Published in final edited form as:

AIDS Behav. 2017 February ; 21(2): 470–480. doi:10.1007/s10461-016-1566-8.

A comparison of adherence timeframes using missed dose items and their associations with viral load in routine clinical care: Is longer better?

HM Crane¹, RM Nance¹, JAC Delaney², RJ Fredericksen¹, A Church¹, JM Simoni³, RD Harrington¹, S Dhanireddy¹, SA Safren⁴, ME McCaul⁵, WB Lober¹, PK Crane¹, IB Wilson⁶, MJ Mugavero⁷, and MM Kitahata¹

¹Medicine, University of Washington, Seattle, WA

²Epidemiology, University of Washington, Seattle, WA

³Psychology, University of Washington, Seattle, WA

⁴Psychology, Massachusetts General, Boston, MA

⁵Psychiatry, Johns Hopkins University, Baltimore, MA

⁶Health Services, Policy & Practice, Brown University, Providence RI

⁷Medicine, University of Alabama at Birmingham, Birmingham, AL

Abstract

Questions remain regarding optimal timeframes for asking about adherence in clinical care. We compared 4-, 7-, 14-, 30-, and 60-day timeframe missed dose items with viral load levels among 1099 patients on antiretroviral therapy in routine care. We conducted logistic and linear regression analyses examining associations between different timeframes and viral load using Bayesian Model Averaging (BMA). We conducted sensitivity analyses with subgroups at increased risk for suboptimal adherence (e.g. patients with depression, substance use). The 14-day timeframe had the largest mean difference in adherence levels among those with detectable and undetectable viral loads. BMA estimates suggested the 14-day timeframe was strongest overall and for most subgroups although findings differed somewhat for hazardous alcohol users and those with current depression. Adherence measured by all missed dose timeframes correlated with viral load. Adherence calculated from intermediate timeframes (e.g. 14-day) appeared best able to capture adherence behavior as measured by viral load.

Corresponding author: Heidi Crane, MD, MPH, University of Washington, Harborview Medical Center, 325 9th Ave, Box 359931, Seattle, WA 98106, 206-744-6649, 206-744-3693 (fax), hcrane@uw.edu.

Findings were previously presented in part at the 9th International Conference on HIV Treatment and Prevention Adherence

Compliance with ethical standards

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study before they completed the clinical assessment.

This article does not contain any studies with animals performed by any of the authors.

Conflict of Interest: There are no conflicts of interest.

Resumen

Aún hay preguntas pendientes relacionadas con los períodos de tiempo óptimos para preguntar sobre el cumplimiento en la atención clínica. Comparamos períodos de tiempo de 4, 7, 14, 30 y 60 días de dosis omitidas de elementos con niveles de carga viral entre 1099 pacientes sometidos a terapia antirretroviral en la atención de rutina. Llevamos a cabo análisis de regresión logística y lineal para examinar relaciones entre distintos períodos de tiempo y cargas virales con el Promediado Bayesiano de Modelos (BMA, por sus siglas en inglés). Llevamos a cabo análisis de sensibilidad con subgrupos de riesgo incrementado de cumplimiento inferior al óptimo (por ejemplo, pacientes con depresión, consumo de drogas). El período de tiempo de 14 días mostró la diferencia media más importante en los niveles de cumplimiento entre los períodos de tiempo con cargas virales perceptibles e imperceptibles. Los cálculos del BMA sugieren que el período de tiempo de 14 días fue el más predominante entre todos y en la mayoría de los subgrupos, aunque los hallazgos difieren un tanto para los consumidores peligrosos de alcohol y las personas que actualmente presentan depresión. El cumplimiento medido para todos los períodos de tiempo de dosis omitidas se correlacionaron con la carga viral. El cumplimiento calculado de períodos de tiempo intermedios (por ejemplo, 14 días) pareció capturar de mejor forma la conducta de cumplimiento, de acuerdo con lo medido por carga viral.

Keywords

adherence; viral load; hazardous alcohol use; substance use; depression

INTRODUCTION

Antiretroviral medication (ARV) adherence is one of the most important determinants of obtaining and maintaining HIV viral suppression and is critical to prevent drug resistance, disease progression, and death and to minimize HIV transmission[1–6]. Detecting and addressing sub-optimal adherence to ARVs therefore is a crucial aspect of HIV clinical care. However, suboptimal ARV adherence is under-detected by providers[2,7,8] and often not recognized until after virologic failure. Finding a widely accepted, easily implemented, standardized approach to routine assessment of ARV adherence behavior in clinical care has remained challenging[9].

More objective adherence measures used in research settings include detection of drugs or metabolites in body fluids, pill counts, and electronic drug monitoring (EDM) devices[10]. While each has advantages, due to expense, logistical issues and intrusiveness, they are not practical for widespread use in clinical care[11,12]. Self-reported ARV adherence measures remain the most practical approach in routine care[10,11,13–15] despite potential limitations, such as concerns about over-reporting ARV adherence[13,16–19]. Self-reported adherence measures have a number of advantages including minimal patient burden, low cost, ease of administration, flexibility in timing and in mode of administration. They are associated with more objective and/or direct adherence measures such as EDM[11,18,20–22] and correlate well with HIV viral load supporting their use for HIV research and clinical management[11,17,21–26]. Ideally they serve as a means of identifying patients experiencing adherence difficulties before they develop viral failure.

