

## **Drug Development: An Overview**

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### **Drug Development: An Overview**

*By Marshall J. Glesby, MD, PhD*

Among the most important challenges facing HIV researchers is the development of new safe and effective drugs for treating HIV infection. Although there have been remarkable therapeutic advances in the past few years, we are clearly in need of additional antiretrovirals which are active against drug-resistant HIV strains, easier to take, and free of major side effects. Developing such drugs is obviously not a simple task. In addition to being costly and laborious, the drug development process is highly dependent on basic scientific discoveries. Fortunately, in the past few years there have been important scientific advances in the understanding of how HIV infects cells and multiplies in the human body. These types of discoveries should lead to the development of new classes of antiretroviral drugs.

### **The Development Process**

Advances in basic science can lead to therapeutic advances through a process known as rational drug discovery. Rather than randomly screening thousands of chemicals for activities against the disease in the test tube, which has been done for HIV as well as for cancer drugs, scientists start with a known chemical structure and use computers to design drugs which may be able to bind to the structure. For example, knowing the chemical structure of HIV's protease enzyme has led to the synthesis of protease inhibitors which bind to and inhibit the function of the enzyme which is critical for HIV replication. Considerable efforts go into modifying the initially conceived parent drug molecule in order to come up with a final drug which has maximal activity against the virus and minimal toxicity.

Extensive testing of a new drug must be undertaken prior to use in humans. These preclinical tests include thorough safety studies in laboratory animals. If the preclinical testing is satisfactory, initial clinical trials, called Phase I studies, are undertaken in humans. Phase I studies involve a small number of subjects who may be healthy volunteers and focus on the pharmacokinetics of the drug—that is, measures of things like the levels of the drug in the bloodstream after a single dose or multiple doses. Phase II studies involve more patients (typically several hundred) and give insight into common toxicities of the drug as well as an initial look at how active the drug is (efficacy). Phase III studies are even larger and yield more definitive safety and efficacy data. Sometimes the different phases are combined (e.g. a Phase II/III trial) to speed up the development process. The data from two Phase III studies are usually submitted to the Food and Drug Administration (FDA) as the key or pivotal studies to demonstrate the safety and efficacy of a new drug.

The average time from discovery of a new drug to its approval for use in people is about 15 years. Fortunately, this timeline has been accelerated somewhat for HIV drugs so that today's

basic scientific discoveries may translate into therapeutic advances in a shorter time frame. Nonetheless, for every 5,000 drugs undergoing preclinical testing, only about five will likely make it into clinical trials, and only one of these five will actually get approved by the FDA. Partly because of this relative inefficiency, the estimated cost of bringing a new drug to market is \$500 million.

Drug development is of particular interest to us at ACRIA because it is an important intersection between the two prongs of our mission-clinical research and treatment education. As a research organization that typically conducts Phase II and III trials, we have extensive experience with investigational drugs before they are approved by the FDA. We are able to incorporate this experience into our treatment education efforts, which has enabled us to become a leading provider of information on new and emerging therapies for HIV infection and its complications to residents of New York City and beyond.

This issue of ACRIA Update focuses on drugs in the pipeline for treating HIV infection and related clinical problems. Tim Horn, a regular contributing writer, has concisely summarized [the current state of antiretroviral drugs in early clinical development](#). To help us understand the targets of these and other potential antiretroviral drugs, David Pieribone, ACRIA's Director of Treatment Education, has sketched out [HIV's life cycle](#) in the centerfold of the periodical.

We initially planned to include information on drugs in the pipeline for opportunistic infections (OIs), but the dramatically decreased incidence of OIs in the developed world as a result of more effective antiretroviral therapy seems to have squelched such drug development. Instead, we are fortunate to have an article by Dr. Mark Sulkowski of Johns Hopkins on a clinical problem of increasing significance for many persons living with HIV infection - [hepatitis C virus \(HCV\) co-infection](#). The principles of rational drug design are actively being applied to HCV drug development, a field in which there have been impressive basic scientific advances in recent years. Finally, Tim Horn has reviewed the epidemiology, current treatment, and drugs in the pipeline for two of the HIV-related cancers which have not disappeared - [Kaposi's sarcoma and non-Hodgkin's lymphoma](#).

