



## **Fuzeon — A Review of the First Entry Inhibitor**

By Cal Cohen, M.D., M.S.

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The Body  
Body Health Resources Corporation  
250 West 57 Street  
New York, NY 10107-0622  
Fax: 212-541-4911

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## Introduction: Why Do We Need a New Class of HIV Medications?

### Reason #1: Resistance to Current Drugs

Treating HIV infection involves many challenges, including occasionally troublesome side effects and the difficulty of taking once- or twice-daily medications for a long period of time.

But one of the most difficult challenges is what to do when a medication no longer has any effect on HIV. When this happens, we say that HIV is “resistant” to a medication. This means that the amount of HIV in your body is able to grow despite the presence of that medication in your body.

Once resistance develops, it’s not the initial return of HIV reproducing inside your body that causes a problem for the immune system; after all, HIV usually doesn’t return in very high numbers. The problem is that once HIV is given even a little leeway to grow, it tends to begin mutating — that is changing its genetic structure — more and more. Each mutation helps HIV thrive, and as it does, it can cause additional immune damage.

And, of course, the more your immune system is damaged, the more vulnerable you are to a host of other, often dangerous, infections. Researchers continue to look for ways in which you can maintain a healthy immune system despite the low-level presence of HIV. In addition, researchers are always looking for combinations of HIV medications that can contain HIV for long periods of time *despite* this low-level presence.

One clear goal of HIV treatment is to avoid resistance and to “suppress” HIV, or stop HIV from reproducing itself. When HIV is fully suppressed, it is “undetectable” in your blood, meaning that although HIV is still present in your blood, we cannot see it with the viral load tests currently available. (It should be noted, however, that viral load tests do *not* measure the presence of HIV in body tissues such as the lymph nodes or the brain, just the presence of HIV in the blood.)

Once HIV is “undetectable,” resistance usually does not occur and treatment will be far more reliable, long-lasting and successful.

### Reason #2: Cross Resistance

Another challenge in HIV treatment is the occurrence of “cross resistance.” Cross resistance occurs when a mutation in HIV allows HIV to “ignore” or resist the effect of more than one medication — including a medication that someone may never have taken. So, despite the fact that we have about 20 different FDA-approved HIV medications, if your HIV becomes resistant to almost any of these medications, there will be some degree of cross resistance to other medications — even though you have not yet used them.

Cross resistance is particularly a concern if, when you were first infected with HIV, you were infected with a strain of HIV that already had some resistance mutations. When this is the case, even before your treatment begins, there may be fewer combinations of HIV medications that will work reliably.

It is important to understand that cross resistance occurs within a specific “class” of antivirals. Researchers categorize each HIV medication within a class based on similarities in the way each medication stops the growth of HIV in the body. For the past several years, HIV treatment has been based on a combination of at least three different medications from one or more of three classes: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).

So, for example, if you develop resistance to one NNRTI such as nevirapine (Viramune), you’re almost guaranteed to have cross resistance with another NNRTI such as efavirenz (Sustiva, Stocrin).

Cross resistance, however, is much more likely to happen with NNRTIs than with NRTIs or PIs. With NRTIs and PIs, another drug within the same class can still be used if you develop resistance to the first one you try. For example, if you are resistant to 3TC (lamivudine, Epivir), which is an NRTI, you will be cross resistant primarily to FTC (emtricitabine, Emtriva), but cross resistant to a much lesser extent with other NRTIs, such as tenofovir (Viread) or d4T (stavudine, Zerit).

It should be noted that even if there is not *complete* cross resistance between two drugs, it is possible for the mutations that made HIV resistant to one drug give HIV a “head start” in creating additional mutations that can eventually make HIV resistant to other drugs.

These problems explain why so many people with HIV now have treatment-resistant strains of HIV. Many HIV-positive people have a hard time finding treatment combinations that will reliably suppress HIV for years and not cause many side effects. Therefore, if their HIV is not completely suppressed, they develop strains of HIV that have become at least partially resistant to several available medications. Furthermore, there are now many people who have at least some degree of resistance to *all three* classes of antivirals used in initial therapy.

Fortunately, cross resistance occurs only *within* a class of drugs, *not* between classes. In other words, if you’ve become resistant to NNRTIs, you’re still probably going to be fully susceptible to NRTIs and PIs (i.e., your HIV will remain vulnerable and able to be attacked by those classes of drugs). And when HIV is fully susceptible to enough new drugs, it can be fully suppressed.

