

Enfuvirtide (T20, Fuzeon)

information on the entry inhibitor
used to treat hiv disease

The Food and Drug Administration (FDA) approved enfuvirtide in spring 2003 to use with other anti-HIV drugs in children age six and older and in adults who have used anti-HIV therapy before. Enfuvirtide is in a new class of drugs called *entry inhibitors*. The drug works at the start of HIV's reproduction cycle by blocking its ability to infect an immune cell. This occurs at the point when HIV fuses to the cell's outer wall in order to gain entry into it (see graphics on page 2). For more information on entry inhibitors, read *New Hope for New Classes of Therapy* in Project Inform's *PI Perspective 35*.

Who should use it?

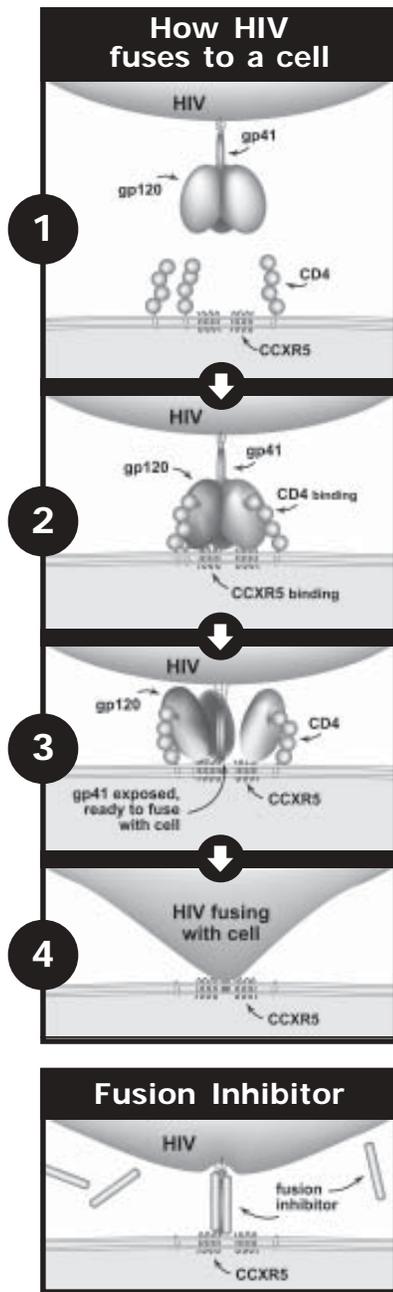
Studies to date include people who have used and who may have resistance to many anti-HIV therapies and who have few options to put together a potent combination of drugs. For these people, enfuvirtide was able to reduce HIV levels and provide benefits. While enfuvirtide shows some activity in people resistant to many or all anti-HIV drugs, studies suggest it may be most effective in reducing HIV levels when used with at least one or two drugs that are still active against HIV (e.g., that a person has not developed resistance to). Because of its cost and the difficulties associated with using it, enfuvirtide is not recommended for first time therapy or after only a few other drugs have been tried.

What does the research show?

Results from two major studies (TORO 1 and TORO 2) were pivotal in the FDA's approval. Both included people with extensive use of anti-HIV therapy who were unable to control viral load. In each study, at study entry, CD4+ cell counts averaged below 100 and HIV levels averaged 100,000 copies/ml. TORO 1 included 491 people and TORO 2 had 504. In both, people used 3–5 anti-HIV drugs with or without enfuvirtide.

More people who used enfuvirtide reached undetectable viral loads and higher CD4+ cell counts. Of those on enfuvirtide, 37% (TORO 1) and 28% (TORO 2) achieved viral suppression below the limit of detection of the test compared to 16% (TORO 1) and 14% (TORO 2) of those not using it. Average CD4+ cell count increases among those on enfuvirtide were 76 (TORO 1) and 65 (TORO 2) compared to 32 (TORO 1) and 38 (TORO 2) in the group not taking the drugs.

Another way to check the success of a regimen is its ability to decrease viral load by 1 log, regardless of whether or not a person reached "undetectable" levels. When combining results from both studies, slightly more than half of those on enfuvirtide had at least a 1 log reduction compared to about 25% of those not using the drug.



