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Enfuvirtide

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Contents

Abstract

▲ Enfuvirtide is the first of a new class of drugs, the fusion inhibitors. It is a synthetic peptide which binds to the HIV glycoprotein 41 (gp41), blocking fusion of the viral and cellular membranes.

▲ HIV isolates with reduced susceptibility to enfuvirtide have been recovered from patients receiving enfuvirtide in combination with other antiretroviral agents.

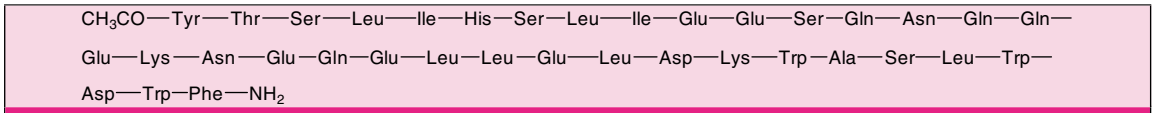
▲ Enfuvirtide 90mg (subcutaneously, twice daily) in combination with optimised background (OB) antiretroviral therapy significantly reduced plasma HIV RNA levels compared with OB alone after treatment for 24 weeks in two randomised trials involving adults with advanced HIV infection. The antiviral efficacy of enfuvirtide was maintained through to 48 weeks.

▲ At 24 and 48 weeks, the increase from baseline in the CD4+ cell count was significantly greater for patients receiving enfuvirtide plus OB than for those receiving OB alone.

▲ Enfuvirtide 30 mg/m^2 or 60 mg/m^2 in combination with other antiretroviral agents reduced plasma HIV RNA levels and increased CD4+ cell counts in a small trial involving paediatric patients with HIV infection.

▲ Local injection-site reactions were common. Lymphadenopathy and pneumonia occurred more often in patients receiving enfuvirtide plus OB than in the control group. The incidence of most other events was similar in each group.

Features and properties of enfuvirtide (Fuzeon™, T-20, DP178)	
Indication	
HIV infection in treatment-experienced patients	
Mechanism of action	
Antiviral	Peptide fusion inhibitor
Dosage and administration	
Recommended dose	Adults 90mg (1mL)
	Children (6–16 years) 2 mg/kg
Route of administration	Subcutaneous injection
Frequency of administration	Twice daily
Pharmacokinetic profile of enfuvirtide after subcutaneous injection of 90mg twice daily for 14 days (unless otherwise stated) in patients with HIV infection	
Peak plasma concentration	5.0 μg/mL
Time to peak plasma concentration	≈4h
Trough plasma concentration	3.3 μg/mL
Area under the plasma concentration-time curve, 0-12h	48.7 μg • h/mL
Bioavailability	84.3% (90mg single dose)
Elimination half-life	3.8h (90mg single dose)
Adverse events	
Most common	Injection-site reactions (98% of patients), lymphadenopathy (7.1 per 100 patient-years), pneumonia (6.7 per 100 patient-years)



Amino acid sequence of enfuvirtide

Recent advances in antiretroviral therapy have markedly improved clinical outcomes for patients with HIV infection.[1-4] However, despite these improvements, many patients exhaust all antiretroviral treatment options as a result of persistent HIV replication. The current standard therapies for HIV infection target either the HIV reverse transcriptase enzyme or the HIV protease enzyme. Selection for drug-resistant viral strains is a common limitation of therapy.[1,2] Often virus strains resistant to one drug will be cross-resistant to other drugs within the same class, which limits a patient's therapeutic options. There is therefore a need for new classes of antiretroviral agents, with novel mechanisms of action.[5]

Enfuvirtide (Fuzeon™[1], T-20, DP178) is the first of a new class of drugs, the fusion inhibitors.[6] It is a 36-amino acid peptide derived from the HIV transmembrane glycoprotein (gp41).[5,7,8] This profile provides a review of the pharmacology, therapeutic efficacy and tolerability of enfuvirtide in patients with HIV infection.

