Acquired immunodeficiency syndrome (AIDS) continues to pose an overwhelming burden on public health. According to estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), 38.6 million adults and 3.2 million children throughout the word were living with human immunodeficiency virus (HIV) infection at the end of 2002. This number is more than 50% higher than the figures projected by WHO in 1991, based on the available data at that time. The Centers for Disease Control and Prevention (CDC) estimates that 850,000 to 950,000 U.S. residents are infected with HIV, with 25% unaware of their current disease state. In 2002, five million people were infected with HIV and a total of 3.1 million people died of HIV/AIDS. Despite the advent of antiretroviral therapy, this number is the highest throughout the world in any year since the beginning of the epidemic.

The pathogenesis of HIV type 1 (HIV-1) has been published extensively. Thus, the knowledge gained paved the way for the development of new antiretroviral agents that are highly active against this strain. Resistance to most of the currently available antiretroviral drugs, however, is common. Although the combinations of these highly active antiretroviral drugs delay the emergence of viral resistance more effectively than monotherapy does, there are no known combinations that can guarantee the prevention of resistance development.

On March 13, 2003, the U.S. Food and Drug Administration (FDA) approved a novel drug, the first in its class for the treatment of resistant HIV-1 infection. Enfuvirtide (Fuzeon®, Roche, Trimeris) represents a new class of antiretroviral agents known as fusion inhibitors. The FDA granted accelerated approval of this drug on the basis of two large clinical trials involving HIV patients who had not responded to conventional antiretroviral therapy.

**PHARMACOLOGY**

Enfuvirtide is a 36-amino acid peptide chain with 14 different amino acids. Linear in nature, its molecule is composed of naturally occurring L-amino acid residues; the N-terminus is acetylated, and the C-terminus is a carboxamide.

Unlike the existing antiretroviral drugs, enfuvirtide has a unique mechanism of action that is designed to block HIV fusion with the human immune cell. The virus is composed of two layers of fatty lipids that consist predominantly of proteins taken from the host cell upon budding and release. HIV also consists of its own surface proteins, called Env. This protein has a strong affinity for the CD4 receptor cell at which binding of the viron particle takes place.

HIV consists of appendages known as glycoprotein 120 and glycoprotein 41 (gp120 and gp41), which aid in viral attachment. gp120 is the capsule that anchors the virus, and gp41 is the domain of gp120 that holds the virus to the CD4 cell. HIV fusion with CD4 cells is accomplished through a series of conformational changes in the HIV envelope as well as in gp120 and gp41. The core structure of glycoprotein 41 is a six-helix bundle composed of a 3N terminal and a 3C terminal helix. The C-helices closely surround the N-helices, and conformational changes, which are manifested by folding into a hairpin shape, occur after binding to the target cell membrane.

The pharmacological structure of enfuvirtide corresponds to the C-helix structure of gp41. Enfuvirtide binds to and inhibits the gp41 protein’s active site and thus disrupts the structural rearrangement that is necessary for the virus to gain entry into a healthy immune cell (Figure 1). Given this unique mechanism of action, enfuvirtide has the potential to act synergistically with the currently available antiretroviral drugs to suppress HIV-1 replication and to diminish the development of resistant mutations.

**PHARMACOKINETICS**

Enfuvirtide is a synthetic peptide and is thus not bioavailable orally. Following a twice-daily subcutaneous injection of 30 to 90 mg, its bioavailability is approximately 84.3%. Comparable absorption of the 90-mg dose has been reported in different injection sites of the abdomen, thigh, and arm.

The time to maximum concentration (T_{max}) ranges from four to eight hours. The volume of distribution (V_d) is 5.5 liters, and the clearance (Cl) rate is 1.4 liters/hour. The area under-the-concentration-time curve (AUC) ranges from 25 to 113 mcg/ml, and the elimination half-life (T_{1/2}) is 3.5 to 4 hours.

Enfuvirtide is bound predominantly to plasma albumin (approximately 92%) and, to a lesser extent, to alpha₂-acid glycoprotein. The drug undergoes hydrolysis to form a deaminated metabolite at the C-terminal phenylalanine residue (Table 1). In clinical trials, enfu-
virtide’s clearance was not affected when the patient’s creatinine clearance was 35 ml/minute or more; however, the effect of the drug’s clearance in patients with a creatinine clearance lower than 35 ml/minute is not known.

It is recognized, however, that enfuvirtide’s clearance is affected by weight and gender. A 20% decrease in total clearance has been reported in low-weight patients (below 40 kg). Conversely, females have been shown to exhibit a 20% decrease in clearance, compared with their male counterparts.