How to use it?

Enfuvirtide cannot be made into pill form for oral use and must be taken by injection. It is injected beneath the skin (not in a vein or muscle), twice a day about 12 hours apart. Each dose is 90mg, for a total daily dose of 180mg. For children weighing less than 94 pounds, doses are based on body weight (2mg/kg twice daily).

The drug is a powder and needs to be mixed with sterile saline solution. A prescription includes these, along with syringes and a sharps container for disposing of used syringes. Your doctor should give you information on how to mix the drug and provide guidance on self administration.

Preparing the mixture and the injection site takes about 45 minutes, including the time it takes for the powder to dissolve. Unfortunately, the drug cannot be prepared ahead of time for several days use and should not be stored in the syringe to use later. Because injection site reactions may occur, it's important to change the injection site. Re-using syringes may lead to serious infections and should be avoided completely.

Both the powder and the saline solution should be stored at room temperature. If it is particularly hot and/or it's not otherwise possible to store the drug at room temperature, it should be refrigerated. After the vial has been prepared (the powder and saline mixed), it can be stored in a refrigerator for up to 24 hours.

A common question people ask about enfuvirtide is, "Why does it need to be injected?" The drug is not absorbed into the body well when taken by mouth (orally) and thus injections are required to achieve adequate blood levels of the drug able to impact HIV.

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What about side effects?

The most common side effect that occurred in almost everyone is some degree of injection site reactions (redness, itching, swelling or skin irritation where the drug was injected into the skin). These reactions may last for seven days or longer. While this can be troublesome, only 5% of people stopped using the drug because of these side effects. In about 9% of people, however, reactions were severe enough to limit their activity and/or need an intervention to manage the reactions.

Following the training given by your doctor for using the drug is critical in minimizing these injection site problems. If you are not given such guidance, speak to your doctor and insist upon it. Other possible side effects, occurring in a small percentage of people taking the drug, include feeling tired (*fatigue*), sleep disturbance (*insomnia*) and pain or tingling in the legs, arms, hands and/or feet (*peripheral neuropathy*).

A small percent of people have a hypersensitivity (allergic) reaction to enfuvirtide, which could be life-threatening. Symptoms may include fever, chills, nausea, vomiting and shivering (*rigors*). People having these symptoms should contact their doctors immediately. Stopping the drug permanently may be necessary. For reasons that remain unclear, a slightly higher rate of bacterial pneumonia occurred among those on enfuvirtide.

What about drug resistance?

As with other anti-HIV drugs, HIV can develop resistance to enfuvirtide. Resistance occurs when the virus changes or mutates and the drug no longer controls the reproduction of HIV. However, studies suggest that enfuvirtide is effective against virus that has developed resistance to all other approved anti-HIV drugs.

Cross-resistance occurs when resistance to one drug makes other drugs less effective. If, or as other drugs like enfuvirtide become available, cross-resistance to similar drugs is possible. However, a similar drug that the company is working on (called T1249) has shown activity against virus that's resistant to enfuvirtide. T1249 will also be an injection, but hopefully will require less frequent ones.

HIV and the brain

Because HIV can infect brain cells, it's important to consider a drug's ability to reach the brain when putting together an anti-HIV regimen. It's probably wise to include at least one drug that has been shown to cross the blood-brain barrier to some useful degree as part of your regimen. These include abacavir, amprenavir, atazanavir, nevirapine, stavudine, zidovudine and to a lesser degree indinavir and lamivudine. Efavirenz has not been shown to cross the barrier to a significant degree, but some experts speculate that it might have some useful effect in impacting HIV in the spinal fluid.

