Two-Year Observational Study in Patients Infected with Drug-Resistant HIV-1 and Treated with the Fusion Inhibitor Enfuvirtide: The ZOOM Cohort

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Summary

The objective of this study was to describe, in real-life settings, the patients treated by the HIV fusion inhibitor enfuvirtide and to evaluate efficacy and safety of this new antiretroviral drug in comparison with the results of the pivotal studies TORO 1 and TORO 2.

Adult HIV-1-infected patients, treated for the first time with enfuvirtide since less than 2 months, were eligible for the study. From September 2004 to May 2006, 364 patients (male, 81%) with a mean (SD) age of 45 (9) years and at CDC stage C for 52% of them were included and followed for 2 years. The median duration of antiretroviral treatment was 10 years with a median number of 11 drugs. Median HIV viral load was 4.7 $\log_{10}$ copies/mL and median CD4 cell count was 155 cells/mm³ (respectively, 5.2 $\log_{10}$ copies/mL and 89 cells/mm³ in TORO studies). Compared to the TORO studies, the proportion of patients on enfuvirtide treatment with HIV RNA < 400 copies/mL in ZOOM study was higher (61 vs. 34% at 1 year; 77 vs. 48% at 2 years). The immunologic benefit was approximately the same at 2 years (+173 cells/mm³ in ZOOM vs. +166 cells/mm³ in TORO studies). Bacterial pneumonia was reported for 5 patients (0.81 case for 100 patient-years).

In conclusion, in real-life settings, the results of the ZOOM study at 2 years confirmed the virologic and immunologic benefits and the favorable safety of enfuvirtide reported in the TORO pivotal trials.

Keywords: Enfuvirtide; Fusion inhibitor; Drug-resistant HIV-1

Introduction

Even with combination antiretroviral therapy (cART) regimen, the durability of HIV control is limited by many factors (adherence to treatment, drug toxicity, bioavailability, among the most important). [1] When salvage therapy is considered, better outcome is expected if antiretroviral regimen includes a class to which the patient has not been exposed previously. Therefore classes of antiretroviral drugs directed at targets other than reverse transcriptase or protease are of potential great interest.[2]

Enfuvirtide, a 36-amino acid synthetic peptide, is the first antiretroviral drug that inhibits the entry of HIV-1 into host CD4 lymphocytes.[3] Enfuvirtide is approved, in combination with other antiretroviral drugs, for the treatment of HIV infection in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral treatment [4].

The TORO (T-20 vs. Optimized Regimen Only) pivotal studies showed the superiority at 24 weeks of enfuvirtide in combination with an optimized background regimen over an optimized background regimen alone in patients with prior experience or prior documented resistance to each of the three classes of approved antiretroviral drugs.[5,6] These results were maintained until 48 and 96 weeks in pooled analyses of the two trials.[7,8]

The pivotal TORO studies evidenced in rigorous experimental conditions the virologic efficacy attributable to enfuvirtide. However, data on enfuvirtide treatment in daily care are scarce. The principal objective of the ZOOM study was to assess in real-life settings the clinical and immunovirologic long-term evolution of HIV-1 patients treated by enfuvirtide during a 2-year follow-up and to describe patient characteristics, practical details on treatment, safety and quality of life.

Patients and Methods

Study design

This study was initiated after a request of the French health authorities (HAS) in June 2004 to conduct a post registration study assessing long-term efficacy and safety of enfuvirtide in HIV-1-infected patients in real-life settings.

This multicenter, prospective, observational cohort study was performed in France. Patients were consecutively included in the study if they met the following criteria: HIV-1 infection, age at least

18 years, enfuvirtide started at inclusion or less than 2 months before inclusion.

An extraction from the French hospital database on HIV (FHDH) which includes data on HIV patients from 62 French hospitals was performed in order to compare the ZOOM cohort population and the population of French patients initiating an enfuvirtide treatment. During the inclusion period of the ZOOM cohort (from September 2004 to May 2006), this database included 617 patients initiating an enfuvirtide treatment (557 experienced-patients and 40 naïve patients).

