Long-Term Assessment of Didanosine, Lamivudine, and Efavirenz in Antiretroviral-Naive Patients: 3-Year Follow-Up

JESÚS SANTOS,1 ROSARIO PALACIOS,1 FERNANDO LOZANO,2 MANUEL LÓPEZ,3 MARÍA CARMEN GÁLVEZ,4 JAVIER DE LA TORRES,5 LUIS FERNANDO LÓPEZ-CORTÉS,6 MARÍA JOSÉ RÍOS,7 and ANTONIO RIVERO8 for the GRUPO ANDALUZ PARA EL ESTUDIO DE LAS ENFERMEDADES INFECCIOSAS (GAEI)

ABSTRACT

The aim of this study was to evaluate the long–term efficacy and safety of didanosine (ddI), lamivudine (3TC), and efavirenz (EFV). This was a follow-up to the VESD study, a 12-month open-label, observational, multicenter study of adult patients with HIV infection who started antiretroviral treatment with the ddI–3TC–EFV once-daily regimen. Of the 167 patients originally included, 106 patients remained on the same triple therapy at the end of the study (1 year), and they were offered an extra 24 months of follow-up; 96 were enrolled in this study (VESD-2). Seventy patients out of the initial cohort were still on the same regimen at month 36, with 97% of them with plasma viral load <50 copies/ml. An intention-to-treat analysis showed that the percentage of patients with plasma viral load <50 copies/ml was 73% at 36 months. CD4 cell counts increased 344 cells/µl over the 36 months. Safety and tolerance were good with no unexpected long-term toxicity. After 3 years of treatment with ddI–3TC–EFV, more than 40% of the patients were still receiving the initial antiretroviral therapy with sustained, durable immunovirological benefit and good acceptance. Long-term toxicity and virological failure were low.

Assessments of durability of highly active antiretroviral therapy (HAART) and long-term safety have seldom been reported but are of major importance in order to select the best initial therapy. Among the nonnucleoside reverse transcriptase inhibitors (NNRTI), efavirenz (EFV) and nevirapine have been evaluated over a 2- to 3-year period in naive patients1–3 but never in association with didanosine (ddI) and lamivudine (3TC). We present the 3-year follow-up results of an open-label, noncontrolled, observational, multicenter study of adult naive patients with HIV who started HAART with a once-daily regimen of ddI–3TC–EFV.4

One hundred and sixty-seven antiretroviral-naive HIV-infected patients with a median baseline CD4 cell count of 142 cells/µl and plasma viral load (VL) of 4.99 log10 received a once-daily regimen of ddI–3TC–EFV, with an initial follow-up of 12 months (VESD study),4 which was later extended 24 months more. All the variables were recorded in a database with the SPSS 12.0 program.

Of the 106 patients eligible for long-term follow-up at month 12, 96 were enrolled in the extended phase of the study. Ten patients were not included for different reasons (loss to follow-up, change of address, patient refusal) and 26 patients had discontinued the initial HAART treatment at month 36 (Fig. 1); therefore, 70 patients (41.9% of the initial cohort) remained on the same regimen and with VL suppressed. CD4 cell counts continued to increase during the second and third years of follow-up by approximately 100 cells/µl per year, independently of the initial CD4 cell counts, and the mean CD4 cell count at

1Hospital Virgen de la Victoria, Málaga, Spain.
2Hospital de Valme, Seville, Spain.
3Hospital Virgen de las Nieves, Granada, Spain.
4Hospital Torrecárdenas, Almería, Spain.
5Hospital Costa del Sol, Marbella, Spain.
6Hospital Virgen del Rocío, Seville, Spain.
7Hospital Virgen Macarena, Seville, Spain.
8Hospital Reina Sofia, Córdoba, Spain.
month 36 was 485 cells/μl (interquartile range 325–614). No patient had pancreatitis or grade 3 or 4 hypertransaminemia, hypertriglyceridemia, hypercholesterolemia, or lactic acidosis over the long term. The adherence questionnaire completed at each visit showed a very high compliance, greater than 90% at the end of the study. The quality of life was good or very good (97%), and the majority of the patients (94%) reported little or no difficulty taking the drug.

