

Impact of a Patient Education Program on Adherence to HIV Medication

A Randomized Clinical Trial

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Abstract: Patients' knowledge of their HIV condition and its treatment, which has been recognized as a factor that influences adherence to antiretroviral therapy, can be improved through educational programs. This prospective, randomized, controlled trial compared an experimental group that participated in an educational program and a control group with standard care. The study evaluated the impact of an educational intervention on adherence to antiretroviral therapy, patients' knowledge, quality of life, and therapeutic response in patients treated with highly active antiretroviral therapy. Three hundred twenty-six patients were analyzed at inclusion. A higher level of adherence was associated with patients who were older, had higher incomes, and did not smoke. CD4 cell count and plasma viral load were correlated with adherence at entry. The educational intervention had an impact on adherence and knowledge in the experimental group at 6 months, which was maintained at 12 and 18 months. A delayed increase in adherence was observed in the control group at 12 months. No significant impact on quality of life was observed over time. The patients' health status improved in 56% of the experimental group subjects and 50% of the control subjects. However, no significant impact was shown on CD4 cell count and plasma viral load. This study shows that an educational intervention improves adherence to antiretroviral regimens and health status and suggests that it should be initiated early in therapy.

Key Words: adherence, HIV, quality of life, patient education, antiretroviral therapy

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The full benefit of highly active antiretroviral therapy (HAART) in HIV-infected patients has been confirmed in long-term clinical practice. HIV infection is now considered to be a chronic, life-long disease. The clinical problem is to educate and encourage patients to maintain their therapeutic regimens. Consequently, increasing attention has been given to how to improve adherence in HIV infection. Adherence is a complex clinical behavior. Some of its determinants are associated with the antiretroviral regimen itself and its usually complex schedule.^{1,2} Others are linked to the patient, to the patient-physician²⁻⁴

relationship, or to the health care providers. Poor adherence to HAART has been identified as an important factor associated with therapeutic failure and possible drug resistance, leading to individual as well as public health consequences.⁵⁻⁷ Patients' knowledge of their therapy was also associated with adherence.⁸

Until now, few reports of educational interventions targeting adherence and knowledge levels have been available in HIV-infected patients. In this prospective, randomized, clinical trial, we evaluated the impact of an educational intervention on adherence to antiretroviral therapy, knowledge, quality of life (QOL), and therapeutic response in a large cohort of chronic HIV-infected outpatients.

PATIENTS AND METHODS

Patients and Study Design

The Ciel Bleu study was a prospective, multicenter, randomized clinical trial that took place in France between May 1999 and June 2001 in 3 hospital-, university-based centers. The study was approved by the Ethics Committee, and all patients gave written informed consent. The experiment compared 2 groups of HIV-1-infected outpatients receiving a stable antiretroviral regimen with at least 3 drugs for at least 3 months. The experimental group participated in an educational program and the control group received standard care over a period of 12 months. All patients from the control group were able to participate in the formal educational sessions after month 12, and the last evaluation point was performed at

month 18. Patients were not included if they had difficulty understanding French, were pregnant, had a partner who was included in the study, or had diagnosed psychiatric problems. HIV diagnosis, therapeutic history, and clinical and laboratory characteristics were collected at inclusion (TO). Then, clinical data, therapeutic changes, standard laboratory data, CD4 cell count, and plasma viral load were recorded every 6 months (T6, T12, T18). Patients completed a questionnaire assessing their QOL, adherence, and knowledge about HIV infection at each visit. In addition, they completed a sociodemographic and lifestyle questionnaire at TO. Patient confidentiality was maintained.

Educational Program

The educational program was an individualized program that took place in each center. It included a personalized educational diagnosis based on problems with adherence. The program used a planning card with self-adhesive stickers showing treatment medications, followed by at least three 1-hour educational sessions during the first 12 months. Pill boxes were distributed. The objectives were to improve patient knowledge regarding HIV infection (disease, transmission mode, monitoring) and treatment and to prepare patients for problems they might encounter in real-life situations. Patients in the control group were given a therapeutic planning card at inclusion. Staff physicians and nurses who participated in the educational program had taken a 4-day course in communication and patient education techniques.

Assessment Tools for the Efficacy of the Educational Program

The efficacy of the educational program was assessed using 4 major criteria: knowledge about HIV and its treatment; adherence; QOL; and therapeutic response. The knowledge questionnaire consisted of 14 items concerning HIV disease. The knowledge score ranged from -11 (all answers incorrect) to +11 (all answers correct). A global adherence score was produced based on items found in the Chesney questionnaire and the Patient Medication Adherence Questionnaire (PMAQ7), combined with 3 qualitative criteria related to instructions for taking medications.^{9,10} The adherence range was 1 (poor) to 4 (good). To complete the adherence questionnaire, a nonadherence factor (NAF) score was calculated from 13 items identifying the reasons for which the patient had not taken his/her medication. The NAF score varied from 0 (virtually no NAF) to 26 (many NAFs). QOL was measured using a validated questionnaire, the HIV-46.¹¹ The scores varied between 0 (poor) and 100 (good). Therapeutic response was measured by a change in plasma viral load and in CD4 cell count. This was used to analyze the impact of the educational program on patients' health status.