Despite an extensive literature on self-reported ARV adherence measures, questions remain regarding the best approaches to implementation across clinical care and research settings and on specific items for optimizing adherence measurement in clinical care[18,19] although routine assessments are recommended[27–29]. Previous studies have used items with a variety of recall time frames. Arguably, shorter time intervals could be preferable due to more accurate recall, while longer time intervals may better capture the full range of non-adherence behaviors because of a wider sampling frame[30].

The purpose of this study was to evaluate adherence measured by self-reported missed dose adherence items of varying timeframes to determine the optimal timeframe for asking about medication adherence in clinical care settings. We compared adherence calculated from 4-, 7-, 14-, 30-, and 60-day timeframes with viral load levels. We used Bayesian Model Averaging (BMA) to identify “best” timeframes. Further, we confirmed these findings in patient populations potentially at increased risk for poor adherence including those with current drug use, hazardous alcohol use, and depression.

METHODS

Study setting

This study was conducted among patients from the University of Washington (UW) Madison HIV clinic which is the largest single provider of HIV care in the northwestern United States. The HIV clinic uses a multi-disciplinary care team approach to provide primary continuity care, on-site specialty care, financial and social case management, and pharmacy services. Study procedures were approved by the UW Institutional Review Board.

Data Collection

The UW HIV data repository captures longitudinal data on the UW HIV cohort. It integrates comprehensive clinical data from all outpatient and inpatient encounters, including results from clinical assessments of patient reported outcomes. The data repository incorporates demographic, clinical, laboratory, medication, and socioeconomic information obtained from electronic health record and other institutional data sources. Laboratory data are uploaded directly from the clinical laboratory system.

Since 2006, consenting patients have completed patient reported measures and outcomes (PRO) based clinical assessments prior to routine physician visits at approximately 4- to 6-month intervals. This began as a research study, however because of the clinical value of the information obtained, the assessment was integrated into routine clinical care procedures with same-day PRO feedback furnished to providers before they see the patient[31,32]. Patients use touch-screen tablets and a web-based survey software application developed specifically for PROs[33–35] in order to self-administer the assessment. Patients who do not speak English or Spanish or who have known cognitive impairment are not offered the assessment.

Study Participants

HIV-infected patients over 18 years of age, receiving ARVs, who attended routine clinical care appointments between July 2009 and June 2013 and completed the adherence items as part of the clinical assessment were eligible for the study. We used the most recent assessment for those patients who completed it multiple times during the study period.

Clinical Assessment Measures

ARV Medication Adherence—Adherence items followed a preamble acknowledging the difficulty of always taking all medications. Patients receiving ARVs receive several medication adherence items including a self-rating scale item that uses a 30-day time frame[18,24], a 30-day visual analogue scale (VAS)[22,36], and several Adult AIDS Clinical Trial Group (AACTG) adherence items[22,37]. The present analysis compared items asking about the number of missed doses over different timeframes ranging from 4 to 60 days. For example, for the 30-day timeframe, the items ask *How many doses of your medication have you missed in the last 30 days?* Response options for the 30-day timeframe were 0, 1, 2–3, 4–5, 6–7, 8–10, 11–15, and >15. Patients select the radio button next to their selected response option. Only one item is seen by a patient at a time, and the timeframe items were intermixed with other adherence items to avoid order effects.

Illicit drug use—We used the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) to assess patients' illicit drug use[38,39]. There are several ways to score the ASSIST[38,39]. Because of the association between illicit drug use and adherence[40,41], we were interested in current use, which we analyzed as a binary variable indicating any use of cocaine/crack, heroin/opiates, and methamphetamines/crystal. We separately evaluated the impact of any current marijuana use. Patients with missing drug use data were assumed to not be current users.

Alcohol Use—We used the consumption items (questions 1 – 3) of the Alcohol Use Disorders Identification Test (AUDIT-C) to identify patients with hazardous alcohol use[42,43] defined as a score of 4 for men and 3 for women to define hazardous alcohol use[44].

Depression—The 9-item Patient Health Questionnaire (PHQ-9) from the PRIME-MD[45,46] measures depressive symptoms experienced over the previous 2 weeks. We scored the PHQ-9 as a severity measure with total scores ranging from 0–27[46]. Patients with depression symptom scores 10 were considered depressed.

CD4+ cell count and HIV-1 RNA levels (viral load)—CD4⁺ cell counts and HIV viral loads were measured as part of routine clinical care. We focused on current values defined as the laboratory value closest in time to the clinical assessment. Of these, 78% were within 30 days and 88% were within 60 days. We categorized CD4⁺ cell count results as <200, 200–349, and 350 cells/mm³. HIV viral load results were examined as both a continuous variable (log_e HIV RNA copy number+1) and dichotomously (as detectable or >400 copies/ml vs. undetectable or 400 copies/ml). We also examined CD4⁺ cell count nadir,

defined as the lowest measured CD4⁺ count prior to the assessment which we categorized as <200, 200–349, and ≥350 cells/mm³.

Statistical Analyses

To ensure that the study sample represented the overall clinic population, we performed bivariate analyses comparing characteristics of study patients to all patients in the UW HIV cohort receiving antiretroviral therapy (ART) using chi-squared tests for categorical variables and *t* tests for continuous variables. We compared characteristics of study participants with detectable current viral loads to study participants with undetectable viral loads. We calculated adherence for each timeframe as the (prescribed doses–missed doses)/prescribed doses * 100. Prescribed doses were identified based on antiretroviral medication regimens in the electronic health record.