drug i.d. chart

GENERIC NAME	TRADE NAME
Protease inhibitor	
amprenavir	Agenerase
atazanavir	Reyataz
fosamprenavir	Lexiva
indinavir	Crixivan
lopinavir + ritonavir	Kaletra
nelfinavir	Viracept
ritonavir	Norvir
saquinavir hgc	Invirase
saquinavir sgc	Fortovase
Nucleoside (NRTI) and nucleotide (NtRTI) analogue reverse transcriptase inhibitor	
abacavir	Ziagen
didanosine (ddI)	Videx
didanosine enteric-coated (ddI EC)	Videx EC
emtricitabine (FTC)	Emtriva
lamivudine (3TC)	EpiVir
stavudine (d4T)	Zerit
stavudine extended release (d4T XR)	Zerit XR
tenofovir	Viread
zalcitabine (ddC)	Hivid
zidovudine (AZT)	Retrovir
3TC/AZT	Combivir
3TC/AZT/abacavir	Trizivir
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	
delavirdine	Rescriptor
efavirenz	Sustiva
nevirapine	Viramune
Fusion inhibitor	
enfuvirtide (T20)	Fuzeon

what about drug interactions?

Studies have been done with other anti-HIV drugs and rifampin, a common tuberculosis medicine. Drug interactions were minor and did not require adjusting the dose of any drug. Whether or not enfuvirtide interacts with other drugs, like methadone, psychiatric medicines or street drugs, is not known. People are encouraged to discuss the possible drug interactions among *all* of the therapies and substances they are taking with their doctor and/or pharmacist.



What is known about this drug for women, people of color, children and the elderly? Enfuvirtide has not been studied in pregnant women. Thus, it's not recommended either for pregnant women or women who are nursing. It is not known if enfuvirtide is found in breast milk. Because HIV can be passed through breast milk, nursing is generally discouraged where alternatives exist. Early results from animal studies do not suggest that there will be a problem with enfuvirtide use during pregnancy. However, animal studies do not always predict safety in humans.

Enfuvirtide appears to clear from the body a little slower in women than men (about 20% lower clearance), even when adjusting for differences in body weight. The combined studies (TORO 1 and 2) included about 10% women (about 100). The studies largely included white people but did include about 8% African Americans. Based on several studies, dose changes are *not* deemed necessary for women, people with lower body weight or Black or Asian people.

Ongoing studies in children (6–16 years) suggest similar effectiveness and safety concerns as those seen in adults. The drug has not been well studied in children under the age of six. Not enough people over 65 were included to provide unique information for the elderly to consider.

How do I get it?

Enfuvirtide is available by prescription. Many states will likely cover enfuvirtide through their AIDS Drug Assistance Programs (ADAP). To find out if you're eligible for your state ADAP and if enfuvirtide is covered through your state's program, contact Project Inform at 1-800-822-7422. Information is also available from AIDS Treatment Data Network at 1-800-734-7104 or www.atdn.org. People who lack insurance, Medicaid, ADAP coverage or other ways to buy the drug might gain access to it through the company's Patient Assistance Program at 1-866-694-6670.

Currently, supplies of the drug are limited, so patients must apply through the "Progressive Distribution Program." Doctors apply on behalf of their patients. Once the supply meets the ongoing needs of the individual, the prescription is "activated" and the drug is shipped either to the patient or doctor. Prescriptions are filled on a first-come, first-serve basis. For more information, doctors should call 1-866-694-6670 to enroll their patients. Thereafter, patients may call directly to check on their status and ask questions. Enrollment forms are available at www.fuzeon.com. Fortunately, the manufacturer announced that it will exceed its previously announced production goals and will have more drug available than first thought.

commentary

Perhaps the most important thing to think about when considering a new drug is how it fits into the arsenal of current therapies. Enfuvirtide will likely never be considered as part of a *first line* regimen—for someone who has never used anti-HIV drugs. This is because it's difficult to prepare and inject, and injection site reactions can be problematic. This drug may not even be very appropriate as part of a *second line* regimen—for someone who has used one regimen and is looking for other options due to drug failure or side effects. Ultimately, the optimal role of this drug is as part of a *third line* (or *salvage*) regimen.

Third line therapy often refers to a regimen for someone who has extensively used anti-HIV drugs and has developed resistance to many drugs in most classes. However, a *true salvage* therapy situation is when prominent resistance occurs to all drugs in all classes. It's fairly rare for people to be in true salvage situations. Often, when looking at resistance test results and evaluating the history of anti-HIV drug use, many if not most people, while working with their doctors, can put together regimens that are active against HIV.

