Limited Patient Adherence to Highly Active Antiretroviral Therapy for HIV-1 Infection in an Observational Cohort Study

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Background: Adherence to highly active antiretroviral therapy (HAART) for human immunodeficiency syndrome type 1 (HIV-1) infection is essential to sustain viral suppression and prevent drug resistance. We investigated adherence to HAART among patients in a clinical cohort study.

Methods: Patients receiving HAART had their plasma concentrations of protease inhibitors or nevirapine measured and completed a questionnaire on adherence. We determined the percentage of patients who reported taking all antiretroviral medication on time and according to dietary instructions in the past week. Drug exposure was compared between patients reporting deviation from their regimen and fully adherent patients. Among patients who received HAART for at least 24 weeks, we assessed the association between adherence and virologic outcome.

Results: A total of 224 of 261 eligible patients completed a questionnaire. Forty-seven percent reported taking all antiretroviral medication on time and according to dietary instructions. Patients who reported deviation from their regimen showed lower drug exposure compared with fully adherent patients (median concentration ratio, 0.81 vs 1.07; P = .001). Among those receiving HAART for at least 24 weeks, patients reporting deviation from their regimen were less likely to have plasma HIV-1 RNA levels below 500 copies/mL (adjusted odds ratio, 4.0; 95% confidence interval, 1.4-11.6) compared with fully adherent patients.

Conclusions: Only half of the patients took all antiretroviral medication in accordance with time and dietary instructions in the preceding week. Deviation from the antiretroviral regimen was associated with decreased drug exposure and a decreased likelihood of having suppressed plasma HIV-1 RNA loads. Patient adherence should remain a prime concern in the management of HIV-1 infection.


Treatment of human immunodeficiency virus type 1 (HIV-1)–infected patients with highly active antiretroviral therapy (HAART) has been shown to be effective with respect to the suppression of plasma HIV-1 RNA below detectable concentrations. However, the effectiveness of HAART to achieve and sustain viral suppression may be hampered by insufficient patient adherence to the antiretroviral regimen. Moreover, suboptimal adherence, allowing ongoing viral replication, facilitates the emergence of HIV-1 variants resistant to the drugs being used. The emergence of drug resistance reduces considerably the treatment options for the individual patient, since cross-resistance exists to a large extent among antiretroviral agents within a therapeutic class. Given the potential for transmission of drug-resistant HIV-1, suboptimal adherence may have significant public health implications.

Adherence to HAART typically includes taking multiple drugs 2 to 4 times a day according to a strict schedule. For several drugs, dietary instructions are necessary. To date, a limited number of studies have investigated the extent to which patients adhere to HAART and have predominantly focused on the proportion of medications taken.

We investigated the extent to which patients report adherence to their antiretroviral regimen, including accurate timing of doses and keeping dietary instructions in a nationwide cohort study in the Netherlands. We compared exposure to protease inhibitors (PIs) and to a nonnucleoside reverse transcriptase inhibitor (NNRTI) between patients who reported taking their antiretroviral medication as prescribed and patients who reported de-
PARTICIPANTS AND METHODS

THE ATHENA PROJECT

From May 1998, consecutive HIV-1–infected patients, 18 years or older, from 22 hospitals in the Netherlands were enrolled in an observational cohort study called the ATHENA project. Eligible patients were either starting or already receiving antiretroviral therapy with at least 1 of the drugs that were licensed in the Netherlands from July 1996, ie, all PIs and NNRTIs, lamivudine, and stavudine. Patients had to be able to complete Dutch or English self-report questionnaires. Plasma concentrations of PIs and nevirapine were determined at routine visits. The study was approved by the institutional review board of all participating centers. All patients gave written informed consent.

ADHERENCE MEASUREMENT

Adherence was assessed by a self-report questionnaire each time plasma concentrations of antiretroviral drugs were determined. Patients were informed that their responses would remain confidential and would have no consequences for their treatment. The completed questionnaire could be returned in a sealed envelope. Patients were asked on which of the past 2 days they had taken all antiretroviral medication, how many days in the past week they had been off schedule by more than 1 hour, and how many days in the past week they had taken their medication according to dietary instructions, if applicable. They were asked about keeping the following dietary instructions: taking didanosine half an hour before or 2 hours after a meal, taking indinavir sulfate 1 hour before or 2 hours after a meal or taking indinavir with a low-fat meal, and taking ritonavir and/or saquinavir mesylate with a meal or within 2 hours after a meal. In addition, patients were asked to what extent their adherence during the past week was comparable with the preceding period. Patients were asked about reasons for nonadherence using a question with 5 response categories and the option for providing additional reasons. Patients could provide more than 1 answer.

