Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia

Lazzarin, A.; Clotet, B.; Cooper, D.; Reynes, J.; Arasteh, K.; Nelson, M.; Katlama, C.; Stellbrink, H.J.; Delfraissy, J.F.; Lange, J.M.A.; Huson, L.; De Masi, R.; Wat, C.; Delehanty, J.; Drobnes, C.; Salgo, M.

DOI
10.1056/NEJMoa035211

Publication date
2003

Published in
The New England journal of medicine

ORIGINAL ARTICLE

Efficacy of Enfuvirtide in Patients Infected with Drug-Resistant HIV-1 in Europe and Australia

Adriano Lazzarin, M.D., Bonaventura Clotet, M.D., Ph.D., David Cooper, M.D., D.Sc., Jacques Reynes, M.D., Ph.D., Keikawus Arasteh, M.D., Mark Nelson, M.B., B.S., Christine Katlama, M.D., Hans-Jürgen Stellbrink, M.D., Jean-François Delfraissy, M.D., Joep Lange, M.D., Ph.D., Les Huson, Ph.D., Ralph DeMasi, Ph.D., Cynthia Wat, M.B., B.S., John Delehanty, Ph.D., Claude Drobnes, Ph.D., and Miklos Salgo, M.D., Ph.D., for the TORO 2 Study Group*

ABSTRACT

BACKGROUND

The T-20 vs. Optimized Regimen Only Study 2 (TORO 2) compared the efficacy and safety of 24 weeks of treatment with the fusion inhibitor enfuvirtide in combination with an optimized background antiretroviral regimen with the efficacy and safety of the optimized background regimen alone.

METHODS

The patients had previous treatment with each of the three classes of antiretroviral drugs, documented resistance to each class, or both and a plasma level of human immunodeficiency virus type 1 (HIV-1) RNA of at least 5000 copies per milliliter. They were randomly assigned in a 2:1 ratio to receive either enfuvirtide (90 mg twice daily) plus a background regimen optimized with the aid of resistance testing (enfuvirtide group) or the background regimen alone (control group).

RESULTS

Of the 512 patients who underwent randomization, 335 in the enfuvirtide group and 169 in the control group received at least one dose of study medication and had at least one follow-up measurement of plasma HIV-1 RNA. The median base-line plasma HIV-1 RNA level was 5.1 $\log_{10}$ copies per milliliter in both groups. The median CD4+ cell count was 98.0 cells per cubic millimeter in the enfuvirtide group and 101.5 cells per cubic millimeter in the control group. Patients had a median of seven years of previous treatment and had received a median of 12 antiretroviral drugs. The background regimen comprised a mean of four antiretroviral drugs in both groups. At 24 weeks, the least-squares mean change from base line in the plasma viral load (intention-to-treat, last observation carried forward) was a decrease of 1.429 $\log_{10}$ copies per milliliter in the enfuvirtide group and a decrease of 0.648 $\log_{10}$ copies per milliliter in the control group, a difference of 0.781 $\log_{10}$ copies per milliliter ($P<0.001$). The mean increase in the CD4+ cell count was greater in the enfuvirtide group (65.5 cells per cubic millimeter) than in the control group (38.0 cells per cubic millimeter, $P=0.02$).

CONCLUSIONS

The addition of enfuvirtide to an optimized background regimen provided significant viral suppression and immunologic benefit over a 24-week period in HIV-1–infected patients who had previously received multiple antiretroviral drugs.

From the Istituto di Ricovero e Cura a Carattere Scientifico, San Raffaele Vita-Salute University, Milan, Italy (A.L.); the Hospital Universitari Germans Trias i Pujol and the Institut de Recerca de la SIDA–Caixa Foundation, Badalona, Barcelona, Spain (B.C.); the National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia (D.C.); the University Hospital of Montpellier, Montpellier, France (J.R.); EPIMED, Vivantes Auguste-Viktoria Hospital, Berlin, Germany (K.A.); the Chelsea and Westminster Hospital, London (M.N.); the Hôpital Pitié-Salpêtrière, Paris (C.K.); the University Hospital Eppendorf, Hamburg, Germany (H.-J.S.); the Centre Hospitalier Universitaire Bicêtre, Assistance Publique–Hôpitaux de Paris, Paris (J.-F.D.); the Academic Medical Center, University of Amsterdam, Amsterdam (J.L.); Roche Products, Welwyn, Hertfordshire, United Kingdom (L.H., C.W.); Trimeris, Durham, N.C. (R.D., J.D., C.D.); and Roche, Nutley, N.J. (M.S.). Address reprint requests to Dr. Lazzarin at the Clinic of Infectious Diseases, IRCCS, San Raffaele Vita-Salute University, Via Stamira d'Ancona 20, 20127 Milan, Italy, or at lazzarin. adriano@hsr.it.

*Members of the TORO 2 (T-20 vs. Optimized Regimen Only Study 2) group are listed in the Appendix.

N Engl J Med 2003;348:2186-95.

THE USE OF HIGHLY ACTIVE ANTIRETROviral therapy has proved extremely successful over the past several years.[1,2] However, in about 50 percent of patients, viral suppression is incomplete, and patients are obliged to switch from one combination of antiretroviral drugs to another to combat resistant virus.[3] Cross-resistance within each of the three classes of approved antiretroviral drugs is extensive and often limits the treatment options for patients who are receiving their third or fourth regimen.[4-6] New classes of drugs directed at targets other than the reverse transcriptase or protease would be of great benefit.

