

# A Simple, Dynamic Measure of Antiretroviral Therapy Adherence Predicts Failure to Maintain HIV-1 Suppression

Robert Gross,<sup>1</sup> Benita Yip,<sup>5</sup> Vincent Lo Re III,<sup>1</sup> Evan Wood,<sup>3,5</sup> Christopher S. Alexander,<sup>5</sup> P. Richard Harrigan,<sup>5</sup> David R. Bangsberg,<sup>2</sup> Julio S. G. Montaner,<sup>3,5</sup> and Robert S. Hogg<sup>4,5</sup>

<sup>1</sup>Division of Infectious Diseases, Department of Medicine, Center for Clinical Epidemiology and Biostatistics, Center for Education and Research in Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania; <sup>2</sup>Epidemiology and Prevention Interventions Center, Division of Infectious Diseases and the Positive Health Program, San Francisco General Hospital, San Francisco, California; Departments of <sup>3</sup>Medicine and <sup>4</sup>Health Care and Epidemiology, Faculty of Medicine, University of British Columbia, and <sup>5</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

**Background.** High levels of antiretroviral therapy adherence are important for human immunodeficiency virus type 1 (HIV-1) suppression, yet the magnitude of adherence required to maintain it is less well characterized. Furthermore, methods to accommodate changes in adherence over time are lacking. In the present study, our objective was to determine the magnitude of antiretroviral therapy adherence needed to maintain HIV-1 suppression by use of a time–updated adherence measure that has the potential to be of use in a clinical setting.

**Methods.** We examined a population-based cohort of HIV-1–infected subjects  $\geq 18$  years of age, residing in British Columbia, Canada, who started receiving antiretroviral therapy between 1 August 1996 and 30 September 2003, who had at least 2 consecutive viral loads  $< 500$  copies/mL and who had prescriptions filled at least 3 times during a follow-up period ending 30 September 2004. Virological failure was defined as the second of 2 consecutive viral loads  $> 1000$  copies/mL. Cox proportional hazards model was used to determine the relationship between virological failure and refill-based, time–updated surrogate measure of adherence.

**Results.** Among the 1634 participants  $\geq 18$  years of age who initiated triple combination therapy during the study, 606 virological failure events were identified. In multivariate analyses, subjects with  $\leq 95\%$  adherence were 1.66 (95% confidence interval, 1.38–2.01) times more likely to experience virological failure than those with  $> 95\%$  adherence.

**Conclusions.** The highest levels of antiretroviral therapy adherence are associated with higher rates of maintained virological suppression. This simple, dynamic surrogate measure of adherence overcomes the limitation of single-point-in-time calculations of adherence and may be useful in real time to determine whether an individual is exhibiting incomplete adherence.

The importance of adherence to antiretroviral therapy (hereafter “adherence”) for achieving undetectable viral loads, for increasing CD4 cell counts, and for overall survival in HIV-1–infected individuals has become clear during the past decade [1–4]. Unfortunately, there are currently no feasible methods to monitor for risk of

virological failure in routine clinical practice. Such a measure would ideally be simple to calculate and easily incorporated into clinical practice so as to alert the care providers of the need for intervention before virological

Received 25 January 2006; accepted 5 June 2006; electronically published 12 September 2006.

Presented in part: 21st Annual International Conference on Pharmacoepidemiology, 24 August 2005, Nashville, Tennessee (abstract 413).

Reprints or correspondence: Dr. Robert Gross, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, 804 Blockley Hall, 423 Guardian Dr., Philadelphia, PA 19104-6021 (rgross@cceb.med.upenn.edu).

**The Journal of Infectious Diseases** 2006;194:1108–14

© 2006 by the Infectious Diseases Society of America. All rights reserved.  
0022-1899/2006/19408-0011\$15.00

Potential conflicts of interest: The following authors have received honoraria, travel grants to attend conferences, and research grants and contracts from pharmaceutical companies working in the area of HIV/AIDS: R.G. (GlaxoSmithKline, Bristol-Myers Squibb, Agouron), R.S.H. (Merck, Abbott, GlaxoSmithKline), V.L.R. (Bristol-Myers Squibb), J.S.G.M. (Abbott, Boehringer Ingelheim, BMS, Gilead Sciences, GlaxoSmithKline, Hoffman–La Roche, Janssen-Ortho, Merck Frosst, Pfizer, Tibotec, Trimeris), C.S.A. (GlaxoSmithKline), and D.R.B. (Pfizer, Bristol-Myers Squibb, Abbott, GlaxoSmithKline). All other authors report no conflicts of interest.