The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research. This study was observational and did not modify the management of patients.

Study procedure

At the screening evaluation and follow-up visits (Months 3, 6, 12, 18 and 24), available data on medical history, clinical status (CDC stage, AIDS-defining events) and other health problems, body weight, previous and present antiretroviral regimens, concomitant treatments, routine laboratory tests (lipids, liver enzymes, blood cell counts, glucose, hemoglobin), CD4 cell counts and plasma HIV-1 RNA level were recorded.

When available, the last genotypic resistance tests before enfuvirtide initiation were recorded at inclusion visit. The genotypic sensitivity score (sum of the active antiretroviral drugs) was calculated by a centralized analysis using the 2006 French National Agency for AIDS Research (ANRS) algorithm (http://www.hivfrenchresistance. org) ; 3TC/FTC was not taken into account to calculate genotypic sensitivity score (it has been previously prescribed in 93% of patients).

The health-related quality of life was evaluated using the MOS-HIV (Medical Outcomes Study HIV Health Survey) questionnaire. It has been specifically developed for HIV-infected patients and its French translation has been validated.[9] Quality of life was assessed at inclusion and at each follow-up visit.

Adherence to enfuvirtide treatment was recorded by each patient in an auto-questionnaire and was assessed as the proportion of patients who performed all enfuvirtide injections during the last four days before each visit.

Statistical analysis

Analyses of virologic and immunologic data were performed on observed data (patients with available data) and on observed data for patients on enfuvirtide treatment. The robustness of the effect of enfuvirtide was evaluated by sensitivity analyses with loss to follow-up, death and missing data attributed to failure.

Univariate and multivariate regression analyses were performed to determine predictive factors of virologic response.
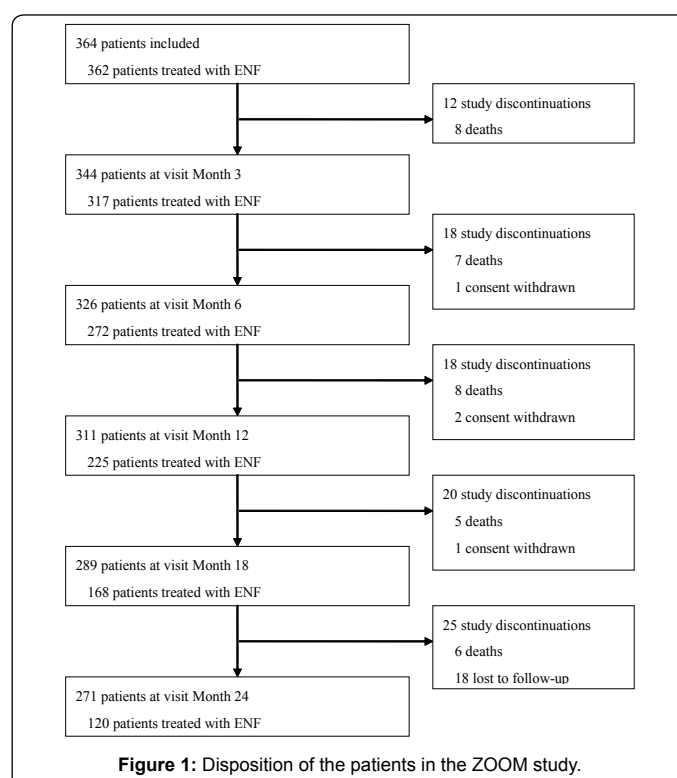
Probability of outcome of one AIDS-defining event or death at 12 months, probability of permanent discontinuation at 12 months and median delay for virologic control (HIV RNA < 50 copies/mL) were assessed by Kaplan-Meier analysis.

