Four year follow-up of simplification therapy with once-daily emtricitabine, didanosine and efavirenz in HIV-infected patients (ALIZE ANRS 099 trial)

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Background: Once-daily combinations of efavirenz and two nucleoside analogues are recommended for the treatment of HIV infection. Long-term efficacy and safety data are scarce for the combination of efavirenz, emtricitabine and didanosine.

Methods: The ALIZE ANRS 099 trial enrolled 355 adults with plasma HIV RNA levels of <400 copies/mL under a protease inhibitor-based regimen, who were randomized to remain on this regimen or to switch to a once-daily regimen of emtricitabine, didanosine and efavirenz for 48 weeks. An extended 4 year follow-up was available for the 178 patients who switched to the efavirenz-containing regimen, and assessed plasma HIV RNA levels, CD4 cell counts, safety and tolerability.

Results: After a median follow-up of 42 months, 121 patients (68%) remained on an efavirenz-based regimen, and 62% and 57% had plasma HIV RNA levels of <400 and <50 copies/mL, respectively, in an intent-to-continue analysis with missing data and treatment discontinuation considered as failure. There was a significant increase in CD4 cell count of 41 cells/mm3. Drug-related adverse events were the main reason for treatment discontinuation in 26 patients (15%), and 15 were reported during the first year of therapy (58%). There was no emergence of clinically defined lipodystrophy, and lipid and glucose profiles were favourable with a significant increase from baseline of high-density lipoprotein cholesterol levels (median increase 12 mg/dL, P<10^-4).

Conclusions: A once-daily regimen of emtricitabine, didanosine and efavirenz provided a durable antiretroviral response and was well tolerated through 4 years of therapy.

Keywords: HIV infection, antiretroviral therapy, treatment outcome, adverse events

Introduction

Combined antiretroviral therapy (cART) with tenofovir and emtricitabine, two nucleoside reverse transcriptase inhibitors (NRTIs), and efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is one of the preferred recommended options in naive HIV-infected patients. Other dual NRTI combinations such as abacavir plus lamivudine, or zidovudine plus lamivudine have
shown lower efficacy and tolerability rates in clinical trials when used with efavirenz.3,4 However, long-term tenofovir use can be associated with renal dysfunction and bone toxicity, and alternative dual NRTI combinations are of interest.5,6 The combination of didanosine and emtricitabine is potentially attractive because of its once-daily dosing, low pill burden, favourable early safety profile and low cost, but because of safety events reported with didanosine (e.g. neuropathy, pancreatitis) and lack of co-formulation, it is less favoured in treatment guidelines.1 Unfortunately, this combination has been investigated with efavirenz in only a few clinical trials and long-term efficacy and safety data are scarce.7–9

In the initial report of the ALIZE ANRS 099 trial, we showed that a switch to a once-daily regimen of emtricitabine, didanosine and efavirenz was able to maintain suppression of plasma HIV-1 RNA levels of <400 copies/mL with good tolerability for 48 weeks in 90.5% of HIV-infected patients previously receiving a protease inhibitor (PI)-based cART.10 This study was extended to 4 years because of the need to continue to provide emtricitabine to these patients until it was marketed, and therefore allowed assessment of the long-term efficacy and safety of this combination. We present here the results of the long-term follow-up of patients randomized to the emtricitabine, didanosine and efavirenz arm of this trial.