Financial support: Michael Smith Foundation for Health Research (Senior Scholar Award to R.S.H.); Canadian Institutes of Health Research (peer-reviewed grant); National Institutes of Health (research grant K08-MH01584 to R.G.); University of Pennsylvania AIDS Clinical Trials Unit (grant U01-AI32783 to R.G.); University of Pennsylvania Center for AIDS Research (grant P30-AI45008 to R.G.); Agency for Healthcare Research and Quality Centers for Education and Research on Therapeutics (cooperative agreement grant HS10399 to R.G.).

failure. Although self-reports can serve this function, they are known to be specific but not sensitive to nonadherence [5] and require subjects to interface with the clinical care team. A refill-based approach does not require subjects to be interviewed and has already been shown to be a valid measure of adherence [5–7]. However, to date, it has been assessed only over a single interval per subject. This is less clinically useful because an individual's adherence changes over time, and, therefore, summarizing adherence over long time frames (e.g., over the course of 1 year [3]) is unlikely to be useful as a real-time measure for alerting providers to their patients' nonadherence. Therefore, we undertook this study to assess whether refill data could be used to calculate a simple, dynamic measure of adherence. In turn, we sought to describe the magnitude of pharmacy-refill adherence needed to maintain undetectable viral loads with individuals who have already achieved initial viral suppression. If high levels of adherence are needed to maintain undetectable viral loads in a large proportion of individuals, then early identification of subjects whose adherence is shown to be faltering by the dynamic pharmacy-refill measure may help in forestalling the ensuing virological failure.

## SUBJECTS AND METHODS

**Study setting.** The distribution and the population-based monitoring of antiretroviral therapy in British Columbia has been extensively described in the literature [3, 8, 9]. Since 1986, 6305 HIV-1-infected men and women have ever received antiretroviral therapy. Prescriptions are distributed through several designated pharmacies or through one of 1200 or more physicians who have ever prescribed antiretroviral therapy. Although the majority of HIV-1-infected men and women who have received therapy are from Vancouver or the surrounding region, eligible treatment recipients have come from all regions in the province.

Since October 1992, the distribution of antiretrovirals has been the responsibility of the HIV/AIDS Drug Treatment Program of the British Columbia Centre for Excellence in HIV/AIDS (hereafter, "the Centre"). The Centre distributes antiretrovirals on the basis of guidelines generated by the Therapeutic Guidelines Committee, which is made up of physicians, pharmacists, virologists, health service researchers, and economists [10]. Because of the anonymous administrative nature of the database, patient consent for inclusion is not required. The Centre's HIV/AIDS Drug Treatment Program has received approval from the University of British Columbia Ethics Review Committee at its St. Paul's Hospital site. The program also conforms with the province's Freedom of Information and Protection of Privacy Act.

**Data collection.** All antiretroviral therapy recipients in the province are entered into an Oracle-based monitoring and evaluation reporting system that uses standardized indicators to

prospectively track the antiretroviral use and clinical and health status of HIV-1-infected individuals. Physicians enrolling an HIV-1-infected individual into the system must complete a drug request enrollment prescription form, which compiles information on the applicant's address, HIV-1-specific drug history, CD4 cell counts, plasma HIV-1 RNA levels, current drug requests, and follow-up physician data. Typically, persons receiving antiretroviral therapy are assessed by physicians at least once every 3 months, at which time prescriptions are renewed or modified. At the time of the first antiretroviral refill, subjects are asked to provide informed consent for accessing electronic medical records and to complete a participant survey, which elicits information on sociodemographic characteristics and clinical and health status. At the same time, the treating physicians are asked to complete a form using the World Health Organization (WHO) clinical staging system [11].