Statistical Analysis

The analysis was conducted using SAS Windows V 8.2 software (SAS Institute, Inc., Cary, NC). At TO, the analyzed population included all randomized patients who had a complete file (97% of patients for clinical and biologic data, and 98% for self-administered questionnaires). At each assessment, the analyzed population included all patients having a complete file at both TO and the point of interest (T6, T12, and T18). Comparisons between groups were realized using nonparametric tests (Mann-Whitney-Wilcoxon, or Kruskal-Wallis or nonparametric covariance and variance analyses) for the qualitative parameters and χ^2 or Fisher exact tests for the quantitative parameters. Analyses of the score developments within each patient group were tested using a signed rank test. The significance threshold was 0.05.

RESULTS

Three hundred sixty-seven patients (179 control and 188 experimental subjects) were randomized. One hundred eighty-seven patients from the experimental group participated in at least 2 educational sessions and 124 of them completed their program within 6 months after inclusion. Despite their randomization to the control group, 19 patients attended at least 1 educational session before T12.

At TO, 326 patients (158 control and 168 experimental subjects) had a complete file. Eighty percent were male, with a mean age of 40.5 years. Consumption of tobacco and alcohol was reported by 44 and 20% of patients, respectively. Thirty-three percent of patients had an AIDS diagnosis. The mean duration of antiretroviral treatment was 4.0 years, and the current regimen included a protease inhibitor in 80% of patients. CD4 cell count was $<200/\text{mm}^3$ in 17% of patients, $200-500/\text{mm}^3$ in 49%, and $<500/\text{mm}^3$ in 34%, whereas plasma viral load was <200 copies/mL in 55% of patients, 200-5000 copies/mL in 22.5%, and >5000 copies/mL in 22.5%. A high percentage of patients had already achieved a maximum score for adherence (46%) or for some QOL dimensions: daily living (62%), role physical (57%), social functioning (47%), role emotional (45%). No significant difference was found between the 2 groups at inclusion.

Patients reported better adherence if they were older ($P < 0.001$), if they had higher incomes ($P = 0.001$), and if they were nonsmokers ($P = 0.01$). A high level of adherence was correlated with a higher CD4 cell count ($P = 0.02$) and a lower plasma viral load ($P < 0.001$).

Patients having a complete file at both TO and the considered visit were analyzed for changes between TO and T6 (118 control and 126 experimental subjects), TO and T12 (130 control and 130 experimental subjects), and TO and T18 (105 control and 121 experimental subjects). The changes in adherence during the study periods are shown in Figure 1. The adherence score increased in the experimental group patients between TO and T6 ($\Delta = +0.25$), as it decreased in the control

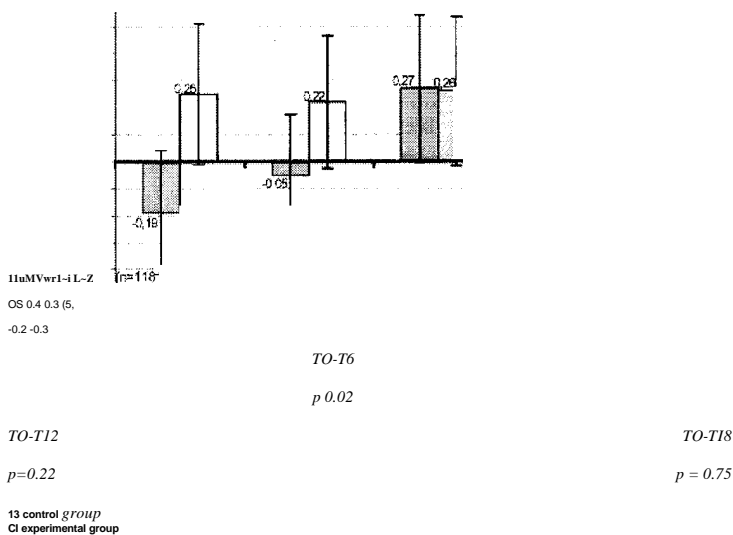


FIGURE 1. Mean change in adherence scores in experimental and control groups at months 6, 12, and 18.

group patients (A = -0.19). This difference was statistically significant (P = 0.025). This adherence benefit was sustained in the experimental group at T12 (A = +0.22) and T18 (A = +0.26). There was a progressive improvement in the adherence score in the control group between TO and T12. This improvement was confirmed at T18, when patients from the control group participated in the educational sessions, while the score in the experimental group stabilized. The NAF score tended to improve in both groups during the study periods, without a significant difference.