For several years now, it has been understood that when you switch from one treatment combination to another after resistance has developed, choosing an “anchor” drug from a new class of medications is among the best ways to reliably reestablish HIV suppression. This is particularly true if most of the drugs available are less than fully potent because you have some degree of cross resistance.

The newest class of HIV drugs is the entry inhibitors, also known as fusion inhibitors. The first approved medication in this class is Fuzeon (enfuvirtide, also known as ENF or T-20). This breakthrough HIV medication offers an important option for people dealing with resistance.

## Entry Inhibitors: A New Class of HIV Medications

### How Does HIV Enter Our Cells?

To damage the immune system, HIV must first get inside your CD4 cells, which are responsible for fighting off diseases inside your body. After HIV enters your CD4 cells, it uses several enzymes to turn the cells into factories that produce more HIV. Two of the key enzymes that HIV uses once it gets inside a CD4 cell are the reverse transcriptase and protease enzymes, which have been the focus of the first three available classes of HIV medications.

Researchers have figured out several of the critical steps that HIV follows to get inside CD4 cells. This has been broken down into a few stages. Here's a play-by-play look at what happens:

- ◆ First, HIV attaches to a CD4 receptor.
- ◆ Then HIV attaches to a “co-receptor.”
- ◆ After this dual attachment (to CD4 and then to a co-receptor), HIV inserts a harpoon-like anchor called a glycoprotein into the CD4 cell wall.
- ◆ Then HIV “zips” together the two ends of this glycoprotein (one end is in the CD4 cell; the other end is still attached to the virus). This action allows HIV to literally pull itself close enough to the CD4 cell wall so it can actually fuse with the CD4 cell.
- ◆ To complete this step of connection (or fusion), an opening is created in the CD4 cell, and — through a process scientists still do not completely understand — HIV inserts its viral RNA into the CD4 cell. This allows HIV to begin the process of completely taking over the CD4 cell.

The goal of Fuzeon, the first entry inhibitor to be approved in the U.S., is to prevent HIV from entering CD4 cells by stopping it from “zipping” together the two ends of the glycoprotein.

## How Does Fuzeon Work?

As mentioned in the last section, HIV inserts a glycoprotein into the CD4 cell wall, and that protein then acts like a zipper to bring HIV directly into contact with the CD4 cell. Fuzeon is like a piece of clothing that gets stuck in the zipper: When Fuzeon attaches to a specific part of the glycoprotein which HIV has inserted into a CD4 cell wall, the glycoprotein can no longer zip itself together, which completely halts the process of HIV fusing with the CD4 cell. Once this process is stopped, as long as Fuzeon remains effective, HIV cannot progress in your body.

That is why entry inhibitors are also known as fusion inhibitors — they stop the *fusion* of HIV to a CD4 cell.

Because fusion is completely unrelated to all the other steps in HIV's life cycle that current HIV medications are designed to block, *no* cross resistance exists between the other classes of HIV medications and Fuzeon. This means that, essentially, everyone with HIV is susceptible to fusion inhibition with Fuzeon. This new class, then, can provide an important "anchor" in a new treatment combination for those who are switching regimens. Therefore, Fuzeon provides a new opportunity to reestablish control of HIV infection.

Fuzeon has several unique features. One is that, unlike all the other HIV medications, Fuzeon must be taken by self-injection. What this means is that to get Fuzeon into your bloodstream, you would be given a small syringe for a simple injection under the skin, similar to how people take insulin. Fuzeon is given as an injection for a similar reason to why insulin is an injection: Fuzeon is a type of molecule that, if taken orally as a pill, will be destroyed in the process of digestion.

Although at first you might feel uncomfortable using a syringe, in most every doctor's office there is someone — usually a nurse — who can teach you how to inject this medication by yourself at home.

## What We Know About Fuzeon

### Efficacy: Just How Good Is This Drug?

In initial studies of Fuzeon, it was given to people alone (not as part of a regimen with other drugs) for about one month. This is the standard way to evaluate how powerful an impact a new drug will have on the ability of HIV to reproduce itself. From these studies, we learned that Fuzeon is about as powerful as most of the other potent HIV medications. We saw that an average person's viral load would decline by about 1.5 logs, or about 96 percent, when Fuzeon was used alone as a single drug.