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

*By Tim Horn*

The anti-HIV drug development pipeline is like a crystal ball: it is filled with an abundance of hope, surprises, and disappointments. Unfortunately, we are still very much dependent on the predictions of the crystal ball. All of the currently available anti-HIV drugs are far from ideal; we still face problems of side effects (both short- and long-term), adherence issues, drug resistance, cost, and potency. Alas, hopes of long-term management and eradication both depend on an ever-growing number of therapeutic options.

Luckily, there are a number of promising drugs in the early stages of development. While it may be some time before these drugs are ready for approval, we can expect some of these to enter large clinical trials over the next year. Here's a look at what the crystal ball has in store:

### **Nucleoside Analogues (NRTIs)**

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) -the class of drugs that includes AZT, 3TC, ddI, d4T and abacavir - are still being developed for the treatment of HIV. Three newer

compounds are currently in the drug development pipeline and may prove to be effective anti-HIV therapies.

Currently in phase I/II studies is **lodenosine (also known as F-ddA)**, an NRTI being developed by U.S. Bioscience. A particular advantage of lodenosine is that, unlike ddI, it can be digested and metabolized in the stomach without an antacid buffer. The antacid buffer in ddI requires that it be taken on an empty stomach and has been suggested to be the root cause of ddI's side effects. According to one preliminary study, lodenosine results in a half-log drop in viral load when taken alone, which is similar to that of other NRTIs. In test tube studies, lodenosine appeared to be active against HIV strains already resistant to AZT, ddC, and ddI, as well as non-nucleoside reverse transcriptase inhibitors (NNRTIs) - good news for patients resistant to these drugs.

Another NRTI in development is **FTC**. The drug is manufactured by Triangle Pharmaceuticals and, at least in test tube studies, appears to be active against both HIV and hepatitis B virus (HBV). At the present time, the drug is being developed using a once-daily formulation (200 mg) and was associated with a 1.4 log drop in viral load after 14 days of use. Unfortunately, individuals already resistant to 3TC may not benefit from taking FTC as one of the most common mutations that confers resistance to 3TC also confers resistance to FTC.

A third NRTI in development is **dOTC (also known as BCH-10652)**. BiochemPharma is the manufacturer and it is currently in Phase I, dose-finding studies. According to the manufacturer, laboratory tests have shown dOTC to be active against HIV strains resistant to 3TC, ddC, adefovir dipivoxil (a nucleotide analogue being developed by Gilead Sciences), and AZT.

#### **Non-Nucleoside Analogues (NNRTIs)**

Currently in phase II studies is **MKC-442**, an NNRTI being developed by Triangle Pharmaceuticals. It is expected that this drug will be used at doses between 750 mg and 1000 mg twice daily. According to results from one preliminary study involving 35 patients, the drug reduced viral loads by more than 1 log during the first week of therapy.

MKC-442 is very similar to today's already approved NNRTIs. For starters, it is associated with rapid resistance, a common occurrence among patients who took either nevirapine or delavirdine as monotherapy in earlier clinical trials; patients who took MKC-442 as monotherapy in a clinical trial began to see their viral loads head back upwards after one week of use. MKC-442 is also associated with rash, a common side effect reported by patients taking nevirapine, delavirdine, and efavirenz. While more data from resistance studies are needed, at least one team of researchers has suggested that MKC-442 is active against HIV strains already resistant to nevirapine. MKC-442 also poses a problem for people looking to avoid drug interactions. Given that the drug is metabolized by the [cytochrome P450 enzyme system](#), interactions with oral contraceptives, protease inhibitors, rifampin, and rifabutin are likely to be discovered. The drug has also been shown to increase AZT levels in the blood by 90%, which will probably require a dose reduction of AZT.

Coming from a biotech group in Japan via Agouron Pharmaceuticals is **S-1153**. The drug is currently in Phase II studies; Phase I study results were presented at the 12th World AIDS Conference in Geneva last summer. According to test tube studies conducted as part of the Phase I trial, the drug may prove to be active against strains of HIV that are cross-resistant to nevirapine, delavirdine, and efavirenz. Like the currently approved NNRTIs, however, resistance is quick to occur with S-1153, at least when taken as monotherapy.

Other NNRTIs in the early stages of development are **carbaxanilide analogues**, **calanolide A analogues**, and the compound **PNU-242721**. Data regarding these drugs are limited, as they are just now entering human studies.