We used Pearson's correlations to investigate the bivariate associations of adherence from each of the missed dose timeframes with each other.

We examined convergent validity of the different timeframes as measured by correlations with viral load values.

We compared mean calculated adherence for each timeframe for those with detectable and undetectable viral load[18]. We repeated these analyses limited to those with viral load values within 30 and 60 days of the assessment. We also calculated the correlation of adherence for each timeframe with viral load as a binary and continuous outcome. In addition, we used a Bayesian Model Averaging (BMA)[47–49] approach to estimate the posterior probability of each specific adherence timeframe being included in the best model for predicting undetectable viral load. We used linear models for predicting log viral load and logistic models for predicting undetectable viral load. This approach allowed us to estimate the uncertainty in model selection and state a direct probability that a specific timeframe would be in the best model. This type of BMA approach has been used to develop predictive models in observational data[50] and may well out-perform traditional model selection approaches in terms of predictive power[51].

We conducted sensitivity analyses among those at potentially increased risk for poor adherence to confirm whether the calculated adherence for each timeframe was performing in the same manner. Specifically, we repeated correlation analyses for patients with depression, hazardous alcohol use, current drug use excluding marijuana use, and marijuana use.

Finally, in addition, due to the concern for the impact of kurtosis in the adherence variable, we also repeated analyses using log-transformed adherence. However, as inferences were the same, results are presented in the more easily-interpretable linear scale.

RESULTS

Overall, 1099 patients on ART completed assessments during the study period and therefore received the adherence items. Atripla (Efavirenz/Emtricitabine/Tenofovir) was the single most common regimen (31%). At the time of the most recent assessment, the mean age of

participants was 45 (SD 10) years, 86% were men, and mean current CD4⁺ cell count was 553 (SD 285) cells/mm³. Refusal rates are low for the clinical assessment (~1%)[31] and characteristics of patients in the study including age, race, and sex were not statistically significantly different from those of all patients on ARVs receiving care in the clinic during the study period (data not shown). Table I shows the demographic and clinical characteristics of the study patient population by viral load status at their most recent assessment. Overall, 5% of these patients on ART had a detectable viral load. Patients with a detectable viral load were more likely to have had a lower current CD4 cell count and CD4 cell count nadir, were more likely to be depressed and to report current illicit drug use (Table I).

Mean calculated adherence at the most recent assessment ranged from 93–97% across the different timeframes with lower mean adherence and wider standard deviations for shorter timeframes (Table II). While these are high rates of adherence, it is worth noting 95% of these patients had an undetectable VL suggesting these may not be overly biased upwards. While calculated adherence was significantly higher with longer timeframes, the percentage of people who reported missing any dose was also significantly higher with longer timeframes (22% for 4-day vs. 54% for 60-day timeframe). We repeated these analyses specifically among patient groups at increased risk for poor adherence to confirm findings across timeframes in higher risk populations. Mean adherence was lower among potentially higher risk groups except for current marijuana users. The pattern of findings was the same with the lowest mean adherence and widest standard deviation calculated from the 4-day shorter timeframe in each case (patients who reported current illicit drug use: mean adherence across timeframes 84–95%; patients who reported current marijuana use: mean adherence 94–98%; patients with depression 90–96%; patients with hazardous alcohol use 92–97%).

Correlations between mean adherence for each pair of timeframes ranged from 0.52–0.89 (Table III). For example, the correlation between mean adherence from the 14 vs. 30-days timeframe items was 0.84. However these correlations were smaller for farther apart time-periods (e.g. for the 4 vs. 60-day timeframe, the correlation between mean adherence levels was 0.52). This same pattern was observed in each of the high-risk populations with lower correlations between farther apart time periods (data not shown).

We compared mean calculated adherence and reported missed doses for each timeframe for those with detectable and undetectable viral load (Table IVa and IVb). Mean adherence levels among those with detectable and undetectable viral loads differed for each timeframe, with the largest mean difference for the 14-day timeframe. Similarly, the percentage reporting a missed dose differed among those with detectable and undetectable viral loads for each timeframe, with the largest percent difference for the 14-day timeframe. We repeated these analyses including only those with viral load values within 30 and 60 days of the assessment (78% and 88% of the study population, respectively), and found similar results (data not shown).

We examined correlations between adherence for each timeframe and HIV viral load status as both a binary and continuous outcome overall and among key subgroups. All correlations were statistically significant (Table V) except for the 60-day timeframe among those

subgroups with current drug use and hazardous alcohol use. In general, the 14-day timeframe correlations were the highest for the overall population and for most of the subgroups except for those with current depression or hazardous alcohol use where the 7-day timeframe correlations were similar or even slightly higher (although not significantly so).

The BMA estimates for the logistic model of the probability of a particular time-frame being included in the best fitting statistical model for the association between calculated adherence and undetectable viral load found a single best timeframe. With this approach, only the 14-day window was more likely to be included in the best fitting statistical model than not (posterior probability of being included in the best fitting statistical model of 59%). Among current drug users, the posterior probability that the 14-day timeframe was in the best fitting statistical model became even higher (90%). Only among the subset of patients with current depression did any other timeframe beside 14-day have a posterior probability of greater than 50% of being included in the final model (7-day, 62%; 14-day 20%). Examining the linear version of the model for the association between adherence and viral load, the 14-day adherence window was certain to be in the best fit model (100% posterior probability) for all groups except hazardous alcohol users (posterior probability of being in the best fitting model of 47%) and those with current depression (posterior probability of being in the best fitting model of 16%). For these groups, the posterior probabilities imply that multiple time windows, particularly the 7-day timeframe, might be included in the best-fitting statistical model, suggesting some benefit in improved model goodness of fit from multiple timeframe measures in these sub-populations.

