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How Long is the Right Interval for Assessing Antiretroviral Pharmacy Refill Adherence?

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To the editors:

Near-perfect adherence to highly active antiretroviral therapy (HAART) results in the highest likelihood of successful HIV outcomes. An adherence measure useful in all settings has not yet been elucidated, and therefore, authorities recommend targeting the adherence measure to the measurement task at hand.¹ The pharmacy refill measure of adherence has been validated against change in viral load over the time interval in which individuals have a 90-day supply of HAART.² However, shorter intervals might allow more rapid detection of non-adherence in clinical practice so clinicians might quickly target individuals for interventions to improve adherence. Yet, if intervals are too short, they might overestimate non-adherence because a relatively few missed doses will drop adherence below the high thresholds desired. If these short periods of temporary non-adherence do not result in treatment failure, then interventions might be overutilized.

We aimed to determine if shorter (i.e., 30- and 60-day supply) intervals of medication adherence measured by refills were as well-correlated with virologic response as the previously validated 90-day supply measure.² These shorter intervals can occur in the first 30 days of a 90-day supply, in the middle 30 days of a 90-day supply, or in the last 30 days of a 90-day supply. Which interval is most strongly correlated with the 90-day supply interval and the viral outcome would provide useful information as to whether these shorter intervals are viable alternatives to the longer interval.

110 subjects on a stable HAART regimen for at least 3 months were recruited from the Philadelphia Veterans' Affairs Medical Center (VAMC).² The study was approved by the Institutional Review Boards at the VAMC, University of Pennsylvania, and Temple University. On the day of study entry, informed consent was obtained from each participant, and a viral load was drawn. The dates for the four most recent refills of the index drug

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(protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or abacavir) preceding the viral load were obtained from automated pharmacy records.

Adherence intervals were defined by the dates of pharmacy refills over the time in which a subject refilled medications for the most recent 90 day supply preceding the study entry day. Typically, these were 30 day prescriptions and the prior 4 prescription dates were used in the calculation of percent adherence during overlapping 30-day, 60-day, and 90-day supply intervals. Percent adherence was calculated for each of these intervals using the following formula: Percent adherence = (Number of days' supply/Number of days between fills) $\times$ 100.

We used Spearman correlations to determine the relationship of pharmacy refill adherence to change in log viral load (from peak viral load to viral load at study entry) for each of the six intervals of interest. A separate correlation was conducted for each 30-day, 60-day, and 90-day supply interval preceding the viral load outcome so that each subject was included only one time in each analysis. These six correlation coefficients were compared to determine which interval best predicted viral load change. Confidence intervals were computed for the Spearman correlations based on Fisher's transformation. We also used Spearman correlations with confidence intervals to compare the six adherence intervals to each other. Finally, the 30-day and 90-day interval adherence estimates were compared to determine the correlation of the paired measures to each other. The sample size of 110 gave 90% power to detect at least 0.75 log change in viral load between good and poor adherers.

In 110 subjects, 89% were male, and median age was 49 years (range 28 to 75). 77% of subjects were African American, 35% were men who have sex with men, and 39% had prior intravenous drug use. Median CD4 count nadir was 122 cells/cm³ (interquartile range (IQR) 57–233); median peak viral load was 49,000 c/ml (IQR 11,000–187,000). Median time on current regimen was 26 months (range 3–65 months).

Table 1 shows the correlations between pharmacy refill adherence estimates measured over varying time intervals and correlations between each adherence estimate and change in log viral load. Pairing the adherence estimates for the first 30-day interval and the 90-day interval by subject demonstrated that the difference between the two adherence estimates was 10% or less for 41.7% of subjects and 20% or less for 71.8% of subjects, and the median difference between the two was 0% (IQR –11.1 to +14.3%). The time frame for measurement of pharmacy refill adherence depended upon the dates of refill and was not usually simultaneous with the viral load outcome. The median gap between the final refill and viral load outcome was 4 days (IQR 0–19 days).

The three 30-day estimates of adherence were equally likely to correlate with adherence over the 90-day interval, but differed in their ability to predict change in viral load. The same was true for adherence estimates for the two 60-day intervals. The shorter duration pharmacy refill measures of adherence that significantly correlated with change in viral load began at least 90 days prior to the viral load outcome. Adherence estimates measured more proximally to the outcome were not significantly correlated with change in viral load, and therefore were poor predictors of viral load.