1. Pharmacodynamic Profile

Mechanism of Action

HIV entry into cells is initiated when the viral surface glycoprotein (gp120) binds to the target cell CD4 molecule and then to the co-receptors. The viral gp41 then undergoes a conformational change that ultimately allows fusion of the viral and cellular membranes.[7,9]

- Enfuvirtide blocks the fusion of cellular and viral membranes, thereby interfering with the entry of HIV into target cells.[9] The drug is a synthetic peptide which corresponds to a 36-amino acid sequence of the heptad repeat sequence 2 of the HIV-1 gp41.[5,7,8] Enfuvirtide competitively binds to the first heptad repeat (HR1) region of gp41, preventing the formation of a six-helix bundle which is critical for membrane fusion to occur.[9,10]

Antiviral Activity *In Vitro*

- Enfuvirtide reduced infection by cell-free HIV_{LAI} and virus-mediated cell-cell fusion by 90% at concentrations of 80 ng/mL and 1–2 ng/mL.[11] The US product information states that the IC_{50} (concentration required to inhibit infection by 50%) for enfuvirtide against laboratory and primary isolates of prominent HIV clades ranged from 18 to 1260 ng/mL.[12] Other reported IC_{50} values for enfuvirtide against HIV isolates include 29–982 ng/mL,[13] 2.5 ng/mL,[14] and 12 and 14 ng/mL.[15]
- In tissue culture, cytotoxicity and cytostasis were observed at enfuvirtide concentrations at least 10^4 to 10^5 times higher than the concentration required to inhibit infection by cell-free HIV.[11]
- Several investigators have reported that HIV enfuvirtide susceptibility is independent of virus co-receptor use.[15-17] In contrast, another group of investigators have shown that a significantly higher concentration of enfuvirtide is required to inhibit CCR5-specific (R5, macrophage-tropic) HIV viruses than that required for HIV viruses that utilise the CXCR4 co-receptor (X4, T cell-tropic viruses).[13,18] In two phase III trials, however, there were no significant differences in mean virological responses between patients predominantly infected with R5 strains at baseline and those predominately infected with X4 strains at baseline (see also section 3).[19] R5 strains usually predominate during transmission whereas X4 viruses are often associated with disease progression.[7]
- In cell culture assays, enfuvirtide exhibited synergistic activity when combined with individual

1 Use of a tradenames is for product identification purposes only and does not imply endorsement.

antiretroviral agents, including zidovudine, lamivudine, nelfinavir and indinavir (combination index = 0.3–0.7, data in abstract form only).[14] The US product information also reports synergistic or additive effects when enfuvirtide is combined with efavirenz.[12]

Viral Resistance

In Vitro

• *In vitro*[20] An HIV clone with two substitutions (glycine to serine at position 36 [G36S] and valine to methionine at position 38 [V38M], GIV→SIM) was resistant to enfuvirtide at concentrations as high as 10 μg/mL. Clones containing one substitution (G36S) exhibited intermediate susceptibility, requiring 0.5–1 μg/mL for a 10-fold reduction in HIV titre. An enfuvirtide concentration of 0.1 μg/mL is sufficient to reduce the wild-type HIV infectious titre by 95–98%.[11] *In vitro* site-directed mutagenesis studies confirmed that, for the development of the resistant phenotype, changes in two of the three amino acid residues were necessary.[20]

In Vivo

The majority of data in this section are available in abstracts or conference posters.

• HIV clinical isolates with reduced susceptibility to enfuvirtide and/or with substitutions in gp41 amino acids have been recovered from patients receiving enfuvirtide;[12,16,21,22] enfuvirtide-resistant mutant viruses appear to be less virulent than the wild-type virus.[23,24] Resistance to other antiretroviral drugs does not confer cross-resistance to enfuvirtide.[12,16,25,26]

• Primary genotypic resistance to enfuvirtide was rare in HIV isolates from enfuvirtide-naive patients, regardless of HIV subtype or prior antiretroviral therapy.[21,25,27-29] In four studies,[25,27-29] the GIV motif at positions 36–38 in gp41 was conserved in 99–100% of isolates.

• HIV clinical isolates with reduced susceptibility to enfuvirtide have been recovered from patients receiving enfuvirtide in combination with other antiretroviral agents.[12,16,19,21,22] In one study, HIV isolates with a single substitution in gp41 amino acids 36, 38, 40 or 43 exhibited a 3.1- to 450-fold decrease in susceptibility to enfuvirtide relative to baseline.[22] Isolates containing substitutions at two amino acids (positions 36, 40, 42, 43, 44 or 45) were associated with a 30- to 632-fold decrease.

• Of the patients in two phase III trials who experienced virological failure within 24 weeks of treatment with enfuvirtide 90mg twice daily, 94% exhibited substitutions in plasma HIV gp41 amino acids 36–45.[19] Valine to alanine at position 38 (V38A) and asparagine to aspartic acid at position 43 (N43D) were the most commonly observed substitutions. HIV isolates from patients who experienced virological failure exhibited a mean 21-fold decrease from baseline in susceptibility to enfuvirtide.[19]

• In three phase II trials, a greater than 10-fold decrease in susceptibility was observed in HIV isolates from 21 of 74 patients with paired baseline and in-treatment isolates.[21] Of these, 18 of 19 HIV isolates with sequence data available harboured substitutions in gp41 amino acids 36–45.