But *how* enfuvirtide fits into the picture of third line therapy is not wholly clear. If people can construct regimens—with the guidance of a doctor and resistance test results—that they believe will be potent without adding enfuvirtide, it may be a great option to hold enfuvirtide

until later if or when options narrow even further. With that said, however, data show that enfuvirtide works best when paired with at least one other drug (preferably two) that's active against HIV. Thus using enfuvirtide in a true salvage situation, when resistance to all drugs is likely, is not the best use of the drug.

For people facing third line therapy choices, enfuvirtide might not be the first option to turn to if other ones are available. A new protease inhibitor called tipranavir looms on the horizon. This drug will likely be available through expanded access programs in late 2003 or so. It appears to be active even in the face of resistance to all other protease inhibitors.

For some making third line therapy decisions, holding off on using enfuvirtide until tipranavir becomes available may still allow for using a viably potent regimen made up of drugs with only partial resistance. For others, in true salvage situations, holding off on using enfuvirtide until tipranavir is available may provide two new and potent drugs to pair up for hopefully better results. Finally, while enfuvirtide appears more potently able to impact HIV when paired with other anti-HIV drugs that are active against a person's virus, it still provides some benefits in true salvage situations, even if it can't be paired with another completely new drug. The results, however, may be short-lived in such situations.



the bottom line on enfuvirtide

Benefits:

- › Can reduce viral load in at least one third of people who are heavily treatment experienced.
- › Relatively mild side effects aside from injection site reactions.

Concerns:

- › Must be injected. Will never be available as an oral drug.
- › Nearly 100% of people will experience injection site reactions that can cause redness, swelling, pain and hardening of the skin.
- › Works better when combined with at least two other drugs to which a person's virus is still sensitive.
- › The virus can develop resistance to enfuvirtide over time.

How to get it:

- › Roche's Patient Assistance Program, call 1-866-694-6670.
- › Available through hospitals and pharmacies.
- › Available through some state AIDS Drug Assistance Programs.

FUZEON INJECTION INSTRUCTIONS

Before you begin

This is a step-by-step guide to injecting Fuzeon (enfuvirtide) that helps remind you about what you learned at your healthcare provider's office. Complete information about Fuzeon is included in the box with your medicine. If you have any questions about using Fuzeon, call your healthcare provider or the pharmacy that provided your Fuzeon. These instructions are for an adult dose of 1mL/cc of Fuzeon. If your prescription is for less than 1mL/cc, or if the prescription is for a child, your healthcare provider may tell you to use different syringes.

Safety tips

- Wash your hands well before starting. Once your hands are clean, do not touch anything except the medicine, supplies, and the area around the injection site.
- Do not touch the needle when holding the syringe. If you touch the needle, you will need to start over with a new syringe. If you run out of syringes, contact your pharmacy.
- Do not touch the tops of the vials once they have been cleaned with an alcohol pad. If you do, clean them again with a new alcohol pad. If you run out of alcohol pads, contact your pharmacy.
- Make sure none of the items in your kit have been opened. Do not use opened materials.
- Never mix Fuzeon with tap water. Use only the sterile water provided to mix Fuzeon.
- Never mix anything or any other medicine in the same syringe as Fuzeon.
- Inject Fuzeon just under the skin (*subcutaneous*). Fuzeon should never be given directly into your veins (*intravenous*) or directly into your muscle (*intramuscular*).
- There should never be any particles floating in the Fuzeon once it is completely mixed with sterile water. If you see any, do not use that vial—contact the pharmacy that provided your Fuzeon.
- Use syringes, vials of Fuzeon and vials of sterile water only one time.

Disposing of used syringes, needles and supplies

- Put all used syringes and needles directly into the sharps container.
- Do not overfill the sharps container.
- Keep the cover on the container and keep it out of the reach of children.
- Once the container is full, it is important to safely dispose of it. Never throw the sharps container into the

trash. Your healthcare provider or the pharmacy that provided your Fuzeon can tell you the right way to dispose of the sharps container.

- Used alcohol pads and vials can be thrown into the trash. If you see any blood on an alcohol pad, put it in the sharps container.
- If you have any other questions about safely disposing of syringes, needles, or supplies, please talk to your healthcare provider or the pharmacy that provided your Fuzeon.