Translating this into viral load: If someone had a viral load of 10,000, a decline of 96 percent would result in a viral load of just under 400. However, since we know that HIV can develop resistance to Fuzeon — just like HIV does with any other drug when more complete suppression of HIV is not established — the largest clinical studies on Fuzeon were all conducted with a combination of medications that included Fuzeon, in order to give everyone the best chance possible of suppressing HIV.

### Clinical Trial Results

The big clinical studies conducted with Fuzeon were called the “TORO” studies. They enrolled about 1,000 people on several continents. To be eligible, people had to be “treatment experienced” — that is, they had to have taken all three of the other classes of HIV medications: NRTIs, NNRTIs and PIs. The researchers made this group the target population primarily because they are most in need of a new class of HIV medications — they are resistant to all three classes of HIV medications and had run out of options for finding a regimen that would durably suppress HIV replication, so they had the most to gain if Fuzeon worked.

The studies were designed to closely resemble what doctors would normally do in their clinical practice, in order to make these trials as easy and as relevant as possible. Patients who were eligible were randomly chosen to receive either the best HIV treatment combination their physician could put together using three to five HIV medications (called the “optimized background”), or this same “optimized background” regimen with Fuzeon added.

To create the optimized background regimen, doctors were allowed to use a combination of three to five of the approved HIV medications that were available at the time. People were given a resistance test before they were accepted into the study so doctors could select the best drugs for them. In addition, doctors had a complete treatment history for each person to help them more accurately choose drugs that would be as well tolerated as possible.

The treatment-experienced patients enrolling in this study had, on average, low CD4 counts and high viral loads. The average CD4 count in these studies was about 90 cells/mm<sup>3</sup>, and the average viral load was just over 100,000 copies/mL. Nobody took a placebo — everyone in the study received either the standard “optimized background” regimen, or an optimized background regimen plus Fuzeon.

There was a humane aspect to the design of these studies. If in the first year a person's regimen failed to suppress HIV while on the background arm, he or she was permitted to “cross over” and receive Fuzeon plus a new background regimen.

The results — which were measured after 24 weeks and again after 48 weeks — demonstrated the importance of adding Fuzeon to a background regimen. Overall, by week 24, those receiving Fuzeon plus an optimized background regimen had approximately *doubled* their chances of achieving viral suppression (to either below 400 copies or even down to below 50 copies). This additional rate of suppression occurred since, on average, Fuzeon made the optimized background regimen almost 90 percent more effective. This means that these people had a nearly 90 percent lower viral load than people who were only taking an optimized background regimen.

Of note, those on just the optimized background had, on average, a total viral load drop of only 0.7 log, which is about the same viral load drop that we see when starting a treatment-naïve patient on just AZT (zidovudine, Retrovir) alone. This study documented just how much resistance there was among treatment-experienced people in this study.

In summary, analyses of this study demonstrated the success of Fuzeon in people who are already resistant to many other HIV medications. For example, when researchers used one definition of success — i.e., a viral load that is at least 90 percent lower than at the start of the study — about twice as many people were able to achieve treatment success after 24 weeks just by adding Fuzeon to their regimen. After 48 weeks, 37 percent of the people taking Fuzeon still had viral load reductions of at least 90 percent, while only 17 percent of people in the optimized background arm were able to maintain such a decline in their viral load.

There are two types of viral load tests: one that can't detect viral loads below 400, and a more stringent one (which is usually used in the U.S.) that can't detect viral loads below 50. Regardless of which measure was used in this study, over twice as many people taking Fuzeon with their regimen had “undetectable” viral loads as people who were not taking Fuzeon. At week 48, for instance, 30 percent of people on Fuzeon had viral loads less than 400 copies, compared to only 12 percent of people on an optimized background regimen alone.

Using the more stringent goal — reaching a viral load of less than 50 — 18 percent of people on the optimized background plus Fuzeon, versus 8 percent on only the optimized background, had an “undetectable” viral load to this degree.

Of note, a similar percentage of people with a viral load of less than 400 and less than 50 copies was noted at weeks 24 and 48. This reinforces the idea that lowering viral load to these levels is one important way to achieve a durable degree of viral suppression. As a result of this improvement in people whose viral load was suppressed, there was a corresponding larger increase in CD4 counts when the study reached week 48 in those receiving Fuzeon plus an optimized background (91 cells/mm<sup>3</sup> increase) versus those people only on an optimized background (45 cells/mm<sup>3</sup>).