• HIV with enfuvirtide resistance-associated mutations did not persist in the plasma of 15 patients who ceased enfuvirtide treatment for 2.7–8.5 months.[23] Forty-eight weeks after recommencing enfuvirtide (45mg subcutaneously twice daily) treatment, these patients had not acquired viruses with enfuvirtide resistance-associated substitutions more frequently than other patients receiving enfuvirtide. In the absence of enfuvirtide in *in vitro* growth competition assays, enfuvirtide-resistant HR1 mutant viruses (identified in patient isolates obtained after treatment) were less virulent than wild-type viruses.[24]

• Enfuvirtide was active in cell culture against baseline virus isolates that were resistant to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).[12,16,25,26]

Immune Effects

• Suppression of interleukin (IL)-12 production during infection with HIV may contribute to host immunosuppression. Enfuvirtide suppressed *in vitro* IL-12 p70 production by human monocytes in res-

ponse to both T-cell-dependent and T-cell-independent stimulation, with maximum inhibition (more than 90%) occurring at less than 10^{-5} mol/L.[30] The concentrations of enfuvirtide required to suppress *in vitro* IL-12 production were less than or equivalent to the levels needed to suppress HIV RNA replication *in vivo*. The suppression was selective for IL-12 in that the production of tumour necrosis factor-α, transforming growth factor-β and IL-10 were unaffected by enfuvirtide. The suppressive effect was not seen with monocyte-derived dendritic cells.[30] The clinical relevance of these data has not been established.

2. Pharmacokinetic Properties

Unless otherwise stated, the data in this section are for adult patients with HIV infection receiving 90mg subcutaneous injections of enfuvirtide. Formal studies investigating the pharmacokinetic profile of enfuvirtide in patients with renal or hepatic impairment have not been conducted.[12]

Absorption

- After 14 days' treatment with twice-daily enfuvirtide plus other antiretroviral agents in 11 patients, the enfuvirtide mean maximum plasma concentration (C_{max}), time taken to reach this concentration (t_{max}), area under the plasma concentration-time curve from 0–12 hours (AUC_{12}) and minimum plasma concentration (C_{min}) were 5.0 μg/mL, 4.1 hours, 48.7 μg • h/mL and 3.3 μg/mL, respectively.[12,31]
- For 12 patients who received a single dose of enfuvirtide the mean absolute bioavailability was 84.3% (using a 90mg intravenous dose as a reference).[32]
- There were no marked differences in mean absorption parameters for twice-daily thigh, arm and abdomen injections in 12 patients (C_{max} 4.71–5.63 μg/mL, C_{min} 2.67–3.66 μg/mL, AUC_{12} 43.3–53.1 μg • h/mL), meaning patients may rotate the site of injection.[33]
- The systemic exposure to twice-daily enfuvirtide 2 mg/kg in paediatric patients was comparable to that previously observed in adult patients receiving 90mg twice daily (data from an abstract and poster).[34] On day 7, the mean AUC_{12} was 54.3 μg • h/mL in 12 children (aged 5–11 years) and 13 adolescents (aged 12–16 years) with HIV infection who received subcutaneous enfuvirtide in combination with other antiretroviral agents. The mean C_{max}, t_{max} and C_{min} were 6.1 μg/mL, 4.6 hours and 2.9 μg/mL, respectively. The pharmacokinetics of enfuvirtide were not significantly affected by puberty stage (as assessed by Tanner Staging), age group, bodyweight or body surface area.[34]

Distribution

- Enfuvirtide has a small volume of distribution (Vd).[1,32] In one trial, the mean steady-state Vd following a single intravenous enfuvirtide 90mg injection was 5.5L (n = 12).[32]
- The US product information states that over a concentration range of 2–10 μg/mL, enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma.[12] It is bound predominantly to albumin and to a lesser extent to α_{-1} acid glycoprotein.

Metabolism and Elimination

- Because enfuvirtide is a peptide, it is expected to undergo catabolism to its constituent amino acids.[12,35] *In vitro* human microsomal data suggest that enfuvirtide is not metabolised by cytochrome P450 (CYP) [data from poster].[35]
- •*In vitro*[12] Plasma concentrations of the metabolite are approximately 15% of those of the parent drug (data from poster).[33]
- Following a single dose of enfuvirtide, the mean elimination half-life and systemic clearance values were 3.8 hours and 1.4 L/h.[32] The US prescribing information reports a mean apparent clearance of 30.6 mL/h/kg in 11 patients who received enfuvirtide 90mg twice daily in combination with other antiretroviral drugs.[12]
- Although no dose adjustment is recommended based on bodyweight or gender, an analysis of plasma concentration data indicates that the clearance of

enfuvirtide is 20% higher in males than females (after adjustment for bodyweight), and clearance is reduced with decreased bodyweight in both males and females (using a bodyweight of 70kg as a reference).[12] Increased bodyweight is associated with increased clearance in males but not females. Analysis of plasma concentration data from several trials indicates that there is no difference in the clearance of enfuvirtide between Blacks and Caucasians or between Asians and Caucasians after adjustment for bodyweight.

