Didanosine, Lamivudine, and Efavirenz versus Zidovudine, Lamivudine, and Efavirenz for the Initial Treatment of HIV Type 1 Infection: Final Analysis (48 Weeks) of a Prospective, Randomized, Noninferiority Clinical Trial, GESIDA 3903

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Background. The combination of didanosine, lamivudine, and efavirenz (ddI/3TC/EFV) for the initial treatment of human immunodeficiency virus type 1 (HIV-1) infection has been insufficiently analyzed in clinical trials.

Methods. We conducted an open-label, randomized study to compare the noninferiority of ddI/3TC/EFV with the lamivudine-zidovudine tablet and EFV (COM/EFV), both administered with food to improve tolerability and convenience. Patients were stratified by HIV-1 RNA level of <5.0 $\log_{10}$ or $\geqslant 5.0$ $\log_{10}$ copies/mL. The primary end point was the percentage of patients with an HIV-1 RNA level of <50 copies/mL at week 48, determined by intention-to-treat analysis.

Results. Three hundred sixty-nine patients were randomized: 186 for ddI/3TC/EFV treatment and 183 for COM/EFV treatment. Both groups were well matched in terms of baseline characteristics; 19.3% of patients received a Centers for Disease Control and Prevention assessment of clinical category C, median HIV RNA level was 5.0 $\log_{10}$ copies/mL, and median $CD4^+$ cell count was 208 cells/μL. At week 48, by intention-to-treat analysis, 70% of patients in the ddI/3TC/EFV group and 63% of patients in the COM/EFV group had an HIV-1 RNA level of <50 copies/mL (treatment difference, 7.1%; 95% confidence interval, −2.39% to 16.59%). Fourteen patients (8%) in the COM/EFV arm and 26 patients (14%) in the ddI/3TC/EFV arm discontinued the study medication because of adverse events ($P = .046$). One patient (1%) in the ddI/3TC/EFV arm and 11 patients (6%) in the COM/EFV arm discontinued medication because of hematological toxicity ($P = .003$).

Conclusions. At week 48, ddI/3TC/EFV administered once per day with food did not have results inferior to those of COM/EFV treatment. A statistically significantly higher proportion of patients in the COM/EFV arm than in the ddI/3TC/EFV arm discontinued therapy because of adverse events, mainly because of hematological toxicity.

Clinical trials registration. NCT00256828.

Current guidelines recommend 2 different types of combination regimen for the antiretroviral therapy (ART)–naive patient: nonnucleoside reverse-transcriptase inhibitor–based regimens, consisting of 1 nonnucleoside reverse-transcriptase inhibitor plus 2 nucleoside (or nucleotide) reverse-transcriptase inhibitors (NRTIs), and protease inhibitor–based regimens consisting of 1 ritonavir-boosted protease inhibitor plus 2 NRTIs [1–3]. The preferred dual-NRTI components in these guidelines are tenofovir-emtricitabine (or lamivudine) and abacavir-lamivudine (or emtricitabine) [1–3].

The lack of comparative data from well-designed randomized clinical trials means that didanosine-lamivudine has not been included in the list of preferred

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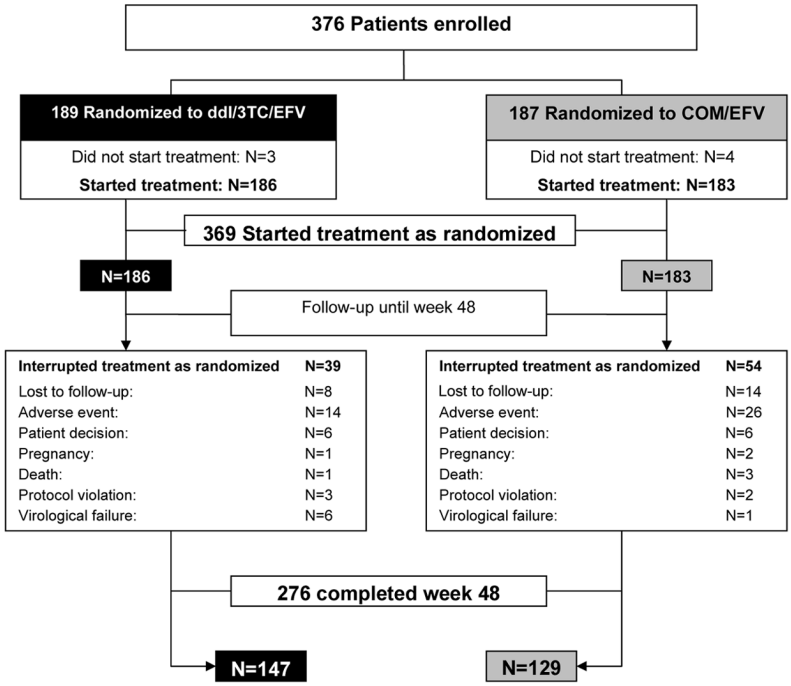