## Protease Inhibitors

Without a doubt, the rapid development of new protease inhibitors (PIs) is one of the most pressing concerns on the minds of both patients and doctors. For all HIV-infected patients, there is a demand for new PIs that are powerful and easier to use (ie., patient-friendly dosing schedules and fewer side effects); for patients who are resistant to the available PIs, there is an urgent need for newer compounds with unique resistance profiles. In turn, the true test of the newest PIs will be their efficacy in patients with prior protease inhibitor experience.

Currently in Phase II clinical trials is **ABT-378**, a protease inhibitor being developed by Abbott Laboratories, the company that produces ritonavir. In test tube studies, ABT-378 has been shown to be 10 times more powerful than ritonavir. When used in combination with small amounts of ritonavir, ABT-378's activity in the blood is prolonged, allowing a twice-daily dosing schedule. In a presentation at the 12th World AIDS Conference, one team of researchers reported some preliminary data from a study comparing two doses of ABT-378 in combination with low-dose ritonavir (100 mg). Thirty-two patients who had never taken a protease inhibitor before were enrolled in the study. After three weeks of ABT-378/ritonavir therapy, the patients' viral loads had dropped by 2 logs; the majority of those treated for 20 weeks had viral loads below the level of detection of the first-generation test (<400 copies).

At the present time, very little is known about ABT-378's resistance profile. However, both the manufacturer and a handful of independent researchers have suggested that it is effective against strains of HIV resistant to ritonavir, indinavir, and saquinavir; data from clinical trials involving patients with a history of protease inhibitor failure are anxiously awaited.

Situated further back in the pipeline is **tipranavir (also known as PNU-140690)**. According to its manufacturer, Pharmacia & Upjohn, tipranavir also appears to be active against several protease inhibitor-resistant strains of HIV, including those resistant to indinavir and ritonavir. At the 12th World AIDS Conference, interim data from a preliminary study of the drug were reported. All patients were hospitalized for the initial 11 days of therapy and then discharged and asked to continue taking the drug under their own supervision. According to the results, tipranavir was well tolerated with no serious adverse events reported during the twelve-week study period. The 24 patients enrolled were taking a double NRTI combination (ie., d4T and 3TC) at the time of entry into the study. After the 11-day hospital phase of the study, most patients saw their viral loads decrease an additional 1.0 - 1.3 logs after eleven days of therapy. Unfortunately, viral load levels began to increase again after twelve weeks of therapy, which the researchers attributed to poor adherence during the outpatient phase of the study.

Other protease inhibitors, most of which seem active against HIV-including both "wild type" and protease inhibitor-resistant strains of HIV-are now in phase I studies. These include **DMP-450** (Triangle Pharmaceuticals), **BMS-232,632** (Bristol Myers-Squibb), and **PD-178390**, a protease inhibitor being developed by Parke Davis.

## Novel Therapeutics

There are several anti-HIV drugs being developed that do not readily fit within any of the above mentioned classes of drugs. These drugs are unique in the way they block HIV replication and may prove to be of substantial benefit when used in combination with standard anti-HIV compounds.

One of the most closely watched compounds in development is **pentafuside (also known as T-20)**, a fusion inhibitor being developed by Trimeris Pharmaceuticals. Unlike reverse transcriptase inhibitors and protease inhibitors which interfere with viral reproduction once HIV is inside the cell, pentafuside prevents HIV from successfully docking with T-cells, protecting the cell from infection. In phase I studies of the drug - with patients not taking other anti-HIV therapies - pentafuside therapy resulted in a 1.5 log reduction in viral load when taken for 14 days; a significant increase in T-cells was also reported.

Another unique approach is the development of zinc finger inhibitors. Zinc fingers are part of the protein responsible for protecting and repackaging HIV-RNA on its way in and out of a cell's nucleus. In the absence of functional zinc fingers, HIV-RNA cannot successfully complete its task of infection and re-assembly. In the early stages of development is **CI-1012**, a drug that acts as a zinc finger inhibitor. Resistance may not be a big problem with this drug, as it interferes with a viral protein that does not readily mutate (as opposed to the reverse transcriptase and protease enzymes).