DISCUSSION

Among 1099 HIV-infected patients on ART who completed missed dose adherence items with multiple timeframes (4-, 7-, 14-, 30-, and 60-day) as part of routine clinical care, the mean adherence at the most recent assessment was high, ranging from 93–97% depending on the timeframe, consistent with the high percentage of patients (95%) with undetectable viral loads. Mean adherence was higher with longer timeframes, however the percentage of people who reported missing any dose was also higher with longer timeframes (22% for 4-day vs. 54% for 60-day timeframe). Correlations between adherence for adjacent timeframes were strong (e.g., for 14- vs. 30-days, the correlation was 0.84), but somewhat more modest for separated timeframes (e.g., for 4- vs. 60-days, the correlation was 0.52). The 14-day timeframe had the largest mean difference in adherence levels between those with detectable and undetectable viral loads. BMA estimates for logistic and linear models of adherence and viral load suggested the 14-day timeframe was strongest overall and for most subgroups, though findings were somewhat different for people with hazardous alcohol use and current depression. Overall, these findings suggested the 14-day timeframe seemed to be best able to capture self-reported adherence behavior as measured by viral load.

We found higher self-reported adherence rates than has typically been reported [2,16,52]. This was a broad clinic-based sample of English- and Spanish-speaking patients in clinical care on ART; we did not target patients at risk for poor adherence but instead included everyone with data obtained as part of a clinical assessment that had been integrated into

routine care. Furthermore, the current treatment era is characterized by more convenient regimens than were available previously; this may also have contributed to the high self-reported adherence rate. Consistent with the high adherence rates, we observed a high rate of viral suppression (95%).

A few studies have compared self-reported adherence across a variety of timeframes. However, many of these studies had a smaller sample size[18,20,21,25,30,53], compared fewer timeframes[20,21,25,30,53], compared items or instruments completed by different groups of patients[25], or compared items that differed both in timeframe and in format[18,21,25,53]. Further, many prior studies assessed adherence separately for each individual ARV medication in a patient's regimen[30,53], adding to the response burden, and is less feasible in routine clinical care. Some studies that addressed timeframe periods and other adherence item comparisons have conducted assessments of instruments collected as part of trials[25,30] rather than in routine clinical care, limiting their generalizability.

One earlier study found little impact of timeframes; however, this study focused on very short intervals using daily recall items of only 1–3 days[30]. Berg *et al.* found that more patients endorsed imperfect adherence with 30-day timeframes compared with a multi-item 7-day measure that examined each antiretroviral medication separately[53]. This finding is consistent with our finding that longer timeframes identified more patients who reported missing at least 1 dose (e.g. 22% for 4-day, 36% for 14-day, 54% for 60-day timeframes) and therefore was less susceptible to ceiling effects.

Lu *et al.* conducted a rigorous study that compared timeframes examining adherence items embedded in a trial setting, and concluded that a 1-month timeframe was preferable to 3- or 7-day timeframes. This study focused more on item formats than timeframe[18]. They reasoned that because viral load depends on adherence over a period of time, a one month or longer timeframe was probably a more clinically relevant time interval than 3 or 7 days[18]. Our study extends their findings by examining a 60-day window, which did not perform better in terms of associations with viral load. We included a 4-day timeframe and consistent with the finding of Lu *et al.* found that short timeframes are undesirable. There are many possible explanations for this finding. For example, shorter timeframes may be more impacted by “white-coat” dosing where patients do better at adherence for the few days before a clinical appointment and therefore shorter timeframes are less representative of overall adherence. Lu *et al.* did not evaluate the 14-day timeframe we found to be optimal in terms of associations with viral load.

We expected to see higher calculated adherence rates with the shorter 4-day timeframe consistent with previously reported over-reporting of good adherence assessed over shorter timeframes[18]. However, we did not confirm these findings. Notably, in this study adherence items were asked as part of a clinical assessment integrated into clinical care that included a number of domains other than adherence. Furthermore, it was completed by patients on touch-screen tablets rather than by an interviewer although patients were aware that providers would view the results. While we did not see greater self-reported adherence rates with the 4-day timeframe, this does not mean that the shorter timeframes were more accurate. A single reported missed dose has more weight with a short timeframe compared

with one reported missed dose with a longer timeframe. Accuracy as assessed by strength of correlations with viral load for the 14-day timeframe was as good as or better than other timeframes most of the time. Additional studies on the pattern of adherence and missed doses would shed further light on the finding of the benefits of the 14-day timeframe over shorter timeframes and whether this was driven by needing a sustained pattern of non-adherence before viral load is influenced.

While ceiling effects are often a key focus for measures such as adherence, adherence behavior has in fact a natural “ceiling” as patients cannot do better than taking all medication doses as directed. A more relevant adherence feature in clinical care would be the measure’s sensitivity to pick up any unsuspected adherence problems. In theory, longer timeframes are more likely to detect unsuspected adherence problems. This is supported by the findings that more patients report missed doses with longer timeframes. However, we did not observe further improvements in viral load associations with timeframes longer than 14-days.

