

## **Anti-HIV Drugs in Development**

### **Contents**

- **Anti-HIV Drugs in Development**
- **HIV Resistance and Resistance Testing**
- **Viral Load Update**
- **Drug Delivery Systems**
- **CRIA News - CRIA Trials – Contributions**

---

### **ANTI-HIV DRUGS IN DEVELOPMENT**

*By Marshall J. Glesby, MD, PhD*

The past two years have been productive from the standpoint of antiretroviral drug development, with approval by the Food and Drug Administration (FDA) of six new drugs to fight HIV infection. Four protease inhibitors and two nonnucleoside reverse transcriptase inhibitors (NNRTIs) were added to the five approved nucleoside analog drugs. Although these 11 drugs can be combined in a large number of ways, due to cross-resistance among drugs in the same class (see page 4), many persons living with HIV/AIDS have exhausted all available options. Furthermore, most of the combination drug regimens are extremely difficult to take and may have considerable side-effects. Given the obvious need for new and improved antiretrovirals, what candidates are in the drug development pipeline?

Instead of addressing this question by compiling an exhaustive listing of drugs in development, this article will focus on the drugs whose new drug applications are closest to being submitted to the FDA for approval. Since very limited clinical data are available on drugs which are earlier on in the development process, some of these drugs will be discussed only briefly.

#### **Efavirenz (DMP 266)**

Efavirenz (Sustiva®), also known as DMP 266, is an investigational NNRTI under development by DuPont Merck. Early clinical studies have generated considerable enthusiasm for this once-daily drug for several reasons.

Combinations of efavirenz with and without protease inhibitors have shown significant HIV viral load reductions. In two small studies of efavirenz in combination with indinavir (CrixivanJ), 94% and 88% of patients achieved viral loads below the level of quantitation (less than 400 copies/ml) at 24 and 48 weeks, respectively. The combination of AZT + 3TC + efavirenz is also being studied, and early results have shown that 22 of 25 (88%) of patients achieved viral loads below 400 copies/ml at 16 weeks. Some experts consider the combination of an NNRTI with two nucleoside analogs (here, efavirenz with AZT and 3TC) to be an attractive approach for initial HIV therapy since patients who fail such a regimen could receive a protease inhibitor subsequently. Others argue for using the best possible combination up front, that is a regimen containing a protease inhibitor. Studies to compare these two approaches are needed.

Preliminary laboratory data suggest that efavirenz may retain potent activity against strains of HIV that have mutations associated with resistance to other NNRTIs (nevirapine and delavirdine). It remains to be seen, however, if the drug can be beneficial clinically in patients who have developed resistance to other NNRTIs.

The side effect profile of efavirenz to date has been favorable. Some patients have experienced lightheadedness, dizziness, and feeling "out of sorts"; these side effects occur less frequently if the drug is taken at bedtime and tend to diminish after a few weeks of treatment. Rash, which occurs in about 20% of patients taking nevirapine or delavirdine, has also been reported with efavirenz. In one study, the same number of rashes were seen in patients taking the combination of efavirenz and indinavir versus indinavir alone. Although there have been cases of severe rash requiring hospitalization, most patients with rashes are able to continue taking efavirenz. Other reported side effects include nausea, vomiting and headache.

Efavirenz is currently in phase III studies, and DuPont Merck will likely seek accelerated approval by the FDA in the first quarter of 1998. An expanded access program for efavirenz was launched in late September 1997. The main eligibility criteria for this program are: age 13 years or older, T cell count of less than or equal to 50 in the last 90 days, and failure or intolerance of the current drug regimen with no other appropriate treatment options. In addition, efavirenz must be used with at least one antiretroviral which the patient has not taken previously. More information about the program can be obtained by calling 800-998-6854.

In addition to one of the phase III trials, CRIA is participating in an open label safety study of efavirenz in combination with one or more investigational antiretrovirals for patients with no other treatment options. To be eligible for this salvage protocol, patients must be failing their current drug regimen based on viral load, CD4 count or clinical deterioration (as specified in the U.S. Public Health Service Guidelines draft) and be able to obtain another investigational agent through expanded access. At this time, adefovir dipivoxil and abacavir (1592U89) are the only other drugs available by this mechanism (see below).

### **Adefovir Dipivoxil**

Adefovir dipivoxil (Preveon™), also known as bis-POM PMEA, is an investigational nucleotide analog under development by Gilead Sciences. Nucleotide analogs differ chemically from nucleoside analogs (the class that includes AZT, ddI, ddC, d4T, and 3TC). In order for nucleoside analogs to be active, they must have phosphate molecules added to their chemical structures by an enzyme inside of the body's cells. This activation step is bypassed for the nucleotide analogs as they already contain the phosphate groups. This property confers a theoretical advantage to the nucleotide class of drugs as they are active in resting cells — including monocytes and macrophages, which are an important reservoir for HIV — and may prime uninfected cells to resist viral replication when subsequently infected by HIV.

Adefovir dipivoxil given alone (monotherapy) demonstrated modest anti-HIV activity in an early study, with an average reduction in HIV viral load of about 0.5 log (70% reduction). This is about the same magnitude of reduction that is seen with AZT monotherapy. Of course, no antiretroviral drug should be given as monotherapy, and adefovir dipivoxil is being studied in a number of different combinations. Like efavirenz, adefovir dipivoxil is taken once daily.

