

Similar Adherence Rates Favor Different Virologic Outcomes for Patients Treated with Nonnucleoside Analogues or Protease Inhibitors

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(See the editorial commentary by Knobel on pages 164–6)

Background. This prospective study verified the effect of adherence on the risk of virologic failure.

Methods. At enrollment in the study, a total of 543 patients who were following a steady (duration, ≥ 6 months) and effective (viral load, < 50 human immunodeficiency virus [HIV] RNA copies/mL) regimen of highly active antiretroviral therapy (HAART) completed a self-reported questionnaire derived from the Adult AIDS Clinical Trials Group Adherence Follow-up Questionnaire. Patients were followed up for the subsequent 6 months to document virologic failure, which was defined as 2 consecutive viral load measurements of > 500 HIV RNA copies/mL.

Results. Only the type of treatment and the adherence rate at baseline were significantly associated with the virologic end point. Among patients who reported an adherence rate of $\leq 75\%$, the rate of virologic failure was 17.4%; this rate decreased to 12.2% for patients whose adherence rate was 76%–85%, to 4.3% for patients whose adherence rate was 86%–95%, and to 2.4% for patients whose adherence rate was $> 95\%$. When analysis was adjusted according to the type of regimen received, patients who were receiving protease inhibitor (PI)–based HAART and who had an adherence rate of up to 85% had a virologic failure rate of $> 20\%$, whereas, only for patients who were receiving nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based HAART and who had an adherence rate of $\leq 75\%$, the virologic failure rate was $> 10\%$. For the comparison of NNRTI-treated patients and PI-treated patients with an adherence rate of 75%–95%, the odds ratio was 0.157 (95% confidence interval, 0.029–0.852). The number of pills and daily doses received correlated with the reported adherence rate.

Conclusions. Patients receiving NNRTIs report a higher rate of adherence than do patients receiving PIs. Adherence is significantly influenced by the number of pills and daily doses received. Low adherence is a major determinant of virologic failure; however, different therapies have different cutoff values for adherence that determine a significant increment of risk.

The positive influence of HAART on survival, disease progression, immune function, and overall quality of life can be tempered by reduced adherence. Many variables, including depression, alcohol and drug use, work schedules, changes in daily routines, and decrease in cognitive function may have an influence on the ability

of an individual to adhere to HAART regimens. The complicated schedules of HAART regimens may also have a negative effect on adherence. The association between low adherence and virologic outcome has been clearly established for therapies that contain protease inhibitors (PIs) [1, 2]. For such regimens, the adherence rate needs to be $> 95\%$ to prevent virologic failure [3]. Much less is known about therapies that involve the use of nonnucleoside reverse-transcriptase inhibitors (NNRTIs). Reducing the pill burden or the number of daily doses associated with an NNRTI-based combination may possibly improve adherence [4, 5], but the adherence rate that ensures a positive virologic outcome is still unclear.

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PATIENTS AND METHODS

The present study was conducted in an infectious diseases outpatient clinic in northern Italy (Ospedali Riuniti, Bergamo). Consecutive patients were enrolled in a prospective cohort study. Patients eligible for participation in the study had been receiving a steady HAART regimen for ≥ 6 months and, at enrollment, had been found to have an HIV RNA level below the limit of detection (i.e., 50 HIV RNA copies/mL).

At enrollment, all patients completed a self-reported questionnaire to ascertain adherence to antiretroviral medications. The adherence measures used in the present trial were adapted from those used in the Adult AIDS Clinical Trials Group (AACTG) survey, which asks patients how many doses of medication they missed during the previous 4 days [6]. To collect data about how patients respected the timing of the administration of their doses of medication, we substituted use of a visual analogue scale based on a 10-cm horizontal line for use of the 5-point scales (i.e., “never” [0], “some of the time” [25%], “about half of the time” [50%], “most of the time” [75%], and “all of the time” [100%]) used in the AACTG questionnaire [7]. Visual analogue scales are sensitive instruments with which to determine patients’ perceptions of descriptive terms that are widely used in medicine [8] and to study the quality of life [9] of patients infected with HIV. Visual analogue scales recently have been validated for the assessment of adherence to HAART [10]. Overall, “100% adherence” was defined as taking all doses and numbers of pills at the time interval prescribed for current medications. Adherence that was $<100\%$ was graded by adjusting the percentage of missed doses or pills for the error in the timing of dose administration. The data on adherence at baseline that were derived from the self-reported questionnaire were cross-linked to the demographic and therapeutic data extracted from the clinic’s computerized database of patient records.