Enfuvirtide (previously known as T-20) is a synthetic 36-amino-acid peptide that binds to the first heptad-repeat region (HR1) of envelope glycoprotein 41 of human immunodeficiency virus type 1 (HIV-1), a protein that is critical for the fusion of the virus with the cell membrane.[7] In phase 1 and 2 clinical trials, enfuvirtide reduced the plasma viral load and was well tolerated when given as short-term monotherapy or as part of long-term combination therapy in patients who had previously been treated with multiple antiretroviral drugs.[8-12]

In the T-20 vs. Optimized Regimen Only Study 2 (TORO 2), a randomized, controlled phase 3 study, we evaluated the efficacy and safety of enfuvirtide therapy in combination with an optimized background antiretroviral regimen in patients who had been treated with multiple antiretroviral drugs, including drugs in all currently available antiretroviral classes. The trial was conducted in centers throughout Europe and Australia. A similar study was conducted in North America and Brazil (the T-20 vs. Optimized Regimen Only Study 1 [TORO 1]).[13]

METHODS

STUDY DESIGN AND PATIENTS

We conducted a randomized, open-label, controlled, parallel-group, phase 3 study involving 67 investigators in France, Spain, Italy, Germany, Australia, the United Kingdom, Belgium, Switzerland, the Netherlands, and Sweden. The study design, patient-selection criteria, conduct, monitoring, and protocol-specific analyses were identical to those of the TORO 1 trial,[13] except for two minor differences in the criteria for inclusion. Patients included in the study were HIV-1–infected adults (defined as persons at least 16 years of age) with a plasma HIV-1 RNA level of at least 5000 copies per milliliter and at least three months of previous treatment with at least one antiretroviral drug from each of the three currently approved classes, demonstrated resistance to each class, or both (whereas TORO 1 required at least six months of previous treatment and treatment with at least two protease inhibitors). Patients provided written informed consent, and the protocol and the provisions for informed consent were reviewed and approved by the independent ethics committee or institutional review board at each center.

Patients were randomly assigned to receive enfuvirtide (90 mg subcutaneously twice daily) plus an optimized background regimen of three to five antiretroviral drugs (enfuvirtide group) or the optimized background regimen alone (control group). Changes to the treatment regimen were permitted for the management of toxic effects or in the event of virologic failure. Virologic failure was defined by one of the following: a decrease from base line in the plasma HIV-1 RNA level of less than 0.5 $\log_{10}$ copies per milliliter on two or three consecutive measurements after week 6, with at least 14 days between the first and last measurements; a decrease from base line of less than 1.0 $\log_{10}$ copies per milliliter on such consecutive measurements after week 14; or a decrease from base line of at least 2.0 $\log_{10}$ copies per milliliter on such consecutive measurements, followed by a rebound of more than 1.0 $\log_{10}$ copies per milliliter from the average of the two lowest values (not necessarily consecutive) after week 6. Patients who had virologic failure after week 8 were allowed to undergo repeated genotypic and phenotypic resistance testing and encouraged to modify their background regimen; if they were in the control group, they could also add enfuvirtide to their regimen.

EFFICACY ANALYSIS

The primary efficacy analysis was conducted at week 24 in the intention-to-treat population, defined as patients who had received at least one dose of study medication and had at least one follow-up measurement of plasma HIV-1 RNA. The primary efficacy end point was the reduction in the plasma HIV-1 RNA level, and secondary efficacy end points included the categorical virologic response, the time to virologic response, the time to virologic failure, and changes in the CD4+ and CD8+ cell counts. Three categories of virologic response were defined on the basis of the plasma HIV-1 RNA load at week

24: less than 50 copies per milliliter, less than 400 copies per milliliter, or a decrease from base line of at least 1.0 $\log_{10}$ copies per milliliter, on two consecutive measurements.

SAFETY ANALYSIS

The safety analysis was conducted in the population of all patients who had received at least one dose of study medication and had follow-up data on safety. Safety end points included adverse events, serious adverse events (including death), adverse events leading to premature withdrawal from the study, injection-site reactions, results of clinical laboratory tests (hematology, serum chemistry, and urinalysis), results on electrocardiography, and vital signs. An additional updated safety analysis combining data from the two phase 3 studies (TORO 1 and TORO 2) has been conducted.[13]

ROLE OF THE STUDY SPONSORS

Roche and Trimeris were the study sponsors. Design of the trial protocol was the responsibility of Roche and Trimeris in collaboration with various health authorities and advisory boards that included certain authors of this report. All statistical analyses were performed by employees of the study sponsor, all of whom were suitably qualified statisticians. Data collection was carried out by Roche Clinical Operations. The data were interpreted by Roche and Trimeris in collaboration with the advisory boards and the clinical trial investigators.

STATISTICAL ANALYSIS

All reported P values are two-sided. Details of the statistical analyses are reported by Lalezari et al.[13]

RESULTS

STUDY POPULATION

A total of 512 patients were enrolled and underwent randomization between February 2001 and July 2001. Three patients randomly assigned to the enfuvirtide group and 1 randomly assigned to the control group withdrew their consent and never received any study medication, leaving 338 subjects in the enfuvirtide group and 170 in the control group (Fig. 1). Of the patients who received at least one dose of the study drugs, one patient in each group had neither follow-up data on safety nor a post-treatment measurement of plasma HIV-1 RNA, and two additional patients in the enfuvirtide group had no post-treatment measurement of plasma HIV-1 RNA. Thus, the intention-to-treat population comprised 335 patients in the enfuvirtide group and 169 patients in the control group, and the population for the safety analysis comprised 337 patients in the enfuvirtide group and 169 patients in the control group.

In the intention-to-treat population, 130 patients in the control group (76.9 percent) met the protocol-defined criteria for virologic failure between week 8 and week 24. Of these patients, 114 (87.7 percent) switched to enfuvirtide. In the enfuvirtide group, 165 patients (49.3 percent) had virologic failure by week 24. A total of 57 patients in the enfuvirtide group (17.0 percent) withdrew from the study by week 24, as did 8 of the 55 patients in the control group who had continued to receive the background regimen alone (14.5 percent) and 9 of the patients in the control group who had switched to enfuvirtide (7.9 percent).

DEMOGRAPHIC AND BASE-LINE CHARACTERISTICS

The demographic characteristics of the intention-to-treat population were similar in the two treatment groups (Table 1). The two groups were also well balanced in terms of previous antiretroviral therapy, with both groups having previous exposures to a median of 12 antiretroviral drugs for a median of seven years. The majority of patients had received treatment with at least five nucleoside reverse-transcriptase inhibitors (84.5 percent in the enfuvirtide group and 89.9 percent in the control group), at least two nonnucleoside reverse-transcriptase inhibitors (56.7 percent in the enfuvirtide group and 58.6 percent in the control group), and at least five protease inhibitors (51.9 percent in the enfuvirtide group and 53.8 percent in the control group). The percentage of patients who had been treated with lopinavir–ritonavir was higher in the enfuvirtide group than in the control group (60.6 percent vs. 52.1 percent). A small percentage of patients in each treatment group had been treated with tenofovir (4.5 percent in the enfuvirtide group and 1.8 percent in the control group).