**CLINICAL TRIALS**

The regulatory submission for enfuvirtide was based on data from two 24-week phase III trials of approximately 1,000 patients. One of these studies, TORO-1 (T-20 versus Optimized Regimen Only, study 1) was a multicenter, randomized, controlled, open-label trial in North and South America. Patients who had at least six months of previous treatment with agents in the three currently available classes of antiretrovirals—nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs)—whose infection showed resistance to agents in these classes were included in the study. The enrolled patients also had median viral loads of 5.2 log10 and median CD4 counts of 75.5 cells/mm3.

Similarly, TORO-2 (T-20 versus Optimized Regimen Only, study 2) enrolled similar patients from Europe and Australia. Participants had to have only a minimum of three months of prior experience with antiretroviral agents and median viral loads of 5.1 log10 copies/ml and median CD4 counts of 98 cells/mm3.

In both clinical trials, patients were randomly assigned, in a 2:1 ratio, to receive 90 mg of enfuvirtide subcutaneously twice daily plus an optimized background regimen consisting of three to five antiretroviral agents or an optimized background regimen only. During the study, the investigational drugs tenofovir (Viread®, Gilead) and lopinavir–ritonavir (LPV/RTV) (Kaletra®, Abbott) were allowed as part of the optimized background regimen. The primary efficacy endpoint was a significant change in the viral load from baseline evaluation at the end of the 24th week.

**EFFICACY**

In both studies, the addition of enfuvirtide to an optimized regimen provided significant antiretroviral and immunological results through 24 weeks of HIV treatment-experienced patients and those with multidrug-resistant HIV infection. TORO-1 showed a decrease in viral loads of 1.7 log10 in the enfuvirtide/optimized background regimen group, whereas a decrease of 0.76 log10 was seen in the optimized background regimen only (control) group (P < .001). Changes in CD4 counts in the enfuvirtide/optimized background regimen group were increased by a median of 76 cells/mm3, whereas controls showed an increase of 32 cells/mm3, respectively (P < .001).

TORO-2 showed similar changes in viral loads, with a decrease of 1.43 log10 for patients receiving the enfuvirtide/optimized background regimen and a decrease of 0.65 log10 in controls (P < .001). The CD4 count rose by 65 cells/mm3 in the patients receiving the enfuvirtide/optimized background regimen, and the controls experienced an increase of 38 cells/mm3. Analysis of both studies revealed a consistent activity of enfuvirtide across baseline immune cell counts, viral loads, age, race, and gender (Table 2).

Lalezari et al. conducted a clinical trial to study the long-term safety and antiviral activity of enfuvirtide in a multicenter 48-week, noncontrolled, open-label rollover study of 71 HIV-infected adults. Baseline HIV RNA levels were 4.8 log10 copies/ml, and the CD4 count

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**Table 1  Pharmacokinetic Parameters of Enfuvirtide**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mcg/ml)</td>
<td>5.0–1.7</td>
</tr>
<tr>
<td>Tmax (hours)</td>
<td>4–8</td>
</tr>
<tr>
<td>AUC (hours/mcg/ml)</td>
<td>25–113</td>
</tr>
<tr>
<td>Elimination half-life (hours)</td>
<td>3.5–4</td>
</tr>
<tr>
<td>Clearance (liter/hour)</td>
<td>1.44</td>
</tr>
<tr>
<td>Vd (liters)</td>
<td>5.5</td>
</tr>
</tbody>
</table>

AUC = area under the curve; Cmax = maximum plasma concentration; Tmax = time to maximum concentration; Vd = volume of distribution.

Data adapted from product information for Fuzeon® (enfuvirtide), Nutley, NJ (Roche) and Durham, NC (Trimeris), March 2003.

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**Figure 1  Structure of the human immunodeficiency virus.** (Adapted from UNAIDS Joint United Nations Programme on HIV/AIDS. AIDS Epidemic Update, December 2002. Available at: www.avert.org.)
Table 2  Outcomes of Randomized Treatment at Week 24 (from Pooled TORO-1 and TORO-2)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Enfuvirtide + Background Regimen (90 mg b.i.d.) (n = 661)</th>
<th>Background Regimen (n = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA log change from baseline</td>
<td>−1.52</td>
<td>−0.73</td>
</tr>
<tr>
<td>(log10 copies/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count change from baseline</td>
<td>+71</td>
<td>+35</td>
</tr>
<tr>
<td>(cells/mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA ≥ 1 log below baseline</td>
<td>342 (52%)</td>
<td>86 (26%)</td>
</tr>
<tr>
<td>HIV RNA &lt; 400 copies/ml</td>
<td>247 (37%)</td>
<td>54 (16%)</td>
</tr>
<tr>
<td>Discontinued because of adverse reactions</td>
<td>40 (6%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Discontinued because of injection-site reactions</td>
<td>20 (3%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Discontinued because of other reasons</td>
<td>36 (5%)</td>
<td>14 (4%)</td>
</tr>
</tbody>
</table>