In a prior study,³ we assessed the relationship between virologic failure and adherence measured using electronic drug monitoring (EDM) over different 90-day intervals staggered by 30 days beginning from the time of viral load outcome and demonstrated that virologic failure was associated with non-adherence occurring 90 days prior to failure. The current study updates these results, in that non-adherence measured over a shorter interval of only 30 days must begin at least 90 days prior to the event in order to predict virologic failure.

This study reconfirms that the accurately captured pharmacy refill measure of adherence measured dynamically over time is associated with viral load outcome.⁴ With this study, we further demonstrate that adherence in individual subjects varies over time and that it is the “upstream” interval of adherence that best predicts viral load outcome. Further, this study also confirms the importance of measuring adherence data in individuals on an ongoing basis given the fact that there was relatively poor correlation of the adherence values within individuals over time.

Shorter intervals of non-adherence measured over a 30 day supply beginning at least 90 days prior to the viral load outcome are significantly associated with and can be used to predict virologic failure. However, since the 90-day intervals of adherence had slight improvement in predicting viral load outcome, there are advantages and disadvantages to measuring adherence over differing lengths of time. For example, in clinical practice, monitoring adherence every 30 days appears to be relevant because adherence varied over time and the shorter 30-day supply measure was useful for picking up non-adherence on which to intervene, before virologic failure occurred. The drawback to this approach is that clinicians might detect non-adherence that would never lead to significant virologic failure and thus might intervene unnecessarily.

We previously assessed the 90-day supply pharmacy refill adherence measure in comparison to EDM adherence.⁵ We found that pharmacy refill adherence correlated poorly with EDM adherence because pharmacy data were difficult to collect from commercial pharmacies without complete data capture. The present analysis was conducted using data collected from the VAMC where the electronic medical record captures all refills obtained from the medical center’s pharmacy and where medications are provided for free, so that it is highly likely that veterans treated for HIV at the medical center obtain all of their refills from the VAMC. Therefore, we believe that we have obtained complete capture of all pharmacy refill data for the subjects in this study.

Our study had several potential limitations for consideration. Pharmacy refill adherence is not perfectly related to viral load outcome as it relies upon the subject’s rate of return to the pharmacy to estimate the maximum number of pills the subject possessed and does not measure pill-taking behavior. Subjects also may have received medications from another source outside of the VAMC system, although this is unlikely as veterans receive free medications in the system. Another possible limitation is our inclusion of subjects regardless of the presence of resistant virus. Resistant virus would weaken the relationship between adherence and viral load change and would decrease the overall association. Therefore, our measure may be even more strongly associated with the outcome than we found. Another possible limitation to the generalizability of our study is our reliance on the VAMC’s unique pharmacy system. Most pharmacy records in developed countries are computerized, but logistical barriers to obtaining pharmacy data remain.⁵

The shorter duration measures of pharmacy refill adherence were significantly related to change in viral load if they began at least 90 days prior to the measure of viral load. These shorter duration measures of adherence correlated with viral load nearly as well as 90-day interval adherence. These results are evidence that upstream measures of adherence were better predictors of viral load outcome than adherence measured more proximally. In clinical practice, measuring adherence every 30 days is likely to be an effective way of identifying patients in need of adherence interventions to improve clinical outcomes.

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Table 1

Correlations between pharmacy refill adherence and change in log viral load from baseline

	90-day adherence	60-day adherence time period 1	60-day adherence time period 2	30-day adherence time period 1	30-day adherence time period 2	30-day adherence time period 3
60-day adherence time period 1	0.842 (0.774– 0.891)	X				
60-day adherence time period 2	0.871 (0.815– 0.911)	0.682 (0.562– 0.774)	X			
30-day adherence time period 1	0.665 (0.542– 0.761)	0.653 (0.525– 0.752)	0.308 (0.122– 0.473)	X		
30-day adherence time period 2	0.619 (0.482– 0.726)	0.819 (0.744– 0.875)	0.672 (0.550– 0.766)	0.212 (0.019– 0.391)	X	
30-day adherence time period 3	0.507 (0.347– 0.639)	0.095 (–0.102– 0.284)	0.548 (0.396– 0.670)	0.270 (0.080– 0.442)	–0.089 (–0.278– 0.106)	X
Difference in Log Viral load	0.265 (0.078– 0.434)	0.229 (0.036– 0.405)	0.184 (–0.007– 0.362)	0.250 (0.059– 0.423)	0.150 (–0.045– 0.334)	0.144 (–0.050– 0.327)