Mutations associated with resistance to protease inhibitors, nucleoside reverse-transcriptase inhibitors, and nonnucleoside reverse-transcriptase inhibitors were found in at least 85 percent, more than 90 percent, and more than 75 percent of patients, respectively, and base-line genotypic and phenotypic sensitivity scores indicated that HIV from the majority of patients was sensitive to fewer than two of the antiretroviral drugs in their background regimen (Table 1).

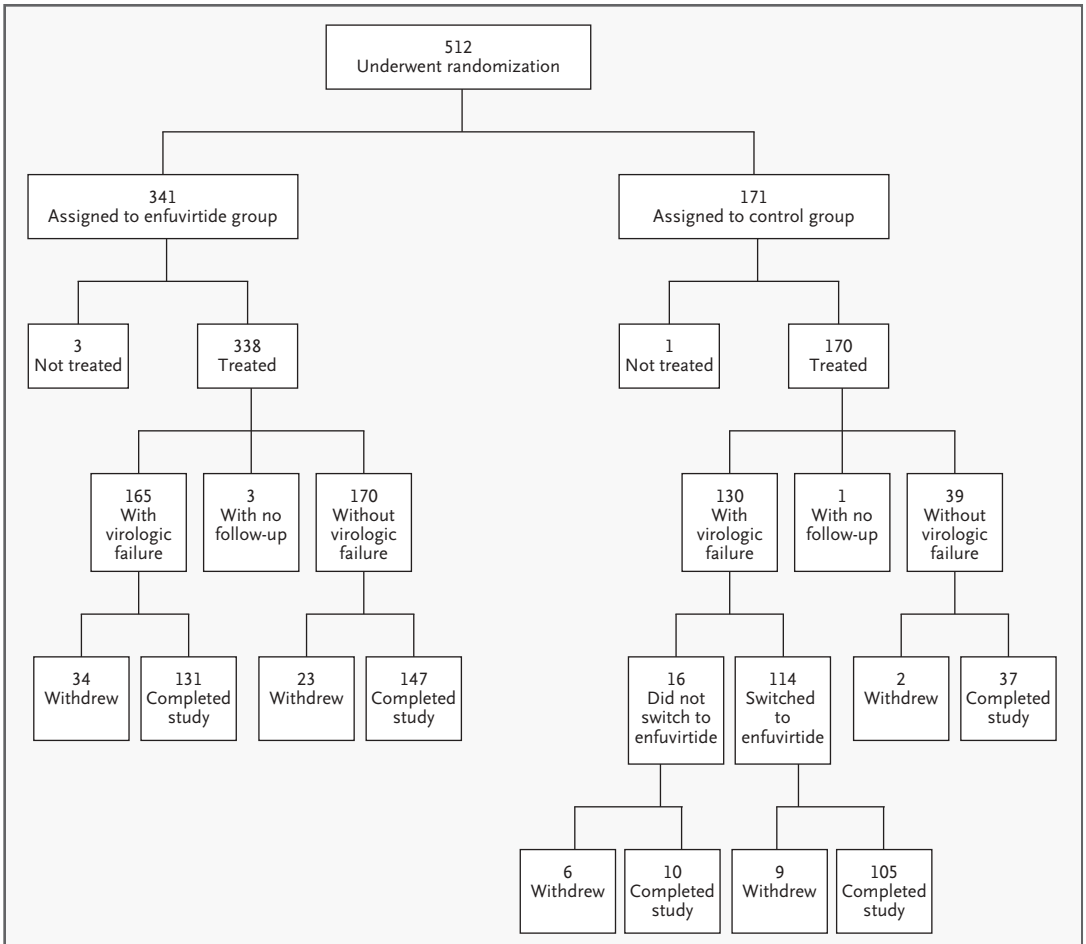

Figure 1. Disposition of All Randomized Patients to Week 24.

Two of the three patients in the enfuvirtide group who are described as having no follow-up had follow-up data on safety but no post-treatment data on the HIV-1 RNA level and therefore could not be classified with respect to virologic failure. Virologic failure was defined as outlined in the Methods section.

The mean (±SD) number of drugs in the optimized background regimen was 3.8±0.8 in the enfuvirtide group and 3.9±0.9 in the control group. The percentage of patients using lopinavir–ritonavir was slightly lower in the enfuvirtide group (35.8 percent [120 patients]) than in the control group (42.0 percent [71 patients]). Otherwise, the two groups were similar in terms of patterns of use of antiretroviral drugs in the background regimen.

VIROLOGIC RESPONSE

At week 24, the least-squares mean change from base line in the plasma HIV-1 RNA level in the intention-to-treat population was a decrease of 1.429 $\log_{10}$ copies per milliliter in the enfuvirtide group and a decrease of 0.648 $\log_{10}$ copies per milliliter in the control group — a significant difference of 0.781 $\log_{10}$ copies per milliliter favoring the enfuvirtide group ($P<0.001$) (Table 2).

Two modified sensitivity analyses with the last observation carried forward, one in which the change from base line in the viral load was set at zero for patients who withdrew from the study and one in which it was set at zero for both patients who withdrew and patients who had virologic failure, also showed a significant difference in favor of the enfuvirtide group ($P<0.001$). In a cohort analysis, the least-squares mean differences favored the enfuvirtide group at all time points up to week 24, and the differences were significant ($P<0.05$) at weeks 4, 8, 12, and 16.