PATIENTS

The present study describes patients who completed a questionnaire at the first pharmacokinetic measurement between May 1998 and June 1999. We included patients who were prescribed indinavir (800 mg 3 times a day), nelfinavir mesylate (750 mg 3 times a day or 1250 mg 2 times a day), saquinavir mesylate (1200 mg 3 times a day), nevirapine (200 mg 2 times a day), or ritonavir (400 mg 2 times a day) combined with saquinavir mesylate (400 mg 2 times a day) as part of their antiretroviral regimen.

ASSESSMENT OF DRUG EXPOSURE

Plasma concentrations of PIs and nevirapine were measured using high-performance liquid chromatography. The timing of the previous dose was recorded on the laboratory form with the timing of the sample drawn. Observed concentrations were divided by the expected concentrations at the corresponding interval between drug ingestion and sampling. The expected concentrations at different time points were obtained from a reference group of HIV-1–infected patients.

RESULTS

ADHERENCE

Between May 1998 and June 1999, CRs were calculated for 261 patients in whom a first pharmacokinetic measurement was performed. Of those, 224 patients (86%) completed a questionnaire within 1 week following pharmacokinetic sampling. None of these patients were using any interacting drugs. Characteristics of patients at the time of completion of the questionnaire are shown in Table 1.

Twenty-three patients (10.3%) reported that they did not take all antiretroviral medication in the past 2 days. Seventy-three patients (32.6%) reported deviation from the schedule in the past week. Forty patients (17.9%) reported deviation from dietary instructions. Deviation from food requirements was reported by 3 (10%) of 31 patients prescribed didanosine, 20 (32%) of 62 patients prescribed indinavir, 10 (18%) of 55 patients prescribed saquinavir, and 16 (24%) of 66 patients prescribed ritonavir.

Of 224 patients, 201 (89.7%) reported taking all antiretroviral medication, 134 (59.8%) reported taking all medication on time, and 119 (53.1%) reported taking all medication on time according to food requirements and were thus considered fully adherent. The Figure shows the percentages of patients within the 4 largest treatment groups who reported taking all antiretroviral medication, on time, and according to food requirements, respectively.

The overall percentage of fully adherent patients was 47% when patients with a nelfinavir-containing regimen, in whom adherence to food requirements was not known, were excluded. In total, 182 patients (81.2%) reported that their level of adherence during the past week was comparable to that during the preceding period. Twenty-three (10.3%) reported that it was better compared with the preceding period, and 19 (8.5%) reported that it was worse.

Reasons for deviation from the regimen were as follows: forgetting (35%), considering it impossible to combine taking medication with activities of that particular moment (24%), feeling sick or ill (22%), having a change in daily routine (19%), and not having the medications available at the requested time (15%).

A total of 178 (79%) of 224 patients were enrolled at 9 sites that included at least 10 patients. The proportion of patients who reported deviation from their regi-
patients using the same drug in the same dosage for whom full pharmacokinetic curves were available. Concentration ratios (CRs) served as measure of relative drug exposure, with 1 indicating a concentration that is equal to the average time-adjusted concentration in the reference population. Patients who were using any interacting drugs were excluded from the analyses.

HIV-1 RNA QUANTIFICATION

Plasma concentrations of HIV-1 RNA were measured with the HIV-1 branched DNA assay (version 1.0 or 3.0, Chiron Diagnostics, Emeryville, Calif) with a lower detection limit of 500 (version 1.0) or 50 copies/mL (version 3.0), the Nuclisens HIV-1 RNA assay (Organon Teknika, Turnhout, Belgium) with a lower detection limit of 400 copies/mL, or the HIV-1 Amplicor Monitor assay (Roche Molecular Systems, Branchburg, NJ) with a lower detection limit of 400 copies/mL, depending on the routine of the particular hospital. We assumed comparability of results of these quantitative HIV-1 RNA measurements.\(^{16}\) We dichotomized virologic outcome into having plasma HIV-1 RNA levels above or below 500 copies/mL.

ANALYSIS

We calculated the percentage of patients who reported taking all antiretroviral medication in accordance with time and dietary instructions in the preceding week. Those patients were considered fully adherent. If no food requirement was applicable, patients were considered adherent with food requirements. The questionnaire did not include the dietary advice that nelfinavir should preferentially be taken with food. Patients treated with nelfinavir who reported taking all antiretroviral medication according to schedule were handled in the analysis as fully adherent.