### **Resistance Still a Danger With Fuzeon**

As with every HIV medication, resistance to Fuzeon can develop. Early studies in which only Fuzeon was used to fight HIV clearly established this. This resistance is made apparent in the form of “genotype mutations,” although there are few if any commercial tests that can do such testing now.

What remains less clear so far is how powerful Fuzeon might be even after resistance develops. Is it like other HIV medications, such as 3TC, where HIV can still be partially suppressed even if there is resistance? While research is ongoing to understand this more fully, the research so far suggests that it's possible. Regardless, with Fuzeon (as with any other HIV medication), it is important to attempt to establish robust suppression — preferably pushing a viral load to less than 50 copies, or at least less than 400 copies.

## Who Fuzeon Works Best For

Is there one type of patient who would most benefit from Fuzeon? After analyzing the TORO studies, researchers discovered four factors that could statistically predict whether a person's viral load will drop below 400 copies after 24 weeks of taking an optimized background regimen with Fuzeon.

People were more likely to be successful on this regimen if, at the time they started it:

- ◆ Their CD4 count was more than 100.
- ◆ Their viral load was less than 100,000.
- ◆ They had already used 10 or fewer HIV medications.
- ◆ They began Fuzeon treatment with at least two other HIV medications that still worked against HIV, as judged by a resistance test.

The TORO studies showed that Fuzeon tends to work better for people with less-advanced HIV infection — a conclusion that is similar to most of the findings for all other HIV medications currently in use. However, what is notable about these results is that they reinforce important issues with regard to the timing of using this drug.

Because Fuzeon was developed for people who had low CD4 counts and who were already resistant to NRTIs, NNRTIs and PIs, doctors might choose to “save” Fuzeon for this late stage of treatment. Clearly, for those with low CD4 counts and few other options, Fuzeon does represent an important breakthrough option, because it might provide at least partial suppression and increase a person's CD4 count.

However, what is clear from these analyses is that there are people with less-advanced disease who may also benefit from the inclusion of Fuzeon in their regimen. For example, someone who has already developed resistance to one NRTI/NNRTI-based regimen and one PI-based regimen — and who is about to start on a third regimen — might also benefit from including Fuzeon as the “anchor” in his or her next regimen. The timing of using Fuzeon is among the most complex discussions that doctors must have with patients when dealing with resistance and treatment options.

In summary: While there are many details that must be considered when deciding on your next regimen and predicting its success, it is at least important, based on the data currently available, to consider adding Fuzeon to your regimen well before you develop complete resistance to virtually all other medications. Waiting until that happens will only limit Fuzeon's benefit.

## Fuzeon's Side Effects

What is clear from the big clinical studies on Fuzeon is that most HIV treatment-experienced people felt physically better once Fuzeon was included in their regimen. Many of the most common side effects reported with other HIV medications — such as nausea or diarrhea — were actually less common in people receiving Fuzeon. This is partly because Fuzeon does not appear to cause these problems, and partly because some of these toxicities were potentially caused by HIV and with HIV under better control, the success of the treatment made these symptoms less common.

Fuzeon's only common side effect is a skin reaction around the area where the drug is injected. While most everyone who takes Fuzeon notices some irritation at the injection site, only about 4 percent of people found this uncomfortable enough to stop the drug within a year.

In clinical studies, about half the people taking Fuzeon rated these reactions as “mild” — which means that they were relatively small, lasted only a day or so and did not require any treatment for discomfort. However, about 25 percent of patients did report having “moderate” reactions. This may mean that the reactions were a bit larger, lasted a bit longer or had made their skin more tender. But again, these side effects were manageable even after people took Fuzeon for one year.

Researchers are trying to assess what techniques might assist people who are dealing with these reactions, in terms of how to inject differently or what to do after receiving an injection. However, a few observations have been shared by many nurses involved in these studies that may be of help:

- ◆ Inject only superficially in the skin. Avoid going deeper — injections anywhere near the muscle are more painful.
- ◆ Avoid injecting near a spot that is already tender, since a second injection might increase that discomfort. It is important to inject in different places.

Other observations are being gathered and will be shared by researchers as they are verified over time. See our ten tips on injecting Fuzeon for more advice.