Figure 1. Grupo de Estudio de SIDA 3903 trial profile at 48 weeks. COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV.

dual-NRTI backbones for initial therapy of HIV infection. To date, only 2 small, randomized clinical trials have been published with this combination [4, 5]. However, the combination of didanosine, lamivudine, and efavirenz (ddI/3TC/EFV) is an attractive regimen for the ART-naive patient. Its main characteristics are the low daily pill burden (3 pills per day), once-daily (QD) dosing, good tolerability, scarce immediate toxicity, and a favorable resistance pattern after treatment failure [6]. The purpose of this trial was to compare ddI/3TC/EFV with zidovudine-lamivudine (coformulated) and efavirenz (COM/EFV) in ART-naive HIV-1–infected individuals. At the time this study was designed, zidovudine-lamivudine was the preferred NRTI backbone for initial therapy for HIV infection.

METHODS

Study individuals. This multicenter, randomized, open-label clinical trial was performed in 48 health care centers in Spain. The protocol was approved by the ethics committee at each center and by the Spanish Medicines Evaluation Agency. To be eligible, patients had to be ART-naive adults (aged ⩾18 years) with chronic HIV-1 infection and confirmed $CD4^+$ cell counts of <350 copies/mL; there were no restrictions on the HIV-1 RNA level. Exclusion criteria were pregnancy or a wish to become pregnant during the study period, acute hepatitis within the 30 days before inclusion, serum aspartate aminotransferase or alanine aminotransferase levels >4 times greater than the upper limit of normal, serum amylase levels >1.4 times greater than the upper limit of normal, peripheral neuropathy of grade ⩾2, alcohol abuse or illicit drug use, and current treatment with methadone. Written informed consent was obtained from all eligible patients before randomization.

Study design. Patients were randomly assigned (1:1 ratio) to receive 1 of the following: (1) ddI/3TC/EFV—that is, 400 mg didanosine QD (250 mg if the patient weighed <60 kg), 300 mg lamivudine QD, and 600 mg efavirenz QD—or (2) 300/150 mg COM/EFV twice daily (BID) plus 600 mg efavirenz QD. In this trial, we used the encapsulated enteric-coated bead formulation of ddI (EC-ddI). Both regimens were administered with food to improve tolerability and patient convenience.

Randomization was centralized and stratified by entry HIV-1 RNA level of <100,000 copies/mL, 100,000 copies/mL, or >100,000 copies/mL. After randomization, patients were assessed at baseline, 4 weeks, 12 weeks, 24 weeks, 36 weeks, and 48 weeks. At each visit, clinical data were collected, and blood specimens were obtained after an overnight fast. The following analyses were performed: complete blood cell count; $CD4^+$ cell count; measurement of plasma HIV-1 RNA, glucose, triglyceride, and total, low-density lipoprotein, and high-density lipoprotein cholesterol levels; and liver, kidney, and pancreatic function. Routine assays were used at all 48 health care sites throughout the follow-up period.

Safety was assessed using reports of adverse clinical events

Table 1. Baseline characteristics of all randomized patients who were exposed to ⩾1 dose of study medication.

Variable	ddI/3TC/EFV (n = 186)	COM/EFV (n = 183)	All (n = 369)	P
Age, median years (IQR)	38 (32–44)	40 (32–46)	39 (32–45)	.499
Female	42 (23)	43 (24)	85 (23)	.466
Weight, median kg (IQR)	68 (60–73)	67 (60–74)	68 (60–74)	.628
HIV-1 risk factors				
Homosexual	73 (39)	78 (43)	151 (41)	.290
Heterosexual	90 (48)	68 (37)	158 (43)	.019
Injection drug use	25 (13)	31 (17)	56 (15)	.214
CDC class C	28 (15)	43 (24)	71 (19)	.125
Positive for hepatitis virus				
B	13 (7)	6 (3)	19 (5)	.096
C	37 (20)	38 (21)	75 (21)	.425
B and C	5 (3)	1 (1)	6 (2)	.120
HIV-1 RNA level				
Median $\log_{10}$ copies/mL (IQR)	5.0 (4.5–5.4)	5.0 (4.5–5.5)	5.0 (4.5–5.5)	.817
⩾100,000 cop/mL	102 (55)	98 (54)	200 (54)	.433
$CD4^+$ cell count				
Median cells/mm^3 (IQR)	205 (93–284)	216 (117–277)	208 (112–280)	.916
<200 cells/mm^3	89 (48)	87 (48)	176 (48)	.518
<50 cells/mm^3	22 (12)	21 (12)	43 (12)	.523