Adefovir dipivoxil appears to be active in the test tube against a variety of viruses that HIV-infected persons are prone to acquire, such as herpesviruses, CMV, and hepatitis B. Studies are underway to test whether adefovir dipivoxil can prevent CMV disease in patients with advanced HIV disease and whether it is effective against hepatitis B.

Another potentially important feature of adefovir dipivoxil is its resistance profile, which appears to be unique thus far. Resistance to adefovir dipivoxil appears to develop slowly, and there appears to be little or no cross-resistance with available antiretroviral drugs. If this resistance profile is verified in clinical trials, the drug may be an important option for persons with extensive antiretroviral drug experience.

The most common side effects seen in early studies of adefovir dipivoxil include nausea, vomiting, diarrhea, elevation of serum creatinine (a measurement of kidney function), protein in the urine, and liver inflammation. Because the drug may deplete the body's supply of carnitine — a natural substance used by the body in energy production — L-carnitine supplements must also be taken once a day.

Adefovir dipivoxil is currently in phase III studies, and Gilead will likely seek accelerated approval by the FDA in 1998. An expanded access program was launched in December 1997 for patients with less than 50 T-cells, viral load greater than 30,000 copies/ml, and no other effective treatment options. More information on this program can be obtained by calling 800-GILEAD-5. CRIA will be participating in this program.

### **Abacavir (1592U89)**

Abacavir, commonly referred to as "1592", is an investigational nucleoside analog under development by Glaxo Wellcome. It appears to be the most potent drug of this class studied to date. Data from small numbers of patients with less than 12 weeks of prior AZT use who received abacavir alone or in combination with AZT had average reductions in viral load of 1.7 to 2.1 logs (98-99% reduction) at 12 weeks. Abacavir has high penetration into the cerebrospinal fluid, the fluid around the brain, and is also being studied as a treatment for HIV-related dementia. Dosing is twice a day.

Preliminary studies of the resistance profile of abacavir suggest that there may be some degree of cross-resistance between it and the available nucleoside analogs. Of particular concern is a mutation in HIV (at position 184) that is associated with resistance to the commonly used drug 3TC (Epivir®). This mutation results in about a three-fold reduction in sensitivity to abacavir in the test tube. It remains to be seen, however, what clinical implications these laboratory findings will have. Preliminary evidence suggests that patients with the 184 mutation may still respond somewhat to abacavir but not to the same degree as those without the mutation.

Side effects seen in early studies of abacavir include nausea, headache, diarrhea, rash with or without fever, insomnia, dizziness, and abdominal pain.

The development of abacavir has generated considerable controversy in the HIV community. Activists have protested what they perceive to be the slow development of a drug that may be a potential option for many who have failed existing therapies and have asserted that Glaxo Wellcome has deliberately dragged its feet to prevent cutting into the market for their leading combination of AZT and 3TC. To explain the delay in broadening access to abacavir, Glaxo cited a lack of safety data in sufficient patients and inadequate supply of drug.

A compassionate use program for abacavir started in July 1997 through approximately 65 clinical trials sites nationwide. Enrollment has been limited to about 100 patients per week, with the demand for the drug far exceeding what Glaxo is supplying, which has led to further protests. To be eligible for enrollment, patients must have a T cell count less than 100, a viral load greater than 30,000 copies/ml, and a history of treatment with two nucleoside analogs and a protease inhibitor or intolerance to combination therapy. Information about study sites can be obtained by calling 800-501-4672. Compassionate use programs also exist for children failing antiretrovirals and adults with dementia. Abacavir is currently in phase III trials, and Glaxo Wellcome will likely seek accelerated approval by the FDA in 1998. A larger expanded access program is planned for March 1998.

### **141W94 (VX-478)**

141W94 is an investigational protease inhibitor under development by Glaxo Wellcome. It is sometimes referred to as the Vertex protease inhibitor because it was discovered by Vertex

Pharmaceuticals and licensed to Glaxo. In animal studies, 141W94 has shown good penetration into the brain.

In an early clinical study, 141W94 taken as monotherapy caused, on average, about a 1.7 log (98%) reduction in viral load. The drug, which is taken twice a day, has been well tolerated in early studies. Side effects to date have included nausea, loose stools, diarrhea, abdominal pain, and headache. Rashes have also been seen, several of which have been severe enough to mandate discontinuation of the drug.

141W94 is currently in phase III trials, and Glaxo Wellcome will likely seek accelerated approval by the FDA some time in 1998. CRIA is participating in one of the phase III trials comparing 141W94 to indinavir (CrixivanJ) in patients with at least 12 weeks of nucleoside analog experience, no prior protease inhibitor therapy, and viral loads greater than 400 copies/ml.

### Drugs in Early Development

Several nucleoside analog drugs are in the early stages of clinical testing, including the following: **Lobucavir** (Bristol-Myers Squibb) has activity in the test tube against CMV, other herpesviruses, hepatitis B and HIV, and is in phase I testing. **F-ddA** (US Bioscience) is chemically related to ddI but does not have to be administered with buffers for stomach acid, which may make it easier to tolerate. It is being [studied](#) at the National Cancer Institute in Bethesda, MD. **FTC** (Triangle Pharmaceuticals), a drug with activity in the test tube against HIV and hepatitis B, is in phase I testing.