## Conclusion: Fuzeon's Role in Treatment

Remember that Fuzeon is, ultimately, not a whole lot different from the HIV medications that came before it. Although it works differently than previously approved HIV medications, and has the novelty and challenge of being injected — requiring a new set of skills by providers and the people using it — it ultimately is just another HIV medication.

The suppression of HIV provided by Fuzeon in combination with other medications can last a long time and help your immune system rebuild itself. This can help your health improve over time.

However, Fuzeon has some of the same vulnerabilities and challenges shared by all medications. Although HIV can develop resistance to it, it works best and lasts longest when it is combined with at least one other working medication, preferably two other potent medications. It can provide substantial HIV suppression when used within an already-working regimen and can more than double the rates of suppression when incorporated into the regimens of people facing resistance to the other drug classes.

Fuzeon is a vital drug to understand as we confront the formidable task of providing effective treatment for the many people facing resistance to prior regimens. It is the only drug from a new class that will be available during the next few years. When used correctly, it has provided real and long-lasting HIV control, and has been a critically important contribution to the fight against HIV.

## Ten Tips on Injecting Fuzeon

By **Karlissa Foy, R.N., B.S.N.** and **Calvin Cohen, M.D., M.S.**

1. Add the Fuzeon powder to the sterile water solution provided. To ensure that the powder dissolves completely into the solution, roll the vial slowly at an angle. It should look like water when it has completely reconstituted.
2. If it's more convenient, while preparing one dose, you can always prepare the "next" dose. This means you can reconstitute two vials at once, using one immediately and refrigerating the second vial (vials can be prepared at most up to 24 hours in advance). However, always make sure the vial is at room temperature before you use it to inject. Some people say that after refrigerating the Fuzeon, it is not only easier to inject it, but there are fewer skin reactions at the spot where they inject.
3. Try a hot bath or shower just before injecting. This may make your skin more supple and easier to inject into.
4. Don't be afraid to try other needles besides those supplied to you by the pharmacist. Ask your doctor about insulin or tuberculin syringes. These have slightly smaller needles (in width) that do not automatically retract. Some people find these needles easier to work with.
5. Be sure to change the places where you inject, so no one spot becomes too tender or develops too severe a reaction. Don't worry if you don't have enough fat under your skin. There is no clear evidence that people with less fat have worse skin reactions.
6. You can inject in your "love-handles" — some patients have noted that they have fewer skin reactions to the injections in areas where there is more fat.
7. Pay attention to the angle of the needle when injecting. If you don't have a lot of fat on your body, pull your skin up a little and make sure you're injecting only into your skin. If you have enough fat under your skin it will be easier. The idea is to avoid muscle injections, which can be painful.
8. Use a clothespin or clip to pinch the skin in areas of injection that you find hard to reach.
9. Vigorously massage the area where you are going to inject the Fuzeon for 3-5 minutes both before and after injection, with the emphasis on "vigorous." Use a vibrator as a tool for vigorous massage!
10. Apply a warm (not hot) towel to the site of injection immediately following injection.

For more information on injecting Fuzeon, visit: [www.thebody.com/fuzeon/redirects/fuzeon\\_injections.html](http://www.thebody.com/fuzeon/redirects/fuzeon_injections.html)

## Glossary

### Anchor

The strongest, most effective medication in an HIV drug combination.

### CD4 (T4) or CD4+ Cells

A type of T cell involved in protecting against viral, fungal and protozoal infections. These cells normally orchestrate the immune response, signaling other cells in the immune system to perform their special functions. Also known as T helper cells. A normal CD4 or T-cell count is between 800 and 1,200.

### Cells/mm<sup>3</sup>

A measurement used to describe the concentration of cells in a cubic millimeter of fluid. This is the standard measurement for determining a person's CD4, or T-cell, count.

### Class

A family of HIV medications. Each class of HIV medications attempts to stop HIV at a different point in its reproductive cycle.

### Copies/mL

A measurement used to describe the concentration of a virus in a milliliter of fluid. This is the standard measurement for determining a person's HIV viral load level.

### Co-Receptor

A molecule on the surface of a cell that HIV attaches itself to in order to begin the process of cell fusion.

### Cross Resistance

Resistance that occurs for more than one drug at the same time. When HIV mutates, some of those mutations may prevent several medications from working correctly — even medications that a person may never have taken before. When this happens, we say that the HIV has become cross resistant to those medications.