At week 24, a greater proportion of patients in

Table 1. Demographic and Base-Line Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Enfuvirtide Group (N=335)	Control Group (N=169)
Male sex — no. (%)	292 (87.2)	148 (87.6)
White race — no. (%)	316 (94.3)	161 (95.3)
Age — yr		
Median	41.0	42.0
Range	22.0–67.0	29.0–82.0
Plasma viral load — $\log_{10}$ copies/ml		
Median	5.1	5.1
Range	3.5–6.7	3.7–6.8
CD4+ count — cells/mm^3		
Median	98.0	101.5
Range	1.0–994.0	1.0–847.0
Previous AIDS-defining event — no. (%)	250 (74.6)	138 (81.7)
Phenotypic sensitivity score — no. (%)		
0	101 (30.1)	59 (34.9)
1–2	151 (45.1)	76 (45.0)
3–4	64 (19.1)	29 (17.2)
≥5	6 (1.8)	4 (2.4)
Missing	13 (3.9)	1 (0.6)
Genotypic sensitivity score — no. (%)		
0	60 (17.9)	31 (18.3)
1–2	199 (59.4)	95 (56.2)
3–4	62 (18.5)	37 (21.9)
≥5	5 (1.5)	5 (3.0)
Missing	9 (2.7)	1 (0.6)

* The numbers of patients in the intention-to-treat population in each country were as follows; 126 in France, 89 in Spain, 59 in Italy, 59 in Germany, 58 in Australia, 49 in the United Kingdom, 25 in Belgium, 22 in Switzerland, 14 in the Netherlands, and 3 in Sweden. Tests for drug resistance were performed at the ViroLogic Clinical Reference Laboratory (South San Francisco, Calif.) with the PhenoSense HIV phenotypic drug-susceptibility assay and the GeneSeq HIV genotypic assay (ViroLogic). The genotypic sensitivity score was defined as the total number of drugs in the background regimen to which a patient's viral isolate showed genotypic sensitivity (according to a modification of a previously published algorithm for interpretation[14]). For tenofovir, the mutation K65R or three or more of the thymidine-analogue–associated resistance mutations (M41L, D67N, K70R, L210W, T215Y, T215F, K219Q, K219E, or K219N), including either M41L or L210W, indicated a lack of sensitivity. The phenotypic sensitivity score was defined as the total number of drugs in the background regimen to which a patient's viral isolate showed phenotypic sensitivity. For tenofovir, patients were assigned a phenotypic sensitivity score that was the same as their genotypic sensitivity score. AIDS denotes the acquired immunodeficiency syndrome.

the enfuvirtide group than in the control group were classified as having a virologic response according to each of the three criteria for response (Table 2). Similar differences between the treatment groups were also seen at week 8 and were significant for all categories of virologic response except a plasma HIV-1 RNA level of less than 50 copies per milliliter.

The enfuvirtide group also had a significantly shorter time to virologic response than the control group when the criterion for a response was an HIV-1 RNA level below 400 copies per milliliter ($P<0.001$ by the log-rank test) and when the criterion was a decrease from base line in the plasma HIV-1 RNA level of at least 1.0 $\log_{10}$ copies per milliliter ($P<0.001$ by the log-rank test). The median time to a virologic response defined as an HIV-1 RNA level of less than 400 copies per milliliter was estimated as 113 days in the enfuvirtide group and could not be estimated in the control group. The median time to a decrease from base line in the plasma HIV-1 RNA level of 1.0 $\log_{10}$ copies per milliliter was estimated to be nine days in the enfuvirtide group; in the control group, the time to this threshold for virologic response could not be estimated.

The percentage of patients with protocol-defined virologic failure was much lower in the enfuvirtide group than in the control group at week 8 (19.1 percent vs. 40.2 percent) and remained so at week 24 (49.3 percent vs. 76.9 percent). The time to protocol-defined virologic failure differed significantly between treatment groups ($P<0.001$ by the log-rank test) (Fig. 2); the median time to failure was approximately 71 days in the control group and could not be estimated in the enfuvirtide group.

IMMUNOLOGIC RESPONSE

In both groups, the CD4+ cell count increased between base line and all time points from week 4 through week 24, with consistently greater increases in the enfuvirtide group. At week 24, the least-squares mean increase from base line in the CD4+ cell count was significantly greater in the enfuvirtide group than in the control group (65.5 cells per cubic millimeter vs. 38.0 cells per cubic millimeter) (Table 2). The CD8+ cell counts increased in both groups, and the least-squares mean change from base line to week 24 in the CD8+ cell count was similar in the two groups.

SAFETY

Local Injection-Site Reactions

Nearly all enfuvirtide-treated patients (97.6 percent) had at least one injection-site reaction, with most having their first such reaction during the first week of the study. Of the 315 patients who reported pain or discomfort from injection-site reactions, 120 (38.1 percent) had mild tenderness at the injection site and 163 (51.7 percent) had moderate pain without limitation of usual activities. The most common signs and symptoms of injection-site reactions were

Table 2. Efficacy in the Intention-to-Treat Population at Week 24.*

Variable	Enfuvirtide Group (N=335)	Control Group (N=169)	Difference between Groups (95% CI)	Odds Ratio (95% CI)	P Value
Least-squares mean change from base line in plasma HIV-1 RNA level — $\log_{10}$ copies/ml†	–1.429	–0.648	0.781 (0.491–1.072)		<0.001
<50 Copies of HIV-1 RNA/ml of plasma — no. of patients (%)	41 (12.2)	9 (5.3)		2.62 (1.22–5.61)	0.01
<400 Copies of HIV-1 RNA/ml of plasma — no. of patients (%)	95 (28.4)	23 (13.6)		2.74 (1.62–4.63)	<0.001
Reduction from base line of ≥1 $\log_{10}$ copies of HIV-1 RNA/ml of plasma — no. of patients (%)	143 (42.7)	35 (20.7)		3.01 (1.94–4.69)	<0.001
Least-squares mean increase in CD4+ count — cells/mm^3	65.5	38.0	27.5 (3.7–51.3)		0.02

* Quantitative analysis of HIV-1 RNA levels was performed by a central laboratory in Switzerland for the sites in Europe (Covance Central Laboratory Services, Geneva) and in the United States for the sites in Australia (Covance Central Laboratory Services, Indianapolis). CD4+ cell counts were assessed centrally with the use of standard techniques for flow cytometry. The last-observation-carried-forward method was used for the analysis of least-squares mean changes. CI denotes confidence interval.
† A negative number represents a decrease.

induration, seen in 318 patients (94.4 percent); erythema, seen in 306 patients (90.8 percent); and nodules and cysts, seen in 237 patients (70.3 percent). Only 11 patients (3.3 percent) in the enfuvirtide group and 3 patients in the control group who switched to enfuvirtide (2.6 percent) discontinued treatment with enfuvirtide owing to injection-site reactions.