The Centre recommends that plasma HIV-1 RNA levels and CD4 cell counts be monitored at baseline, 4 weeks after starting antiretroviral therapy, and every 3 months thereafter. Plasma HIV-1 RNA levels were determined using the Roche Amplicor Monitor assay (versions 1.0 and 1.5; Roche Diagnostics) via either the standard method or the ultrasensitive adaptation. CD4 cell counts were measured by flow cytometry, followed by fluorescent monoclonal antibody analysis (Beckman Coulter).

**Study subjects.** All HIV-1-infected subjects in the current study were entered into the Centre's monitoring and evaluation system when they were first prescribed antiretrovirals. Eligible study subjects were  $\geq 18$  years of age, achieved at least 2 consecutive HIV-1 viral loads  $< 500$  copies/mL, and were receiving antiretroviral therapy with prescriptions filled at least 3 times since initial viral load suppression. Subjects were first given triple combination therapy between 1 August 1996 and 30 September 2003 and had their CD4 cell counts and plasma HIV-1 RNA levels measured within 6 months before the first antiretroviral therapy start date. Study data from eligible subjects were extracted from the Centre's HAART (highly active antiretroviral therapy) Observational Medical Evaluation and Research cohort and were followed up through 30 September 2004.

**Outcome measure.** The primary end point in this analysis was time to virological failure, defined as the time to plasma viral load  $\geq 1000$  copies/mL on at least 2 consecutive measurements. This virological cutoff was chosen because it is used clinically to define whether an individual is maintaining virological response [12] and because there is ongoing debate as to the significance of lower quantifiable viral loads [13–16]. The time to virological failure was defined as the interval of time between the first of 2 consecutive viral loads  $< 500$  copies/mL after initiating therapy and the time of the second of 2 consecutive viral loads  $\geq 1000$  copies/mL.

The event date was chosen to be the date of the second of 2 consecutive viral loads  $\geq 1000$  copies/mL because a single viral load is insufficient evidence to confirm treatment failure; that is, the time of the second viral load  $\geq 1000$  copies/mL is the time at which a provider identifies an individual as clinically having experienced treatment failure.

**Adherence and other exposure measures.** The adherence measure was based on medications dispensed, not prescribed; this is also commonly referred to as “refill adherence/compliance.” Subjects received new prescriptions at various time intervals ranging from monthly to, at most, every 3 months. Adherence was assessed over multiple time intervals per subject. An adherence interval was defined as the duration between 3 refills, as depicted in figure 1. The 3 refills represent 2 contiguous refill periods (figure 1), and this period was chosen because of concerns that shorter periods may not reflect a sufficiently stable measure of an individual’s pill-taking behavior [5].

The intended duration (days supplied) varied from subject to subject and within subjects over time; that is, prescriptions early in therapy (i.e., first months) generally provided 30 days’ supply. Refills later in therapy were generally extended to 60 days’ and then 90 days’ supply if the subjects returned appropriately for refills and evidenced a virological response.

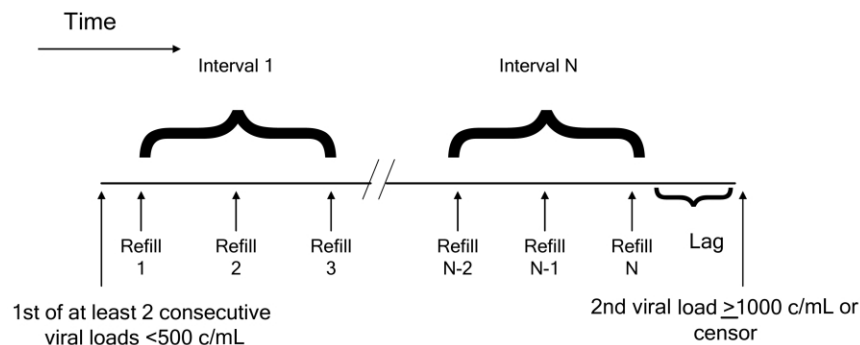
Adherence was defined as days’ supply of medications dispensed divided by days between prescription fills (expressed as a percentage) [17]. Although patients with undetectable viral loads less commonly have medications changed, the regimens can change because of toxicity or other medical reason. These changes can result in staggering of refills, which would stagger the measurement of adherence. Therefore, no index drug was used. Rather, any prescription for antiretroviral medication filled  $>10$  days after a prior antiretroviral drug prescription was filled was considered a refill. If any antiretroviral was dispensed within 10 days after a prior fill, only the earlier fill was used to represent the start of that refill period. Furthermore, a win-