For the 6 months subsequent to enrollment in the study, patients were prospectively followed up on the basis of their HIV RNA blood levels, which were measured using the assay routinely available at the study center; the lower limit of detection of this assay was 50 HIV RNA copies/mL. A viral load of >500 HIV RNA copies/mL, which was confirmed by a successively measured viral load yielding the same result, was considered to denote virologic failure.

The univariate association between variables at baseline and virologic outcome was tested using the χ^2 test or Fisher’s exact test for categorical variables. Pearson’s correlation test and Student’s *t* test were used for continuous variables, unless the variables were not normally distributed, in which case the Kruskal-Wallis and Mann-Whitney *U* tests were used.

Logistic regression (a forward stepwise model) was used for multivariate analyses of the association between variables and

virologic outcome. Variables were selected for inclusion in the multivariate model on the basis of their significance ($P < .05$) in univariate analysis. The magnitude of the univariate association between adherence to medication and virologic outcome and the effect of the type of HAART on this association were expressed as ORs and 95% CIs.

Data were analyzed using SPSS software, version 10.0 for Windows (SPSS). All tests were 2-sided, and $P < .05$ was considered to be statistically significant.

RESULTS

At the baseline visit, 560 patients were interviewed about their adherence to their medications, and they also completed the self-reported questionnaire on adherence. Six patients were excluded from the study because the HIV RNA load determined at their baseline visit was not below the limit of detection (i.e., 50 HIV RNA copies/mL). Eleven other patients were excluded from the study because, during the 6 months after the baseline visit, they either failed to return to the clinic for the programmed controls (i.e., were temporarily lost to follow-up; 2 patients), changed therapy within a simplification program (3 patients), or entered a structured treatment interruption program (6 patients). Therefore, the study included a total of 543 patients.

The characteristics at baseline of the patients included in the study are shown in table 1. All patients were receiving a 3-drug regimen: 76 patients were receiving 3 nucleoside reverse-transcriptase inhibitors (NRTIs), 314 patients were receiving 2 NRTIs and 1 NNRTI (178 were receiving efavirenz, and 136 were receiving nevirapine), and the remaining 153 patients were receiving 2 NRTIs plus either a PI or a boosted PI (12 patients were receiving saquinavir and ritonavir; 63, nelfinavir; 33, indinavir; 12, amprenavir and ritonavir; and 33, lopinavir and ritonavir). To verify the use of drugs according to patient status (i.e., therapeutic [drug] history), we categorized therapies as “first-line therapy” (i.e., the first HAART regimen received by drug-naïve patients), “second-line therapy” (i.e., a HAART regimen received after the receipt of a first HAART regimen and in the presence of alternative therapeutic options), or “salvage therapy” (i.e., a HAART regimen for patients who had exposure to triple-class HAART and who had resistance to ≥ 1 drug in each class). For patients treated with 3 NRTIs, the percentage of patients receiving each category of therapy was as follows: 14.5% received first-line therapy, 61.8% received second-line therapy, and 23.7% received salvage therapy. The percentages of patients receiving first-line, second-line, and salvage therapy were 36.6%, 58.9%, and 4.4%, respectively, among patients receiving NNRTIs, and they were 22.9%, 60.8%, and 16.3%, respectively, among patients receiving PIs ($P < .01$). Furthermore, the percentages of patients who had previously experi-

Table 1. Characteristics, at baseline, of patients included in the analysis.

