration of HIV diagnosis, years (IQR)	4.9 (2.3–10.6)	11.7 (2.8–14.4)	.30
Employed, <i>n</i> (%)	34 (32%)	3 (43%)	>.5
On first ART regimen, <i>n</i> (%)	60 (59%)	5 (71%)	>.5
Four-drug regimen, <i>n</i> (%)	15 (14%)	1 (14%)	>.5
Median CD4 at entry (IQR)	436 cells/mm ³ (229–572)	328 cells/mm ³ (283–434)	.38
Nadir CD4 (IQR)	139 cells/mm ³ (39–262)	104 cells/mm ³ (6–296)	>.5

Note: IDU = intravenous drug use; ART = antiretroviral treatment; IQR = interquartile range.

Table 2

Comparison of percent adherence at varying times prior to censor between failure and nonfailure groups

Percent adherence by time period	No failure (<i>n</i> = 109)	Failure with viral load > 1000 copies/mL (<i>n</i> = 7)	<i>p</i>
Immediately prior to censor (IQR)	96% (83%–100%)	38% (12%–100%)	.03
30 days prior to censor (IQR)	96% (86%–100%)	63% (24%–100%)	.08
60 days prior to censor (IQR)	96% (87%–100%)	71% (42%–96%)	.04
90 days prior to censor (IQR)	95% (86%–100%)	57% (51%–72%)	.03