dow period of 30 days was allowed before classifying a subject as  $<100\%$  adherent, so as to account for potential stockpiles at home or provider-prescribed temporary medication stoppage (e.g., for adverse effects, medical procedures, etc.); that is, each subject was each subject was allowed a 30-day grace period for which a  $<30$ -day gap between refills was considered continuous therapy. In secondary analyses, this grace period was removed in the calculation of adherence, so as to determine the impact that it had on the results. Of note, although refill-derived adherence can be  $>100\%$  if subjects obtain refills before the expected refill dates, we truncated the adherence measure at 100%.

The following baseline explanatory variables were also measured for inclusion as potential confounders of the relation between adherence and virological failure: age, sex, CD4 cell count, plasma HIV-1 RNA level, prior AIDS diagnosis, protease inhibitor use, current or past injection drug use, subject’s physician’s experience with HIV-1 treatment (defined as the number of HIV-1-infected patients the physician had previously treated at the time the study subject was first prescribed antiretrovirals by the HIV/AIDS Drug Treatment Program), and start of antiretroviral therapy after August 1997 (the time at which therapeutic guidelines changed so that triple combination HAART was available to all with baseline viral loads  $>5000$  copies/mL or CD4 cell counts  $<500$  cells/mm<sup>3</sup>).

**Statistical analyses.** The analyses included 2 definitions of the outcome: whether the subject had a virological failure at the end of the study period and time to virological failure. Time zero in the time to failure analysis was the first of at least 2 viral loads  $<500$  copies/mL. The event date was the second of at least 2 consecutive viral loads  $\geq 1000$  copies/mL. Event-free subjects were right censored at the last viral load  $<1000$  copies/mL until 30 September 2004.

The analysis included adherence in 4 different ways: (1) dichotomized at  $\leq 95\%$  or  $>95\%$  [2] and included only for the



**Figure 1.** Schema for adherence assessment. Small arrows represent prescription refill dates. Intervals represent the time between temporally adjacent refill periods. Interval N represents the final adherence interval before the event date or censor date. The lag duration is the time from the final refill date to the event date. Adherence was calculated for each interval and was defined as follows: (days supply between refill date 1 and date 3)/(duration of interval)  $\times 100\%$ .

**Table 1. Associations between baseline variables and adherence in subjects receiving antiretroviral therapy with at least 2 consecutive viral loads <500 copies/mL.**

Variable	Value in subject with		P
	>95% adherence during final interval (n = 1379)	≤95% adherence during final interval (n = 255)	
Male sex	1166 (84.6)	210 (82.4)	.376
History of injection drug use	303 (22.0)	80 (31.4)	.001
AIDS diagnosis	235 (17.0)	37 (14.5)	.319
Protease inhibitor use	820 (59.5)	183 (71.8)	<.001
Age, median (IQR), years	39.0 (33.4–45.8)	37.6 (32.3–43.8)	.023
CD4 cell count, median (IQR), cells/mm <sup>3</sup>	200 (80–340)	200 (90–370)	.847
Plasma viral load, median (IQR), log <sub>10</sub> copies/mL	>5 (4.68 to >5)	>5 (4.79 to >5)	.208
Physician's experience, <sup>a</sup> median (IQR)	69 (8–176)	38 (4–123)	<.001

**NOTE.** Data are no. (%) unless otherwise indicated. IQR, interquartile range.

<sup>a</sup> Defined as the no. of HIV-1-infected patients the subject's physician had previously treated at the time the subject was first prescribed antiretrovirals by the HIV/AIDS Drug Treatment Program.

subject's final observed adherence period; (2) categorized as >95%, 70%–95%, and <70% [4] and included only for the subject's final observed adherence period; (3) dichotomized as ≤95% or >95% and included as a time-varying variable for each of the subjects' observed adherence periods; and (4) as a continuous measure in 10% decrements as a time-varying variable for each of the subjects' observed adherence periods.