Characteristic	All patients (<i>n</i> = 543)	Patients with virologic failure (<i>n</i> = 29)	<i>P</i> ^a
Male	414 (76.2)	24 (82.8)	.504
Age, mean years ± SD	40 ± 6.9	39 ± 5.0	.468
Risk factor for HIV infection			.759
Injection drug use	246 (45.3)	14 (48.3)	
Heterosexual sex	206 (37.9)	12 (41.4)	
Homosexual sex	80 (14.7)	3 (10.3)	
Other	1 (2.0)	0	
CDC 1993 classification			.581
AIDS	328 (60.4)	18 (62.0)	
Non-AIDS	215 (39.6)	11 (38.0)	
Duration of HAART, mean months ± SD	63.7 ± 44.2	61.6 ± 42.6	.702
HAART regimens received, mean no. ± SD	2.9 ± 2.4	2.7 ± 1.9	.456
Category of HAART received			.442
First-line	161 (29.7)	9 (31.0)	
Second-line	325 (59.9)	19 (65.5)	
Salvage	57 (10.5)	1 (3.4)	
Previous virologic failure	143 (26.3)	6 (20.7)	.665
Duration of current HAART regimen, mean months ± SD	21.3 ± 16.5	21.6 ± 17.9	.764
Pills received for current HAART regimen, mean no. ± SD	6.9 ± 3.5	7.4 ± 3.3	.352
Type of HAART received			.037
3 NRTIs	76 (14.0)	5 (17.2)	
2 NRTIs + 1 NNRTI	314 (57.8)	9 (31.0)	
2 NRTIs + 1 PI	153 (28.2)	15 (51.7)	
Adherence rate, mean % ± SD	92.3 ± 12.5	78.9 ± 22.6	<.0001

NOTE. Data are the no. (%) of patients, unless otherwise indicated. Data for categorical variables are presented as the no. (%) of patients, and data for continuous variables are presented as mean values ± SD. CDC, Centers for Disease Control and Prevention (Atlanta, GA); NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

^a Univariate association with the virologic outcome.

enced virologic failure associated with HAART were 26.3%, for patients treated with 3 NRTIs; 21.6%, for patients treated with NNRTIs, and 35.9%, for patients treated with PIs (*P* = .04).

However, when analyzed for their correlation to the virologic end point of the study, only 2 of the variables considered—namely, the type of HAART received and the rate of adherence reported at baseline—showed a statistically significant association in univariate analysis and also maintained the statistical predictive value in multivariate analysis (*P* < .0001, for the adherence rate, and *P* = .037, for the type of HAART received) (table 1). We observed a statistically significant (*P* < .0001) linear association between the reported adherence rate and the rate of virologic failure in the 6 months after the baseline visit (figure 1). Among patients who reported an adherence rate of ≤75%, the rate of virologic failure was 17.4%; this percentage decreased to 12.2% for patients whose adherence rate was 76%–

85%, to 4.3% for patients whose adherence rate was 86%–95%, and to only 2.4% for patients whose reported adherence rate was >95%.

However, when adjusted for the type of regimen—namely, NNRTI- and PI-based HAART (the 2 most-represented drug combinations)—the risk of virologic failure was not equally distributed. Patients who followed a PI-based regimen and who had an adherence rate of up to 85% demonstrated a virologic failure rate of >20%, whereas, only for patients who followed an NNRTI-based HAART regimen and who had an adherence rate of ≤75%, the virologic failure rate was >10% (figure 1). For cumulatively analyzed NNRTI-based therapies, the OR for virologic failure was 0.271 (95% CI, 0.116–0.635), but this result was influenced by and was statistically significant because of the risk observed for patients with intermediate adherence. For patients who were treated with an NNRTI-based regimen and