Last but not least is **zintevir (also known as AR-177)**, a drug being developed by Aronex Pharmaceuticals. Zintevir is an inhibitor of integrase, the third of three retroviral enzymes long considered by researchers to be an ideal therapeutic target (the other two are reverse transcriptase and protease). Integrase is the enzyme responsible for integrating viral RNA into a host cell's DNA. Because zintevir effectively disrupts the integrase process, HIV cannot effectively take over the cell's nucleus, thereby preventing infection. Phase I studies of the drug suggest that it is safe. However, the drug is currently being studied in an intravenous (IV) formulation; it is still not clear if an oral version of the drug will be made available.

### Conclusion

While the drug-development crystal ball seems to be filled with hopeful prospects, it is also filled with a great number of uncertainties. Of course, these uncertainties are to be expected; very few of the compounds discussed above have entered large-scale clinical trials. As a result, data regarding efficacy-in both antiretroviral-naïve and experienced patients-are still hard to come by, as is information about the safety and resistance profiles of these drugs.

*Tim Horn is the Executive Editor of **The PRN Notebook**, published by Physicians' Research Network in New York.*

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### Drugs in Development

#### NUCLEOSIDE ANALOGUES

- Iodenosine (F-ddA)
- FTC
- dOTC (BCH-10652)

#### NON-NUCLEOSIDE ANALOGUES

- MKC-442
- S-1153

#### PROTEASE INHIBITORS (PI's) OTHER ANTIVIRALS

- ABT-378
- tipranavir (PNU-140690)
- DMP-450
- BMS-232, 632
- PD-178390
- CI-1012
- Pentafuside (T-20)
- Zintevir

### The HIV Lifecycle

*By David Pieribone*

Understanding how the human immunodeficiency virus (HIV) works inside the human cell gives scientists important clues on how to attack it at its most vulnerable points. Knowing the secrets of how the virus functions and reproduces itself, a process called its lifecycle, can help scientists design new drugs that may both be more effective suppressing HIV and have fewer side effects.

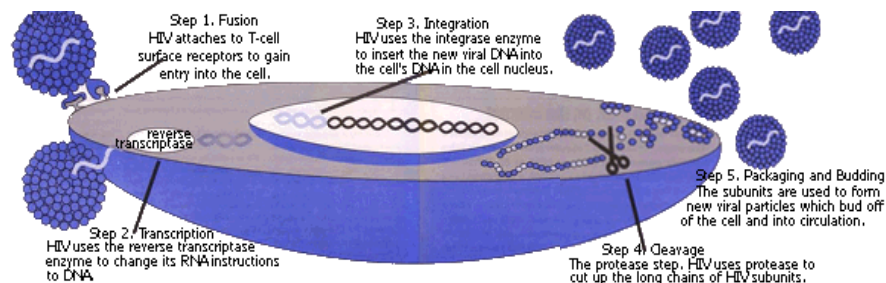
For people living with HIV and AIDS, knowing how HIV works can make it easier to understand how the drugs work in the body and why it so important to take them exactly as they are prescribed.

Viruses cannot reproduce themselves without the aid of a living cell. HIV prefers to infect an immune cell called the T-cell, or more specifically a CD4+ helper cell. T-cells are an important part of the immune system because they help control the body's response to many common but potentially fatal infections. They are like the commanders of the immune system, and without enough of them, the body's immune system will be unable to defend against life-threatening infections. By ways that are not yet understood, HIV's lifecycle directly or indirectly causes a reduction of the number of T-cells in the body, eventually resulting in an increased risk of infections.

After HIV enters the body-through the usual means of unsafe sex, sharing contaminated needles, blood transfusions or from mother to child (vertical infection) - it waits to bump into its favorite host cell-the T-cell. When this happens, HIV will reprogram the host cell to make copies of the virus. HIV has to complete many steps in order for this to happen. At each step of HIV's lifecycle, it is theoretically possible to design a drug that will stop the virus. These steps are outlined in the following section.

## Fusion

Once an HIV particle has come into contact with a T-cell, it must attach itself to the cell so that it may inject its instructions into it. (see figure below, step 1) Only recently have scientists come to better understand this process, known as fusion. On the surface of a T-cell are molecules called receptors that are like communication devices for the cell. Two in particular, CD4 and a chemokine receptor, are used by HIV to attach onto the cell in order to gain access inside the cell. With these two receptors, HIV attaches to the cell and fuses with the cell's membrane, or outer surface. Scientists are developing drugs called fusion inhibitors which block this process by binding to or altering the receptor sites. In addition, scientists have found that people who lack these receptors because of a mutation in their genes, or those who have them blocked by natural chemokines (chemical messengers), may not get infected as readily with HIV or may progress more slowly to AIDS. In addition to fusion inhibitors, scientists are examining vaccines that may help the body block these receptors on its own.