All tests were bilateral at the level 0.05. The analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Characteristics of the patients at inclusion

From September 2004 to May 2006, 371 patients were enrolled by 149 HIV specialists who were spread over the French territory. Seven patients who did not meet the inclusion criteria were excluded. The disposition of patients during the follow-up visits is described in (Figure 1). The population analysis included 364 patients: 81% of patients were male with a mean (SD) age of 45 (9) years (Table 1). At initiation of enfuvirtide treatment, 52% of patients presented a severe condition with history of AIDS-defining events and 17% were coinfected with HCV. They had a high median HIV viral load (4.7

Figure 1: Disposition of the patients in the ZOOM study.

Characteristics	n	
Gender, n (%) of male	364	293 (81)
Mean age (SD), years	358	45 (9)
Mean weight (SD), kg	361	65 (13)
HIV transmission, n (%)		
Sexual	364	281 (77)
Drug addiction	364	53 (15)
Blood transfusion or blood exposure accidents	364	13 (4)
Other or unknown	364	17 (5)
CDC stage C, n (%)	362	189 (52)
HBV coinfection (HBsAg), n (%)	364	15 (4)
HCV coinfection (anti-HCV), n (%)	364	60 (17)
Mean (SD) delay since HIV infection diagnosis, years	266	15 (4)
Median (range) number of prior antiretroviral drugs	352	11 (1–21)
Median (range) CD4 cells/mm^3	338	155 (1–937)
< 200 cells/mm^3, n (%)	338	207 (61)
≥ 200 cells/mm^3, n (%)	338	131 (39)
Median (range) HIV-1 RNA, $\log_{10}$ copies/mL	333	4.7 (1.3–6.5)
Genotypic sensitivity score, n (%)*		
0	327	49 (15)
1	327	129 (39)
2	327	125 (38)
3	327	22 (7)
4	327	2 (1)

*The number of active antiretroviral molecules was assessed in 327 patients with genotypes available at inclusion (3TC/FTC was not taken into account).

Table 1: Characteristics of cohort patients at inclusion.

$\log_{10}$ copies/mL) and a low median CD4 cell count (155 cells/mm³). The mean delay since HIV infection diagnosis was 15 years and transmission was mainly through sexual contacts (77%).

For antiretroviral treatment-experienced patients (97% of the patient population), the median duration of antiretroviral treatment was 10 years before inclusion in the study; patients had been previously treated by a mean (SD) of 11 (4) antiretroviral drugs and by at least 10 antiretroviral drugs for 70% of them. Before initiation of enfuvirtide, patients had received a median of 6 nucleoside reverse transcriptase inhibitors (NRTI; isolated or in combination), 1 non nucleoside reverse transcriptase inhibitor (NNRTI) and 4 protease inhibitors (PI).

Among the 327/364 patients with genotypes available at inclusion, patients with large resistance to NRTI (at least 3 thymidine-associated mutations; TAMs), NNRTI (at least one resistance mutation) and PI (at least 4 major resistance mutations) were 56, 48 and 53%, respectively. More than half of patients (54%) had a genotypic sensitivity score < 2; 78% of patients had one or two active molecules in the antiretroviral combination associated to enfuvirtide (Table 1).

These characteristics were similar to the 617 patients treated with enfuvirtide included in the French hospital database on HIV who initiated enfuvirtide between September 2004 and May 2006: median age, 43 years; male gender, 78%; AIDS stage, 53%; coinfection HCV, 17%; median plasma HIV RNA, 4.8 $\log_{10}$ copies/mL; median CD4 counts, 136 cells/mm³; median of previous antiretroviral treatments, 11; median of duration of antiretroviral treatments, 10 years. Therefore, the patient population of our observational study was representative of the French population of HIV-1-infected patients treated with enfuvirtide.

Therapeutic management of patients

The treatment by enfuvirtide was administered at initiation according to the recommended dosing for 363/364 patients with 90 mg injected twice daily. For one patient, dosing was once daily injection of 90 mg enfuvirtide at treatment initiation (patient request) and was maintained for the entire follow-up in the study (2 years). During the follow-up, treatment was modified for only one patient (from twice to once daily injection at the Month 6 visit at patient request).