In this study, ddI–3TC–EFV once daily showed sustained and durable antiviral activity, with CD4 counts still increasing each year. Nearly half the initial cohort (41.9%) was still on the same regimen at 36 months. It is worth emphasizing that these results were obtained despite many losses to follow-up given the observational nature of the study and the absence of inclusion criteria in addition to the features of the cohort, with a very high proportion of patients having AIDS or a coinfection, receiving replacement therapy with methadone, and severely immunosuppressed at baseline. The immunological data were similar to those reported for other triple-therapy combinations with EFV, even in patients with low baseline CD4 cell counts. There were only two long-term virological failures, and both clearly were associated with lack of compliance. Long-term safety was very satisfactory, with no unexpected toxicities. The global percentage of withdrawals due to adverse effects through 36 months is similar to that reported in other studies of combinations of EFV and another backbone, and it was also similar to that in the 5-year follow-up study with 3TC–stavudine (d4T)–lopinavir/ritonavir reported by Abbott.

Concerning hepatotoxicity, four cases were seen in the initial cohort but during the extended study period no grade 3–4 hepatotoxicity was detected. This is highly notable in this cohort, in which 48% had positive HCV serology. Another point of note in a long-term study is the lipid profile. Only one patient had hypertriglyceridemia in the initial cohort and no cases of grade 3–4 hypertriglyceridemia or hypercholesterolemia were found in the long-term study.

These results are even better than with other nucleoside reverse transcriptase inhibitors (NRTI), such as emtricitabine ( FTC)–tenofovir or abacavir–3TC. Nor were there any cases of pancreatitis, polyneuropathy, or lactic acidosis over the long term. These disorders were seen with a certain frequency with the NRTI combination of ddI and d4T, but they are fairly uncommon with ddI at the recommended doses and 3TC or FTC. Therefore, the mitochondrial toxicity due to the ddI–3TC combination is much less common than initially foreseen. The quality of life and patient satisfaction with the drugs were as high as in the initial study, and the long-term degree of compliance was similar to that during the first year, representing the good acceptance of this regimen and lack of effort needed to adhere to it. The lipodystrophy syndrome was not evaluated in this study so that no data are available.

In summary, our findings on the durability of the antiviral and immunological response, and the absence of related long-term toxicities, suggest that the initial regimen with ddI–3TC–EFV is a possible alternative to other EFV backbone regimens. This simple, well-tolerated, efficient regimen helped the patients to maintain adherence and achieve a good quality of life and satisfaction with the therapy.

APPENDIX: MEMBERS OF THE VESD GROUP

Coordinators: J. Santos and R. Palacios, Hospital Virgen de la Victoria, Málaga. Participants: J. De la Torre and A. del Arco, Hospital Costa del Sol; E. Nuño and S. Fernandez, Hospital de la Axarquía, Velez-Málaga; F. Ofate, Hospital Carlos Haya, Málaga; M. Grana and F. Salgado, Hospital de la Serranía, Ronda; A. Fernández, Hospital Comarcal de Melilla; M.C. Gálvez, Hospital Torrecárdenas, Almería; A.B. Lozano, Hospital de Poniente, Almería; V. Gutierrez-Ravé, Hospital de Santa Ana, Motril; M López, J. Pasquau, and M.A. López-Ruz, Hospital Virgen de las Nieves, Granada; L. Muñoz and J. Hernández, Hospital San Cecilio, Granada; A. Rivero, Hospital Reina Sofia, Córdoba; L.F. López-Cortés, Hospital Virgen del Rocío, Sevilla; F. Lozano, Hospital Virgen de Valme, Sevilla; M.J. Ríos and D. Morales, Hospital Virgen Macarena, Sevilla; M. Torres, Hospital Punta de Europa, Algeciras; M. Pérez, Hospital La Línea de la Concepción; A. Vergara, Hospital Puerto Real, Cádiz; A. Terrón, Hospital de Jerez de la Frontera.
REFERENCES


Address reprint requests to:
Jesús Santos
Infectious Diseases Unit
Hospital Universitario Virgen de la Victoria
29010 Málaga, Spain
E-mail: med000854@saludalia.com