Adverse Events

After 24 weeks of treatment, the adverse-event profiles (excluding injection-site reactions) in the two treatment groups were similar and were generally consistent with common side effects of antiretroviral medication, underlying HIV infection, or both. Aside from injection-site reactions, 241 patients in the enfuvirtide group (71.5 percent) had at least one adverse event that was considered to be related to the study medication, as compared with 114 patients in the control group (67.5 percent). The most frequently reported treatment-related adverse events in both groups were diarrhea and nausea (Table 3). Most treatment-related adverse events were mild or moderate, and their rates differed between treatment groups by less than 5 percentage points. Overall, 106 patients in the enfuvirtide group (31.5 percent) and 38 patients in the control group (22.5 percent) had at least one severe adverse event. The higher percentage of severe adverse events in the enfuvirtide group was not attributable to any specific type of event.

Adverse events led to withdrawal from the study by 26 patients in the enfuvirtide group (7.7 percent) and 2 patients in the control group (1.2 percent). The most frequent adverse event leading to withdrawal was depression (in six patients, all in the enfuvirtide group [1.8 percent]). Vomiting and hypersensitivity each led to the withdrawal of two patients in the enfuvirtide group (0.6 percent). All other adverse events that led to withdrawal occurred in only one patient in either treatment group. Eight patients in the control group who switched to enfuvirtide (7.0 percent) had adverse events that began after the switch to enfuvirtide and subsequently led to withdrawal; each type of event that led to withdrawal was reported by only one patient.

The percentages of patients who died (1.8 percent [6 patients] in the enfuvirtide group and 0.6 percent [1 patient] in the control group) or had a serious adverse event (23.7 percent [80 patients] in the enfuvirtide group and 24.3 percent [41 patients] in the control group) while receiving the treatment to which they had been randomly assigned were similar in the two treatment groups.

Updated Safety Analysis

The update on safety combining data from the two phase 3 studies (including 663 patients in the enfuvirtide groups and 334 patients in the control groups) was completed after a longer exposure to the study drugs (813 patient-years of exposure for patients in the enfuvirtide groups [median, 1.48 years per patient; range, <0.01 to 1.92] and 163 patient-years of exposure for patients in the control

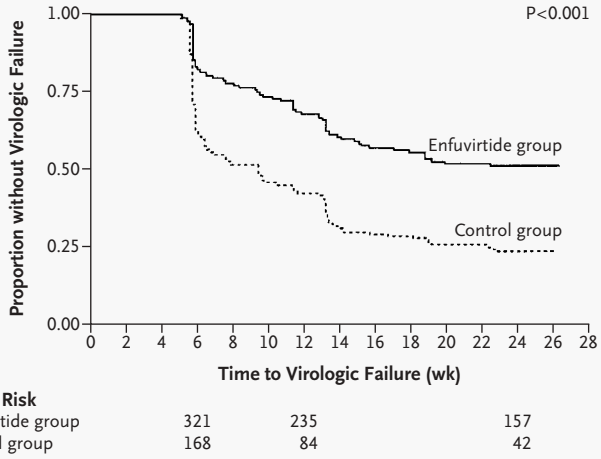

Figure 2. Kaplan–Meier Estimates of Time to Virologic Failure, as of Week 24.
Data were censored at the time of discontinuation of treatment. The analysis was conducted according to the intention-to-treat principle. The P value was determined by the log-rank test.

groups [median, 0.35 year per patient; range, 0.04 to 1.60], for a ratio of 5:1). The results of this analysis are described by Lalezari et al.[13] The safety profile seen in the 24-week review was generally confirmed. Sepsis and pneumonia, primarily bacterial, occurred more frequently in the enfuvirtide group than in the control group; however, the difference between groups in the exposure-adjusted rates was significant only for pneumonia (P=0.02).

Two cases of systemic hypersensitivity reaction (both in TORO 1) were considered to be related to enfuvirtide treatment, and both recurred on rechallenge. Rash, fever, and vomiting developed in one patient, and the other reaction took the form of membranoproliferative glomerulonephritis; on rechallenge with the antiretroviral regimen, severe respiratory distress developed in the patient with the latter reaction.[13] Eosinophilia (>700 cells per cubic millimeter) that emerged with treatment was more common in patients who received enfuvirtide (74 of 662 patients who could be evaluated [11.2 percent], or 11.5 patients per 100 patient-years) than in the control group (8 of 332 patients who could be evaluated [2.4 percent], or 4.9 patients per 100 patient-years) but was not associated with clinical events suggestive of systemic hypersensitivity.

Aside from eosinophilia, differences between the treatment groups in the incidence of grade 3 or grade 4 laboratory abnormalities that emerged with treatment were small. No consistent pattern was evident to suggest a definitive association of enfuvirtide with any particular laboratory abnormality.

ADHERENCE

Adherence to the overall regimen was high in both groups, with 298 patients in the enfuvirtide group (89.0 percent) and 145 patients in the control group (85.8 percent) achieving adherence of at least 85 percent. In the enfuvirtide group, 314 patients (93.7 percent) had adherence of at least 85 percent to the twice-daily injections of enfuvirtide.

DISCUSSION

TORO 2 was an open-label, randomized, phase 3 trial designed to evaluate the incremental virologic and immunologic benefit of adding a new class of antiretroviral drug (enfuvirtide, 90 mg twice daily) to an optimized background regimen of conventional antiretroviral drugs, as compared with the use of the optimized background regimen alone. The patients included in this study had received extensive previous treatment. Genotypic and phenotypic resistance tests were used to select the optimized background regimen for all patients in the study; the benefit of such testing is suggested by the relatively high proportion of patients who had a response to treatment, even in the control group (20.7 percent with a reduction of at least 1 $\log_{10}$ copies of HIV-1 RNA per milliliter of plasma at week 24). This rate of response compares well with that seen in patients in other trials who had previously been treated with all three available classes of antiretroviral drugs.[15,16]

The reduction in the plasma HIV-1 RNA level evident in both groups during the first 24 weeks of treatment was substantial, given the degree of antiretroviral resistance in this population of patients. Even so, the difference in the decrease in viral load at week 24 favoring enfuvirtide was clinically relevant and statistically significant. The results of the sensitivity analyses confirm the robustness of this primary response. The effect of enfuvirtide was also statistically significant at week 24 according to all criteria for virologic response in analyses using the intention-to-treat population and the conservative data-handling rules according to which patients with virologic failure and patients who withdrew from the study were considered to have treatment failure. Recent analyses indicate that the absolute magnitude of antiviral response in patients who are treated with enfuvirtide is greatest in those receiving a combination of enfuvirtide and at least two drugs

to which the patient's virus is sensitive.[17,18] The reductions in plasma viral load at week 24 in both treatment groups were accompanied by a corresponding increase in CD4+ cell counts, with significantly greater increases in the enfuvirtide group. Given that patients entered the trial with a median CD4+ cell count of approximately 100 cells per cubic millimeter, the increase in CD4+ cell counts observed at 24 weeks in the enfuvirtide-treated patients (65.5 cells per cubic millimeter) is likely to be clinically relevant.