Potential for Drug Interactions

- Following a study in 12 patients, investigators concluded that there was minimal potential for drug interactions between enfuvirtide and agents that are substrates of CYP1A2, CYP2E1, CYP3A4, CYP2D6, CYP2C19 or N-acetyltransferase.[36] Patients received enfuvirtide for 7 days, and the five-drug 'Pittsburgh cocktail' (caffeine, chlorzoxazone, dapsone, debrisoquine, mephenytoin) 15 days before the first enfuvirtide injection, and again on day 6.[36]
- The pharmacokinetics of enfuvirtide were not affected to a clinically relevant extent when enfuvirtide was coadministered with ritonavir (an inhibitor of CYP3A4 isoenzymes), rifampicin (an inducer of several CYP isoenzymes) or saquinavir plus ritonavir to 12 patients with HIV infection.[35]

3. Therapeutic Efficacy

The efficacy of twice-daily subcutaneous enfuvirtide has been studied in adults and children.

Adults

TORO (T-20 vs Optimised Regimen Only) Trials

The efficacy of enfuvirtide in combination with other antiretroviral agents is being evaluated in two ongoing phase III trials (T-20 vs Optimised Regimen Only [TORO] 1 and TORO 2), for which 24-week data have been published in full[37,38] and pooled 48-week data are available as a poster.[39] Both are randomised, open-label multicentre trials, enrolling a total of almost 1000 patients with advanced HIV infection.[37,38]

Patients were required to have prior treatment with antiretroviral drugs from three classes (NRTIs, NNRTIs and PIs, treatment experience ≥6 months in TORO 1, ≥3 months in TORO 2) and/or documented resistance to at least one member in each of the three classes.[37,38] Patients had prior treatment with a median of 12 antiretroviral drugs for a median of 7 years (US product information).[12] At baseline, the median HIV load was approximately 5 $\log_{10}$ copies/mL.[37,38] The median CD4+ cell counts for the enfuvirtide and control groups were 76 and 87 cells/μL in TORO 1[37] and 98 and 102 cells/μL in TORO 2.[38]

In both studies, an optimised background (OB) regimen of three to five antiretroviral agents was selected for each patient based on their prior treatment history and baseline genotypic and phenotypic HIV resistance measurements. Patients were then randomised in a 2 : 1 ratio to receive enfuvirtide or no additional treatment. Enfuvirtide 90mg was self-administered twice daily.[37,38]

The primary efficacy endpoint in both trials was defined as the change from baseline to 24 weeks in plasma HIV RNA level.[37,38] Secondary endpoints included the proportion of patients with viral loads reduced to <400 or <50 copies/mL or with a decrease in viral load ≥1 $\log_{10}$ copies/mL and the changes from baseline in CD4+ cell count. In both trials, efficacy data were analysed for the intention-to-treat population.

- After 24 weeks in both trials, enfuvirtide plus OB was significantly more effective than OB alone for both the mean reduction in viral load (primary endpoint) and the proportion of patients with HIV RNA levels <400 or <50 copies/mL (figure 1).[37,38] The response to enfuvirtide plus OB was approximately 2-fold greater than that to OB alone in both trials.[37,38] The percentage of patients with a ≥1 $\log_{10}$ copies/mL reduction in viral RNA levels relative to baseline was significantly greater in the enfuvirtide group than in the comparator group (TORO 1, 51.8% vs 29.1%, $p \leq 0.0001$; TORO 2, 42.7% vs 20.7%, $p \leq 0.001$).[37,38]