Using the \(\chi^2\) test, the proportion of patients who reported deviation from their regimen was compared across hospitals that enrolled at least 10 patients.

We compared CRs between fully adherent patients and patients who reported deviation from their regimen by the Mann-Whitney test. In patients prescribed ritonavir combined with saquinavir, the lowest CR of both drugs was used.

We analyzed data from patients who completed a questionnaire within 1 week following pharmacokinetic sampling, because questions referred to the past week. We additionally analyzed the data of patients who completed a questionnaire on the same day the pharmacokinetic sample was taken.

Among patients who had received HAART for at least 24 weeks, we investigated the association between adherence and virologic outcome. We calculated the odds ratio (OR) and 95% confidence interval (CI) on having plasma HIV-1 RNA levels above 500 copies/mL in patients who reported deviation from their regimen compared with patients who reported being fully adherent by logistic regression analysis. In a second logistic regression analysis, we adjusted for age, sex, antiretroviral therapy before initiation of HAART, prior change of HAART because of therapy failure, Centers for Disease Control and Prevention (CDC) stage at initiation of HAART, HIV-1 transmission category (homosexual vs other), and PI or NNRTI used as part of the current HAART regimen. Two-sided \(P\) values less than .05 were considered to indicate statistical significance. Data analyses was performed using the SPSS software for Windows version 8.0.2 (SPSS Inc, Chicago, Ill).

ADHERENCE AND DRUG EXPOSURE

Three patients (2 taking indinavir, 1 taking ritonavir and saquinavir) had undetectable plasma concentrations of PIs. All 3 reported being not fully adherent. For all treatment groups combined, patients who reported deviation from their regimen showed significantly lower CRs, indicating lower drug exposure, compared with patients who reported being fully adherent (Table 2). A CR of 1 indicates a concentration that is equal to the average time-adjusted concentration in the reference population. The median CR of patients who reported deviation from their regimen was below 1, whereas it approximated 1 in fully adherent patients. Median CRs within treatment groups are also shown in Table 2. To date, the minimal effective CR has been established for indinavir only. This minimal effective CR should be higher than 0.75, which corresponds with an indinavir trough concentration of 0.10 mg/L.\(^{17}\) Similar minimal effective indinavir trough levels have been established by others, using a different method.\(^{18,19}\) The median CR of patients in the indinavir group who reported deviation from their regimen was below this minimal effective threshold.

When CRs were compared between fully adherent patients and patients in whom nonadherence was based only on deviation from schedule and dietary prescriptions, ie, those who reported taking all their medications but not in accordance with time and/or dietary prescriptions (\(n=82\)), the latter group had statistically significantly lower CRs (Mann-Whitney test, \(P=.002\)), with a median of 0.78.

A total of 185 patients had completed a questionnaire on the same day the pharmacokinetic sample was taken. A comparison of CRs between fully adherent patients and patients who reported deviation from their regimen within this group led to similar results. The median CR in fully adherent patients was 1.05, whereas it was 0.82 in patients who reported deviation from their regimen (Mann-Whitney test, \(P=.001\)).

ADHERENCE AND VIROLOGIC OUTCOME

There were 156 patients who had received HAART for at least 24 weeks; in 137 (88%) of these patients a plasma HIV-1 RNA measurement was performed at completion of the questionnaire. Of those 137 patients, 107 (78.1%) had plasma HIV-1 RNA levels below 500 copies/mL, 82 (59.9%) had received antiretroviral therapy before initiation of HAART, and 36 (26.3%) had previously changed their HAART regimen because of therapy failure.
Twenty (28%) of 72 patients who reported deviation from their regimen had plasma HIV-1 RNA levels above 500 copies/mL compared with 10 (15%) of 65 patients who reported being fully adherent (OR, 2.1; 95% CI, 0.9-4.9) (Table 3). After adjustment for antiretroviral therapy before initiation of HAART, prior change of HAART because of therapy failure, and CDC stage at initiation of HAART, the OR was 4.0 (95% CI, 1.4-11.6). Adjustment for age, sex, HIV-1 transmission category, and PI or NNRTI used did not significantly improve the fit of the model, did not alter results, and did not lead to statistically significant ORs. They are therefore not reported.