**MKC-442** (Triangle Pharmaceuticals) is a nucleoside analog that functions as an NNRTI. Preliminary data have shown about a 1 log (90%) reduction in viral load at the highest dose studied to date, with headache and loose stools as the most common side effects. **Loviride** (Janssen Pharmaceutica) is an NNRTI that has been studied outside of the U.S. in several large studies. Little benefit was seen in one study when the addition of loviride plus 3TC was compared to adding 3TC alone to background therapy with other nucleoside analogs. Loviride is apparently not going to be studied in the U.S. at this time. **HBV 097** (Hoechst/Bayer) is an NNRTI with a unique chemical structure that has caused reductions in viral load of about 1.5 logs (97%) as monotherapy in an early study. Phase II studies are underway.

There are a handful of second generation protease inhibitors in preclinical and early clinical development. **ABT-378** (Abbott Laboratories) appears to be a very potent drug that is chemically similar to ritonavir (Norvir®) but ten times more active against HIV in the test tube. It has been studied only in healthy, HIV-negative volunteers to date but should be entering early clinical trials for HIV-infected patients soon. **PNU-140690** (Pharmacia & Upjohn) is one of the more exciting drugs in early clinical development. Unlike the available protease inhibitors, it has a completely different type of chemical structure, and laboratory studies suggest that it may have activity against HIV strains that are resistant to protease inhibitors such as ritonavir and indinavir. It remains to be seen whether this will hold up in clinical studies. Bristol-Myers Squibb recently acquired two protease inhibitors that were originally being developed by Ciba-Geigy (Novartis). One of these drugs, **BMS-234475** (formerly CGP-73547), is in phase I testing. Other protease inhibitors with chemical structures that differ from the currently available drugs — and thus have the potential to be active against resistant HIV strains — are in preclinical development.

Two nucleotide analogs are in early clinical development by Gilead Sciences: **PMPA** is given intravenously and the prodrug, **bis-poc PMPA**, is an oral form of PMPA which gets converted into active drug in the body. A small phase I study of PMPA demonstrated about a 1 log (90%) reduction in viral load at the highest dose tested, though this may not be the highest dose that can be given.

Fusion inhibitors are drugs which are designed to interfere with the attachment of HIV to cells. Several fusion inhibitors are in early clinical development. **Pentafuside (T-20)** (Trimeris, Inc.) is given intravenously, and a phase I study showed about a 1.5 log (97%) reduction in viral load at two weeks. **FP-21399** (Fuji) works by a similar mechanism.

Integrase inhibitors are designed to inhibit HIV's integrase enzyme, which, like reverse transcriptase and protease, is essential for its replication. The function of integrase is to bind to HIV DNA, which reverse transcriptase copies from the viral RNA, and integrate it into the cell's genetic material. **Zintevir** (AR 177; Aronex Pharmaceuticals) works by inhibiting the binding of integrase to the HIV DNA, rather than inhibiting the enzyme's activity per se. It is given intravenously and is being studied in a [phase I/II trial](#) at NY Hospital-Cornell Medical Center. Zinc fingers are structures that help package HIV genetic material into newly created viruses and appear to play a role in an earlier stage of the viral life cycle. **CI-1012** (Parke Davis) is a zinc finger inhibitor in phase I development at the National Cancer Institute. A Dutch company (Van de Velde) is developing a similar type of drug called **ADA (azodicarbonamide)** in Europe.

Antisense drugs are small molecules, usually short pieces of DNA, that are designed to enter HIV-infected cells and inhibit the action of viral genes. **GEM 91** (Hybridon, Inc.) is an antisense compound in phase II development. Based on studies in the test tube, it appears to inhibit several stages of the HIV life cycle, including the absorption of HIV into cells, the reverse transcription of viral RNA into DNA, and the production of proteins needed in the latter stages of virus production. Given intravenously, it has resulted in short term reductions in virus levels within cells of up to 90%. An intramuscular formulation of the drug is also under development.

Some of these drugs in the early stages of development offer the hope of increasing the treatment options of those who are exhausting the currently available drugs. In particular, drugs in new classes that attack different stages of the HIV life cycle may circumvent the problem of cross-resistance within existing classes of drugs. More data are certainly needed on the safety and efficacy of these investigational drugs before we can even begin to speculate what impact they might have on treating HIV infection. Information about participating in clinical trials of many of the drugs mentioned in this article can be obtained by calling 800-TRIALS-A or by contacting the [AIDS Treatment Data Network](#) (800-734-7104). For more information about CRIA's clinical trials, call 212-924-3934. Dr. Marshall J. Glesby is the Medical Director of CRIA.

*Dr. Marshall J. Glesby is the Medical Director of CRIA.*

## **HIV Resistance and Resistance Testing**

*By David Pieribone*

In the era of Highly Active Antiretroviral Therapy (HAART), serious problems still exist that keep some people living with AIDS (PLWAs) from benefiting from these powerful drug combinations. One of the greatest problems is resistance. Resistance means that a drug which was effective in treating or suppressing a certain infection no longer works against the pathogen (disease causing agent) which causes the infection. The failure of anti-HIV drugs has been linked to the emergence of drug resistance. Resistance can arise to treatments for many types of infections (e.g. viral, bacterial, and fungal).

Resistance to a particular drug often arises from a genetic mutation in the pathogen. Simply put, a resistance mutation can be thought of as a change in the genetic material of the pathogen which allows it to evade a particular drug that previously inhibited its growth.

HIV mutations are actually mistakes made during HIV's reproduction. The HIV virus is prone to make mistakes since it does not proofread the copies of its genetic material (RNA) which it makes to form new viruses. It is estimated that over one half of the HIV viruses produced in the body have mutations that prevent them from successfully infecting new cells. For HIV, this is an advantage because some of these mutations could allow it to become resistant to a particular drug, which enables the virus to continue multiplying in the presence of the drug. Resistance has been documented with all classes of the currently approved anti-HIV drugs.