The knowledge score, estimated by the number of correct answers, also tended to increase at T6, T12, and T18 compared with TO in the 2 groups, with a higher improvement in the experimental group at T6 and T12. However, the number of incorrect answers remained stable in both groups during the study. The QOL scores tended to increase in the experimental group over time; however, no significant difference was found between the 2 groups.

There was no direct impact of the educational program on CD4 cell count and plasma viral load. However, a benefit of the health status, based on concordant changes in CD4 cell count and plasma viral load between TO and T6, was found in 56% of patients in the experimental group and 50% in the control group. This benefit was confirmed at T12 and was similar in the 2 groups, with an improvement in 59% of patients.

DISCUSSION

In this study, the benefit of an educational intervention on patient adherence to antiretroviral therapy was demonstrated in the experimental group at month 6 and was maintained at month 12 and 18. A consistent impact on knowledge and NAFs was found. CD4 cell count and plasma viral load were correlated with adherence at baseline. However, although the global health status improved in our patients, improvement

of adherence did not translate into measurably better immunologic or virologic outcomes. No evidence of a specific impact on QOL was found.

In a population of patients initiating a new treatment regimen, Tuldra et al¹² showed that a psychoeducative intervention resulted in a higher adherence level in the experimental group (94%) compared with the control group (69%) and a better virologic response (89% in the experimental group vs. 66% in the control group had a plasma viral load <400 copies/mL). Bentz et al¹³ also found an impact on adherence and virologic response in pretreated patients. Fogarty et al¹⁴ assessed adherence intervention effectiveness in HIV treatment from 11 reports, with discordant results. The differences between the study populations and between the educational programs could explain the various effects of interventions on treatment response. A strength of our study is the long-term follow-up, of the patients showing a sustained effect of the educational program.

Measurement of adherence is difficult, particularly in a randomized study aimed at improving adherence, as measuring adherence may, in itself, improve adherence. The best way to measure adherence remains controversial.^{1,15} In our study, previously validated self-reported questionnaires were used. The majority of our patients showed an adherence of 100% (number of pills taken/number of pills prescribed) during the study period. The adherence score we used combined this percentage with other variables that explored infrequently missed pills and respect of manufacturers' instructions. This adherence score was improved in the experimental group, with statistical evidence at T6.

Interestingly, we observed an increased adherence score in the control group at T12 compared with inclusion, confirmed at T18. This effect paralleled the effect observed in the experimental group at T6 but was delayed in the control group. We hypothesized that a diffusion or Hawthorne effect occurred in the control group and control staff members within the 3 study sites. This would have modified the practice of ambulatory HIV care, as the trained staff found it unethical to withhold information that they felt might improve the level of adherence of all patients. In addition, some patients in the control group participated in educational sessions. Increasing adherence in the control group by diffusion of the educational intervention only would be a conservative interpretation of our findings. Future studies should consider a randomized cluster design to avoid this bias.

We are aware of the potential limitations of this study. First, we used a single measurement of adherence. Second, the absence of questionnaires was the major source of missing data in this study, as at least 20% of patients did not return their questionnaires at each visit. However, we searched, but did not find, any statistical link between baseline adherence scores or any other baseline criterion and dropout from the study. Third, we did not demonstrate any effect of the intervention on CD4 cell count or on plasma viral load. However, the sample of

patients included in the study was probably not ideal for measuring a therapeutic impact associated with improved adherence. Forty percent of patients had persistent viral replication while treated and even an improvement of adherence could not overcome possible drug resistance. Furthermore, a high level of adherence existed at baseline; patients with low adherence levels could be more likely to respond to the intervention.

The impact of educational interventions on QOL was not evaluated in previously published studies addressing patients treated with HAART, although QOL is of major concern in this population.¹⁶ However, our educational program did not demonstrate a significant effect on QOL. This could be explained by a ceiling effect, as our study included mostly asymptomatic outpatients, who, at baseline, expressed a high level of QOL for most of the variables studied.

There has been increasing concern about adherence in the treatment of HIV-infected patients in recent years, because of the complexity of HAART regimens, the long period of treatment, and the high rate of adherence required to achieve good outcomes.¹⁷ Educational interventions must be carried out early in the course of treatment, before drug resistance arising from nonadherence develops and alters the ultimate therapeutic prognosis in an irreversible way. The results from our study should encourage physicians to follow recent guidelines that recommend patient education and adherence monitoring in all HIV primary care encounters and include adherence goals in treatment plans and interventions.

APPENDIX

The participants in the Ciel Bleu Study are Pr. J. F. Delfraissy, Dr. C. Goujard, B. Vagnaux, M. Ody, A. Kriaa, V. Morin, B. Levy, P. Lezeau, and Y. Buisson (Kremlin Bicêtre Hospital), Pr. D. Peyramond, Dr. J. Lippmann, and Dr. C. Leclercq (Lyon: Croix-Rousse Hospital); Pr. J. Beylot, Dr. N. Bernard, Dr. E. Vimard, and M. H. Trainaud (Bordeaux: St. André Hospital), O. Sanchez and D. R. Bertholon.

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