An important aspect of this study is the timeframes were compared among different patient groups including those at higher risk for adherence difficulties. While the calculated mean adherence rate among those with current illicit drug use was somewhat lower than others, BMA models still strongly suggested the 14-day timeframe was preferable for most but not all groups. In contrast, those with hazardous alcohol use had less clear BMA results with evidence similarly strong for both 7-day and 14-day timeframes. Finally, among those with depression, the BMA evidence for the 7-day item was in fact stronger than for the 14-day timeframe. This is in contrast to the findings for the overall study population or most of the subgroups. These results do not clarify why those with hazardous alcohol use or depression may have different findings and in particular may benefit from slightly shorter timeframes; more work is needed to understand if this is due to increased memory impairments or other reasons. These results highlight the importance of evaluating measurement properties in key subgroups such as those with hazardous alcohol use and considering whether different measurement approaches may be needed for these subgroups.

Our BMA approach is a unique. Most statistical approaches ignore the uncertainty in the model selection process. It is common to pick a single “best” model based on a parameter like goodness of fit. However, there is always some uncertainty as to whether models with similar goodness of fit are being eliminated based on sampling variability. We used BMA because it is a technique that considers possible statistical models and estimates the posterior probability that each model is the “best” model based on the data (given that the true model is in the set of models considered)[49]. The classic BMA approach averages many models together, each weighted by their posterior probability. One alternative is to sum up the posterior probabilities of all of the models that have a specific variable present, and use that as the probability that this variable is in the “best” model. This alternative approach creates a more parsimonious model than classic BMA, which will have some variables included with very low posterior probabilities (and thus extremely small coefficients). We used this alternative approach to evaluate the probability that a variable was in the best model and included all variables with a posterior probability of > 50% in our final model. This model was then fit as a traditional statistical model, using the selected variables of interest and

determined the 14-day item timeframe was certain to be in the best-fit model for all groups of individuals except those with hazardous alcohol use and depression.

Strengths

There are several notable strengths to this study. Patients answered identically formatted self-reported adherence missed dose items using different timeframes allowing a direct comparison of timeframes. The adherence items were integrated into a comprehensive clinical assessment to limit the Hawthorne effect. Participants were asked about their doses and not about a medication being specifically monitored as part of a study or trial so likely there was less pressure for over-reporting.

We focused on general missed dose items rather than day-by-day or dose-by-dose recall items. These more complex recall items such as sometimes used in the early ACTG studies[37] are more time-consuming and confusing and are thus of limited feasibility for wide-spread use in routine clinical care where regimens vary. Items were not adjusted to target specific medications or specific days and were not adjusted based on the number of doses of medications per day, greatly reducing burden and enhancing their incorporation into routine clinical care. We did not limit analysis to just those on their initial regimen but instead had an “all-comers” approach further enhancing generalizability.

This study evaluated both mean adherence for each timeframe as well as percentage who missed a dose. This dual approach has advantages in that the impact of each missed dose is much greater on mean adherence at shorter timeframes than longer ones. They are therefore measuring slightly different constructs with the missed dose percentage picking up a much greater number of people with missed doses and potential adherence issues with the longer timeframes than would be captured using a mean adherence cutoff.

These data focused on patients in care during recent years (2009–2013), so patients were on regimens from the current treatment era. The assessment was done using tablets rather than phone or interviews likely decreasing social desirability bias and over-reporting of adherence behavior. The adherence items were included in an assessment as part of routine clinical care including standardized instruments measuring depression, illicit drug use, and a number of other domains using validated instruments, rather than as part of a specific adherence study; again thereby decreasing pressure on patients to focus on and over-report adherence. Finally, this study included sensitivity analyses in key subgroups such as those with hazardous alcohol use who may be at increased risk for poor adherence and in whom understanding differences in how adherence items work may be of particular importance.

Limitations

This study has several limitations worth noting. The clinical assessment was available only in English or Spanish, and the data were from a single clinical site, possibly limiting the generalizability of our findings. We did not conduct qualitative work with patients to further evaluate our results. This study focused specifically on missed dose items with varying timeframes. It is possible that other item formats might have performed better among people with limited health literacy or health numeracy[54]. However, these missed dose items did not require patients to calculate percentages or more complicated number-related tasks. We

compared timeframes specifically for missed dose format adherence items. However, our findings might be different using other types of adherence items. We compared self-reported adherence to viral load, which is an indirect measure of adherence but is impacted by factors beyond adherence. Nevertheless, we do not suspect that this impact would be different based on responses across the different missed dose items. More direct adherence measurements such as electronic drug monitoring are often considered the gold standard for adherence, but these measures have limitations including expense and logistical issues that make them impractical for widespread use in clinical care.

In conclusion, this study compared self-reported adherence calculated from missed dose items of various timeframes with measured viral loads. While assessing and addressing issues with adherence in clinical care settings before patients develop virologic failure or resistance has clear advantages, questions remain regarding the best approach. We found that intermediate timeframes (e.g. 14-day) may be the most clinically useful timeframe for most patient groups. Consistent with prior studies, our data support the assertion that very short timeframes such as the commonly used 4-day timeframe may be less accurate than longer timeframes such as 14 days. Furthermore, we did not see further improvement in terms of the association with viral load using extremely long windows (60-days). While confirmation of these results in other studies and populations would be ideal, our findings suggest that of the 5 timeframes examined, the 14-day appeared best able to capture adherence behavior as measured by viral load, the biological correlate of medication adherence. Interestingly, subgroups of patients, particularly those with hazardous alcohol use and current depression, may benefit from modified strategies of measuring adherence. This study advances our understanding of adherence assessments that can be implemented within clinical care settings and can lead to improvements in adherence that translate into better clinical outcomes.