The mean (SD) duration of follow-up in the study was 20.5 (7.1) months for a mean total duration of enfuvirtide treatment (defined as time between first and last injection) of 15.2 (8.9) months. Exposure to enfuvirtide (defined as total duration of enfuvirtide treatment less periods of transient treatment discontinuations) was 14.7 (8.9) months.

The median number of antiretroviral drugs administered in combination with enfuvirtide was 3 at the initiation of enfuvirtide treatment. Fifty-four percent of patients had zero or one active

molecule in the combination associated to enfuvirtide at its initiation (Table 1).

The most frequent antiretroviral combinations administered with enfuvirtide were: 1 PI plus 2 NRTI (29%), 1 PI plus 1 NRTI (12%), 2 PI plus 2 NRTI (11%) and 2 PI (9%). The main combinations of antiretroviral drugs prescribed at initiation of enfuvirtide treatment were close to the combinations associated to enfuvirtide in the French hospital database on HIV for the same period for the 577 treatment-experienced patients (1 PI plus 2 NRTI, 30%; 1 PI plus 1 NRTI, 10%; 2 PI plus 2 NRTI, 7%).

During the follow-up, there was at least one modification of the antiretroviral treatment (excluding enfuvirtide) for 59% of patients (median number of change: one). New molecules became available during the study follow-up and therefore were used increasingly: darunavir (from 16 patients at enfuvirtide initiation to 77 patients at Month 24; 4 to 21%), etravirine (0 to 25 patients; 0 to 7%), raltegravir (0 to 33 patients; 0 to 9%), maraviroc (3 to 5 patients; 0.8 to 1.4%). Tipranavir was frequently prescribed at the initiation of enfuvirtide treatment (113 patients at enfuvirtide initiation and 144 at Month 24; 31 and 40%).

Enfuvirtide treatment discontinuation

There was a definitive discontinuation of enfuvirtide treatment during the study for 59% of patients (216/364) and at least one transient discontinuation for 11% of patients (40/364). Permanent discontinuations were due to patient or physician request (47%), injection-site adverse events (22%), virologic failure (22%), immunologic failure (10%) and poor treatment adherence (11%).

The probability of permanent discontinuations at 12 months was 34.6% (95% confidence interval [CI]: 29.9 to 39.9%; Kaplan-Meier analysis). This rate of discontinuation of enfuvirtide treatment at 12 months was close to the value from the French hospital database on HIV (32%; 95% CI, 27 to 37).

There was at least one study visit after permanent discontinuation for 191/216 patients. After enfuvirtide discontinuation, 30% of patients (58/191) were treated with new antiretroviral molecules not received before (tipranavir, darunavir, raltegravir or maraviroc).

Virologic and immunologic efficacy

The median viral load decreased from 4.7 to 1.69 $\log_{10}$ copies/mL between baseline and Month 24 with a median viral load drop of -2.46 $\log_{10}$ copies/mL.

The proportion of patients with a virologic response increased during the follow-up with 74% of patients with HIV-1 RNA < 400 copies/mL and 56% with HIV-1 RNA < 50 copies/mL at Month 24 (observed data)(Table 2). For patients on enfuvirtide treatment at Month 24, these proportions were 77 and 57%, respectively (Table 2 and Figure 2).

	ZOOM Study N=364			TORO 1 and 2 Pooled analysis [4, 8] N=661	
	Observed data (patients with viral load available)	Observed data for patients on enfuvirtide treatment	Sensitivity analysis on total population Missing = Failure	Intent-to-treat	On treatment
HIV RNA < 400 copies/mL					
6 months	63%	64%	47%	37%	NA
12 months	61%	61%	41%	30%	34%
24 months	74%	77%	43%	27%	48%
HIV RNA < 50 copies/mL					
6 months	41%	42%	31%	23%	NA
12 months	39%	40%	26%	18%	23%
24 months	56%	57%	32%	18%	32%