b.i.d. = twice a day; HIV = human immunodeficiency virus; N/A = not available; RNA = ribonucleic acid; TORO = T20 versus Optimized Regimen Only, study 1 and study 2.

Data adapted from product information for Fuzeon® (enfuvirtide).4

SAFETY

During trials, patients tolerated enfuvirtide well. By far, the most common adverse drug events (ADEs) were reactions at the injection site. At the end of the 24 weeks in TORO-1 and TORO-2, nearly all patients in the enfuvirtide group (98.2%) reported at least one injection-site reaction, with most patients experiencing their first reaction during the first week. About 42% to 49% of patients also reported either mild-to-moderate tenderness and pain without limitation of their usual daily activities. Only 8.7% of these patients had pain or discomfort and needed oral analgesic agents, and none of the patients required hospitalization. Other common signs of injection-site reactions included erythema (87%), induration (84%), and nodules or cysts (82%).

Other ADEs that were noted during the study were thought to be related to the optimized treatment regimen. The enfuvirtide group included a total of 74.5% of patients who also experienced ADEs. ADEs included diarrhea (79%), nausea (72%), fatigue (64%), and vomiting (25%), respectively. Patients also experienced insomnia, headache, dizziness, flatulence, and weight loss (Table 3).3,4,8,9

An increased rate of bacterial pneumonia was observed in subjects receiving enfuvirtide, compared with the control arm, but it is unclear whether this increase was related to enfuvirtide per se. Hypersensitivity reactions were associated with enfuvirtide therapy, including rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum liver transaminase levels.3,4 These reactions may occur upon rechallenge.3

The manufacturer suggests careful monitoring of bacterial pneumonia and hypersensitivity. Results from the phase II 48-week study of the drug’s long-term safety and efficacy suggest that ADEs do not increase with prolonged exposure. Furthermore, enfuvirtide is well tolerated in both adults and children with HIV infection.11,12

DRUG–DRUG INTERACTIONS

Clinical studies involving enfuvirtide are limited. No clinically significant drug interaction was reported when this medication was used in combination with the other antiretroviral drugs.4 In cell culture media essays, enfuvirtide exhibited additive-to-synergistic effects when it was combined with individual members of various antiretroviral agents, such as zidovudine (AZT, Retrovir®), (Glaxo-SmithKline), lamivudine (3TC, Epivir®), (GlaxoSmithKline), nelfinavir (NFV, Vira-cept®, Agouron), indinavir (IDV, Crixivan® Merck), and efavirenz (EFV, Sustiva®, Bristol-Myers Squibb Virol-ogy).4 A human microsomal study in vitro suggests that enfuvirtide is neither an inducer nor an inhibitor of cytochrome P-450 (CYP-450) enzymes or its substrates.1,2,4

The HIV Netherlands, Australia, Thailand Research Collaboration (HIVNAT) Study Group conducted three pharmacokinetic interaction trials. In each study,

Table 3  Percentage of Patients with Treatment-Emergent Adverse Events Excluding Injection-Site Reactions (from Pooled TORO-1 and TORO-2)4

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Enfuvirtide + Background Regimen (%) (n = 663)</th>
<th>Background Regimen (%) (n = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>8.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Depression</td>
<td>8.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.7</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>7.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Influenza</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5</td>
<td>2.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>2.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

TORO = T20 versus Optimized Regimen Only, study 1 and study 2.