If we use the HIV protease as an example, it is easy to understand the concept of how a viral mutation can lead to drug resistance. After HIV has infected a cell and reprogrammed it to reproduce HIV, the cell becomes a factory for making HIV. The infected cell now reproduces HIV particles continuously. It is estimated that up to 10 billion HIV particles are produced daily in the body. A crucial step in the life cycle of the virus occurs when the protease enzyme cuts up a string of proteins (some of HIV's building blocks) so that they can be assembled to form new infectious virus particles. For purposes of explanation, let's think of this protease as a pair of scissors which does the cutting. One class of drugs called protease inhibitors stop this scissors from cutting. Picture the protease inhibitor as a clamp holding the two blades together and preventing them from cutting.

As HIV reproduces itself millions of times, it produces a few mutated copies of this protease enzyme which do not look like a scissors but look like, say, a box cutter or a knife. This new enzyme can still cut up the string of proteins like the scissors did but now the protease inhibitor can no longer prevent its function since a clamp (the protease inhibitor) is no use against a single blade. This is how a mutation results in drug resistance. Mutations that lead to resistance have been identified for all of the four approved protease inhibitors.

A similar process leads to the mutation of another enzyme called reverse transcriptase. This enzyme, which constructs DNA from viral RNA, can be inhibited with another class of drugs called reverse transcriptase inhibitors. When mutations arise in this enzyme, the virus becomes resistant to drugs that once inhibited it. Mutations have been identified which cause resistance to all the approved RT inhibitors.

### **Cross-Resistance**

Presently there are three classes of anti-HIV drugs on the market: nucleoside analogs, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. Drugs within each class act on the same target of HIV's life cycle. HIV that has become resistant to one drug within a class may also be resistant to other drugs in the same class. This phenomenon is called cross-resistance. For example, HIV which is resistant to the protease inhibitor ritonavir seems to invariably be resistant to indinavir, another protease inhibitor.

**Table 1**

**Codon changes associated with resistance to antiviral drugs**

**Nucleoside Analog Reverse Transcriptase (RT) inhibitors**

<b>Drug</b>	<b>RT Gene Codon</b>
Zidovudine (AZT)	41, 67, 70, 215, 219
Didanosine (ddl)	65, 74, 184

Zalcitabine (ddC)	65, 69, 184
Lamivudine (3TC)	184
Stavudine (d4T)	50?, 75?
1592U89	65, 74, 115, 184

#### **Non-Nucleoside RT Inhibitors**

<b>Drug</b>	<b>RT Gene Codon</b>
Nevirapine	103, 106, 108, 181, 188, 190
Loviride	103, 181
Delavirdine	181, 236
DMP-266	100, 108, 179, 181

#### **Protease Inhibitors**

<b>Drug</b>	<b>Protease Gene Codon</b>
Saquinavir	10, 48, 54, 63, 71, 90
Ritonavir	20, 33, 36, 46, 54, 71, 82, 84, 90
Indinavir	10, 20, 24, 46, 54, 63, 64, 82, 84, 90
Nelfinavir	30, 35, 36, 46, 71, 77, 84, 88
141W94	10, 46, 47, 50, 8

#### **Some Causes of Drug Resistance**

Individuals with advanced HIV disease, low CD4 cells (T-cells) and high HIV viral loads seem to be more likely to develop drug-resistant HIV. Viral mutation is directly related to viral production. The more virus produced, the greater the chance of mutation and thus resistance. ( As less virus is produced, there is less chance of mutation.) Therefore the goal of therapy is maximal suppression of HIV replication. Suppression of virus must be continuous since any viral replication, in theory, can lead to resistance. If a drug or combination of drugs only partially suppresses HIV production, the viruses produced will eventually become resistant and the new strain of resistant virus will predominate in the body.

If inadequate levels of a drug are present in the body, viral production can continue. There are many possible reasons for inadequate drug levels. Firstly, and most importantly, is non-adherence to the drug regimen. If a person fails to take the medications in the right dose, in the correct way (e.g. with or without food) or at the right times, the result may be inadequate drug levels, which allows the virus to reproduce. Secondly, certain concomitant medications can

interfere with the absorption of the antiviral drugs, or can increase the metabolism of these drugs thus causing inadequate drug levels. Lastly, many of the antiretroviral drugs do not penetrate certain areas of the body, such as the brain, thus allowing HIV to replicate unchecked in these areas.

Some individuals who have previously taken anti-HIV drugs as monotherapy (one drug at a time) may have developed resistance to the drugs due to inadequate suppression of HIV replication. It is important for healthcare providers who are prescribing combination therapy to evaluate a patient's past medication history in order to aid in the choice of drugs to which a person's HIV will hopefully be sensitive.

### **Preventing Resistance**

In theory, it is possible to eliminate resistance if viral production is completely suppressed. Small studies of triple drug combination therapy which have demonstrated suppression of viral production below the available level of quantification have also delayed or eliminated the onset of drug resistance, at least in the short term. Larger, long term studies are required to validate this. It is still not known whether all viral replication has actually stopped when an individual's viral load is undetectable by the current tests(see p.6). It is possible that even if a small amount of HIV is being produced, a mutation will occur that can confer resistance.