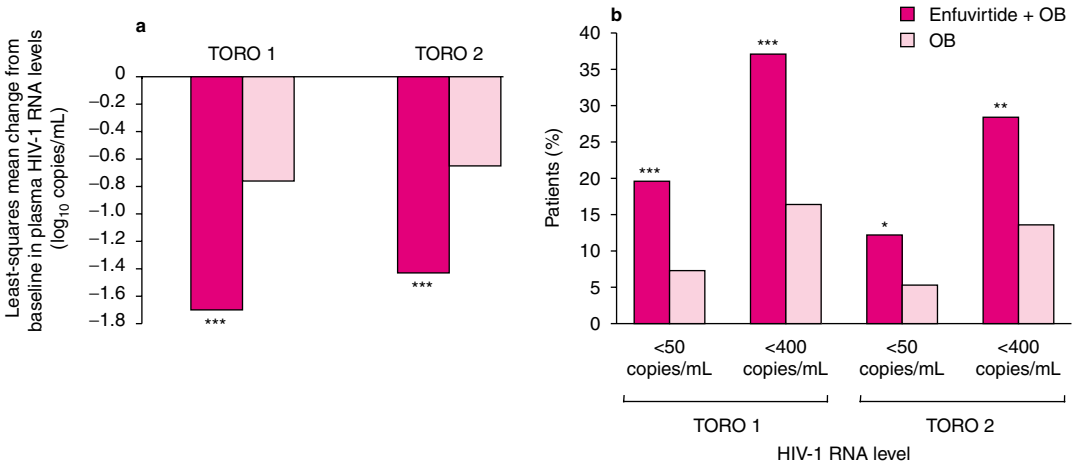


Fig. 1. Viral suppression with enfuvirtide in treatment-experienced patients with HIV infection. Data shown are 24-week results (intention-to-treat analysis) from two phase III randomised, open-label, multicentre trials, TORO 1 (n = 491)[37] and TORO 2 (n = 504).[38] Patients had at least 3–6 months prior treatment with and/or resistance to three classes of antiretroviral agents. Patients received an optimised background (OB) regimen (3–5 antiretroviral agents) plus enfuvirtide (90mg subcutaneous, twice daily) or no additional treatment (2 : 1 ratio). The median viral load at baseline was approximately 5 $\log_{10}$ copies/mL. The primary efficacy endpoint was the mean change from baseline in plasma HIV RNA level (**a**). The percentages of patients achieving a viral load reduction to <400 or <50 copies/mL were secondary endpoints (**b**). **TORO** = T-20 vs Optimised Regimen Only; * $p \leq 0.01$, ** $p \leq 0.001$, *** $p \leq 0.0002$ vs OB.

- In a pooled analysis of 24-week data from both TORO 1 and TORO 2, mean virological responses were not significantly affected by baseline viral co-receptor tropism or clade (see also section 1).[19] The mean reductions from baseline in plasma HIV RNA for patients predominately infected with X4, R5 or dualtropic strains were 1.34, 1.55 and 1.64 $\log_{10}$ copies/mL, respectively. Reductions for patients predominately infected with clade B and non-B HIV were 1.55 and 1.92 $\log_{10}$ copies/mL.[19]

- The antiviral efficacy of enfuvirtide was maintained through to 48 weeks of treatment in these trials.[39] In a pooled analysis of 48-week data for TORO 1 and 2, the mean adjusted reduction from baseline in HIV RNA levels was 1.48 $\log_{10}$ copies/mL for enfuvirtide plus OB recipients compared with 0.63 $\log_{10}$ copies/mL for those receiving OB alone ($p < 0.0001$). A significantly higher percentage of patients in the enfuvirtide groups had viral RNA levels reduced to <400 copies/mL (30.4% vs 12.0%, $p < 0.0001$) or <50 copies/mL (18.3% vs 7.8%, $p < 0.0001$).[39]

- At 24 weeks, the increase from baseline in the mean CD4+ cell count was significantly greater in the enfuvirtide group than in the OB group in both TORO 1 (76 vs 32 cells/μL, $p \leq 0.001$) and TORO 2 (66 vs 38 cells/μl, $p \leq 0.02$).[37,38] For pooled 48-week data, the mean adjusted increase from baseline in CD4+ cell count was 91 cells/μL in enfuvirtide plus OB recipients compared with 45 cells/μL in OB recipients ($p < 0.0001$).[39]

- A Markov model, based on pooled 24-week data from the TORO trials and published mathematical models of disease progression, predicted that enfuvirtide plus OB will extend average overall survival by 1.6 years compared with OB alone (6.2 vs 4.6 years, data from an abstract and poster, statistical analysis not reported for any parameter).[40] The predicted overall survival was more favourable with enfuvirtide plus OB than OB alone regardless of baseline CD4+ cell counts and genotypic sensitivity scores. Patients with higher genotypic sensitivity scores or a CD4+ cell count ≥100 cells/μL derived more benefit from enfuvirtide plus OB. The projected mean overall survival for enfuvirtide plus OB recipients with baseline genotypic sensitivity scores of 0, 1 and ≥2 were 4.2, 5.4 and 7.2 years, respectively. Respective projections for patients with base-

line CD4+ cell counts of <100 cells/μL and ≥100 cells/μL were 3.8 and 8.1 years.[40]