### Deoxyribonucleic Acid (DNA)

The molecular chain found in genes within the nucleus of each cell, which carries the genetic information that enables cells to reproduce. DNA is the principal constituent of chromosomes, the structures that transmit hereditary characteristics.

### Efficacy

How well something works. Often used when describing the strength of HIV medications and drug combinations.

### Enzyme

A protein that causes a chemical reaction to take place.

### Fusion

The process in which HIV attaches to and combines with a CD4 cell.

**Glycoprotein**

A specific type of protein that has one end sticking out from the outer wall of a cell.

**Immune System**

The body's complicated natural defense against disruption caused by invading foreign agents (e.g., microbes, viruses).

**Molecule**

The smallest particle of a compound that has all the chemical properties of that compound. Molecules are made up of two or more atoms, either of the same element or of two or more different elements. Ionic compounds, such as common salt, are made up not of molecules, but of ions arranged in a crystalline structure. Unlike ions, molecules carry no electrical charge. Molecules differ in size and molecular weight as well as in structure.

**Mutation**

A genetic change. When HIV mutates, it can prevent HIV medications from working correctly; when this happens, we say that the HIV has become resistant to that medication.

**Optimized Background**

A type of combination drug regimen that has been specially chosen for a person so that it works as well as any drug combination can for him or her.

**Placebo**

A fake pill. In many studies, researchers will give some people a placebo so they can measure how much better (or worse) people do when they are given the real medication. Placebos are usually nothing more than sugar pills.

**Reconstituted**

Completely dissolved in a liquid.

**Resistance**

The ability of HIV to reproduce itself despite the presence of HIV medications in the body. When HIV develops mutations, it can prevent HIV medications from working correctly; when this happens, we say that the HIV has become resistant to that medication.

**Resistance Test**

A medical test used to determine whether the HIV within a person is able to reproduce itself even if the person is taking medications designed to keep it from doing so.

**Ribonucleic Acid (RNA)**

A nucleic acid, found mostly in the cytoplasm of cells, important in the synthesis of proteins. The amount of RNA varies from cell to cell. RNA, like the structurally similar DNA, is a chain made up of subunits called nucleotides. In protein synthesis, messenger RNA replicates the DNA code for a protein and moves to sites in the cell called ribosomes. There, transfer RNA (tRNA) assembles amino acids to form the protein specified by the messenger RNA. Most forms of RNA (including messenger and transfer RNA) consist of a single nucleotide strand, but a few forms of viral RNA that function as carriers of genetic information (instead of DNA) are double-stranded. Some viruses, such as HIV, carry RNA instead of the more usual genetic material DNA.

**Superficially**

On the surface; skin-deep.

**Suppression**

The prevention of HIV's ability to reproduce itself.

**Tolerated**

This word usually appears when talking about medication side effects. A person is said to “tolerate” a drug if he or she doesn't experience any side effects severe enough to make them stop taking it, or if a person doesn't quit taking the drug because of the way it must be taken (e.g., by injection, or by swallowing a large number of pills several times a day).

**Treatment Experienced**

Used to describe a person who has already taken many of the available medications to treat a disease.

**Treatment History**

A detailed rundown of the previous medications a person has taken, as well as when those medications were taken, why they were stopped and any health problems a person experienced while taking them.

**Treatment Naive**

Used to describe a person who has never taken any of the available medications to treat a disease.

**Undetectable**

An HIV viral load that is so low it cannot be seen using existing viral load tests.

**Viral Load**

The amount of HIV in a person's blood. Monitoring a person's viral load is important because of the apparent correlation between the amount of virus in the blood and the severity of the disease: sicker patients generally have more virus than those with less advanced disease. A sensitive, rapid test — called the viral load test for HIV-1 infection — can be used to monitor the HIV viral burden. This procedure helps clinicians to decide when to give anti-HIV therapy. It may also help researchers determine more quickly if experimental HIV therapies are effective.

## About the Author



**Calvin "Cal" J. Cohen, M.D., M.S.**

Dr. Cohen is Research Director of the Community Research Initiative of New England and is a clinical instructor in ambulatory care and prevention at Harvard Medical School in Boston. In addition, he works as an HIV clinical management consultant and internist at Harvard Pilgrim Health Care, and is affiliated with Harvard Vanguard Medical Associates.

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