Having someone help you with injections

Certain injection sites, such as the upper arms, can be hard to use at first. If you need help, ask your partner, a friend or a family member. Anyone who will be helping you should know how to inject Fuzeon to lower the chance of getting an accidental needlestick or giving you an infection. They should:

- Meet with your healthcare provider to learn the safe way to give injections.
- Read the *Caregiver's Guide to Injecting Fuzeon*.

Injection sites and NMT syringe information

Injection sites

Changing where you inject Fuzeon on your body each time is an important way to lessen how bad your injection site reactions get. For more detailed information about each injection site, see *Your Guide to Taking Fuzeon*.

About the NMT safety syringe

- There are two different-sized NMT Safety Syringes, a 3-mL (large) syringe and a 1-mL (small) syringe
- NMT Safety Syringes are included with Fuzeon because the used needle springs back by itself into the syringe after use, lowering the chance of accidental needlesticks.

IMPORTANT! When first picking up the NMT Safety Syringe or injecting air or sterile water into vials, do not push the plunger past the 0.2-mL/cc mark on the barrel of the 3-mL (large) syringe or past the 0.05-mL/cc mark on the barrel of the 1-mL (small) syringe. This could make the needle spring back into the barrel of the syringe or make it hard to pull the plunger back.

- Your healthcare provider may recommend other types of syringes for use with Fuzeon.
- Never throw your used syringes into the trash. Put them in the sharps container.

FUZEON INJECTION INSTRUCTIONS

Getting started

Gather supplies

Gather the following supplies for each dose and put them on your Fuzeon Preparation Mat or a cleaned surface:

- One vial of Fuzeon—at room temperature
- One vial of sterile water
- One 3-mL/cc (large) syringe with a 1-inch needle
- One 1-mL/cc (small) syringe with a ½ inch needle
- Alcohol pads
- Sharps container

Mixing two doses

- To save time, you can mix both of your daily doses of Fuzeon at the same time, but you will need to keep the second vial of mixed Fuzeon in the refrigerator. Do not store mixed Fuzeon in the syringe.
- Once sterile water has been added to the Fuzeon, the vial can be placed in the refrigerator. The Fuzeon will dissolve in time for your next dose.
- Before using the dose of refrigerated Fuzeon, be sure it is clear and allow it to warm to room temperature.
- Mixed Fuzeon must be used within 24 hours.
- The instructions below are for mixing a single dose. If you want to mix two doses at the same time, be sure to use new alcohol pads, syringes, medicine and sterile water.
- Write the date and time on the vial when mixed if you are mixing the dose to be used later.

Prepare supplies

- Open the syringe packages and take the caps off the vials.
- Throw the syringe packages and vial caps into the trash

Wash hands

- Wash your hands well using soap and warm water and dry them with a clean towel.
- Once your hands are clean, do not touch anything other than the medicine, supplies and the area around the injection site.

Clean vial tops

- Wipe each vial top with a new alcohol pad and let the tops air-dry.
- If you touch the rubber tops after cleaning them, clean them again with a new alcohol pad.

Mixing Fuzeon

Draw up sterile water

- Gently tap the Fuzeon vial to loosen the powder.
- Using the 3-mL/cc (large) syringe, slowly pull the plunger back to get 1.1 mL/cc of air.
IMPORTANT! To avoid causing the needle to spring back into the barrel of the syringe, do not push the plunger past the 0.2-mL/cc mark.
- Before turning the sterile water vial upside down, slowly inject the air into the vial—and keep the needle in the vial.
- Turn the vial upside down. Make sure the tip of the needle is always below the surface of the water to help keep air bubbles from entering the syringe.

TIP! Gently tap or flick the barrel and push and pull the plunger to remove extra air and bubbles. To be sure you end up with 1.1 mL/cc of sterile water in the syringe, you may need to pull the plunger past the 1.1 mL/cc mark.

- Slowly pull the plunger back to get 1.1 mL/cc of sterile water into the syringe.
- Carefully remove the needle and syringe from the vial.

Inject sterile water into Fuzeon

- Insert the syringe with sterile water into the Fuzeon vial at an angle.
- Inject the sterile water slowly, so that it drips down the side of the vial into the Fuzeon powder.
- Remove the needle from the vial. Push the plunger all the way down with the tip of your thumb until you hear a snap. This will make the needle spring back into the syringe.
- Put the used syringe in the sharps container.