NOTE. Data are no. (%) of patients, unless otherwise indicated. CDC, Centers for Disease Control and Prevention; COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV; IQR, interquartile range.

and abnormal laboratory results. The severity of adverse events and laboratory abnormalities were graded according to the World Health Organization Toxicity Grading Scale [7]. Clinical assessment and physical examination to detect lipoatrophy and lipoaccumulation were also scheduled at each visit, as described elsewhere [8]; the evaluated body areas were the face, extremities, hips/buttocks, abdomen, and dorsocervical region. Adherence to ART was calculated at each visit after baseline by the simplified medication adherence questionnaire, a validated instrument that classifies adherence as a dichotomous variable (adherent/nonadherent) [9].

Definitions. Virological failure was defined as 1 of the following: (1) reduction in HIV-1 RNA level by <1 log during the first 4 weeks of therapy, (2) failure to achieve an HIV-1 RNA level of <50 copies/mL by week 24, and (3) rebound to an HIV-1 RNA level >50 copies/mL on 2 consecutive occasions after achieving HIV-1 RNA determinations of <50 copies/mL. In cases of virological failure, serum samples were obtained and tested locally for resistance. Baseline HIV genotyping was not required in this trial. Progression to AIDS was defined as the occurrence of any new clinical event included in category C of the 1993 classification of the Centers for Disease Control and Prevention [10].

End points. The primary study end point was the percentage of patients with HIV-1 RNA levels <50 copies/mL at 48 weeks, by intention-to-treat (ITT) analysis. Secondary end points included the percentage of patients with HIV-1 RNA concentrations of <400 copies/mL at 48 weeks by ITT analysis, percentage of patients with HIV-1 RNA concentrations of <50 copies/mL and of <400 copies/mL at 48 weeks by on-treatment analysis, changes in $CD4^+$ cell counts, proportion of patients who experienced virological failure, development of genotypic resistance at treatment failure, adverse events leading to study-drug discontinuation, percentages of laboratory abnormalities (grades 3–4) through week 48, lipid elevations, changes in body composition, and adherence to ART.

Statistical analysis. The hypothesis was that ddI/3TC/EFV QD is not inferior to COM/EFV BID, on the basis of the proportion of patients achieving HIV-1 RNA levels of <50 copies/mL at 48 weeks by ITT analysis. The ITT analysis included all randomized patients who were exposed to ⩾1 dose of study medication (ITT-E), with consideration of missing or discontinuation of any drug as treatment failure. ddI/3TC/EFV QD can be considered not to be inferior to COM/EFV BID if the 95% CI for the difference in response rates is entirely greater than −12%. In relation to sample size, we estimated that, with 185 patients per arm, on the basis of having ⩾75% efficacy in the ddI/3TC/EFV QD arm at 48 weeks, the study would have 83% power for the primary noninferiority comparison at the 1-sided .05 level of significance (70% for a 2-sided comparison).