### **Resistance Testing**

Recently a number of laboratories have begun offering resistance testing. There are two types of resistance tests available: genotypic and phenotypic. These tests use two different approaches to determine if an individual's virus has become resistant to particular drugs. Though some doctors are using these tests in an effort to determine which drugs to use for a patient who has failed a particular combination, other doctors do not use them since the tests have not yet been studied adequately and may provide misleading information. The most widely available test is genotypic testing.

### **Genotypic Testing**

Genotypic testing looks at changes in the RNA of the virus. Similar to DNA, RNA contains the virus' genetic instructions or genes that program the manufacture of the protease and reverse transcriptase enzymes, as well as a host of other proteins. Each protein or enzyme consists of specific building blocks called amino acids. Each amino acid is added to a protein that is being built in a cell based on a code in the RNA. The code in the RNA that specifies a particular amino acid is called a codon. Genotypic resistance test results are shown as changes in individual amino acids due to mutations at specific codons in the RNA. Mutations at one or more codons are associated with resistance to particular drugs. Often a sequence of mutations are needed to confer resistance to a particular drug or class of drugs. Researchers have identified many but not all of the mutations that lead to drug resistance. Table 1 summarizes the key mutations that have been associated with resistance to particular anti-HIV drugs. Genotypic testing is less expensive and takes less time than phenotypic testing. However, since it only detects the predominant viral population (it can't quantify mixtures of virus), it may not accurately detect all mutations, making the results difficult to interpret. In addition, since all mutations which lead to resistance have not been characterized, the absence of known mutations does not necessarily mean the absence of resistance.

### **Phenotypic Testing**

Unlike genotypic testing, phenotypic testing does not look at the actual genes or RNA of the virus but looks at the ability of the virus to replicate in a test tube when a particular drug is present. Test results are given as the amount of drug necessary to suppress the virus. HIV that is not resistant will be completely suppressed by appropriate levels of drug. Resistant HIV requires adding considerably more of the drug to completely suppress the virus. Since most anti-HIV drugs are already given at the maximum tolerated dose, it is not possible to add more of the drug without causing major toxicities. Phenotypic testing is a more direct measure of resistance than

genotypic testing, which allows easier interpretation of the results. However, phenotypic testing takes longer and is more expensive to perform.

### **Limitations of the Tests**

Because these tests usually are able to evaluate only the most predominant strains of virus in the blood, it is not always possible to tell accurately if other drug resistant strains are contained within an individual. For example, consider a person who took AZT + 3TC in the past and failed, as manifested by an increased viral load. His drug regimen was changed to three new drugs which initially lowered his viral load, but six months later he had a rebound in viral load. Since he has not taken AZT/3TC for many months, perhaps only a very small population of the virus in his body is still resistant to these drugs. This may not show up on resistance testing. Yet, if he were to take AZT/3TC again, the resistant strain would likely predominate in a short period of time, and the drugs would not work effectively.

Neither phenotypic nor genotypic testing has been tested adequately in clinical trials, so their accuracy and validity have not been established. For this reason most insurance companies and drug assistance programs will not pay for them. The current cost of genotypic resistance testing is from \$ 300-400 and phenotypic resistance testing costs about \$1000. Currently a few clinical trials are being conducted to evaluate the utility of these tests.

Since we have no hard information on how to interpret resistance tests, use of these tests is not standard clinical practice. In the future, if studies prove the validity of these tests they may be used to make treatment decisions. By combining both genotypic and phenotypic resistance testing it may be possible to get more relevant information than using just one test by itself. However, this approach has also not been validated and is expensive.

*David Pieribone is CRIA's Treatment Education Director, a member of the [Treatment Action Group](#) and a community representative for the American Foundation for AIDS Research.*

### **Viral Load Update - How much is too much?**

*By Spencer Cox*

The viral load tests, which serve as the basis for the recent Public Health Service Guidelines on HIV Treatment, are still relatively new tests, and much information is being learned every day about how they are best interpreted. While the guidelines state that the goal of antiviral therapy is to reduce HIV levels in the blood to levels that are not detectable by current tests, there is currently much debate about what "undetectable" means.

The standard PCR test, known as the Roche Amplicor™ HIV test, measures virus levels of more than 400 copies/milliliter of blood. While test results may find 200 or 300 copies, these numbers are considered unreliable. An experimental version of the Amplicor™ test, known as the "Ultradirect" assay, can measure as few as 20-50 copies of virus/milliliter of blood. Studies suggest that people who have undetectable viral load measures according to the standard test, but not from the Ultradirect test, have viral rebound at about the same rate as people who have low levels of detectable virus according to the standard test. In other words, people who have 50-400 copies of virus have increases in virus levels at about the same rate as people who have somewhat more than 400 copies of virus. On the other hand, people who are undetectable according to the Ultradirect assay tend to maintain viral suppression indefinitely.

Although the Ultradirect assay is not yet approved by the Food & Drug Administration (FDA), and is therefore not widely available, some researchers are suggesting that that test, and not the currently available test, should be the standard measure of viral load in patients taking potent

combinations of anti-HIV drugs. This controversy will be resolved as the newer, more sensitive tests become available.

Another viral load test which has been used in a number of research studies is known as the bDNA or Quantiplex™ test and is manufactured by Chiron Corporation. The second generation bDNA test measures below 500 copies/ml, though some scientists have questioned the reliability of measurements below 1200-1500 copies/ml. The test is not yet approved by the FDA, and an application has been pending for some time. A third generation bDNA test is under development, and a recent study suggests that it reliably measures down to about 50 copies/ml

*Spencer Cox is the Director of the Antiviral Project of the [Treatment Action Group](#) and a CRIA board member.*

## **Drug Delivery Systems**

*By Dudley Saunders*

As the prospect of lifetime HAART (highly active antiretroviral therapy" looms, so does the unlikelihood that HAART's difficult and unforgiving regimens can be maintained by patients over the long haul. Fortunately, the thirty year old drug delivery industry may hold the key.