Acknowledgments

We thank the patients, staff, and providers of the University of Washington (UW) Harborview Medical Center Madison HIV Clinic. This work was supported by the National Institutes of Mental Health (NIMH) at the National Institutes of Health [R01 MH084759] and the Office of Behavioral and Social Sciences Research at the National Institutes of Health [U01AR057954-S]. Additional support came from the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health [CNICS R24 AI067039, UW CFAR NIAID Grant P30 AI027757] and the National Institutes of Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health [U24AA020801, U01AA020793 and U01AA020802].

Funding: This work was supported by the National Institutes of Mental Health (NIMH) at the National Institutes of Health [R01 MH084759] and the Office of Behavioral and Social Sciences Research at the National Institutes of Health [U01AR057954-S]. Additional support came from the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health [CNICS R24 AI067039, UW CFAR NIAID Grant P30 AI027757] and the National Institutes of Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health [U24AA020801, U01AA020793 and U01AA020802].

REFERENCES

1. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 $\times 10^9$ cells/L. *Ann Intern Med*. 2003 Nov 18; 139(10):810–816. [PubMed: 14623618]
2. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000 Jul 4; 133(1):21–30. [PubMed: 10877736]

3. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*. 2000 Mar 10; 14(4):357–366. [PubMed: 10770537]
4. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*. 2001 Jun 15; 15(9):1181–1183. [PubMed: 11416722]
5. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? *AIDS*. 2003 Mar 28; 17(5):711–720. [PubMed: 12646794]
6. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. 2010 Jun 12; 375(9731):2092–2098. [PubMed: 20537376]
7. Gross R, Bilker WB, Friedman HM, Coyne JC, Strom BL. Provider inaccuracy in assessing adherence and outcomes with newly initiated antiretroviral therapy. *AIDS*. 2002 Sep 6; 16(13):1835–1837. [PubMed: 12218400]
8. Bangsberg DR, Hecht FM, Clague H, et al. Provider assessment of adherence to HIV antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001 Apr 15; 26(5):435–442. [PubMed: 11391162]
9. Bangsberg DR. Monitoring adherence to HIV antiretroviral therapy in routine clinical practice: the past, the present, and the future. *AIDS Behav*. 2006 May; 10(3):249–251. [PubMed: 16783537]
10. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005 Aug 4; 353(5):487–497. [PubMed: 16079372]
11. Knobel H, Alonso J, Casado JL, et al. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. *AIDS*. 2002 Mar 8; 16(4):605–613. [PubMed: 11873004]
12. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination. Is this patient taking the treatment as prescribed? *JAMA*. 1993 Jun 2; 269(21):2779–2781. [PubMed: 8492406]
13. Kimmerling M, Wagner G, Ghosh-Dastidar B. Factors associated with accurate self-reported adherence to HIV antiretrovirals. *Int J STD AIDS*. 2003 Apr; 14(4):281–284. [PubMed: 12716500]
14. Wagner G. Utility of self-reported antiretroviral adherence: Comment on Simoni et al. (2006). *AIDS Behav*. 2006 May; 10(3):247–248. [PubMed: 16783536]
15. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. *Pediatrics*. 2007 Jun; 119(6):e1371–e1383. [PubMed: 17533177]
16. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med*. 2001 May 15; 134(10):968–977. [PubMed: 11352698]
17. Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clin Infect Dis*. 2001 Oct 15; 33(8):1417–1423. [PubMed: 11550118]
18. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav*. 2008 Jan; 12(1):86–94. [PubMed: 17577653]
19. Wilson IB, Carter AE, Berg KM. Improving the self-report of HIV antiretroviral medication adherence: is the glass half full or half empty? *Curr HIV/AIDS Rep*. 2009 Nov; 6(4):177–186. [PubMed: 19849960]
20. Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS*. 2002 Jan 25; 16(2):269–277. [PubMed: 11807312]
21. Oyugi JH, Byakika-Tusiime J, Charlebois ED, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *J Acquir Immune Defic Syndr*. 2004 Aug 15; 36(5):1100–1102. [PubMed: 15247564]
22. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. *AIDS Behav*. 2006 May; 10(3):227–245. [PubMed: 16783535]