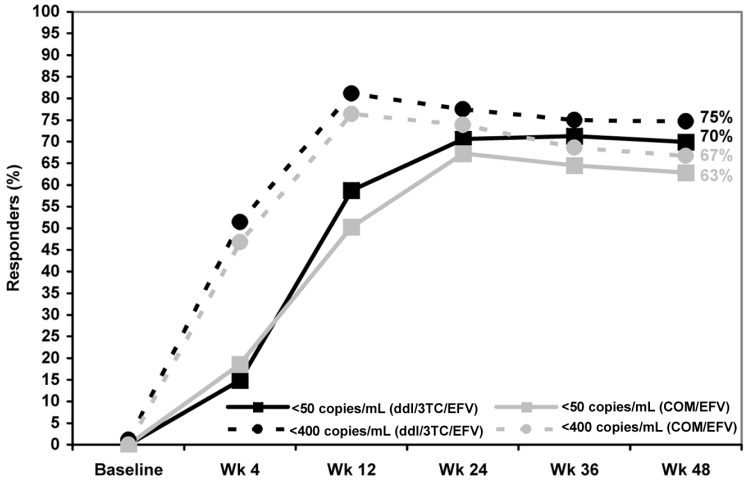

Figure 2. Percentages of all patients with HIV-1 RNA levels <50 copies/mL and <400 copies/mL, as determined by intention-to-treat analysis of all randomized patients who were exposed to ⩾1 dose of study medication, with missing or discontinuation of any drug considered to be treatment failure. HIV-1 RNA levels <50 copies/mL: treatment difference for combination of didanosine, lamivudine, and efavirenz (ddI/3TC/EFV) versus lamivudine-zidovudine tablet and EFV (COM/EFV), 7.1% (95% CI, −2.39% to 16.59%). HIV-1 RNA levels <400 copies/mL: treatment difference for ddI/3TC/EFV versus COM/EFV, 8% (95% CI, −1% to 17%). Wk, week.

RESULTS

Patient characteristics and disposition. During the recruitment period (June 2004 through December 2005), 369 patients from 48 centers were randomized (ddI/3TC/EFV arm, 186; COM/EFV arm, 183) (figure 1). In total, 276 (75%) of the 369 patients in the ITT-E population completed week 48. Therefore, the on-treatment population included 276 patients (ddI/3TC/EFV arm, 147; COM/EFV arm, 129).

Baseline characteristics were similar for the 2 treatment groups (table 1), except that there were fewer cases of heterosexual infection transmission in the COM/EFV group than in the ddI/3TC/EFV group. Eighty-five (23%) of the ITT-E population was female; the median age of all participants was 39 years, 13 (15%) had acquired HIV infection by injection drug use, 16 (19%) had prior AIDS-defining conditions, 4 (5%) were positive for hepatitis B surface antigen, and 18 (21%) had antibodies against hepatitis C virus. The median HIV-1 RNA level was 5.0 $\log_{10}$ copies/mL, and the median $CD4^+$ cell count was 208 cells/mm^3.

Efficacy. At week 48, by ITT-E analysis, the percentage of

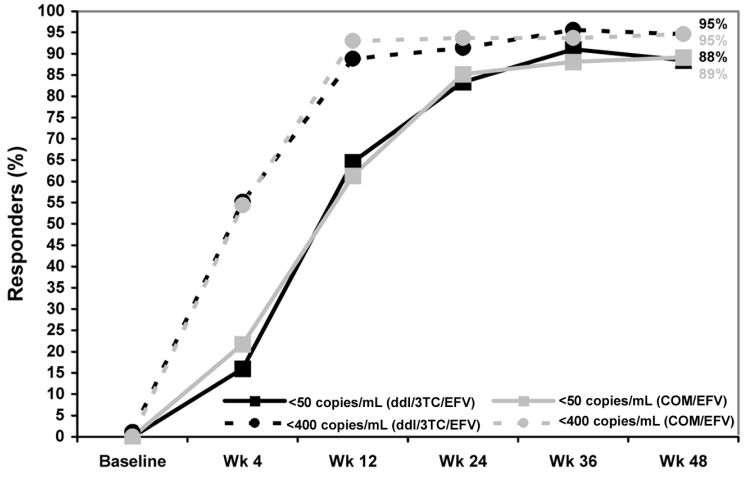

Figure 3. On-treatment analysis. Percentages of on-treatment patients with HIV-1 RNA <50 copies/mL and <400 copies/mL. HIV-1 RNA levels <50 copies/mL: treatment difference for combination of didanosine, lamivudine, and efavirenz (ddI/3TC/EFV) versus lamivudine-zidovudine tablet and EFV (COM/EFV), −3% (95% CI, −7% to 6%). HIV-1 RNA levels <400 copies/mL: treatment difference for ddI/3TC/EFV versus COM/EFV, 0% (95% CI, −5% to 5%). Wk, week.