Currently, anti-HIV drugs are delivered to the body in a remarkably crude fashion: simply put, the highest tolerable dose is administered by pill, and then readministered just before the drug falls below therapeutic levels in the body. This method of dosing drugs can cause several problems. It is the high blood levels of drug shortly after each dose that seem to cause the vast majority of side effects. Furthermore, individuals metabolize and clear drugs from their bodies at different rates. For example, someone who metabolizes a protease inhibitor drug rapidly may have blood levels of the drug that are too low to inhibit HIV at several times throughout the day prior to each new dose. When the drug levels are too low to keep HIV from replicating, resistance to the drug may set in.

The drug delivery industry develops systems for "continuous infusion." This means their goal is a system that delivers a drug to the body at a particular, steady rate over a long period of time, thereby eliminating the initial "peak" levels of a drug that cause side effects, as well as the low, or "trough," levels that leave a drug ineffective and allow the pathogen an opportunity to develop drug resistance. Just as important, these systems are developed for infrequent administration, and usually eliminate any food restrictions associated with a drug's oral formulation, making it far easier for patients to adhere to therapy.

Although these systems hold out the likelihood of maintaining patients on a single regimen in perpetuity, as well as reaching out to the historically non-compliant population who are currently being denied HAART by some medical providers, the pharmaceutical industry has only begun to talk to the drug delivery industry, and only one system developer, Alza Corporation, has tested a protease inhibitor in one of their devices. Drug companies weighing an investment are likely to be responsive to community pressure, if for no other reason than to assure them of marketplace demand.

Dudley Saunders is a writer, and member of the [Treatment Action Group](#).

**CRIA NEWS**

**CRIA TRIALS NOW ENROLLING**

### **Adefovir Dipivoxil for Antiretroviral Naive Patients**

CRIA is participating in a 48 week study of Gilead Sciences' nucleotide analog drug adefovir dipivoxil (formerly called bis-POM PMEA). Adefovir is a new type of drug that is active against HIV as well as some other viruses such as CMV, hepatitis B virus, and herpes viruses. The study is of HIV+ persons with more than 100 T-cells and HIV viral load of greater than 5,000 who have not taken other anti-HIV drugs in the past. Participants will be assigned to one of five treatments, all of which include the protease inhibitor indinavir (Crixivan™). Participants will be reimbursed \$15 per scheduled visit after enrollment.

### **DMP 266**

DMP 266 is DuPont Merck's new non-nucleoside reverse transcriptase inhibitor (NNRTI) that appears to be quite active against HIV in early clinical studies when used in combination with other drugs. CRIA is participating in a study of DMP 266 for people with more than 50 T-cells and HIV viral loads greater than 10,000 who have not taken a protease inhibitor drug, 3TC, nevirapine, or delavirdine. Participants will be assigned to one of three combinations: AZT + 3TC + indinavir (Crixivan™), AZT + 3TC + DMP 266, or indinavir + DMP 266. The study will last 60 weeks and participants will be reimbursed \$15 per scheduled study visit after enrollment.

### **Oxandrolone for Women with Weight Loss**

Oxandrolone is BTG's anabolic steroid hormone which has shown promise as a treatment for AIDS-related wasting in small, preliminary studies and, unlike testosterone, can be taken as a pill. CRIA is participating in a multicenter studies of oxandrolone for AIDS-related wasting in women. In this study, different doses of oxandrolone will be compared with inactive pills (placebo) for 12 weeks, followed by a 24 week period during which all participants will receive oxandrolone. Participants must be HIV+ with unintentional weight loss of 10-20% of their usual body weight. Participants will be reimbursed \$15 per scheduled study visit after enrollment.

### **141W94 protease inhibitor**

CRIA is participating in a 48 week study that compares Glaxo Wellcome's investigational drug 141W94 to indinavir (Crixivan™). To be eligible, participants must have taken nucleoside drugs (e.g., AZT, 3TC, ddI, ddC, d4T) for the past 12 weeks, have detectable viral load (greater than 400), and never have taken a protease inhibitor drug. Participants, in conjunction with their doctors, are encouraged to change at least one of their nucleoside drugs at the time of starting the study. Participants will be reimbursed \$15 per scheduled study visit after enrollment.

### **SMART/EST Women's Project**

CRIA is participating in a multicenter study to test a 10 week stress management program to teach women how to cope more effectively with their illness and everyday problems. Two approaches —individual and group relaxation training— are being compared. Women 18 years of age and older with a diagnosis of AIDS may be eligible. Participants will be reimbursed \$25 per visit after enrollment (up to \$575). Free child care and refreshments will be provided. For more information, call Debra Munger at 212- 924-3934.

### **Protease Inhibitor and Blood Sugar Study**

CRIA is conducting a study to examine the effects of protease inhibitor use on responses to the oral glucose tolerance test (measurement of blood sugar levels after taking a drink with a high sugar content). To be eligible, participants must be about to start treatment with a protease inhibitor drug for the first time. Participants will be reimbursed \$30 for each of the first two visits and \$50 at the final visit.