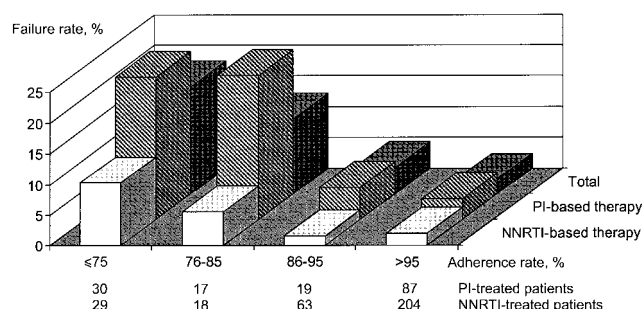


Figure 1. Proportion of patients experiencing virologic failure, according to their reported rate of adherence to a HAART regimen. Data shown are for analysis of adherence to all HAART regimens and for adjusted analysis based on the type of HAART regimen received. NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

who had a low adherence rate ($\leq 75\%$), the OR was 0.379, with the confidence interval embracing the unit (i.e., a risk of 1 [not significant]; 95% CI, 0.088–1.639), whereas, for patients with an adherence rate of $>75\%$, the OR was 0.309 (95% CI, 0.105–0.911). These results were also confirmed when patients with optimal adherence (i.e., 100% adherence) were excluded from analysis (OR, 0.157 [95% CI, 0.029–0.852]).

We observed a statistically significantly different ($P = .018$) adherence rate for patients who received an NNRTI-based therapy (mean adherence rate, 93.6% [95% CI, 92.3%–94.8%]), compared with patients who received a PI-based HAART regimen (mean adherence rate, 89.9% [95% CI, 87.7%–92.0%]). The only 2 parameters that were significantly correlated with the reported adherence rate were the number of pills in the prescribed regimen ($P = .021$) and the number of daily doses that the prescribed regimen required. With respect to these variables, the mean adherence rate was significantly higher for patients receiving once-daily regimens (94.8% [95% CI, 90.2%–99.3%]), compared either with patients receiving a twice-daily regimen (mean adherence rate, 92.0% [95% CI, 90.8%–93.2%]; $P = .042$) or with patients receiving a regimen requiring >2 daily doses (mean adherence rate, 91.9% [95% CI, 89.0%–94.9%]; $P = .009$). The difference in the adherence rates of patients following a twice-daily regimen and patients following a regimen requiring >2 daily doses was not statistically significant ($P = .199$).

DISCUSSION

Of the participants in the present study, more than one-third (36%) reported 100% adherence to the HAART regimen prescribed by their physicians. These data may have resulted from the very strict definition of optimal adherence used in the present study—that is, taking all pills at the right time interval as prescribed. Although rates of adherence to HAART vary considerably from study to study, many studies report adherence

rates of $\sim 60\%$ for their study populations when thresholds of 80%–90% are used to define adherence as acceptable [11, 12]. In the present study, use of an adherence rate of 80% as a threshold value would have led to 69% of the patients having their adherence rate defined as acceptable. Even when the possible tendency of patients to overestimate their adherence is considered, these results are consistent overall, keeping in mind that we selected a population that showed complete control of viral replication. That the cohort in the present study showed complete control of viral replication may explain some other findings. The rate of virologic failure was not influenced by the previous therapeutic experiences of the patients, nor was it influenced by previous virologic failure, both of which are factors that are known to reduce the efficacy of HAART. However, the fact that the design of the study required the selection of patients who had been receiving effective HAART for ≥ 6 months annulled this effect and canceled the differences observed for this characteristic of therapy among the different HAART regimens.

Several aspects of the present study may be highlighted. The enrolled cohort was large and underwent follow-up at a single center. Patients are well characterized regarding their history of disease progression and exposure to antiretroviral drugs. Data were not collected in a monitored clinical trial setting, which further limited the reasons to overreport adherence. The cohort was unselected and included a substantial proportion of former drug users, and it was highly representative of a general population of HIV-infected individuals.

We are aware of several limitations of the present study. First, self-reporting by patients is known to overestimate adherence to therapy. However, the patients' reports of lower adherence to therapy are usually reliable, and the underestimation (resulting from measurement bias) of the number of patients with low adherence would be conservative in our findings. We did not directly investigate the occurrence of "drug holidays" (i.e., voluntary discontinuation of HAART over a brief period), which frequently occur during weekends and which have been discussed as an independent predictor of virologic failure [13, 14]. However, during the pilot study of AACTG adherence instruments, it was found that asking about adherence that occurred during a 4-day period, as we did in the present study, was optimal, because it increased the likelihood of including data for a weekend day in the analysis but still focused on recent adherence and, therefore, maximized the participants' recollection [6, 15].