Methods

Study design

Details of the study design and results through 48 weeks have previously been reported.10 Briefly, 355 antiretroviral-experienced adults with a CD4 cell count of ≥100 cells/mm³ and plasma HIV-1 RNA levels of <400 copies/mL for at least 6 months under a regimen including a PI and two NRTIs, were prospectively enrolled in this randomized controlled trial between May 2000 and April 2001 in 58 clinical centres in France. At baseline, patients were NNRTI naive, had not experienced virological failure under a PI-based regimen and had laboratory values within acceptable limits. Suboptimal antiretroviral therapy with NRTIs alone before PI-based therapy was not an exclusion criterion, providing that the patients had not received didanosine monotherapy, and were receiving lamivudine at baseline. Patients with a history of pancreatitis or peripheral neuropathy were not eligible. Patients were randomly assigned 1:1 to switch to a once-daily combination of emtricitabine, didanosine and efavirenz, or to continue their PI-based antiretroviral regimen. In the switch arm, patients received the following combination of drugs, once daily at bedtime: emtricitabine (one 200 mg capsule daily), didanosine (one 400 mg enteric-coated capsule daily for patients weighing ≥60 kg, and one 250 mg enteric-coated capsule daily for patients weighing <60 kg) and efavirenz (600 mg daily, three 200 mg capsules for the first year, then one 600 mg capsule daily). The study was approved by the ethics committee of the Hôpital Saint-Louis, Paris, and the Institutional Review Board of the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS). All patients gave written informed consent at entry into the trial, and at each amendment proposed to extend the follow-up of the study. Indeed, the study was initially designed to last only 48 weeks but, according to the very good short-term efficacy and safety data, and the need to provide emtricitabine to these patients until it was approved, the study follow-up was extended to 48 months. We report here data from patients randomized to the once-daily emtricitabine, didanosine and efavirenz arm of the trial.

Assessments

Participants were followed clinically and by routine laboratory monitoring every 4 weeks until week 8, every 8 weeks until month 12, every 12 weeks until month 24, every 6 months until year 4. At each visit, clinical data were collected through an interim medical history and physical examination, and blood specimens were obtained. Routine analyses were performed at each site throughout the study period, and included a complete blood count, measurement of plasma HIV-1 RNA levels (Chiron and Roche assays were allowed in this study but a patient had to be followed with the same assay throughout the study), CD4 cell count, and tests of liver, kidney, muscle and pancreatic function. In patients experiencing virological failure, defined by two successive plasma HIV RNA levels of >400 copies/mL while on study drugs, a genotypic resistance test was performed during the first 48 weeks.

Safety was assessed through the reporting of adverse clinical events and abnormal laboratory measurements. For this study, only treatment-limiting adverse events and all grade 3–4 events, according to the ANRS toxicity grading scale (http://etudes.isped.u-bordeaux2.fr/TELECHARGEMENT/UB897/CMG-EC/ANRS_EP11_GrillesGravite.pdf), were analysed. At baseline and at months 12, 24, 36 and 48, patients were also assessed for lipodystrophy by their physician using a specific questionnaire. Patients were categorized as having lipoatrophy (face, limbs, buttocks, prominent superficial veins), lipo hypertrophy (neck, breast, abdomen) or both (mixed syndrome), as previously described.11 Each clinical sign of lipodystrophy was also graded by the physician as mild (noticeable only when specifically sought), moderate (obvious to the patient or the physician) or severe (obvious by any casual observer). No objective measurements of body composition were performed.

The data were gathered at study centres by site investigators and study coordinators, and sent to INSERM U897 (Bordeaux, France) for monitoring, data entry and statistical analysis.

Statistical analysis

The sample size (n = 355) was initially calculated to demonstrate non-inferiority of the once-daily arm as compared with the PI arm on the proportion of patients with 1 year of sustained viral suppression (<400 copies/mL) with a non-inferiority margin of 15%.

The primary efficacy endpoint for this long-term study was the proportion of patients having plasma HIV-1 RNA levels of <400 and <50 copies/mL, in an intent-to-treat analysis where missing data were considered as failures. In this analysis, patients discontinuing the randomized treatment (defined as a discontinuation or change of at least one drug in the regimen), were also considered as failures whether or not their plasma HIV RNA level was controlled. The primary efficacy endpoint was also analysed in an on-study medication analysis, including all randomized patients, but censoring follow-up after discontinuation of study medication, lost to follow-up, withdrawal from study or death, with missing plasma viral load data considered as failure.