### **Combination Study for Antiretroviral Naive Patients**

CRIA will be participating in a study comparing the three drug combination of Combivir™ (AZT/3TC) plus nelfinavir with the four drug combination of Combivir™ plus 1592U89 plus the 141W94 protease inhibitor. To be eligible for the study, which will begin in early 1998, participants must have a T-cell count of 50 or greater and a viral load of 5,000 or greater. The only prior

treatment allowed is up to one week of 3TC or a protease inhibitor and up to four weeks with other nucleoside analog drugs. Participants will be reimbursed for scheduled study visits after enrollment.

### **Testosterone and MET-Rx™**

CRIA is sponsoring a study of testosterone and MET-Rx™, a high protein nutritional supplement for treatment of AIDS-related wasting. Participants will receive testosterone or placebo injections in combination with MET-Rx or standard nutritional supplement. Participants must be HIV+ men with T-cell counts of less than 400, low testosterone levels, and weight loss or loss of lean body mass. For information, call Dr. Judith Rabkin 212-543-5762.

For more information on any of these studies, please call Dr. Avinash Desai or Dr. Douglas Mendez at (212) 924-3934, or visit our World Wide Web page ([www.criany.org](http://www.criany.org))

### **CRIA's Treatment Education Program**

Demand for CRIA's Treatment Education Program, an initiative which we began in July 1997, has been overwhelming. In the past five months alone, CRIA has provided critical education on the newest HIV/AIDS treatments to over 750 PLWAs at AIDS service organizations in all five boroughs of New York City. Nearly 30 Treatment Education Partnerships (TEPs) have been established with groups to provide regular ongoing services to their clients and patients. Many more ASOs have expressed interest to become TEPs.

We are pleased to announce that several major funders have come forward to help us meet the demand for our HIV/AIDS treatment education services. Recently, the State of New York Department of Health AIDS Institute awarded CRIA a seven month grant to provide treatment education within neighborhoods in northern Manhattan, the Bronx, and Queens. The New York Community Trust - Royal S. Marks Foundation Fund is providing a two-year grant for our program, and the Liz Claiborne Foundation has recently provided CRIA with a grant to expand our treatment education services specifically for women living with AIDS.

Due to the increasing demand for HIV/AIDS treatment education, CRIA is expanding the program's staff. We are pleased to welcome Eduardo Guzman as a new Treatment Educator. Eduardo's experience with the Spanish speaking community will enable CRIA to provide critical information to an even broader audience.

If you are interested in learning more about CRIA's treatment education services or you would like to schedule a treatment education workshop, please call David Pieribone, CRIA's Treatment Education Director, at 212-924-3934, or write to CRIA, Treatment Education Program, 275 Seventh Avenue, 20th Fl, NY, NY 10001.

### **Protease Inhibitors and Blood Glucose Levels study**

CRIA has started a new study designed to examine the effect of protease inhibitor drugs on blood glucose (sugar) levels. The basis for the study is the apparent onset of diabetes in a relatively small proportion of persons taking protease inhibitors. As of May 1997, 83 cases of high blood sugars or diabetes were reported to the Food and Drug Administration (FDA), 14 of whom had a worsening of control of pre-existing diabetes. All four FDA-approved protease inhibitors have been implicated as potentially causing high blood sugars. Whether the protease inhibitors themselves actually cause diabetes or high blood sugars is not definitively known.

In the CRIA study, HIV-infected persons without a diagnosis of diabetes who are about to start treatment for the first time with a protease inhibitor will undergo a glucose tolerance test, which measures blood glucose levels before and after taking a drink with a high sugar content. The test

will be repeated on two occasions after starting the protease inhibitor to see if the results are affected by the drug. Participants will be reimbursed for their time.

For more information about participating in this study, call 212-924-3934.

### **Expanded Access for Adefovir Dipivoxil and Efavirenz**

CRIA is participating in protocols designed to make adefovir dipivoxil (Preveon®) and efavirenz (DMP 266, Sustiva®) available to persons with advanced HIV disease and limited treatment options. If you fit into this category and your medical provider or clinic is not participating in these programs, we can work with you and your medical provider to see if you are eligible.

To be eligible for the adefovir dipivoxil protocol, you must have a T-cell count of 50 or less and a viral load of 30,000 or more within the past two months, and your medical provider must be unable to come up with an alternative combination of drugs that is likely to be viable.

To be eligible for the efavirenz safety protocol, you must be failing current antiretroviral therapy (based on rising viral load, falling T-cell count, or clinical deterioration) and not have the option of treatment with at least two marketed anti-HIV drugs. In addition, you must have access to at least one other investigational drug (1592U89 or adefovir dipivoxil).

For more information about these protocols, you or your medical provider may call CRIA at 212-924-3934.

### **Coming Soon to CRIA....**

In early 1998, CRIA will be participating in an international, multicenter study designed to determine whether a four-drug combination is more effective than a three-drug combination as initial treatment of HIV infection. The study, sponsored by Glaxo Wellcome, will compare the combination of Combivir™ (AZT/3TC), abacavir (1592U89), and 141W94 with one of the more commonly prescribed initial regimens — Combivir™ plus nelfinavir (Viracept™). An interesting feature of this study is the plan to utilize genotypic and phenotypic resistance testing to help guide the choice of drugs in participants who do not have sustained suppression of viral replication (to a viral load of less than 120 copies/ml).

To be eligible for this study, participants must be HIV-positive adults with T-cell counts of at least 50 cells/mm<sup>3</sup> and HIV viral load of at least 5,000 copies/ml. Potential participants must be antiretroviral naive —the only prior treatment allowed is up to one week of treatment with 3TC or a protease inhibitor and up to four weeks with other nucleoside analog drugs. For more information about this study, call Dr. Avinash Desai at 212-924-3934.