Levels of response equivalent to those seen in the enfuvirtide group (42.7 percent with a reduction of $\geq 1 \log_{10}$ copies of HIV-1 RNA per milliliter of plasma and 28.4 percent with fewer than 400 copies per milliliter at week 24) have been seen in studies using regimens of more than five antiretroviral drugs with or without an interruption of treatment before the switch to the study regimen.[16,19] These multidrug regimens of "mega–highly active antiretroviral therapy" require a high level of patient commitment for good adherence and may also be associated with greater toxicity.

The development of resistance to all three currently available classes of antiretroviral drugs represents a substantial challenge to the successful treatment of HIV. It is therefore important to understand the potential influence of resistance to fusion inhibitors. A recently presented analysis of resistance to enfuvirtide in TORO 1 and TORO 2 found that 94 percent of patients with protocol-defined virologic failure and demonstrated suboptimal viral suppression had virus with amino-acid substitutions at codons 36 through 45 of the viral glycoprotein 41 (known to be associated with resistance to enfuvirtide).[20,21] These substitutions were associated with a wide range of decreases (by a factor of 5 to 401) in susceptibility to enfuvirtide.

Overall, with the exception of local injection-site reactions, the safety and tolerability of enfuvirtide in combination with an optimized background regimen were similar to those of the background regimen alone during 24 weeks of therapy. The pooling of the data from TORO 1 and TORO 2 for an updated safety analysis offered a larger population with a longer duration of exposure, so that we could better characterize the safety profile of enfuvirtide; this pooled analysis was appropriate because the studies had similar designs, patient-selection criteria, conduct, monitoring, and protocol-specified analyses. The results of this analysis showed higher rates of bacterial pneumonia and sepsis among patients receiving enfuvirtide than among patients in the control groups. There was a higher incidence of eosinophilia in the enfuvirtide group than in the control group, even after adjustment for exposure. A review of data for individual patients with eosinophilia did not reveal any clinical adverse events that were suggestive of systemic hypersensitivity to enfuvirtide.

Table 3. Frequent Treatment-Related Adverse Events at Week 24.*

Adverse Event	Enfuvirtide Group (N=337)	Control Group (N=169)
	no. (%)	
Gastrointestinal disorders		
Diarrhea, not otherwise specified	67 (19.9)	34 (20.1)
Nausea	38 (11.3)	25 (14.8)
Vomiting, not otherwise specified	25 (7.4)	14 (8.3)
General disorders		
Fatigue	29 (8.6)	11 (6.5)
Asthenia	24 (7.1)	7 (4.1)
Pyrexia	19 (5.6)	9 (5.3)
Skin and subcutaneous-tissue disorders		
Dermatitis, not otherwise specified	26 (7.7)	7 (4.1)
Pruritus	17 (5.0)	5 (3.0)
Nervous system disorders		
Headache	20 (5.9)	13 (7.7)
Peripheral neuropathy, not elsewhere classified	17 (5.0)	9 (5.3)
Psychiatric disorders		
Insomnia, not elsewhere classified	19 (5.6)	10 (5.9)
Depression, not elsewhere classified	18 (5.3)	4 (2.4)

* Frequent adverse events were defined as those occurring in at least 5 percent of the patients in either group. Local injection-site reactions were excluded from the analysis.

The most common adverse events associated with enfuvirtide treatment were injection-site reactions, which occurred in 97.6 percent of enfuvirtide-treated patients. However, only a very small number of patients discontinued enfuvirtide use because of an injection-site reaction (3.3 percent of patients in the enfuvirtide group and 2.6 percent of patients in the control group who switched to enfuvirtide), and adherence to enfuvirtide therapy was high (≥85 percent in 93.7 percent of patients). Research continues into ways of minimizing local injection-site reactions and ways of managing them more effectively.

The week 24 findings of this study are supported by similar results obtained in TORO 1 in North America and Brazil.[13] The results of these two concomitant studies of an HIV-1 fusion inhibitor provide firm proof of principle that HIV-1 glycoprotein 41 can be a viable target for the effective treatment

of HIV-1 infection. The promising efficacy and tolerability profile of enfuvirtide suggests that the introduction of this new antiretroviral agent could represent a major advance in the care of previously treated patients.

Supported by Roche and Trimeris.

Dr. Lazzarin reports having received consulting or lecture fees from Merck and GlaxoSmithKline and grants from Chiron, GlaxoSmithKline, Bristol-Myers Squibb, and Roche; Dr. Clotet lecture fees from Bristol, Gilead, GlaxoSmithKline, and Roche; Dr. Cooper consulting or lecture fees from Bristol-Myers Squibb, Boehringer Ingelheim, Chiron, GlaxoSmithKline, Merck, Pfizer, Roche, and Schering-Plough and grant support from Boehringer Ingelheim, Roche, Johnson and Johnson, and Schering-Plough; Dr. Reynes consulting or lecture fees from Abbott, Boehringer Ingelheim, Gilead, GlaxoSmithKline, and Roche; Dr. Arastéh lecture fees and grant support from Bristol-Myers Squibb, Roche, GlaxoSmithKline, and Boehringer Ingelheim; Dr. Nelson consulting and lecture fees and grant support from Roche; Dr. Katlama consulting or lecture fees from Boehringer Ingelheim and Gilead; Dr. Stellbrink consulting or lecture fees from Bristol-Myers Squibb, Gilead, Merck, and Roche and grant support from Roche and GlaxoSmithKline; Dr. Delfraissy consulting or lecture fees from Bristol-Myers Squibb, Glaxo, Merck, and Roche; and Dr. Lange consulting or lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Gilead, and GlaxoSmithKline.