All secondary endpoints were analysed on treatment, based on observed data up to study medication discontinuation (plus 1 month for event-type endpoints). They included the median change from baseline in CD4 cell counts, the proportion of patients having experienced clinical progression to AIDS or death, severe non-AIDS events (including severe cardiovascular, liver and renal diseases and cancers), grade 3 or 4 adverse events, treatment-limiting adverse events, lipodystrophies, those who discontinued study medications and median changes from baseline in plasma glucose and lipid concentrations. Trend in the proportion of patients with lipodystrophy between weeks 0 and 48 was tested.
through a logistic regression for repeated data, and trend in more severe grades of lipodystrophy through a log-linear model for repeated data.

Statistical analyses were performed with the use of SAS software (SAS Institute, Inc., Cary, NC, USA).

Results

Study patients and disposition (Figure 1)

Median age at enrolment was 41 years, 85% of patients were male and 28% had AIDS. Plasma HIV RNA levels were <400 and <50 copies/mL in 100% and 92% of patients respectively. Median CD4⁺ T cell count was 509 cells/mm³. At baseline, NRTI combinations included zidovudine plus lamivudine in 42% of patients, stavudine plus lamivudine in 46% and stavudine plus didanosine in 8%. For PIs, nelfinavir was prescribed in 38% of patients, indinavir in 37% and ritonavir-boosted-PI combination in 15%. Median duration of cART at enrolment was 36 months.

The median duration of follow-up in this study was 42 months (interquartile range 38–44) representing 571 patient-years of follow-up. One hundred and twenty-one patients [68%, 95% confidence interval (CI) 59–76] were still on study treatment at the end of follow-up (Figure 1). The overall median duration of study regimen was 3.5 years (interquartile range: 2.3–3.6).

Overall 57 patients (32%, 95% CI 25–39) did not complete follow-up. The main reasons for study or study medication discontinuation were drug-related adverse events (n = 26) including one suicide death, patient’s choice (n = 9), patients lost to follow-up (n = 7), virological failure (n = 6), physician’s choice (n = 5), pregnancy or a wish to become pregnant (n = 3) and immunological failure (n = 1).

Antiretroviral activity (Figure 2)

In the intent-to-treat analysis with missing data or study medication discontinuation considered as failure, 62% of patients (111/178; 95% CI 55–69) had plasma HIV RNA levels of <400 copies/mL at the end of follow-up, and 57% (102/178; 95% CI 50–65) had <50 copies/mL (Figure 2). The proportions of patients with plasma HIV-1 RNA levels <400 and <50 copies/mL in the on-treatment analysis were 92% (111/121, 95% CI 85–96) and 84% (102/121, 95% CI 76–90), respectively.

Ten patients had two successive plasma HIV RNA levels >400 copies/mL, seven during the first 48 weeks and three thereafter. Among the five subjects whose genotype was available, mutations associated with efavirenz resistance were detected in all (K103N in four and L100I in two); none of which was present at baseline on proviral DNA. Also, five genotypes carried the M184V mutation associated with emtricitabine resistance and one the L74V associated with didanosine resistance.

Changes in CD4 cell counts and clinical progression (Figure 2)

Modest but significant increases in CD4 cell counts were observed on the study regimen, with a median increase from

![Flow chart of the ALIZE ANRS 099 study over 4 years of follow-up; when patients stopped study treatment first, then study follow-up, the first occurrence only is presented. FTC-ddI-EFZ, emtricitabine–didanosine–efavirenz.](image)
baseline to the end of follow-up of +41 cells/mm³ (interquartile range: –88, +181). The proportion of patients with CD4 cell counts ≥500 cells/mm³ rose from 49% at baseline to 59% at year 4, whereas the proportion of patients with counts of <200 cells/mm³ remained stable at 3%. One patient discontinued the study treatment because of insufficient CD4 cell count.

Two patients experienced a new AIDS-defining event (invasive cervical cancer and pulmonary tuberculosis), and two experienced a relapse of an AIDS-defining event (Kaposi sarcoma and ocular toxoplasmosis). Six patients (3%) reported minor HIV-associated events on treatment: herpes zoster (n = 2), oral candidiasis (n = 3) and thrombocytopenia (n = 1).