When we compared virologic outcome between fully adherent patients and patients in whom nonadherence was only based on deviation from schedule and dietary prescriptions, ie, those who reported taking all their medications but not in accordance with time and/or dietary prescriptions, the latter group tended to be more likely to have a viral load above 500 copies/mL (OR, 2.1; 95% CI, 0.9-5.2). When taking into account antiretroviral therapy before initiation of HAART, prior change of HAART because of therapy failure, and CDC stage at initiation of HAART, the OR was 5.5 (95% CI, 1.6-18.4).

We took a closer look at the association among adherence, virologic outcome, and prior therapy failure. In the group of patients without prior therapy failure, 10 (59%) of 17 patients who reported deviation from their regimen had plasma HIV-1 RNA levels above 500 copies/mL compared with 9 (47%) of 19 patients who reported being fully adherent (OR, 1.6; 95% CI, 0.4-5.9; P = .49). The finding that a substantial number of patients did not succeed in taking HAART as prescribed illustrates failure, 10 (59%) of 17 patients who reported deviation from their regimen had plasma HIV-1 RNA levels above 500 copies/mL compared with 9 (47%) of 19 patients who reported being fully adherent (OR, 1.6; 95% CI, 0.4-5.9; P = .49).

### Table 1. Characteristics of the 224 Patients

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Fully Adherent</th>
<th>Not Fully Adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>(n = 119)</td>
<td>(n = 105)</td>
</tr>
<tr>
<td>Indinavir sulfate</td>
<td>(n = 30)</td>
<td>(n = 32)</td>
</tr>
<tr>
<td>Nelfinavir mesylate</td>
<td>(n = 42)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Ritonavir and saquinavir mesylate</td>
<td>(n = 32)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>(n = 21)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>(n = 16)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>(n = 7)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>Nelfinavir mesylate</td>
<td>(n = 3)</td>
<td>(n = 3)</td>
</tr>
<tr>
<td>Indinavir sulfate</td>
<td>(n = 30)</td>
<td>(n = 32)</td>
</tr>
<tr>
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<tr>
<td>Saquinavir</td>
<td>(n = 21)</td>
<td>(n = 28)</td>
</tr>
</tbody>
</table>

*Values are given as medians (interquartile ranges). P = .001 for fully adherent vs not fully adherent (Mann-Whitney test).
the difficulty of consistently taking antiretroviral medication according to all requirements. To date, it is not known what level of adherence to HAART is precisely needed to prevent viral rebound and the emergence of drug-resistant virus variants, although “less than excellent adherence” has been considered to be insufficient. There is evidence that rates of virologic failure significantly increase when less than 93% of prescribed doses of PIs are actually taken. The degree to which one can deviate from a specific antiretroviral regimen without increasing the risk of treatment failure will depend on characteristics of the particular drugs that are used, such as the plasma elimination half-life and the degree to which drug exposure is dependent on food intake. In the present study, we found that the group of patients treated with an indinavir-containing regimen, a PI sensitive to accurate adherence to both timing of drug intake and specific dietary requirements, who reported deviation from this regimen had a median CR that was below the minimal effective threshold. Since the consequences of poor adherence will differ across various antiretroviral regimens, we believe the present study underlines the importance of considering the patients’ ability to adhere when choosing among different treatment options.

Studies investigating the extent of adherence to HAART have predominantly focused on the proportion of pills being taken. Median adherence rates from 84% to 92% have been reported, as well as 70% of patients taking more than 95% of prescribed medication, 50% taking 100% of prescribed medication, and 58% taking more than 90%. In the present study, we found that 90% reported taking all prescribed medication. When the timing of doses and food requirements were taken into account, the percentage of patients who reported having taken HAART medication as prescribed decreased to 47%. Supposedly, this result may be representative for a number of other cohorts as well: 78% of our patients who took HAART for at least 24 weeks had suppressed plasma HIV-1 RNA loads, which is comparable to results reported in other prospective cohort studies. Patients who reported taking all their medications but not in accordance with time and dietary prescriptions also had lower CRs and were more likely to have a viral load above 500 copies/mL compared with patients who reported being fully adherent. This suggests that there is more to adherence than whether or not someone takes one’s dose. Patients also need to take it properly.

We found that the association between adherence and virologic outcome was affected by prior therapy failure. Other studies found the proportion of patients achieving undetectable plasma HIV-1 RNA concentrations on the first HAART regimen to be higher than that of subsequent regimens. In the present study, adherence was significantly related with virologic outcome in patients without prior therapy failure but not in patients with prior therapy failure. This could possibly be explained by decreased drug sensitivity in the group with prior therapy failure. Clearly, this finding needs further investigation and corroboration in other studies.