Gently mix Fuzeon

- Gently tap the Fuzeon vial with your fingertip for 10 seconds to start dissolving the powder. Then gently roll the Fuzeon vial between your hands to reduce the mixing time. Make sure no Fuzeon is stuck to the vial wall. After tapping, it could take up to 45 minutes to dissolve.

IMPORTANT! Never shake the Fuzeon vial. Shaking will make the medicine foam and it will take much longer to dissolve.

- Once the powder starts to dissolve, just set it aside and it will completely dissolve.

FUZEON INJECTION INSTRUCTIONS

Inspect Fuzeon

- When completely mixed, the liquid Fuzeon should be clear.

IMPORTANT! Completely dissolved Fuzeon should be clear and without foam. If the Fuzeon is foamy, allow more time for it to dissolve.

- If you see bubbles, gently tap the vial until they disappear.
- If you see any particles in the Fuzeon once it is completely mixed, do not use that vial. Contact the pharmacy that provided it.
- Mixed Fuzeon must be used right away or stored in the vial in the refrigerator and used within 24 hours. Do not store mixed Fuzeon in the syringe.

Giving the injection

Choose the injection site

- Using your Fuzeon Planner to help you, choose a site different from the one you used for your last injection

IMPORTANT! With the tips of your fingers, feel for any hard bumps. Do not inject in or near bumps or any other types of reactions from past injections. Also, do not inject into moles, scars, bruises, your belly button or areas that could be irritated by a belt or waistband.

- Clean the injection site with a new alcohol pad. Start in the center, apply pressure and clean in a circular motion, working outward. Allow the site to air-dry.

Draw up Fuzeon

- Clean the Fuzeon vial top again, using a new alcohol pad. Allow it to air-dry.
- Using the 1-mL/cc (small) syringe, pull back the plunger to get 1 mL/cc of air.
- Insert the syringe into the vial of mixed Fuzeon.
- Before turning the vial upside down, slowly inject the air into the Fuzeon, and keep the needle in the vial.

IMPORTANT! To avoid causing the needle to spring back into the barrel of the syringe, do not push the plunger past the 0.05-mL/cc mark.

- Gently turn the vial upside down.
- Make sure the tip of the needle is always below the surface of the Fuzeon to help keep air bubbles from entering the syringe. Slowly pull the plunger to get 1 mL/cc of Fuzeon.

TIP! Gently tap or flick the barrel and push and pull the plunger to remove extra air and bubbles. To be sure

you end up with 1 mL/cc of Fuzeon in the syringe, you may need to pull the plunger past the 1-mL/cc mark.

- Carefully remove the needle and syringe from the vial.

Inject Fuzeon

- Pinch and hold a fold of skin around the injection site
- Pierce the skin at a 45° angle. The needle should be inserted 3/4 of the way in.

TIP! Your healthcare provider may teach you to inject in a different way.

- With the tip of your thumb, slowly push the plunger all the way to inject Fuzeon. The needle will pull out of the skin and spring back into the syringe by itself when you are done.

TIP! Do not force the needle deeper into the skin while trying to make the needle spring back into the barrel. If you are having a problem, remove the needle from the skin and right away press the plunger down all the way until the needle springs back into the barrel of the syringe.

- Put the used syringe in the sharps container.
- Cover the site with a small bandage if you see any blood or medicine.

Safety information

What are the possible side effects of Fuzeon?

Injection site reactions

Fuzeon causes injection site reactions. Almost all people get injection site reactions with Fuzeon. Reactions are usually mild to moderate, but occasionally may be severe. Reactions on the skin where Fuzeon is injected include:

- Itching
- Swelling
- Redness
- Pain or tenderness
- Hardened skin
- Bumps

These reactions generally happen within the first week of Fuzeon treatment and usually happen again as you keep using Fuzeon. A reaction at one skin injection site usually lasts for less than 7 days.

Injection site reactions may be worse when injections are given again in the same place on the body, or when the injection is given deeper than it should be (for example, into the muscle).