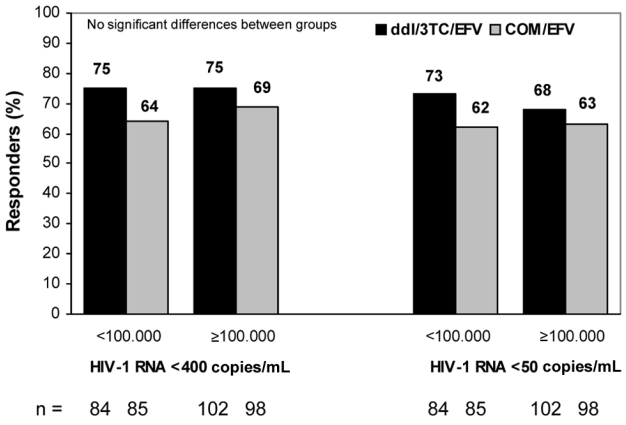

Figure 4. Proportions of patients with HIV-1 RNA levels <50 copies/mL and <400 copies/mL; by baseline HIV-1 RNA, as determined by intention-to-treat analysis of all randomized patients who were exposed to ⩾1 dose of study medication, with missing or discontinuation of any drug considered to be treatment failure. COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV.

patients with HIV-1 RNA levels <50 copies/mL was 70% in the ddI/3TC/EFV group and was 63% in the COM/EFV group. The treatment difference was 7.1% (95% CI, −2.39% to 16.59%), thereby establishing noninferiority of ddI/3TC/EFV to COM/EFV (figure 2). Noninferiority was also demonstrated by ITT-E for those patients who achieved an HIV-1 RNA level of <400 copies/mL and for those who achieved an HIV-1 RNA level of <50 copies/mL and <400 copies/mL, as determined by on-treatment analysis (figures 2 and 3). Treatment response assessed by baseline HIV-1 RNA strata or by baseline $CD4^+$ cell count showed consistent results between groups and across strata (figures 4 and 5).

Immunologic response. A significant increase in $CD4^+$ cell counts was observed in both arms, with a 48-week median increase of 158 cells/mL in the ddI/3TC/EFV arm (interquartile range, 88–270 cells/mL) and 163 cells/mL in the COM/EFV arm (interquartile range, 77–230 cells/mL) ($P = .412$) (figure 6).

Clinical disease progression. Eleven AIDS-defining diseases (tuberculosis, 6 cases; pneumocystosis, 2 cases; toxoplasmosis, 1 case; non-Hodgkin lymphoma, 1 case; and *Cytomegalovirus* retinitis, 1 case) were diagnosed in 11 patients after a median period of 52 days (range, 9–261 days): 5 (3%) in the ddI/3TC/EFV arm and 6 (3%) in the COM/EFV arm ($P = .177$). Four deaths were reported during the study period: 1 (<1%) in the ddI/3TC/EFV arm (motor vehicle accident, 1 patient) and 3 (2%) in the COM/EFV arm (non-Hodgkin lymphoma, 2; suicide, 1). These deaths were not related to the study medication.

Virological failure and genotype analysis. Protocol-defined virological failure was documented in 6 patients (3%) in the ddI/3TC/EFV arm and in 1 patient (<1%) in the COM/EFV arm ($P = .122$). Genotypic resistance testing was performed for the 7 patients who experienced protocol-defined virological failure (table 2). Of these, 6 patients had efavirenz-associated mutations, 5 patients had the M184V/I mutation, 3 patients had thymidine analogue–associated mutations, and 1 patient had the ddI-associated mutation L74V. International AIDS Society–USA–defined major protease inhibitor mutations were not detected in any of the patients [11]. Baseline genotyping was performed in 3 of the 6 patients in the ddI/3TC/EFV arm with protocol-defined virological failure. Two patients were infected with a wild-type virus, whereas 1 patient was found to be infected with a virus harboring the K103N mutation.

Adherence. After 48 weeks, the rate of patient adherence to ART (as determined by the simplified medication adherence questionnaire) was 82% (153 patients) in the ddI/3TC/EFV arm and 80% (146 patients) in the COM/EFV arm ($P = .754$). If we exclude the need to take the medication at the indicated time, the percentages of patients who adhered to ART were 84% (156 patients) and 83% (152) in the ddI/3TC/EFV and COM/EFV arms, respectively ($P = .869$).

Safety. There were fewer premature discontinuations of study medication because of adverse events in the ddI/3TC/EFV arm than in the COM/EFV arm (14 [8%] vs. 26 [14%]; $P = .046$) (table 3). This difference stems from a significantly lower frequency of hematological toxicity that led to study-drug discontinuation in the ddI/3TC/EFV arm than in the COM/EFV arm (1 [<1%] vs. 11 [6%]; $P = .003$). Of note, no single case of clinical pancreatitis was seen in any of the treatment groups.