Cox proportional hazards models were constructed for the association between adherence as a time-varying variable and time to virological failure. The relation between adherence category during the final interval (figure 1, interval N) and the proportion of subjects maintaining suppression was assessed using the test for trend.

Analyses were performed using SAS software (version 8.02; SAS Institute). All tests of significance were 2-sided, with *P* < .05 used as the threshold of statistical significance.

## RESULTS

Between 1 August 1996 and 30 September 2004, a total of 2217 antiretroviral-naïve subjects ≥18 years of age initiated triple combination therapy consisting of 2 nucleosides plus a protease inhibitor (boosted or nonboosted) or a nonnucleoside reverse-transcriptase inhibitor, and 1715 (77.4%) achieved confirmed suppression (i.e., at least 2 consecutive viral loads <500 copies/mL). Of the 1715 eligible subjects, 1634 (95.3%) met the minimum requirement of having 3 refill dates after suppression and were, therefore, included in the study.

Subjects included achieved their first 2 consecutive viral load measures <500 copies/mL over a median interval of 93 days (interquartile range [IQR], 50–189 days). At the time of initiation of antiretroviral therapy, the median age was 39 years (IQR, 33–46 years), the median CD4 cell count was 200 cells/mm<sup>3</sup> (IQR, 80–350 cells/mm<sup>3</sup>), the median plasma HIV-1 RNA

level was >100,000 copies/mL (IQR, 48,000 to >100,000 copies/mL), and the subjects' physicians had cared for a median of 63 patients with HIV-1 infection (IQR, 7–167 patients). There were 383 (23.4%) subjects who had a history of injection drug use. A total of 272 (16.6%) study subjects had a prior diagnosis of AIDS. The overall median follow-up time for study subjects was 29 months (IQR, 15–49 months). As of 30 September 2004, a total of 606 (37.1%) subjects experienced a virological rebound during the observation period, with a median time to rebound of 22 months (IQR, 13–39 months).

In table 1, we compare the baseline characteristics between subjects with >95% adherence at the final interval and those with ≤95% adherence. Those with >95% adherence over the final interval were less likely to be injection drug users, were less likely to have received a protease inhibitor in the first regimen, were slightly older (median age, 39.0 vs 37.6 years; *P* = .023), and were more likely to have received follow-up from physicians with more HIV-1 treatment experience (median no. of HIV-1-infected patients under the physician's care, 69 vs. 38; *P* < .001) than subjects with ≤95% adherence at the final time point.

Overall, adherence was high, with 1379 (84.4%) of the subjects having >95% adherence over the final interval. When the final adherence period was categorized as <70%, 70%–95%, or >95%, there was a statistically significant trend toward a higher proportion of subjects having virological failures as adherence decreased. There were 465 (33.7%) subjects with virological failure among those with >95% adherence, whereas 34 (40.5%) of the 84 with 70%–95% adherence had virological failure, and 107 (62.6%) of the 171 with <70% adherence had virological failure (*P* for trend < .001).

Table 2 displays the baseline characteristics and time-updated adherence measures and their associations with virological re-

**Table 2. Univariate and multivariate analyses of the baseline and time-updated factors associated with time to virological failure.**

Variable	Hazard ratio (95% CI)	
	Crude	Adjusted
Age, years	0.98 (0.97–0.99)	0.98 (0.98–0.99)
Male sex	0.76 (0.62–0.95)	0.89 (0.72–1.12)
Protease inhibitor regimen	1.05 (0.88–1.24)	...
Physician experience <sup>a</sup> /100 patients	0.96 (0.89–1.04)	...
AIDS diagnosis	0.66 (0.52–0.84)	0.84 (0.65–1.08)
Injection drug use	1.52 (1.28–1.81)	1.37 (1.15–1.63)
Treatment started after August 1997	1.31 (1.07–1.61)	1.40 (1.13–1.73)
Baseline CD4 cell count/100-cell/mm <sup>3</sup> decrement	0.91 (0.88–0.94)	0.93 (0.89–0.96)
Baseline plasma viral load $\geq$ 100,000 copies/mL	0.87 (0.74–1.02)	1.06 (0.89–1.26)
Time-updated adherence $\leq$ 95%	1.78 (1.47–2.15)	1.66 (1.38–2.01)