One patient died of suicide after 3 years in the study while on study treatment. This patient had a history of depression at baseline.

Also, three male patients presented with severe non-AIDS events. Two had myocardial infarctions, which occurred after the third year of follow-up. These two patients were smokers, had no history of coronary disease, and one had high baseline LDL cholesterol levels (6.03 mmol/L). The third one had urethral cancer.

**Adverse events**

The study treatment was generally well tolerated during the 4 years of the study, and overall only 26 patients (15%, 95% CI 10–21) discontinued the study because of drug-related adverse events.

Most (n=15) of these adverse events were sensorineural (abnormal dreams n=6, dizziness n=3, peripheral neuropathy n=2, others n=4). Other drug-related treatment-limiting adverse reactions were metabolic (increased concentrations of triglycerides n=2 and liver aminotransferase n=1, pancreatitis n=1, lactic acidosis n=1), psychiatric (suicide attempts n=3, acute psychosis n=1) and non-specified (n=2). Among the three patients who made suicide attempts, one patient died of suicide as stated above, and that could be treatment related.

Fifteen of these treatment-limiting adverse events occurred during the first year of the study (58%), and six (23%) occurred during the first 4 weeks of treatment.

In addition, a total of 35 patients (20%, 95% CI 15–27) developed serious (grade 4) adverse events on study treatment, 18 (51%, 95% CI 43–58) during the first year of the study. Only 11 of these events were considered by the investigators to be
related to the study drugs (4 cases of elevated liver aminotransferases levels, 2 cases of increased CPK levels, 3 suicide attempts including 1 death, 1 hallucination, 1 pancreatitis).

**Metabolic and morphological changes (on-treatment analysis)**

Median values at different timepoints for total, HDL and LDL cholesterol, triglycerides and glucose concentrations are shown in Table 1. There was a significant increase from baseline to year 4 in HDL cholesterol level (+12 mg/dL, interquartile range (+4, +20), P<10^-4). Also, no patient was prescribed lipid-lowering agents during follow-up. In addition, there was no trend towards a decrease in cardiovascular risk scores over time.

Lipodystrophy was assessed by the investigators during the study: at baseline, year 1 and then every year thereafter. Overall, the prevalence of lipodystrophy (P=0.92), lipoatrophy (P=0.59) or lipohypertrophy (P=0.51) remained stable from baseline to year 4. No patient discontinued study treatment because of worsening lipodystrophy. There was no trend to more severe grades of lipodystrophy over time (P=0.79) (data not shown).

Overall, median body weight increased from 69 kg at baseline to 73 kg at year 4 (P=0.003), with an increase in body mass index from 22.8 kg/m^2 to 23.8 kg/m^2 at year 4 (P=0.006).

**Discussion**

In this extended follow-up to almost 4 years of the ALIZE ANRS 099 trial, we confirm that the once-daily combination of emtricitabine, didanosine and efavirenz provides a potent and durable antiretroviral response in initially well-controlled patients. Virological response obtained in the present study (57% of patients with plasma HIV RNA of <50 copies/mL at 4 years in an intent-to-treat analysis with missing values and treatment changes considered as failures), compares favourably with long-term results obtained in other efavirenz-based cART. In the 144 week follow-up of the 903 study, 71% and 68% of patients in the tenofovir, lamivudine and efavirenz arm reached a plasma viral load of <400 and <50 copies/mL, respectively. Similarly, in the 168 week follow-up of the DP-006 study, 48% and 42% of patients had HIV RNA levels of <50 and <400 copies/mL, respectively, with a cART including efavirenz, zidovudine and lamivudine. In the 144 week follow-up of the 934 study, excluding patients who did not