The overall incidence of grade 3–4 laboratory abnormalities was similar in both arms, except for a statistically significantly

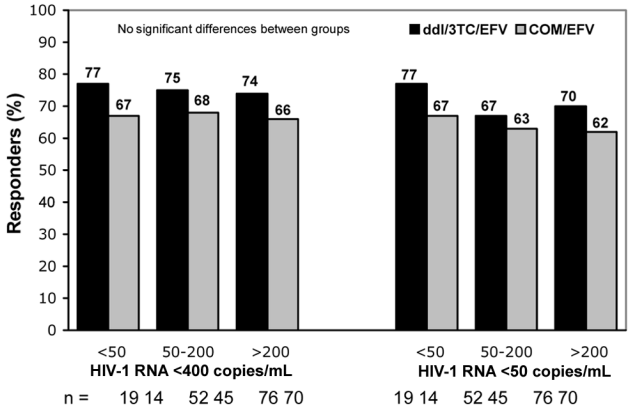

Figure 5. Proportions of patients with HIV-1 RNA <50 copies/mL and <400 copies/mL at week 48, as determined by baseline $CD4^+$ cell count and intention-to-treat analysis of all randomized patients who were exposed to ⩾1 dose of study medication. COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV.

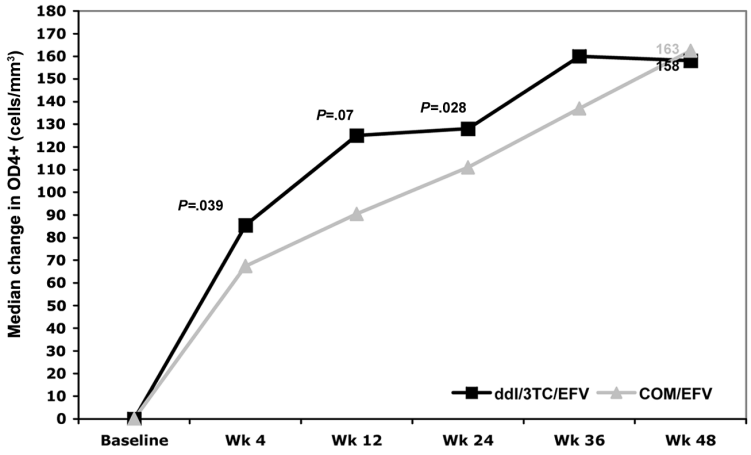

Figure 6. CD4 median change in cell count from baseline, as determined by intention-to-treat analysis of all randomized patients who were exposed to ⩾1 dose of study medication. COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV. Wk, week.

lower percentage of neutropenia ($<0.75 \times 10^9$ cells/L) in the ddI/3TC/EFV arm than in the COM/EFV arm (1% vs. 8%; $P = .005$) (table 4). The frequency of grade 3–4 elevations of serum amylase was low and not statistically significantly different between the ddI/3TC/EFV arm and the COM/EFV arm (4% vs. 5%; $P = .742$).

In the on-treatment population, the maximum median changes from baseline in fasting lipid levels (interquartile range) in the ddI/3TC/EFV arm and in the COM/EFV arm were as follows: triglycerides, 47.0 mg/dL (23.0–102.5 mg/dL) versus 45.5 mg/dL (12.0–100.0 mg/dL; $P = .455$); total cholesterol, 59.0 mg/dL (40.0–82.0 mg/dL) versus 44.0 mg/dL (30.0–70.0 mg/dL; $P = .001$); low-density lipoprotein cholesterol, 35.0 mg/dL (17.0–60.0 mg/dL) versus 29.0 mg/dL (16.0–49.0 mg/dL; $P = .118$); and high-density lipoprotein cholesterol, 21.0 mg/dL (15.25–29.0 mg/dL) versus 18.0 mg/dL (12.0–25.0 mg/dL; $P = .055$). Lipid-lowering medications were administered to 6 patients (4%) in the ddI/3TC/EFV arm and to 9 patients (7%) in the COM/EFV arm ($P = .6$).

At 48 weeks, investigator-defined lipoatrophy (any grade) in the on-treatment population was reported with similar frequency in both the ddI/3TC/EFV and COM/EFV arms: 11 (7%) of 147 patients and 11 (9%) of 129 patients, respectively ($P = .840$). The frequency of lipoaccumulation was similar in both the ddI/3TC/EFV and the COM/EFV arms: 20 patients (14%) versus 16 patients (12%) ($P = .858$).