23. Nieuwkerk PT, Oort FJ. Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis. *J Acquir Immune Defic Syndr*. 2005 Apr 1; 38(4): 445–448. [PubMed: 15764962]
24. Feldman BJ, Fredericksen RJ, Crane PK, et al. Evaluation of the single-item self-rating adherence scale for use in routine clinical care of people living with HIV. *AIDS Behav*. 2012 Oct 30; 17(1): 307–318.
25. Mannheimer S, Thackeray L, Huppler Hullsiek K, et al. A randomized comparison of two instruments for measuring self-reported antiretroviral adherence. *AIDS Care*. 2008 Feb; 20(2): 161–169. [PubMed: 18293124]
26. Simoni JM, Huh D, Wang Y, et al. The validity of self-reported medication adherence as an outcome in clinical trials of adherence-promotion interventions: Findings from the MACH14 study. *AIDS Behav*. 2014 Dec; 18(12):2285–2290. [PubMed: 25280447]
27. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med*. 2012 Jun 5; 156(11):817–833. [PubMed: 22393036]
28. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med*. 2015 Dec; 5(4):470–482. [PubMed: 26622919]
29. Amico KR, Zuniga JM, Wilson IB, Gross R, Young B. Provider guidance for linking patients to antiretroviral therapy adherence interventions: recommendations from an IAPAC advisory committee on adherence monitoring and support. *Journal of the International Association of Providers of AIDS Care*. 2013 Mar-Apr; 12(2):79–83. [PubMed: 23520402]
30. Pearson CR, Simoni JM, Hoff P, Kurth AE, Martin DP. Assessing antiretroviral adherence via electronic drug monitoring and self-report: an examination of key methodological issues. *AIDS Behav*. 2007 Mar; 11(2):161–173. [PubMed: 16804749]
31. Fredericksen RJ, Crane PK, Tufano J, et al. Integrating a web-based patient assessment into primary care for HIV-infected adults. *Journal of AIDS and HIV Research*. 2012; 4(2):47–55. [PubMed: 26561537]
32. Crane, H., Fredericksen, R., Feldman, B., et al. The effect of pre-visit reports to providers of patient reported outcomes (PROs) in routine clinical care; 6th International Conference on HIV Treatment and Prevention Adherence; Miami, Florida. 2011.
33. Crane HM, Lober W, Webster E, et al. Routine collection of patient-reported outcomes in an HIV clinic setting: the first 100 patients. *Curr HIV Res*. 2007 Jan; 5(1):109–118. [PubMed: 17266562]
34. Crane HM, Grunfeld C, Harrington RD, Uldall KK, Ciechanowski PS, Kitahata MM. Lipoatrophy among HIV-infected patients is associated with higher levels of depression than lipohypertrophy. *HIV Med*. 2008 Oct; 9(9):780–786. [PubMed: 18754804]
35. Lawrence ST, Willig JH, Crane HM, et al. Routine, self-administered, touchscreen, computer-based suicidal ideation assessment linked to automated response team notification in an HIV primary care setting. *Clin Infect Dis*. Apr 15; 50(8):1165–1173.
36. Amico KR, Fisher WA, Cornman DH, et al. Visual analog scale of ART adherence: association with 3-day self-report and adherence barriers. *J Acquir Immune Defic Syndr*. 2006 Aug 1; 42(4): 455–459. [PubMed: 16810111]
37. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care*. 2000 Jun; 12(3):255–266. [PubMed: 10928201]
38. Newcombe DA, Humeniuk RE, Ali R. Validation of the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): report of results from the Australian site. *Drug and Alcohol Review*. 2005 May; 24(3):217–226. [PubMed: 16096125]
39. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addiction*. 2002 Sep; 97(9):1183–1194. [PubMed: 12199834]

40. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med.* 2003 May; 114(7):573–580. [PubMed: 12753881]
41. Ingersoll K. The impact of psychiatric symptoms, drug use, and medication regimen on non-adherence to HIV treatment. *AIDS Care.* 2004 Feb; 16(2):199–211. [PubMed: 14676026]
42. Bradley KA, Bush KR, Epler AJ, et al. Two brief alcohol-screening tests From the Alcohol Use Disorders Identification Test (AUDIT): validation in a female Veterans Affairs patient population. *Arch Intern Med.* 2003 Apr 14; 163(7):821–829. [PubMed: 12695273]
43. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med.* 1998 Sep 14; 158(16):1789–1795. [PubMed: 9738608]
44. Gual A, Segura L, Contel M, Heather N, Colom J. AUDIT-3 and AUDIT-4: effectiveness of two short forms of the alcohol use disorders identification test. *Alcohol and Alcoholism.* 2002 Nov-Dec; 37(6):591–596. [PubMed: 12414553]
45. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA.* 1999 Nov 10; 282(18):1737–1744. [PubMed: 10568646]
46. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001 Sep; 16(9):606–613. [PubMed: 11556941]
47. Raftery A, Madigan D, Hoeting J. Bayesian model averaging for linear regression models. *J Am Statist Assoc.* 1997; 92(437):179–191.
48. Raftery A. Bayesian model selection in social research. *Sociological methodology.* 1995; 25:111–163.
49. Hoeting J, Madigan D, Raftery A, Volinsky C. Bayesian model averaging: a tutorial. *Statistical Science.* 1999; 14(4):382–417.
50. Volinsky C, Madigan D, Raftery A, Kronmal R. Bayesian model averaging in proportional hazard models: Assessing the risk of a stroke. *Applied Statistics.* 1997; 46(3):443–448.
51. Viallefont V, Raftery AE, Richardson S. Variable selection and Bayesian model averaging in case-control studies. *Stat Med.* 2001 Nov 15; 20(21):3215–3230. [PubMed: 11746314]
52. Nieuwkerk PT, Sprangers MA, Burger DM, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Arch Intern Med.* 2001 Sep 10; 161(16):1962–1968. [PubMed: 11525698]
53. Berg KM, Wilson IB, Li X, Arnsten JH. Comparison of antiretroviral adherence questions. *AIDS Behav.* 2012 Feb; 16(2):461–468. [PubMed: 21181252]
54. Wilson IB, Fowler FJ Jr, Cosenza CA, et al. Cognitive and Field Testing of a New Set of Medication Adherence Self-Report Items for HIV Care. *AIDS Behav.* 2013 Sep 28.