Data adapted from product information for Fuzeon® (enfuvirtide). Nutley, NJ (Roche) and Durham, NC (Trimeris), March 2003.4
12 patients infected with HIV-1 received one of the following regimens with enfuvirtide: 1,000 mg of saquinavir (Fortovase®, Roche) twice daily, boosted with 100 mg of ritonavir (Norvir®, Abbott), 200 mg of ritonavir twice daily, or 600 mg of rifampin (e.g., Rifadin®, Aventis) once daily. Boyd and colleagues reported a low potential for drug–drug interactions that were consistent with the expectations of a peptide drug such as enfuvirtide.13

**DRUG RESISTANCE**

HIV-1 resistance to enfuvirtide was assessed in TORO-1 and TORO-2. In both trials, the researchers studied samples from baseline values and at treatment failure. Currently, no standard assays are available for fusion inhibitors. Consequently, the investigators used a susceptibility test, developed by ViroLogic, to determine enfuvirtide resistance and sequencing of the gp41 amino acids at positions 36 to 45.4 They evaluated the ability of this susceptibility assay to determine which patients had baseline resistance that might predict subsequent drug failure and assessed the differences between susceptibility to enfuvirtide at baseline and after treatment failure.

Greenberg et al. studied genotypic resistance in the patients who did not respond to therapy and noted a large number of mutations in the gp41 amino acids 36–45.14 Mutations at positions 36, 38, and 43 are common and tend to produce reduced susceptibility.14 Mutations at these positions were found either alone or in combination and resulted in varying degrees of enfuvirtide-reduced susceptibility.4,14

Kilby et al. also studied the pharmacokinetics, safety, and resistance parameters of enfuvirtide.15 In a randomized group of six, 78 patients received 12.5, 25, 50, or 100 mg of subcutaneous enfuvirtide plus an optimized background regimen. The investigators performed genotyping between amino acids 1 and 175 of the gp41 protein using a Perkin-Elmer ABI Model Prism™ DNA 377 sequencing system. It was found that the incidence of genotypic or phenotypic resistance in the groups receiving the smaller dose was lower (19%) than in the high-dose groups (50%).15 Current and previous studies suggest that laboratory susceptibility to enfuvirtide varies among patients; however, the differences in laboratory susceptibility have not translated into clinical failure.14

Several other agents indicated for use against viral entry, called entry inhibitors, are in various stages of preclinical studies. These agents include the second-generation fusion inhibitor T-1249 as well as some attachment and chemokine coreceptor inhibitors.13 Preliminary results of an open-label, 10-day dosing trial of T-1249 in patients not responding to an enfuvirtide regimen were presented at the Tenth Conference on Retroviruses and Opportunistic Infections. At day 11, T-1249 exhibited potent but short-term activity in most patients who did not respond to T-20 therapy.10,17 Given these favorable outcomes, T-1249 might be an option for patients who do not improve with enfuvirtide therapy.17

**INDICATION**

As a result of two 24-week clinical trials, enfuvirtide is currently indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.2,3

**DOSE AND ADMINISTRATION**

Enfuvirtide injection is available in the form of single-use vials. Each vial contains 108 mg of enfuvirtide, with 1.1 ml of sterile water needed for reconstitution before administration. The dose for adults is 90 mg subcutaneously twice daily; for pediatric patients six years of age or older, the recommended dose is 2 mg/kg, or a maximum of 90 mg given subcutaneously twice daily.3,4 The Pediatric AIDS Clinical Trial Group (PACTG)3 is currently investigating dosing recommendations for children younger than six years of age.

**COST**

The price of a month’s supply of enfuvirtide is approximately $1,715, with an annual cost of approximately $20,570.12 The high cost of this medication may discourage some patients from using it and third-party payers from providing coverage. Other antiretroviral agents are less expensive, ranging from less than $300 per month (e.g., didanosine [Videx®, Bristol-Myers Squibb Immunology]) up to $700 or more per month (e.g., ritonavir and nelfinavir).18 Comparative costs of some antiretroviral agents are presented in the August 2003 issue of P&T on page 539.

**CONCLUSION**

HIV-1 resistance to the currently available antiretroviral drugs is common. In addition, a high pill burden and deleterious side effects of the current agents are major contributing factors to noncompliance in HIV-infected patients. Consequently, there is a dire need to develop other medications that do not have these shortcomings.

In light of its unique mechanism of action, favorable safety profile, and ease of administration, enfuvirtide may bring a new optimism to the treatment of HIV infection. Enfuvirtide’s accelerated approval was based on results from two major clinical studies sponsored by Roche laboratories, and these studies suggest that this medication offers a therapeutic alternative for resistant HIV-1 infection.

Compared with the other antiretroviral drugs, however, the high cost of enfuvirtide might limit its use to a small group of patients. It is estimated that 50,000 to 100,000 HIV patients are suitable candidates for enfuvirtide therapy.3

**REFERENCES**

8. D’Souza MP, Cairns JS, Plager SF. Current evidence and future directions for continued on page 583