Our study had several limitations. We assessed patient adherence by self-report. This is a method known to overestimate adherence but to reliably assess nonadherence. Therefore, it is likely that our results represent the highest estimate of the extent to which patients are adhering to HAART.

Patients enrolled in the study needed to be literate in Dutch or English because adherence was assessed by a self-report questionnaire; therefore, our results might not be generalized to patients with insufficient language skills to complete a self-report questionnaire.

We used a time frame of 7 days in our adherence questionnaire. This might have caused some recall bias. However, other studies investigating adherence to HAART by self-report have suggested a reasonable validity of using a time frame of 7 days or longer. We therefore believe that the use of a 7-day time frame was justifiable.

We used CRs as a measure of relative drug exposure. Concentration ratios may be affected by individual variability in pharmacokinetic profiles. Theoretically, a patient with a profile characterized by a high peak and a low trough level could obtain a more favorable CR compared with a patient with a profile characterized by a low peak and a high trough level, depending on whether the sample is drawn, whereas a more favorable virologic response would be expected in the latter patient. However, CRs have previously been used as a measure of exposure to PIs among groups of HIV-1–infected patients and have been shown to be related with adherence and virologic treatment failure.

### Table 1. Odds Ratios of Having Plasma HIV-1 RNA Concentrations Above 500 Copies/mL Among Patients

<table>
<thead>
<tr>
<th>Outcome (referent)</th>
<th>Univariate OR (95% CI)</th>
<th>P</th>
<th>Multivariate OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not fully adherent</td>
<td>2.1 (0.9-4.9)</td>
<td>.08</td>
<td>4.0 (1.4-11.6)</td>
<td>.01</td>
</tr>
<tr>
<td>ARVT before HAART</td>
<td>5.9 (1.9-18.1)</td>
<td>.002</td>
<td>3.1 (0.9-11.0)</td>
<td>.09</td>
</tr>
<tr>
<td>Prior change in HAART</td>
<td>9.1 (3.7-22.6)</td>
<td>&lt;.001</td>
<td>8.1 (2.8-23.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CDC stage at initiating HAART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (referent)</td>
<td>3.2 (1.1-9.0)</td>
<td>.06</td>
<td>1.5 (0.4-5.1)</td>
<td>.27</td>
</tr>
<tr>
<td>B</td>
<td>3.0 (1.1-8.7)</td>
<td></td>
<td>2.7 (0.8-9.2)</td>
<td></td>
</tr>
</tbody>
</table>

**HIV-1** indicates human immunodeficiency virus type 1; **CR**, odds ratio; **CI**, confidence interval; **ARVT**, antiretroviral therapy; **HAART**, highly active antiretroviral therapy; and **CDC**, Centers for Disease Control and Prevention.

*Prior change in HAART because of therapy failure†

†Rise in plasma HIV-1 RNA concentration, decrease in CD4 cell count, or increase in HIV-1–related symptoms.
therefore believe that there is sufficient support for the use of CRs as measure of drug exposure at a group level.

In the questionnaire, we had not included the dietary advice that nelfinavir should preferentially be taken with food. This advice had been overlooked in designing the questionnaire. Patients treated with nelfinavir who reported taking all antiretroviral medication according to schedule were handled in the analysis as being fully adherent. This might have decreased our ability to differentiate between the level of adherence of patients who were treated with a nelfinavir-containing regimen.

We found significantly lower drug exposure in patients who reported deviation from their regimen compared with patients who reported being fully adherent. However, we observed considerable variability in CRs within both groups of patients. We found a median CR greater than 1 in the group of fully adherent patients, although the median CR was not statistically significantly greater than 1. A median CR greater than 1 in fully adherent patients could be explained by the large interpatient variability in plasma drug concentrations that is particularly common for PIs. This could result in observed concentrations being slightly higher compared with the time-adjusted reference concentrations, since reference values had been determined in relatively small reference groups and, therefore, by chance could have been lower.

Within the group of patients who reported being fully adherent, we observed CRs that were lower than 1. This might be indicative of a too favorable self-reported level of adherence.

In conclusion, only half of the patients reported taking all antiretroviral medication in accordance with time and dietary instructions in the preceding week. Patient adherence should remain a prime concern in the management of HIV-1 infection.

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