NA: not available

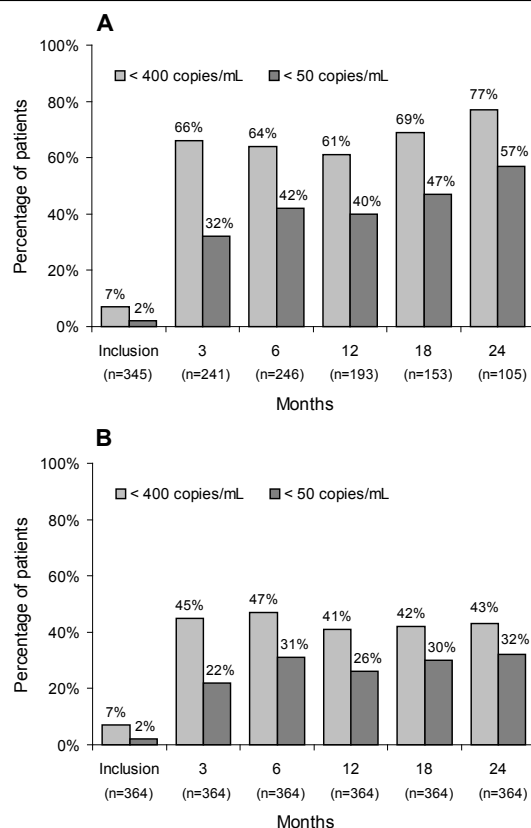**Table 2:** Description of virologic outcome in ZOOM and TORO studies.

Figure 2: Virologic response during the follow-up: A. Patients on enfuvirtide treatment with available data; B. Total population of the cohort (Missing = Failure).

A sensitivity analysis (Missing = Failure) showed that the patients with virologic responses were 47 and 31% (for HIV-RNA < 400 and 50 copies/mL) at Month 6 and virologic response was maintained up to Month 24 for 43 and 32% of patients, respectively (Table 2 and Figure 2).

For the group of patients with a viral load ≥ 50 copies/mL at treatment initiation (n=327), the median delay for virologic control (< 50 copies/mL) was 12.5 months (95% CI, 7.5 to 22.0; Kaplan-Meier analysis).

Using a multivariate analysis, the following predictive factors at initiation of enfuvirtide treatment for virologic response (HIV-1 RNA < 50 copies/mL) at Month 24 were evidenced: HIV-1 RNA < 100 000 copies/mL (odds-ratio [OR] = 2.0; CI 95%, 1.0 to 3.7), no NNRTI mutation (OR = 1.7; 95% CI, 0.9 to 3.1) and less than 7 PI mutations (OR = 6.0; 95% CI, 1.3 to 28.0).

The median CD4 count increased during the study: from 155 cells/mm^3 at baseline to 323 cells/mm^3 at Month 24. The median immunologic benefit was +173 cells/mm^3 at Month 24; 39% of patients had at least an increase of 100 CD4 cells/mm^3 between inclusion and Month 24 (Figure 3).

Forty-two patients presented 61 AIDS-defining events during the study (including 11 esophageal candidiasis). The probability of outcome at Month 12 of one AIDS-defining event or death was 12% (CI 95%, 9 to 16; Kaplan-Meier analysis) and was comparable to the probability in the French hospital database on HIV (13%; CI 95%, 10 to 17). The probability was higher in patients with at least one previous AIDS-defining event as compared to patients without event (at one year, 19.8 vs. 2.9%; p<0.0001).

Safety

Thirty-four deaths occurred during the 2-year follow-up (17 patients were on enfuvirtide treatment and 17 patients had discontinued enfuvirtide treatment). For the 17 patients on enfuvirtide treatment, death occurred for 47% of them (8/17) before the third month after inclusion.

Main causes were AIDS-related deaths (35%; n=12; including 5 AIDS-defining cancers), liver disease (15%; n=5), non-AIDS defining cancers (9%; n=3), septic shock (9%; n=3).