DISCUSSION

The results of GESIDA (Grupo de Estudio de SIDA) 3903 showed that a regimen of ddI/3TC/EFV administered QD with food provides a potent antiretroviral response in the treatment of HIV-1 infection in ART-naive adults with chronic HIV-1 infection. Noninferiority of the ddI/3TC/EFV regimen to the COM/EFV regimen was confirmed at week 48 of the study, for the primary end point of HIV-1 RNA level <50 copies/mL by ITT-E analysis. It was also confirmed for secondary virological end points, including those patients with an HIV-1 RNA level <400 copies/mL by ITT-E analysis and those patients with an HIV-1 RNA level <50 copies/mL and <400 copies/mL, as

Table 2. Summary of protocol-defined confirmed virological failure and drug-associated resistance by week 48.

Patient	Regimen	Failure, week	HIV-1 RNA, copies/mL	Resistance mutations	Baseline genotyping
1	COM/EFV	36	27,500	K103N, M184V, and K219E	Not available
2	ddI/3TC/EFV	36	19,157	K103N, V108I, and M184V	Wild type
3	ddI/3TC/EFV	12	1,750,000	K103N, M184V, and L74V	K103N
4	ddI/3TC/EFV	36	4574	K103N, V108I, M184V, and T215Y	Not available
5	ddI/3TC/EFV	12	61,415	K103N and M184V	Wild type
6	ddI/3TC/EFV	24	470,000	R211K and G190E	Not available
7	ddI/3TC/EFV	24	292,000	K103N, Y188L, and M184I	Not available

NOTE. COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV.

Table 3. Adverse events leading to study-drug discontinuation at week 48.

Adverse event	No. (%) of patients, by treatment		
	ddI/3TC/EFV (n = 186)	COM/EFV (n = 183)	P
All	14 (8)	26 (14)	.046
Hematological toxicity			
All	1 (1)	11 (6)	.003
Anemia	0 (0)	11 (6)	.000
Neutropenia	1 (1)	4 (2)	.212
Rash	7 (4)	7 (4)	.785
CNS toxicity	2 (1)	3 (2)	.683
Psychosis	1 (1)	0 (0)	.99
Stevens-Johnson syndrome	1 (1)	0 (0)	.99
Malaise	1 (1)	1 (1)	.99
Gastrointestinal intolerance	1 (1)	1 (1)	.99
Myopathy	0 (0)	1 (1)	.496
Cytomegalovirus retinitis	0 (0)	1 (1)	.496
Viral hepatitis	0 (0)	1 (1)	.496

NOTE. COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV.

determined by on-treatment analysis. In addition, treatment response assessed by baseline HIV-1 RNA strata (<100,000 and ⩾100,000 copies/mL) or by baseline $CD4^+$ cell count (<50, 50–200, and >200 cells/mL) was similar for both regimens.

We found a more rapid increase in $CD4^+$ cell response in the ddI/3TC/EFV arm than in the COM/EFV arm, as revealed by a statistically significantly higher median increase from baseline at weeks 4, 12, and 24. However, we did not find statistically significant differences in the $CD4^+$ cell response between treatment groups at week 48. In other clinical trials, a lower $CD4^+$ cell response was found with ART regimens containing zidovudine-lamivudine than with other NRTI combinations, such as stavudine-didanosine [12], stavudine-lamivudine [13], abacavir-lamivudine [14], and tenofovir-emtricitabine [15]. This may have been because of a leukopenic effect of zidovudine.

Protocol-defined virological failure was uncommon and not statistically significantly different between groups: 6 patients in the ddI/3TC/EFV arm and 1 patient in the COM/EFV arm experienced failure. The genotypic resistance tests performed at the time of failure showed resistance-associated mutations in all instances. Predominant mutations detected in viruses from patients treated with ddI/3TC/EFV were the EFV-associated mutation K103N, followed by the 3TC-associated mutation M184V/I. Interestingly, the ddI-associated mutation L74V was detected in only 1 patient, for whom baseline genotyping showed the presence of the K103N mutation. These results are more consistent with those of Maggiolo et al. [4], who found that none of the viruses recovered from patients who experienced treatment failure with the ddI/3TC/EFV regimen had the L74V mutation, than it is with those of Santos et al. [16], who detected the L74V mutation (as well as the M184V/I and K103N mutations) at the time of failure in viruses recovered from 6 of 7 patients who received ddI/3TC/EFV.