Effects on Health-Related Quality of Life

At baseline and various other times including 24 and 48 weeks in both the TORO studies, patients completed the Medical Outcomes Study (MOS)-HIV questionnaire which examines patients' health-related quality of life (reported in an abstract and poster).[41] The MOS-HIV questionnaire includes two summary scores: physical health, which summarises six scale scores, and mental health, which summarises four scale scores. At baseline, there were no significant differences for any of the scores between the enfuvirtide plus OB group and the OB group. Patients also assessed the ease of enfuvirtide self-injection (reported in a poster)[42] and the impact of enfuvirtide treatment on their daily lives (abstract plus poster).[43]

- After treatment for 24 and 48 weeks, enfuvirtide plus OB recipients showed significantly greater improvement from baseline than OB recipients for the mental health summary score and for four of the scale scores: general health, energy/fatigue, health distress and quality of life ($p < 0.05$).[41] All other scores did not differ significantly between the two treatment arms.
- The changes from baseline in all scores were very similar at 48 weeks to those observed at 24 weeks.[41] At 48 weeks, the improvement in the mental health summary score for the enfuvirtide group was approximately 2 compared with <0.5 for the OB group ($p = 0.01$). For the four scale scores for which enfuvirtide plus OB recipients showed a greater improvement compared with OB alone, approximate changes from baseline were as follows: general health +4 vs −1.2 ($p = 0.002$); energy/fatigue +5 vs +2 ($p < 0.05$); health distress +8 vs +3.5 ($p = 0.02$) and quality of life +3.5 vs −1 ($p = 0.02$).[41]
- At weeks 8, 24 and 48, approximately two-thirds of patients in TORO 1 and TORO 2 assessed self-injection of enfuvirtide as very easy (≈30%) or easy (≈40%) and approximately 20% were neutral.[42] Although there was no significant difference between the distribution of ease of injection scores from week 8 to week 48, investigators noticed a trend towards patients finding self-injection easier over time. Of patients who rated self-injection as difficult at week 8, 42% were neutral or found it easy at week 48.[42]
- At 24 weeks, the majority of patients (70–89%) reported enfuvirtide treatment had little or no effect on their familiar routines, including work, sleep and social life. Nearly all patients (95–98%) reported little or no effect on basic activities of daily living such as bathing, toileting and preparing meals.[43]

Phase II studies

- At 48 weeks in two phase II trials (reported in abstracts) enfuvirtide 90mg twice daily as a component of combination therapy regimens reduced mean HIV RNA loads by approximately 2–3 $\log_{10}$ copies/mL in moderately and heavily treatment-experienced patients (all patients were PI experienced).[31,44]
- Enfuvirtide plus other antiretroviral therapy reduced viral load by >2 $\log_{10}$ copies/mL in a randomised dose-ranging open-label study in 70 PI-experienced, NNRTI-naive patients.[44] At 48 weeks, median reductions from baseline in HIV RNA levels ranged from 2.10 to 2.62 $\log_{10}$ copies/mL for patients receiving enfuvirtide 45, 67.5 or 90mg twice daily plus abacavir, amprenavir, ritonavir and efavirenz, compared with 1.9 $\log_{10}$ copies/mL for the same regimen without enfuvirtide (study not powered to show statistical differences). At the same timepoint, 54.9% and 47.1% of enfuvirtide recipients had plasma HIV RNA levels ≤400 and ≤50 copies/mL. The median increase from baseline in CD4+ cell counts was 132 cells/μL for enfuvirtide recipients compared with 90 cells/μL for the control group.[44]

Paediatric studies

The efficacy of enfuvirtide in combination with other antiretroviral drugs has also been investigated in children with HIV infection; 24-week results from one trial have been published,[45] a second trial which is ongoing does not yet have efficacy data available.[12,46] Unless stated otherwise, statistical analyses were not reported.

• At 24 weeks, enfuvirtide (30 mg/m^2 or 60 mg/m^2 twice daily) plus background antiretroviral therapy reduced the viral load from baseline by at least 1 $\log_{10}$ copies/mL in 10 of 14 children (aged 4–12 years) with HIV infection.[45] There was a significant increase in CD4+ cell count from baseline to 24 weeks (146 cells/μL, p-value not stated [on-treatment analysis, 11 evaluable patients]). At baseline, the median plasma HIV load and CD4+ cell count were 4.4 $\log_{10}$ copies/mL and 523 cells/μL. After seven days of treatment, each patient's background regimen was changed to include new antiretroviral agents including at least one from an antiretroviral class to which the patient had little or no previous exposure.[45] At this stage of treatment, the numbers of patients with a decrease from baseline in HIV load of >0.7 $\log_{10}$ and ≥1 $\log_{10}$ copies/mL were 11 and 8 of 14.