Table I

Demographic and clinical characteristics at most recent clinical assessment by viral load status (detectable vs. undetectable) among HIV-infected patients in clinical care (N=1099)

Characteristic	Viral load		p-value
	Undetectable N=1042 %	Detectable N=57 %	
Sex			0.2
Male	86	81	
Female	14	19	
Language			0.8
English	96	96	
Spanish	4	4	
Race/ethnicity			0.08
White	58	56	
Black	18	26	
Hispanic	15	5	
Other/unknown	9	12	
HIV transmission risk factor			0.9
Men who have sex with men	57	54	
Injecting drug use	24	26	
Heterosexual	19	19	
Other/unknown	1	0	
Age, years			0.6
< 30	7	11	
30 – 39	21	19	
40 – 49	39	44	
50	33	26	
CD4⁺ cell count current, cells/mm³			<0.001
< 200	8	40	
200 – 349	15	19	
350	77	40	
Depression			0.03
Yes	22	35	
No	78	65	
Hazardous alcohol use			0.7
Yes	14	16	
No	86	84	

Characteristic	Viral load		p-value
	Undetectable N=1042 %	Detectable N=57 %	
Illicit drug use (current)			0.04
Yes	16	26	
No	84	74	
Marijuana use (current)			0.3
Yes	20	26	
No	80	74	

Table II

Summary statistics for adherence timeframe items from most recent clinical assessment among HIV-infected patients in clinical care (N=1099)

Timeframe	Mean Adherence[*] (%)	Standard Deviation	Median Adherence	Percentage who reported missing any doses[*] (%)
4-day	93	18	100	22
7-day	95	11	100	25
14-day	95	12	100	36
30-day	96	7	100	48
60-day	97	4	99	54

^{*} The trend in mean adherence and the trend in percentage reporting missing any doses across the timeframes were both significant

Table III

Correlations between mean calculated adherence for each pair of timeframes among HIV-infected patients in clinical care (N=1099)

Timeframe	4-day	7-day	14-day	30-day
7-day	0.74			
14-day	0.69	0.85		
30-day	0.63	0.81	0.84	
60-day	0.52	0.70	0.71	0.89

Bolded correlations are statistically significantly different from 0 at $p < 0.05$

Table IV

a. Mean calculated adherence for each time frame by viral load status among HIV-infected patients in clinical care (N=1099)

HIV viral load				
	Undetectable	Detectable		p value
Timeframe	Mean adherence (SE*)	Mean adherence (SE)	Mean adherence difference (SE)	
4-day	0.93 (0.005)	0.81 (0.04)	0.12 (0.04)	0.003
7-day	0.96 (0.003)	0.84 (0.03)	0.11 (0.03)	<0.001
14-day	0.96 (0.003)	0.82 (0.04)	0.14 (0.04)	<0.001
30-day	0.97 (0.002)	0.89 (0.02)	0.08 (0.02)	<0.001
60-day	0.98 (0.001)	0.94 (0.01)	0.04 (0.01)	<0.001

b. Percentage of participants who reported missing a dose for each time frame by viral load status among HIV-infected patients in clinical care (N=1099). Chi-square tests determined the p-value.

HIV viral load				
	Undetectable	Detectable		p value
Timeframe	% Reporting a missed dose	% Reporting a missed dose	Difference in % reporting a missed dose	
4-day	21	44	23	<0.001
7-day	24	53	29	<0.001
14-day	35	68	34	<0.001
30-day	46	79	33	<0.001
60-day	53	79	26	<0.001

SE: standard error

Table V

Correlation between calculated adherence for each timeframe and HIV viral load status both as a binary (detectable vs. undetectable) and continuous outcome among HIV-infected patients in clinical care (N=1099)

Timeframe	Detectable HIV viral load (binary)					HIV viral load (continuous variable, log)				
	All	Patients reporting:				All	Patients reporting:			
		current substance use	current marijuana use	current depression	current risk alcohol use		current substance use	current marijuana use	current depression	current risk alcohol use
4-day	-0.15	-0.21	-0.28	-0.20	-0.22	-0.17	-0.22	-0.34	-0.23	-0.25
7-day	-0.22	-0.26	-0.36	-0.27	-0.23	-0.24	-0.27	-0.42	-0.31	-0.27
14-day	-0.25	-0.35	-0.38	-0.25	-0.24	-0.27	-0.34	-0.45	-0.28	-0.26
30-day	-0.24	-0.26	-0.35	-0.23	-0.17	-0.25	-0.25	-0.39	-0.25	-0.19
60-day	-0.21	-0.14	-0.27	-0.21	-0.03	-0.21	-0.12	-0.31	-0.22	-0.03

Bolded correlations are statistically significantly different from 0 at $p < 0.05$

Posterior probabilities* of the best fitting statistical model for estimating associations between adherence and viral load including adherence from each timeframe using a Bayesian model averaging approach among HIV-infected patients in clinical care (N=1099)

Table VI

Timeframe	Undetectable HIV viral load (binary)					HIV viral load (continuous variable, log)				
	Patients reporting:					Patients reporting:				
	All	current substance use	current marijuana use	current depression	current hazardous alcohol use	All	current substance use	current marijuana use	current depression	current hazardous alcohol use
	% in model	% in model	% in model	% in model	% in model	% in model	% in model	% in model	% in model	% in model
4-day	0	5	6	9	24	0	5	4	5	22
7-day	9	10	39	62	26	0	5	7	89	49
14-day	59	90	45	20	27	100	100	100	16	47
30-day	39	15	22	13	14	9	14	8	5	12
60-day	6	7	7	10	10	5	23	17	5	50

* Posterior probabilities are directly interpretable as the probability of a predictor being in the model given the data