CRIA plans to have other new protocols available in early 1998, at least one of which will be designed for persons failing protease inhibitor treatment. For an updated listing of our trials, please call us or visit our World Wide Web page ([www.aidsinfonyc.org/cria](http://www.aidsinfonyc.org/cria)).

### **New Board Members at CRIA**

CRIA is pleased to announce the addition of three new Board Members elected at the November 19, 1997 board meeting.

#### **Jill A. Cadman**

brings an in-depth background in HIV/AIDS research advocacy, prevention and treatment education to CRIA. She has been a staff member of the [Gay Men's Health Crisis](#) since 1993, and currently serves as Associate Editor of that agency's monthly treatment newsletter, Treatment Issues.

**Barbara W. Liberman, Ph.D**

adds a new perspective to CRIA's community based Board as a psychologist who has conducted extensive research into the areas of improving mental health for people living with AIDS (PLWAs). Dr. Liberman has been active in a number of charitable causes in New York City, including her involvement in several leading AIDS service organizations. She currently serves as Managing Director of the Metropolitan Opera Association.

**Carlos J. Sandoval, Esq.**

has long been an AIDS activist through his volunteer work at a number of AIDS service organizations over the past years, including CRIA. In addition to his personal understanding of the challenges faced by people living with AIDS and a deep commitment to the pursuit of improved HIV treatments, Mr. Sandoval brings to CRIA's Board an expertise in the legal affairs of non-profits and PLWAs.

CRIA's staff looks forward to the direction and guidance that we will receive from our new Board Members to make our programs most effective at meeting the needs of PLWAs in the coming months and years.

**CRIA UPDATE****Editor in Chief**

J Daniel Stricker

**Managing Editor**

David L. Pieribone

**Medical Editor** Marshall J. Glesby, MD, Ph.D.

**CRIA Board of Directors**

Ross Bleckner, *President*

Donald Kotler, MD, *Vice President*

George N. Stathakis, *Treasurer*

Robert Levy, Esq., *Secretary*

Jill Cadman

Marisa Cardinale

Bob Colacello

Spencer Cox

Douglas Dieterich, MD

Charles Franchino, DC

Michael Goff

Brian L. Heyman

Barbara W. Liberman, Ph.D.

Judith Rabkin, PhD, MPH

Carlos J. Sandoval, Esq.

David Seidner

**In Memoriam**

Don Hall

Kiki Mason

Hon. Jason Worth

**Executive Director**

J Daniel Stricker

**Medical Director**

Marshall J. Glesby MD, Ph.D.

CRIA is an independent, non-profit, community-based AIDS research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. CRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of *CRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information call Meredith Snow at 212-924-3934.

**Copyright** © 1998

*Community Research Initiative on AIDS.*

*All rights reserved. Non-commercial reproduction is encouraged provided appropriate credit is given.*

**CRIA**

275 Seventh Avenue, 20th Floor  
New York, NY 10001  
Phone: (212) 924-3934  
FAX: (212) 924-3936  
Internet address: [www.criany.org](http://www.criany.org)

**acknowledging our friends...**

## GENEROUS CONTRIBUTORS

**The following persons, corporations and organizations made major donations between September 1 and December 15 to support CRIA's search for effective AIDS treatments:**

Patrice G. Adcroft  
Bristol Myers Squibb Company  
Calvin Klein, Inc.  
Central tree Service, Inc.  
CFDA  
Chase Manhattan Foundation  
Patricia & Gustavo Cisnero  
Claudia Cohen  
Bob Colacello  
Computer Associates  
*Conde Naste House and Garden*  
Ellen & William D'Amico  
Estate of Salvatore Saraceno  
Sandy Gallin  
Stephane & Alison Gerson  
Maureen Griffen  
Agnes Gund & Daniel Shapiro  
Fredric Hanson  
Gale Hayman  
Fred Hochberg & Tom Healy  
Wilma Hockett  
*In Style Magazine*  
Duane Jeske  
Katherine Kagan

KJ Kaminski Consulting  
Robert A. Landau  
Harriet Leve  
Liz Claiborne Foundation  
Martha Nelson  
Phillip Morris Companies  
Roche Diagnostic  
Roche Laboratories  
Nancy Rose  
Michael Roth  
Royal s. Marks Foundation  
James & Ruth Scheuer  
David Seidner  
Serono Laboratories, Inc.  
Sony Europe  
Stephen Sills  
Jeffrey B. Soref  
Nadja L. Swarovski  
Richard S. Swenson  
Ted, Inc.  
The David Geffen Foundation  
Jann Wenner

**Thoughtful donations in memory of the following people remind us of what is at stake in the fight against AIDS:**

Allen Barnett  
Barry Binkowitz, MD  
Philip Blasucci  
Irving Cooperberg  
Nelson Gross  
Paul A. Kaplan  
Jeffrey L. Mitchell  
Carl Parisi  
Brian Riordan

**Contributions in support of CRIA's vital research initiatives were made in honor of the following individuals:**

Anthony John F. Aloï  
Jack Battaglia  
Leo Sosnoski  
Ross Bleckner  
Ched Chinery  
Bob Colacello  
Ben Fishner  
J.A. Forde  
Brian Heyman & Ian Heslop  
Richard Jacobs  
Ron Rossi  
Chris Seelig  
Jeff Scheuer  
J Daniel Stricker