**NOTE.** CI, confidence interval.

<sup>a</sup> Defined as the no. of HIV-1-infected patients the subject's physician had previously treated at the time the subject was first prescribed antiretrovirals by the HIV/AIDS Drug Treatment Program.

bound, based on Cox proportional hazards models. After controlling for all the other factors in multivariate analyses, younger age, higher baseline CD4 cell count, starting treatment after August 1997, and being an injection drug user ever were all significantly associated with the likelihood of virological failure, irrespective of adherence. Time-updated adherence  $\leq$ 95% was strongly associated with an increased hazard of rebound, with a 66% increased risk (hazard ratio [HR], 1.66 [95% confidence interval {CI}, 1.38–2.01]) in multivariate models when compared against those with adherence  $>$ 95%. When time-dependent adherence was expressed as a continuous variable in these models, there was an 11% increased risk of failure for every 10% decrease in adherence (HR, 1.11 [95% CI, 1.07–1.15]). In secondary analyses, the grace period was removed, and adherence for each interval was recalculated. Time-updated adherence  $\leq$ 95% remained associated with an increased hazard of rebound in fully adjusted models, although to a somewhat attenuated degree (HR, 1.42 [95% CI, 1.21–1.68]).

It is important to note that the time-updated measure of adherence was not assessed at the exact time of virological rebound. Because the adherence measure was based on refill dates and refills were not linked to viral load measurements, there was a time lag between the adherence measure and the event/censor date (see figure 1). This lag was a median of 84 days (IQR, 41–161 days).

## DISCUSSION

This study demonstrates that, among individuals with prior virological suppression, high adherence, as estimated using a refill-based, time-updated measure, is associated with a lower risk of confirmed virological failure. Furthermore, our findings show that the high levels of adherence required for *maintaining* virological suppression are similar to the levels needed to

*achieve* viral suppression in individuals newly starting therapy [1, 2, 18]. Importantly, as in prior work [1, 2], we did not identify a clear threshold effect for adherence; that is, greater adherence conferred a greater likelihood of maintained suppression even below the 95% threshold. As such, although the highest levels of adherence are an appropriate ideal, if not attainable, incremental increases in adherence at levels  $<$ 95% should still be viewed as a worthwhile goal.

Our results demonstrate that the dynamic measurement approach to adherence is associated with virological outcome. This use of the adherence measure is unique in that it is able to account for changes in an individual's adherence pattern over time. This time-updated method overcomes the problem of other approaches that assign an individual's adherence on the basis of a single time point or summarized over the entire study period, thereby failing to address the important dynamic of adherence change over time.

The novel use of this time-varying adherence measure opens the possibility of innovative uses of this technique. By having a measure of adherence that is frequently updated, it is possible that clinicians can use this tool as an early warning system alerting them to their patients' nonadherence before virological failure. In essence, this measure could operate as a form of "virtual" directly observed therapy. The mechanism by which directly observed therapy improves adherence has been well described [19]. Only testing this strategy in the setting of a randomized clinical trial will confirm whether this theoretical advantage is real.

There are several features of the present study that should be highlighted. First, the present study was performed within a province-wide treatment program in which all subjects had access to medical attention, combination antiretroviral therapy, and laboratory monitoring free of charge. We are confident,