The safety analysis revealed statistically significantly fewer premature discontinuations of study medication attributable to adverse events in the ddI/3TC/EFV arm than in the COM/EFV arm. This finding is consistent with the results of other studies that have found clinically significant anemia associated with the use of zidovudine [14, 15]. Other than hematological toxicity, the incidence of adverse events was comparable between both regimens over the 48-week period. Of note, no single case of clinical pancreatitis was seen in this trial, and the frequency of grade 3–4 hyperamylasemia was not statistically significantly different between the groups. Both groups showed similar changes from baseline in fasting lipid values at week 48, and the use of lipid-lowering medications was similar in both study arms.

Investigator-defined lipodystrophy (lipoatrophy and lipoaccumulation) was uncommon and similar in both study arms. However, we must emphasize the limitation of our study in this regard, because the period of observation was only 48 weeks, and there were no objective measurements of body composition.

In this trial, patients assigned to the ddI/3TC/EFV arm took all of the pills together at night with food. As mentioned before, we used EC-ddI, a formulation that is equivalent to the buffered didanosine tablet [17]. It is recommended that EC-ddI be taken on an empty stomach, a recommendation based on the finding that the bioavailability of EC-ddI can be reduced by 20%–25% with food [18]. It should be taken into account, however, that the absorption of other NRTIs is also reduced when they are taken with food. For example, food reduces drug exposure by 20% for zidovudine [19, 20] and by 27% for zalcitabine [21], but there are no data to support that taking these drugs with food may cause therapeutic failure. The results of our trial show that the clinical significance of such moderate reductions in ddI exposure with food, especially as part of a HAART regimen, is null. They also support administering EC-ddI at the same time as lamivudine and efavirenz, with food, as a compact QD regimen.

At the time that this study was designed, the results of different clinical trials [22, 23] supported the inclusion of zidovudine-lamivudine as the preferred NRTI backbone for initial therapy of HIV infection. However, zidovudine-lamivudine performed less well than tenofovir-emtricitabine in a clinical trial, presumably because of its requirement for BID dosing and the higher frequency of intolerance of the regimen [15]. Our study showed that ddI/3TC/EFV QD administered with food was not inferior to COM/EFV BID over 48 weeks. It also showed that a statistically significantly higher proportion of

Table 4. Percentages of patients with laboratory abnormalities (grades 3–4) at 48 weeks.

Laboratory finding	No. of patients, by treatment		
	ddI/3TC/EFV (n = 186)	COM/EFV (n = 183)	P
Hemoglobin level <8 g/dL	1	4	.112
Total neutrophils $<0.75 \times 10^9$ cells/L	1	8	.005
Platelet count $<50 \times 10^9$ cells/L	4	4	.99
Serum glucose level >250 mg/dL	0	0	…
Serum creatinine level >3× ULN	2	3	.713
Bilirubin level >2.5× ULN	4	5	.765
Aspartate aminotransferase level >5× ULN	4	6	.569
Alanine aminotransferase level >5× ULN	7	5	.597
Alkaline phosphatase level >5× ULN	0	1	.496
γ-Glutamyl transpeptidase level >5× ULN	21	19	.757
Amylase level ⩾2.1× ULN	4	5	.742
Triglyceride level >750 mg/dL	4	1	.213
Cholesterol level			
Total, >300 mg/dL	9	5	.221
LDL, ⩾190 mg/dL	18	12	.234

NOTE. COM/EFV, lamivudine-zidovudine tablet and efavirenz (EFV); ddI/3TC/EFV, didanosine, lamivudine, and EFV; LDL, low-density lipoprotein; ULN, upper limit of normal.

patients in the COM/EFV arm than in the ddI/3TC/EFV arm discontinued therapy because of adverse events, mainly hematological toxicity. Moreover, it showed no increased risk of pancreatitis, peripheral neuropathy, or other mitochondria-associated toxicities associated with the use of ddI. Limitations of this study include its open-label design, which might bias assessment of safety but would be less likely to bias virological and immunological end points. Another limitation is the absence of baseline genotyping. Despite these shortcomings, we believe that the findings of our study may have implications for the use of ddI/3TC/EFV in the initial therapy of HIV infection.

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