4. Tolerability

Unless otherwise stated, the results in this section are from an analysis of pooled 48-week data from TORO 1 and 2, which is available as a conference poster.[47]

• The most frequent adverse effects associated with the use of enfuvirtide were local injection-site reactions (ISRs). After 48 weeks of treatment, 98% of enfuvirtide plus OB recipients had reported at least one ISR.[47] Frequent symptoms of ISRs included pain/discomfort, erythema, induration, and the presence of nodules or cysts (96%, 91%, 90% and 80% respectively). Eleven percent of patients experienced ISRs that were severe, required analgesic agents or limited usual activities, and 4.4% of patients discontinued treatment because of ISRs.[47]

• Excluding ISRs, the adverse events that occurred at a rate of at least 5 per 100 patient-years and quantitatively more frequently in enfuvirtide recipients are illustrated in figure 2.[47] The only two adverse events that occurred with a frequency of at least 5 per 100 patient-years higher in the enfuvirtide plus OB treatment group than the OB alone group were lymphadenopathy (7.1 vs 1.2 per 100 patient-years: risk ratio 5.75: 95% CI 1.51, 48.48) and pneumonia (6.7 vs 0.6: risk ratio 10.78; 95% CI 1.84, 435.2). The pneumonia was primarily caused by bacterial infections, and the incidence was within the expected range for this patient population. It is unclear whether the increased incidence of pneumonia was related to enfuvirtide use. The most frequently reported adverse events in both the enfuvirtide and control groups, all of which were reported more frequently in the OB group, were diarrhoea (37.1 vs 73.4 per 100 patient-years: risk ratio 0.51; 95% CI 0.40, 0.63), nausea (26.2 vs 50.0: risk ratio 0.52; 95% CI 0.40, 0.69) and fatigue (25.0 vs 37.6: risk ratio 0.66; 95% CI 0.49, 0.90).[47]

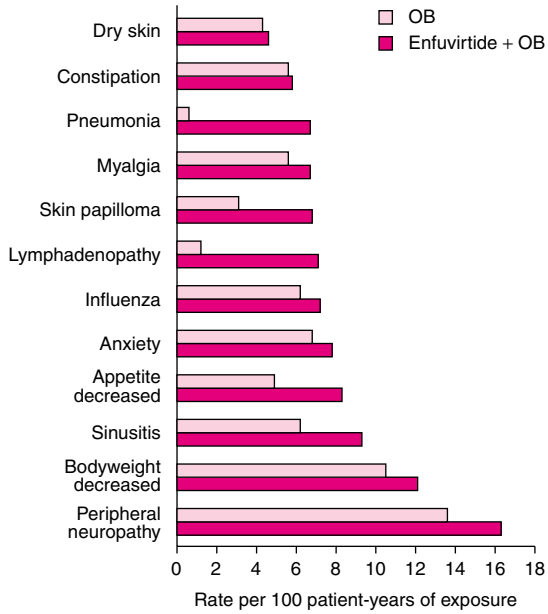


Fig. 2. Tolerability of enfuvirtide (excluding injection site reactions) in treatment-experienced patients with HIV infection. Data shown are a pooled analysis of 48-week results from TORO 1 and TORO 2, which are phase III, multicentre, randomised, open-label trials.[47] The analysis was based on a total of 997 patients who had at least one safety follow-up. Only events occurring at a rate ≥5 per 100 patient-years and quantitatively more frequently in the enfuvirtide groups are shown. Patients had at least 3–6 months' prior treatment with and/or resistance to three classes of antiretroviral agents. Patients received an optimised background (OB) regimen (3–5 antiretroviral agents) plus enfuvirtide (90mg subcutaneously, twice daily) or an OB regimen alone (2 : 1 ratio). Risk ratios for the adverse events shown, with the exception of lymphadenopathy (5.75) and pneumonia (10.78), ranged from 1.04 to 2.20. **TORO** = T-20 vs Optimised Regimen Only.