therefore, that our results are not influenced by access-to-therapy-related issues, which have often compromised the interpretation of similar population or cohort-based studies. Second, despite the potential limitations that our measure of adherence is only a surrogate marker of actual pill taking and had not previously been used in a time-updated manner, surrogate measures of adherence have been validated in several studies to date [3–6], have been found to be associated with virological suppression to a magnitude similar to results obtained by use of microelectronic monitors, and have been correlated with untimed plasma antiretroviral concentrations [8] and survival [3]. Third, although the highest levels of adherence were associated with the highest rates of suppression, there were still substantial proportions of subjects who are able to adhere to lesser degrees and maintain suppression. Therefore, our conclusion that high levels of adherence are desirable is relevant only on a population basis. Fourth, despite allowing a 30-day grace period when categorizing a subject as <100% adherent, we still showed a strong association between the measure and outcome. If we were to eliminate this allowance, the measure may be even more sensitive to nonadherence. However, it would likely increase the misclassification of individuals who have been following prescribed orders to stop taking the medications temporarily or who have stockpiles at home. Such misclassification would explain the slightly attenuated results obtained when the grace period was removed in the secondary analysis. Fifth, the number of days supplied increased from 30 days to up to 90 days if subjects exhibited virological responses over time. These longer refill intervals are likely to result in detection of nonadherence later than shorter refill intervals would because the adherence calculation requires the refill dates. Therefore, our measure may be less sensitive to nonadherence for subjects who are switched to longer refill intervals. Sixth, when regimens changed, subjects would be considered adherent when in fact they were not taking the medications but had not notified the pharmacist that they had stopped taking the medications. These regimen changes unknown to the pharmacists may have resulted in overestimates of adherence. Seventh, because this study focused exclusively on subjects who had achieved virological suppression, the result cannot be generalized to the relation between adherence and virological control in subjects who never achieve suppression. Finally, despite a time lag between the date of adherence measurement and the event date, we were still able to show a relation between adherence and outcome. Because the suboptimal adherence in the present study began, on average, 2–3 months before confirmed virological failure, it is possible that this measure of adherence may be clinically useful as a data element for incorporation into strategies for improving adherence.

In conclusion, the present study demonstrates that high levels of adherence result in the highest proportion of subjects main-

taining suppression of viral load over time. Furthermore, our results support the conclusion that incorporating refill-based measures of adherence into clinical practice may allow for the early identification of subjects destined to experience virological failure because of poor adherence. Consideration should be given to automating this measure and providing it to the clinical care team so as to alert them to occult nonadherence, with the goal of intervening before virological failure. This strategy is ripe for testing in a clinical trial.

## Acknowledgments

We thank Jennifer Adachi, Bonnie Devlin, Elizabeth Ferris, Nada Gataric, Kelly Hsu Myrna Reginaldo, and Peter Vann for their research and administrative assistance.

## References

1. Gross R, Bilker WB, Friedman HM, Strom BL. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS* **2001**; 15:2109–17.
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**; 133:21–30.
3. 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 × 10(9) cells/L. *Ann Intern Med* **2003**; 139:810–6.
4. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. The impact of adherence on CD4 cell count responses among HIV-infected patients. *J Acquir Immune Defic Syndr* **2004**; 35:261–8.
5. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. *J Clin Epidemiol* **2004**; 57:1107–10.
6. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. *J Acquir Immune Defic Syndr* **2000**; 23:360–1.
7. Kitahata MM, Reed SD, Dillingham PW, et al. Pharmacy-based assessment of adherence to HAART predicts virologic and immunologic treatment response and clinical progression to AIDS and death. *Int J STD AIDS* **2004**; 15:803–10.
8. Alexander CS, Asselin JJ, Ting LS, et al. Antiretroviral concentrations in untimed plasma samples predict therapy outcome in a population with advanced disease. *J Infect Dis* **2003**; 188:541–8.
9. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* **2001**; 286:2568–77.
10. British Columbia Centre for Excellence in HIV/AIDS. Therapeutic guidelines for the treatment of HIV/AIDS and related conditions. Vancouver: University of British Columbia, Ministry of Health, British Columbia, **1999**.
11. Proposed 'World Health Organization staging system for HIV infection and disease': preliminary testing by an international collaborative cross-sectional study. The WHO International Collaborating Group for the Study of the WHO Staging System. *AIDS* **1993**; 7:711–8.
12. Yeni PG, Hammer SM, Carpenter CC, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *JAMA* **2002**; 288:222–35.
13. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to < 400 copies/ml. *AIDS* **2002**; 16:1521–7.
14. Havlir DV, Bassett R, Levitan D, et al. Prevalence and predictive value

- of intermittent viremia with combination HIV therapy. *JAMA* **2001**; 286:171–9.
15. Lo Re V 3rd, Gasink L, Kostman J, Leonard D, Gross R. Natural history of patients with low-level HIV viremia on antiretroviral therapy. *AIDS Patient Care STDS* **2004** 18:436–42.
  16. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA* **2005**; 293:817–29.
  17. Steiner JE, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* **1997**; 50:105–16.
  18. 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**; 14:357–66.
  19. Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. *Lancet* **2000**; 355:1345–50.