## Transcription

After HIV successfully attaches and fuses with the cell, it is ready to transfer the instructions which will reprogram the cell to reproduce many copies of the virus (step 2). These instructions, known as RNA, are similar to the DNA instructions contained in virtually all cells of the body. But HIV needs to translate these RNA instructions into DNA so that the cell can understand them. To do this, HIV uses an enzyme known as reverse transcriptase. This enzyme takes the single strand of viral RNA and transcribes it into a double strand of DNA which the cell can read. A class of drugs known as reverse transcriptase inhibitors can stop this process.

## Integration

After HIV has successfully translated its instructions from RNA to DNA, it is ready for the next

step in its life cycle-integration. Integration is the process by which HIV inserts its DNA into the cell and "reprograms" the cell with its instructions or blueprints on how to make copies of itself (step 3). In order for these instructions to take effect, they must be added to the DNA of the cell. In each cell there is a structure called the cell nucleus, which is like the command center of the cell. This is where all of the DNA is stored. Normally this cellular DNA tells the cell how to function as a T-cell, but the new viral DNA will reprogram it to make HIV. HIV uses another enzyme called integrase to insert the viral DNA (proviral DNA) into the cell nucleus where it will be used as a blueprint to make new HIV as soon as the cell is activated. Integrase is responsible for moving the viral DNA to the nucleus and inserting it into the cell's existing DNA. Drugs that inhibit integration (integrase inhibitors) are in clinical testing.

### **Cleavage**

Once the cell has the virus' instructions in its nucleus and becomes activated, it is ready to make new HIV particles. The cell's nucleus commands the cell to reproduce HIV, and soon the building blocks for the new HIV viruses are produced in the cell in the form of chains of subunits. The next step in HIV's lifecycle is called cleavage (step 4). HIV uses another enzyme called protease to act like a scissors which cuts up the long chains of subunits so they can come together to form the new virus. The class of drugs called protease inhibitors are able to block the cutting action of the enzyme, thus preventing the reassembly of the new HIV.

### **Packaging**

Once the subunits are cut by the protease enzyme they are ready to be put together to form the new viruses. This stage, known as packaging (step 5), is not fully understood, but there are some steps within this stage that have been identified and may be possible targets for new drugs. In one of these steps, HIV's instructions, the RNA, is wound tightly to fit into its nucleocapsid, similar to the cell's nucleus. This step is the target of a class of drugs known as zinc finger inhibitors. HIV uses a configuration of zinc atoms in the shape of a "finger" to wrap its genetic material (RNA) tightly enough to fit into the capsid to be stored. Researchers have identified a number of possible zinc finger inhibitors that can interfere with this packaging stage.

### **Budding**

As the packaging step is completed, HIV moves to the outer part of the cell to escape. This process is known as budding (step 5). HIV actually uses part of the cell's outer wall, known as the cell membrane, to complete its final structure. Once this process is completed the new HIV particles leave the cell in search of new cells to infect and start the whole process over. Once HIV-infected, the cell can produce thousands of new HIV particles.

During HIV's life cycle, the T-cell, known as the host cell, is altered and perhaps damaged, causing the death of the cell. Scientists are not sure exactly how the cell dies but have postulated a number of scenarios. First, after the cell becomes infected with a virus or other pathogen, internal signals may tell it to commit suicide. This is known as apoptosis or programmed cell death-like a self-destruct program that is used to kill the cell with the hopes of killing the virus too. A second possible mechanism for the death of the cell is that, as thousands of HIV particles bud or escape from the cell, they compromise or damage the cell membrane that protects the cell, and the cell dies. Another possible cause for the cell's death is that other cells of the immune system, known as killer cells, recognize that the cell is infected and inject it with chemicals that destroy it. Whatever the mechanism of the cell's death there is one less T-cell in the body, and with this happening on a monumental scale, T-cells begin to decline. Over time, there are not enough T-cells to defend the body. At this stage, a person is said to have Acquired Immunodeficiency Syndrome, or AIDS, and becomes susceptible to infections that a healthy immune system could deal with. If this process of immune destruction is halted in time, preliminary evidence indicates that a damaged immune system may be able to repair some of the damage over time.