Overall, 93% of patients had at least one injection-site reaction during the follow-up: induration (89%), nodule (86%), pain (85%), erythema (73%), pruritus (43%) and bruise (40%). The intensity of local reactions was most frequently mild to moderate.

At least one general adverse event related to enfuvirtide treatment according to the investigator was reported for 40% of patients. These adverse events were heterogeneous; the most frequent, asthenia, was reported for 13% of patients.
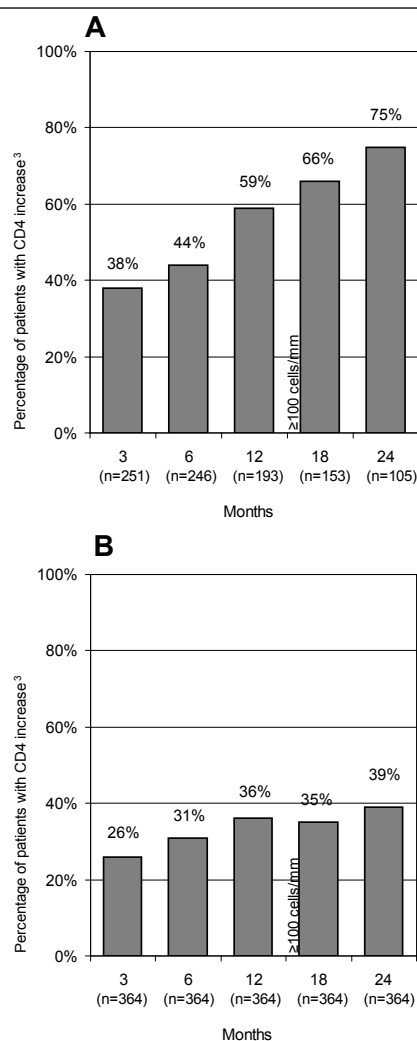

Figure 3: Imunologic response during the follow-up: A. Patients on enfuvirtide treatment with available data; B. Total population of the cohort (Missing = Failure).

Five cases of bacterial pneumonia were reported in 5 patients (1.4%; 0.81 cases for 100 patient-years). The characteristics of these patients were the followings: 4 patients with CDC stage C (with at least 2 AIDS-defining events for 3 of them), 2 patients with HIV-1 RNA > 100 000 copies/mL, 2 patients with past smoking. Four patients with bacterial pneumonia have been hospitalized and 2 patients deceased during the study follow-up (one was still on enfuvirtide treatment).

Treatment adherence

The treatment adherence was reported by the patient in an auto-questionnaire at each visit. Among patients on enfuvirtide treatment during the 24-month follow-up, 82 to 91% of them reported to have performed all enfuvirtide injections in the last 4 days before the visit.

Approximately half of patients on enfuvirtide treatment considered that the enfuvirtide treatment was easy or very easy to take (48% at inclusion, 51% at Month 6 and 41% of patients at Month 12 and Month 24).

Quality of life

Analysis of quality of life was performed in the subgroup of patients who returned at least two auto-questionnaires including one at baseline (n=264). Among the 11 dimensions (each noted from 0 to 100) of the MOS-HIV questionnaire, some were improved during the follow-up: "general health perception" (median score, +5), "health distress" (+5) "quality of life" and "energy/fatigue" (+5). Among the 216 patients who stopped definitively enfuvirtide treatment, 100 returned auto-questionnaires at least at baseline and at treatment discontinuation. An improvement of some scores between inclusion and treatment discontinuation was observed for "mental health" (median score, +4), "general health perception" (+5) and "health distress" (+5.8).

Discussion

This large observational study included 364 patients who were comparable to patients initiating enfuvirtide treatment in the large French hospital database on HIV-infected patients (FHDH database).