We are indebted to all the investigators and patient volunteers involved in the TORO 2 trial.

APPENDIX

In addition to the authors, the TORO 2 Study Group included the following institutions and persons: D. Blanckenberg and M. Nievaard (Academic Medical Center, University of Amsterdam, Amsterdam); J.F. Hoy and J.J. Roney (Alfred Hospital and Monash University, Melbourne, Australia); M. Fisher and N. Perry (Brighton and Sussex University Hospitals, Brighton, United Kingdom); J. Anderson and J. Patching (Carlton Clinic, Carlton, Victoria, Australia); A. Lafeuillade and G. Hittinger (Centre Hospitalier Intercommunal, Toulon, France); A. Nguyen-Wartel (Centre Hospitalier Universitaire Bicêtre, Assistance Publique–Hôpitaux de Paris, Paris); V. Baillat and L. Cotte (Centre Hospitalier Universitaire, Montpellier, France); D. Rey and J.-M. Lang (Centres d'Information et de Soins de l'Immunodéficience Humaine, Hôpitaux Universitaires Strasbourg, Strasbourg, France); A. Winston and C. Fletcher (Chelsea and Westminster Hospital, London); G. Carosi and S. Casari (Clinica di Malattie Infettive e Tropicali, Brescia, Italy); E. Wilkins and R. Daintith (Department of Infectious Diseases and Tropical Medicine, North Manchester General Hospital, Manchester, United Kingdom); S. De Wit and K. Kabeyat (Department of Infectious Diseases, Centre Hospitalier Universitaire St. Pierre, Brussels, Belgium); J.-M. Molina and N. Colin de Verdiere (Department of Infectious Diseases, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris, Paris); K. Gyllensten, A. Sönnenborg, and M. Christianssen (Department of Infectious Diseases, Karolinska Institutet, Huddinge University Hospital, Stockholm, Sweden); L. Flamholc and U.M. Akerholm (Department of Infectious Diseases, Malmo University Hospital, Malmo, Sweden); G. Di Perri and S. Bonora (Department of Infectious Diseases, University of Turin, Turin, Italy); J. Rockstroh and K. Schneider (Department of Medicine I, University of Bonn, Bonn, Germany); T. Harrer and M. Baeuerle (Department of Medicine III, University of Erlangen–Nuremberg, Erlangen, Germany); A. Telenti and M. Cavassini (Division of Infectious Diseases, University Hospital, Lausanne, Switzerland); B. Hirschel and L. Kaiser (Division of Infectious Diseases, Geneva University Hospital, Geneva); F. Maggiolo and G. Gregis (Division of Infectious Diseases, Ospedali Riuniti, Bergamo, Italy); M. Battegay and N. Khanna (Division of Infectious Diseases, University Hospital, Basel, Switzerland); M. Flepp and B. Hasse (Division of Infectious Diseases, University Hospital Zurich, Zurich, Switzerland); F. Mazzotta and S. Locaputo (Divisione di Malattie Infettive Ospedale S.M. Annunziata, Antella–Florence, Italy); A. Moll and F. Schlote (EPIMED–Vivantes Auguste-Viktoria Hospital, Berlin, Germany); M.E. van der Ende and R. Deenenkamp (Erasmus University Medical Center, Rotterdam, the Netherlands); M. Bloch and D. Austin (Holdworth House General Practice, Darlinghurst, Sydney, Australia); G. Banabdelmoumen and J. Gerbe (Hôpital Bichat–Claude Bernard, Paris); H. Gallais and C. Dhivers (Hôpital de la Conception, Service des Maladies Infectieuses, Marseilles, France); D. Vittecoq and E. Teicher (Hôpital Paul Brousse et Agence du Médicament, Paris); N. Ktorza and E. Bertrand (Hôpital Pitié-Salpêtrière, Paris); J.-A. Gastaut and I. Poizot-Martin (Hôpital Sainte Marguerite, Hôpital de Jours, Centres d'Information et de Soins de l'Immunodéficience Humaine Sud, Marseilles, France); W. Rozenbaum and L. Slama (Hôpital Tenon, Paris); J. Gonzalez-Lahoz and L. Martin-Carbonero (Hospital Carlos III, Madrid); K. Aguirrebengoa and M. Goeketxea (Hospital Cruces, Baracaldo, Spain); S. Moreno and J. Oliva (Hospital Ramon y Cajal, Departmento de Enfermedades Infecciosas, Madrid); A. Bonjoch and A. Ballesteros (Hospital Universitari Germans Trias i Pujol y Institut de Recerca de la SIDA-Caixa Foundation, Badalona, Barcelona, Spain); J. Pachon-Diaz and R.M. Alcazar-Caballero (Hospital Virgen del Rocio, Department of Infectious Diseases, Seville, Spain); C. Trepo and L. Cotte (Hôtel-Dieu Hospital, Lyons, France); A.D. Stoehr and A. Plettenberg (Institut für Interdisziplinäre Infektiologie und Immunologie, Hamburg, Germany); A. Antinori and G. Liuzzi (III Divisione, Istituto Nazionale per la Malattie Infettive Lazzaro Spallanzani, Rome); E. Ortega-Gonzalez and A. Martin-Herrera (Infectious Disease Unit, Hospital General Universitario, Valencia, Spain); A. Allworth and N. Gerns (Infectious Diseases Day Therapy Unit, Royal Brisbane Hospital, Brisbane, Australia); J.M. Gatell and J.L. Blanco (Infectious Diseases Unit, Clinical Institute of Infectious Diseases and Immunology, Hospital Clinic, Barcelona, Spain); F. Raffi and C. Allavena (Infectious Diseases Unit, University Hospital, Nantes, France); R. Colebunders and A. De Roo (Institute of Tropical Medicine, Antwerp, Belgium); A. Danise and H. Hasson (Istituto di Ricovero e Cura a Carattere Scientifico, San Raffaele Vita-Salute University, Milan, Italy); P.J. Easterbrook and A. Waters (Kings College Hospital, Caldecott Road, London); S. Staszewski and C.J. Stephan (Klinikum der J.W. Goethe-Universität, Zentrum der Inneren Medizin, Frankfurt, Germany); E. Bouza and J.-A. Pérez-Molina (Microbiology and Infectious Disease Division, Hospital General Universitario Gregorio Marañon, University of Madrid, Madrid); R. Fielden and S. McLeod (National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia); N. Roth and H. Wood (Prahran Market Clinic, South Yarra, Australia); C. Leen and S. Morris (Regional Infectious Disease Unit, Edinburgh, United Kingdom); J. Chung (Roche, Nutley, N.J.); B. Atkins and D. Herath (Roche, Welwyn Garden City, United Kingdom); I. Williams and D. Cornforth (Royal Free and University College Medical School, London); M. Johnson and Z. Cuthbertson (Royal Free Hospital, London); P. Chavanet and C. Lequeu (Service des Maladies Infectieuses, Hôpital du Bocage, Dijon, France); P. Dellamonica and J. Durant (Service d'Infectiologie, Hôpital Archet 1 Centre, Hospitalier Universitaire de Nice, Nice, France); N. Bodsworth and R. Finlayson (Taylor Square Private Clinic, Darlinghurst, Sydney, Australia); L. Smiley and G.D. Miralles (Trimeris, Durham, N.C.); M. Torralba and C. Cepeda (Unidad Infección Virus de Inmunodeficiencia Humana, Hospital 12 de Octubre, Madrid); J. González-García and A. Lorenzo (Unit HIV, La Paz Hospital, Madrid); G. Pastore and P. Maggi (Università Policlinico, Istituto di Malattie Infettive, Bari, Italy); E. van Wijngaerden and H. Bobbaers (Universitaire Ziekenhuizen, Gasthuisberg, Leuven, Belgium); J. van Lunzen and O. Degen (University Hospital Eppendorf, Hamburg, Germany); J.C.C. Borleffs and P. Ellerbroek (University Medical Center Utrecht, Utrecht, the Netherlands).