There is much that is not known about the lifecycle of the HIV virus. More research about HIV's lifecycle will enable scientists to coax HIV to give up its secrets of survival in the body, this in turn will allow the development of new drugs and vaccines designed to stop it.

## **Hepatitis C Virus and HIV Co-Infection**

*By Mark S. Sulkowski, MD*

Since its discovery, AIDS has been marked by the development of opportunistic infections, which cause significant illness and death. Recently, advances in prophylactic and antiretroviral therapies have dramatically reduced the incidence of these diseases and their impact on AIDS mortality. However, obscured by the headlines announcing reductions in AIDS deaths, is the increasing importance of chronic hepatitis C virus (HCV) infection among HIV-infected persons.

Due to shared routes of transmission, HCV and HIV co-infection is common, affecting 60-95% of those with blood exposures, such as injection drug users and recipients of transfused blood products. Sexual transmission of HCV is less common, but may be facilitated by concurrent HIV infection. As a result, the HCV disease burden among HIV-infected adults is substantial, particularly in urban settings where injection drug use is common. For example, one-half of all patients followed in Baltimore, Maryland at the Johns Hopkins HIV clinic are infected with HCV.

Similar to HIV, most persons do not experience symptoms during HCV infection, and have a long, period of clinically silent infection. However, natural history studies show that HCV infection can cause progressive hepatic (liver) inflammation and scarring (fibrosis), which may lead to cirrhosis, liver cancer, and liver failure in up to 25% of persons over a period of 20 to 30 years. Among HIV-infected persons, the progression of HCV-related liver disease may be quite rapid (< 10 years), particularly in those with advanced immunodeficiency. Several studies have shown the synergistic effect of HIV infection on the development of HCV-related liver disease and emphasize the emerging risk of death due to liver disease among HIV/HCV co-infected persons. Among HCV-infected hemophiliacs in the United Kingdom, liver-related deaths were almost 20 times higher than the general population among men with only HCV infection, and an astounding 94 times higher among men with both HIV and HCV infection. This and other studies demonstrate the increasing importance of HCV co-infection as deaths from AIDS and other opportunistic diseases decline, and underscore the need to develop effective HCV treatment strategies.

### **Today's Treatment Strategies**

As with HIV, successful treatment strategies will be based on an understanding of the virus itself. Hepatitis C is an RNA virus with a very rapid replication rate; each day about 367 billion hepatitis C virions are produced and survive in the blood about 8 hours before being replaced by new virus. HCV does not have "proof-reading" capabilities and is prone to make frequent errors or mutations during replication, which may lead to rapid resistance to anti-viral drugs. An understanding of such viral dynamics led to the development of successful, multi-drug "cocktails" against HIV, and these same principles will guide the development of new anti-HCV drugs.

Viral mutations or diversity may also explain some of the shortcomings of currently available treatments. Alfa interferon is the only FDA-approved drug with anti-HCV activity. Interferon, administered as a single dose, can result in dramatic decreases in HCV blood levels within 24 hours, and administered over longer periods of time, such as 12 -18 months, can result in the eradication of hepatitis C virus from the blood. However, sustained virologic response, defined as a undetectable plasma hepatitis C viral load six months after the discontinuation of therapy, is achieved in only 20-30% of patients with interferon monotherapy.

Among HIV-infected patients, interferon therapy may be less effective, but few well designed studies of alfa interferon for the treatment of HCV among HIV-infected persons have been performed. The largest published study, conducted by the Hepatitis-HIV Spanish Study Group, reported sustained virologic responses in 20% of HIV-infected patients who took interferon injections three times a week for 12 months. Patients with CD4 cell counts > 500 cells/mm<sup>3</sup> were more likely to respond to treatment. Moreover, for patients who fail to respond virologically, interferon therapy may have beneficial effects on the liver. Most clinical trials have found decreased hepatic inflammation by liver biopsy after interferon therapy, and several studies have shown that interferon therapy can delay progression to liver cancer or failure.