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Only fasting values were used for these timepoints. IQR, interquartile range; NA, not available.
agree to continue follow-up beyond 96 weeks, 71% and 64% of patients in the tenofovir, emtricitabine and efavirenz arm reached a plasma viral load of <400 and <50 copies/mL, respectively, whereas 58% and 56% of patients in the zidovudine, lamivudine and efavirenz arm reached a plasma viral load of <400 and <50 copies/mL, respectively. Similarly, in the 3 year follow-up of the NEFA study, 46% of patients randomized in the efavirenz arm met the definition of failure. These results confirm that a once-daily regimen combining emtricitabine, didanosine and efavirenz is able to maintain a durable antiviral response similar to that obtained with recent efavirenz-based regimens. In addition, a recent meta-analysis also supports the safety and efficacy of didanosine in the NRTI backbone as initial cART. Another report, however, demonstrated lower antiviral efficacy of this dual NRTI combination when used with unboosted atazanavir as compared with two efavirenz-based cARTs, but differences between arms might be attributed to the use of unboosted atazanavir rather than didanosine and emtricitabine. The low rate of treatment discontinuation attributed to treatment-related adverse events (15% of patients at 4 years) in this study also demonstrates the favourable tolerability profile of this combination. Efavirenz-related CNS adverse events remained the most frequent adverse events observed with this regimen during the first weeks of treatment but were usually transient. However, one patient, with a pre-existing history of depression, died by suicide that could be related due to the use of efavirenz. Nevertheless, a subanalysis of the ALIZE trial did not show evidence of efavirenz having a causal effect on the risk of depression or suicide attempt even up to 36 months of use but rather showed that age and history of depression were associated with depression. The long-term safety of the dual NRTI combination of didanosine and emtricitabine was very good. Only one patient presented with pancreatitis, with no renal failure or bone marrow toxicity. This favourable safety profile of the didanosine/emtricitabine/efavirenz combination has been previously reported, with similar data using the didanosine/lamivudine backbone. However, we acknowledge a potential lack of power to detect rare adverse events that could be related to the long-term use of didanosine, such as peripheral neuropathy or non-cirrhotic portal hypertension, due to the relatively small sample size of study. Also, a high rate of discontinuation, descriptive study and lack of comparator make it difficult to draw firm conclusions.

Interestingly, the cardiovascular tolerability of this combination seems attractive, with no change in lipid parameters except for a favourable significant increase in HDL cholesterol levels, already reported with NNRTIs and in particular nevirapine. Moreover it is noteworthy to observe a stability in triglyceride, total and LDL cholesterol levels with this combination, since efavirenz alone has been associated with less favourable changes. In addition, the Framingham score remained unchanged during follow-up in our patients. The two patients who developed a myocardial infarction during follow-up had multiple cardiovascular risk factors. However, this study was not designed, and remains underpowered, to assess cardiovascular disease endpoints.

In this study, as well as in other efavirenz-based regimens, the emergence of mutations in the reverse transcriptase gene was reported in patients with virological failure. However, rescue regimens could easily be identified in these patients as PIs, thymidine analogues and tenofovir usually retained full activity against these resistant viral isolates.

Body changes in this study were only assessed using a clinical definition. Nevertheless, the prevalence of clinically significant lipodystrophy after 4 years of follow-up was similar to baseline with this cART, as this regimen did not include thymidine analogues. Indeed, in another trial using the same combination of emtricitabine, didanosine and efavirenz in naive patients and where the assessment of lipodystrophy was blinded, only 1% of patients were reported with lipodystrophy after 1 year. However, since most patients switched from stavudine- and/or zidovudine-containing regimens, an improvement in lipodystrophy might have been expected to occur.

In summary, the 4 year extended follow-up of the ALIZE ANRS 099 trial has shown the durable antiretroviral activity and safety of a once-daily combination of emtricitabine, didanosine and emtricitabine, and supports its use in the treatment of HIV infection.

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Members of the ALIZE study group

References


Author contributions

As principal investigator, J-M. M. had full access to the data in this study and takes full responsibility for the integrity of the data and the accuracy of its analyses. Study concept and design: S. G., V. J., G. C. and J-M. M.

Acquisition of the data: G. C., W. R., F. S., S. G., V. R. and V. J. have nothing to disclose.

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