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
2. Murphy EL, Collier AC, Kalish LA, et al. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. Ann Intern Med 2001; 135:17-26.
3. Deeks SG. Determinants of virological response to antiretroviral therapy: implications for long-term strategies. Clin Infect Dis 2000;30:Suppl 2:S177-S184.
4. Rousseau MN, Vergne L, Montes B, et al. Patterns of resistance mutations to antiretroviral drugs in extensively treated HIV-1-infected patients with failure of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001;26:36-43. [Erratum, J Acquir Immune Defic Syndr 2001;26:395.]
5. Race E, Dam E, Obry V, Paulous S, Clavel F. Analysis of HIV cross-resistance to protease inhibitors using a rapid single-cycle recombinant virus assay for patients failing on combination therapies. AIDS 1999;13:2061-8.
6. Van Vaerenbergh K, Van Laethem K, Albert J, et al. Prevalence and characteristics of multinucleoside-resistant human immunodeficiency virus type 1 among European patients receiving combinations of nucleoside analogues. Antimicrob Agents Chemother 2000;44:2109-17.
7. Wild C, Greenwell T, Matthews T. A synthetic peptide from HIV-1 gp41 is a potent inhibitor of virus-mediated cell-cell fusion. AIDS Res Hum Retroviruses 1993;9:1051-3.
8. Kilby JM, Hopkins S, Venetta TM, et al. Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. Nat Med 1998; 4:1302-7.
9. Kilby JM, Lalezari JP, Eron JJ, et al. The safety, plasma pharmacokinetics, and antiviral activity of subcutaneous enfuvirtide (T-20), a peptide inhibitor of gp41-mediated virus fusion, in HIV-infected adults. AIDS Res Hum Retroviruses 2002;18:685-93. [Erratum, AIDS Res Hum Retroviruses 2003; 19:83.]
10. Lalezari JP, DeJesus E, Northfelt DW, et al. A controlled phase II trial assessing three doses of enfuvirtide (T-20) in combination with abacavir, amprenavir, ritonavir, and efavirenz in non-nucleoside reverse transcriptase inhibitor–naive HIV-infected adults. Antiviral Ther (in press).
11. Lalezari JP, Eron JJ, Carlson M, et al. A phase II clinical study of the long-term safety and antiviral activity of enfuvirtide-based antiretroviral therapy. AIDS 2003;17:691-8.
12. Drobnes C, Fang L, Nelson E, et al. Tolerability of enfuvirtide (T-20) during chronic therapy in phase II trials. In: Program and abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif., September 27–30, 2002. Washington, D.C.: American Society for Microbiology, 2002:262. abstract.
13. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003;348: 2175-85.
14. EuroGuidelines Group for HIV Resistance. Clinical and laboratory guidelines for the use of HIV-1 drug resistance testing as part of treatment management: recommendations for the European setting. AIDS 2001; 15:309-20.
15. Hammer SM, Vaida F, Bennett KK, et al. Dual vs single protease inhibitor therapy following antiretroviral treatment failure: a randomized trial. JAMA 2002;288:169-80.
16. Katlama C, Dominguez S, Duvivier C, et al. Long term benefit of treatment interruption in salvage therapy (GIGHAART ANRS 097). In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003: 81. abstract.
17. Lalezari J, Henry K, O'Hearn M, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone: week 24 response among categories of treatment experience and baseline (BL) HIV antiretroviral (ARV) resistance. In: Program and abstracts of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif., September 27–30, 2002. Washington, D.C.: American Society for Microbiology, 2002:266. abstract.
18. Lange J, Lazzarin A, Clotet B, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone: week 24 response among categories of baseline (BL) demographics, treatment experience, and HIV antiretroviral (ARV) resistance. In: Program and abstracts of the Sixth International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, November 17–21, 2002:17-8. abstract.
19. Grossman H, Frechette G, Reyes F. Mega-HAART: complex protective regimens for HAART failure. In: Program and abstracts of the Second International Workshop on Salvage Therapy for HIV Infection, Toronto, May 19–21, 1999:246. abstract.
20. Rimsky LT, Shugars DC, Matthews TJ. Determinants of human immunodeficiency virus type 1 resistance to gp41-derived inhibitory peptides. J Virol 1998;72:986-93.
21. Greenberg ML, Melby T, Sista P, et al. Baseline and on-treatment susceptibility to enfuvirtide seen in TORO 1 and TORO 2 through 24 weeks. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003:108. abstract.