• The proportion of enfuvirtide plus OB recipients who discontinued study treatment because of ad-

verse events was 8.9% versus 10.7% of OB recipients.[47] After treatment with enfuvirtide plus OB for 24 weeks, the most frequent adverse events leading to treatment discontinuation were vomiting and nausea in the TORO 1 trial[37] and depression, vomiting and hypersensitivity in the TORO 2 trial. [38]

- After 48 weeks' treatment, five patients (<1%) had systemic hypersensitivity reactions that were attributed to enfuvirtide therapy; some of them recurred on rechallenge.[47] Reactions included rash, fever, nausea and vomiting, chills, rigors, hypotension, elevated serum liver transaminases and one case each of glomerulonephritis and Guillain-Barré syndrome.
- At 24 and 48 weeks, eosinophilia (>700 cells/mm^3) was the only treatment-related laboratory abnormality that occurred in a markedly greater proportion of patients in the enfuvirtide group than in the control group (24 weeks pooled TORO data, 11.5 vs 4.9 patients per 100 patient-years;[37] 48 weeks, 12.9 vs 5.5[47] [statistical analysis not reported for either timepoint]). After treatment for 24 weeks, other grade 3 or 4 laboratory abnormalities that occurred in ≥2 of patients and more frequently in patients receiving enfuvirtide were elevated amylase, lipase, triglycerides, alanine aminotransferase, aspartate aminotransferase, creatine phosphokinase, and α-glutamyl transferase and reduced haemoglobin.[12]
- Eleven of 14 paediatric patients experienced at least one ISR during treatment with enfuvirtide for 24 weeks.[45] None of the reactions caused a patient to discontinue treatment. The US prescribing information states that adverse events were similar to those reported in adult patients for 35 paediatric and adolescent patients (aged 6–16) who received enfuvirtide (treatment duration ranged from 1 dose to 48 weeks).[12]

5. Cost Effectiveness

Three cost-effectiveness analyses for enfuvirtide have been conducted; two are available as posters and abstracts[48,49] and the other is available as an abstract and therefore recounts only limited design details.[50] One analysis was conducted from the US healthcare perspective[48] and one from the UK health payer perspective:[49] the perspective was not reported for the other trial.[50]

The US[48] and UK[49] analyses both used a Markov model, based on pooled 24-week data from the TORO trials and published mathematical models of disease progression. The cost of therapy for the OB regimen was based on four drugs (the average number used in the trials), assumed to include two NRTI agents and a boosted PI agent (2003 prices used for both regimens).[48,49] Published estimates, with inflation adjustments where necessary, were used to determine treatment costs for an AIDS-defining event (ADE) and monthly costs for non-ADE-related care. Published reports of patients with HIV were used to make quality-of-life adjustments; these were stratified by CD4+ cell count. One-way sensitivity analyses were performed using variables based on published data.[48,49] Discount rates used were 3% for costs in the US analysis[48] and 6% for costs and 1.5% for quality-adjusted life years (QALY) in the UK analysis.[49] The other analysis used a simulation model of HIV disease and treatment and 24-week data from TORO 1.[50]

- In the US analysis, the incremental cost-effectiveness ratio for the use of enfuvirtide plus OB compared with OB alone was estimated to be $US32 795 per life year gained and $US43 607 per QALY gained.[48] Respective estimates for the UK analysis were £18 859 and £23 200.[49] In both analyses, the investigators concluded that the calculated level of cost effectiveness was acceptable by current standards.[48,49]
- The variables most likely to influence the cost effectiveness (change the ratio by at least $US10 000[48] or £5000[49]) were as follows: risk of a new ADE, time to virological failure and baseline CD4+ cell count in both analyses,[48,49] and quality of life in the US analysis.[48] Subgroup analyses in the UK investigation showed that the cost effectiveness of enfuvirtide plus OB was improved for patients with higher genotypic sensitivity scores or CD4+ cell counts.[49]
- In the other analysis, for which assumptions were not stated, the cost-effectiveness ratio for enfuvir-

tide plus OB compared with OB alone was $74 400 per QALY gained, based on an enfuvirtide cost of $21 000/person/year.[50]

6. Dosage and Administration

The recommended dosage of enfuvirtide for adults is 90mg (1mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen.[12] For paediatric and adolescent patients aged 6–16 years, the recommended dosage is 2 mg/kg twice daily up to a maximum of 90mg twice daily. Each injection should be given at a site different from the preceding one, and only where there is no current ISR.

7. Current Status

Enfuvirtide is approved in the EU, the US, and several other countries. It is indicated for use in combination with other antiretroviral agents. In the US, enfuvirtide is indicated for the treatment of HIV infection in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy.[12] In the EU, patients must have experienced treatment failure with at least one agent from each of the PI, NNRTI and NRTI classes, or have intolerance to previous antiretroviral regimens. In large phase III trials, enfuvirtide has shown efficacy in reducing plasma HIV RNA levels when used in addition to optimised therapy and, with the exception of ISRs, was generally well tolerated.

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