It is generally accepted that an adherence rate of $>95\%$ is needed to prevent virologic failure [3, 16]. This statement is largely based on previous experience [3] in which older PI-based regimens without boosting were used. How this conclusion directly applies to more-recent PI-based regimens or to treatment schedules not including a PI is still debated.

Nobody doubts that anything inferior to excellent adherence may result in a viral breakthrough or in the emergence of drug-resistant strains. However, absolute adherence, although a reference standard, is very difficult to achieve and maintain. Knowledge of reliable cutoff values for adherence may help clinicians to provide the best advice to their patients. In the present study, approximately one-third of the PI-treated patients were receiving a boosted regimen. Nonetheless, for HAART that included a PI, the results of the present study are quite similar to previously reported data [3], although (1) a slightly lower proportion of virologic failure was observed among patients with similar adherence rates and (2) a possible cutoff value for adherence, indicating a marked increment of the risk of virologic failure, could be drawn at 85% (for a 5.3%–23.5% reduction in the risk of virologic failure).

Results were markedly different for NNRTI-based therapies. The risk of virologic failure was significantly reduced among patients treated either with a nevirapine-based therapy or with an efavirenz-based therapy. In particular, the risk was significantly reduced (OR, 0.157) for patients with adherence that was defined as being in the “gray zone” between very poor adherence (i.e., <75% adherence) and optimal adherence (i.e., 100% adherence). This observation is of particular relevance because patients with such adherence could have a higher risk of developing viral resistance [17, 18]. Why patients who were treated with NNRTI-based regimens reported a higher adherence rate may be explained by the greater convenience of NNRTI-based regimens. A lower number of pills in a prescribed HAART regimen and a lower number of required daily doses were both independent predictors of increased adherence.

It is more difficult to explain why patients who received PIs and who reported a given adherence rate experienced a greater proportion of virologic failure, compared with patients who had the same adherence rate but were treated with an NNRTI. The extremely long half-life of NNRTIs may offer a possible explanation. Single or sporadic dose omissions may result in an adherence rate of 75%–95%, but the same number of omissions may be, at least in part, “forgiven” by the long-lasting concentrations of NNRTIs, especially if the incorrect behavior does not necessarily imply complete omission of the dose but, rather, erroneous timing of dose administration (i.e., a “delayed dose”). In this regard, a recently published study confirms that, when efavirenz is included in the regimen, virologic suppression occurs even after a 7-day period of no therapy and that measurable and active amounts of efavirenz may be still present in blood [19]. The results of the present study are also consistent with the data for smaller cohort studies [20, 21], which also showed how highly nonadherent individuals have a significantly higher risk of developing virologic resistance if they are treated with an NNRTI-based HAART regimen.

A final observation can be derived from the design of the

present study. We assessed adherence in a cross-sectional way and prospectively followed up the patients for the 6 months after the baseline visit occurred. Our measures of adherence therefore refer solely to a precise “time zero.” Nevertheless, these measures predicted, in a linear and statistically significant way, the virologic outcome during the subsequent interval, which was quite wide. It may be inferred that the adherence behavior of a single patient tends to reiterate over time. Simple tools, such as the visual analogue scale that we used, could therefore be part of the clinical routine used to identify those patients who have a greater risk, so as to allow the use of specific educational and control measures to minimize the risk of virologic rebound and HAART failure.

In conclusion, we found that patients treated with NNRTIs reported a greater adherence rate than did patients treated with PIs. Adherence is significantly influenced by the number of pills and daily doses involved in the prescribed regimen. Low adherence is a major determinant of virologic failure; however, different therapies seem to have different cutoff values for adherence that determine a significant increment of risk. In this respect, at least for an intermediate level of adherence (adherence rate, 76%–99%), NNRTI-based regimens appear to be more “forgiving” than PI-based HAART regimens.

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