Patients who started enfuvirtide treatment were at an advanced state of the disease with median HIV RNA at 4.7 $\log_{10}$ copies/mL, median CD4 cell count at 155 cells/mm³, history of AIDS-defining events for 52% of them; 97% of patients were antiretroviral treatment-experienced with a median exposition of 10 years. Nevertheless, the patients of the ZOOM study had a virologic and immunologic profile more favorable as compared to patients of the TORO pivotal studies (median HIV RNA, 5.2 $\log_{10}$ copies/mL; median CD4 cell count, 89 cells/mm³).[8] The better immunovirologic profile in ZOOM study most probably reflects changes in the management of patients in years 2004–2006 with a greater number of new efficient antiretroviral drugs and earlier management.

The more favorable profile at baseline of patients of the ZOOM study explains most probably the higher rates of virologic responses in comparison with TORO studies (Table 2). The immunologic benefit was however approximately the same in ZOOM and TORO studies: the median increase after 2 years was +173 and +166 CD4 cells/mm³ with 39 and 32% of patients who had an increase ≥ 100 CD4 cells/mm³, respectively.

Data on discontinuations of enfuvirtide and switch to other antiretroviral drugs are scarce. In our study, there was a definitive discontinuation of enfuvirtide for 59% of patients during the 2-year follow-up. The most frequent reasons were patient or physician request, injection-site reaction and virologic failure. In the TORO studies, the rate of permanent discontinuation before 48 weeks was only 26.5%.[10] This difference could be explained by the increasing availability of new efficient antiretroviral treatments in years 2004–2006 and patients who discontinued permanently enfuvirtide during the ZOOM study were frequently treated with tipranavir, darunavir, raltegravir or maraviroc. Another explanation could be the expected higher adherence to treatment for patients included in a clinical trial compared to patients of an observational cohort.

After 2 years, 11.5% of patients of the ZOOM study and 15.2% patients of the TORO studies experienced at least one AIDS-defining event. Esophageal candidiasis was the most frequent AIDS-defining event both in ZOOM and TORO studies.[8]

There were 34 deaths (9%) in the ZOOM study; the frequency of deaths was lower both in the TORO studies (5%) and in the French hospital database on HIV (5%). The causes of death in the ZOOM study were comparable to those reported in a French national survey performed in 2005: AIDS (35 vs. 36%), liver diseases (15 vs. 15%), non AIDS-defining cancers (9 vs. 17%).[11]

Overall, 93% of patients reported site-injection adverse events (98.5% in TORO studies) and 15% of patients were prematurely withdrawn for local or general intolerance related to enfuvirtide (21% in the TORO studies).

In TORO trials, pneumonia was significantly more frequent in patients treated with enfuvirtide (6.7 vs. 0.6 events per 100 patient-years), although the incidence remained within the expected ranges for this population.[11] During the ZOOM follow-up, bacterial pneumonia was reported for 5 patients, i.e. 0.81 for 100 patient-years, which is comparable to the incidence reported in enfuvirtide-treated patients in a recent study on the data from the French hospital database on HIV (0.65 for 100 patient-years)[12] or in the PI-treated patients of the APROCO cohort (0.8 for 100 patient-years).[13] The study of Kousignian et al concluded that enfuvirtide-containing regimens were not associated with a significantly higher risk of bacterial pneumonia than other antiretroviral regimens.[12]

The results of quality of life with the MOS-HIV questionnaire were in agreement with the TORO trials with improvement of the dimensions "general health perception", "energy/fatigue", health distress" of the MOS-HIV questionnaire.[14]

The proportion of patients who declared they had performed all the injections in the last 4 days was high during the whole follow-up of the ZOOM study (82 to 91%) and comparable to the treatment adherence in the TORO studies (89% of patients reported an adherence of at least 90%).

Finally, during the ZOOM study, the conditions of use of enfuvirtide were closely in line with the recommendations of the Summary of Product Characteristics (dosing, number of daily injections).

In conclusion, in real-life settings, the results of the ZOOM study at 2 years in the French population confirmed the virologic and immunologic benefits and the favorable safety of enfuvirtide reported in the TORO pivotal trials.

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