### **New Approaches**

Recently, therapy with the combination of interferon with ribavirin has been shown to improve the rate of sustained virologic response. The combination is marketed in the United States as Rebetron®, and may lead to sustained virologic response in up to 50% of patients. While clearly an advance in the treatment of HCV-infection, this may not represent true "combination" therapy. Ribavirin alone has no anti-HCV effect, and viral inhibition studies show no synergy between interferon and ribavirin. The mechanism of action of ribavirin is not known, but it appears to prevent the recurrence of HCV in the blood when therapy is stopped in patients who initially respond to treatment. No studies have been published on the use of this combination for the treatment of HCV in HIV-infected patients; AmFAR is currently sponsoring a multicenter clinical trial to evaluate its safety and effectiveness in co-infected persons.

In light of the increasing impact and the availability of effective drugs, many co-infected persons should be considered for anti-HCV therapy. However, interferon with or without ribavirin may not be for everyone. Interferon, given by an injection under the skin, may cause low white blood cell and platelet counts, anemia, depression, hair loss, and thyroid dysfunction. Ribavirin, taken orally, may cause a dose-related anemia during the first 4 weeks of treatment, typically a moderate decrease in the concentration of hemoglobin. In addition, ribavirin is a nucleoside analogue, like zidovudine (AZT) and other antiretroviral drugs, and some preliminary studies of ribavirin and zidovudine (AZT) in a test tube have antagonism between these drugs. However, practical implications, if any, of this laboratory finding are not known. Nonetheless, the limited effectiveness and side effect profile of the current treatment options emphasizes the need for new anti-HCV drugs.

Easier to use, slowly released alfa interferons, bound to polyethylene glycol (PEG), have been developed, and can provide continuous exposure to interferon with a once-weekly injection. Studies evaluating the effectiveness of PEG-interferon and ribavirin are underway. However, novel designer drugs that target specific HCV sites essential for viral replication are urgently needed. As with HIV treatment, these drugs will be used in combination with other drugs, including interferon, to prevent the development of HCV resistance. Several potential targets have been identified within the HCV molecular structure. HCV has a protease, which differs significantly from the HIV protease, but is essential for cleaving large proteins into smaller segments during the virus life cycle. HCV also uses a helicase enzyme, which unwinds the double RNA complex as the virus copies itself. The complex, molecular structures of these targets have been determined, and drugs to inhibit these sites are being developed.

A third enzyme that is critical to HCV replication is an RNA-dependent RNA polymerase, representing another potential target for inhibition. HCV protein production is also dependent on a viral region called the internal ribosomal entry site (IRES), which may be blocked by anti-HCV IRES drugs. In addition, novel approaches, such as the development of antisense molecules, which may prevent the production of HCV proteins and degrade HCV RNA, are being pursued. However, despite aggressive research efforts, progress in the development of these new drugs is impeded by the lack of a cell or animal model that would allow rapid screening of candidate drugs. Current expectations are that some of these new drugs may be available over the next 2 to 5 years for the combination therapy of HCV infection.

Thus, while exciting HCV therapies are under development, the impact of HCV-related liver disease among HIV-infected patients is already being felt in HIV clinical practices around the world. Co-infected patients should be evaluated for significant HCV-related liver disease, which may require a liver biopsy to examine the extent of hepatic disease. The decision to pursue hepatitis C treatment with interferon with or without ribavirin should be addressed on an individual patient basis, taking into account HIV and HCV factors as well as the medication side effect profile. Until the promise of new drugs is realized, more co-infected persons must be treated with interferon or interferon/ribavirin to stem the emerging epidemic of hepatitis C-related deaths among HIV-infected persons.

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### **Emerging Therapies for Chronic Hepatitis C Virus Infection and Estimated Date of Availability**

DRUG CLASS	MECHANISM OF ACTION	DATE
Pegylated-interferon + Ribavirin	Interferon chemically bound to polyethyleneglycol (PEG); allows for the slow, continuous release of interferon	1999
Helicase inhibitors	Prevents unwinding of double-stranded viral RNA during HCV replication	2001-2003
Protease inhibitors	Prevents cleavage of large viral protein into smaller segments	2001-2003
RNA-dependent RNA polymerase	Prevents replication or copying of the HCV genome	2001-2003
IRES (internal ribosomal entry site) inhibitors	Prevents the expression of viral proteins	2001-2003
BDNA vaccines	Bind to interferon resistance sites	2008
Antisense nucleotides	Stimulate cytotoxic T-cell activity	2008
Dominant negative mutants	Block viral protein production	2008

### **HIV-Related Cancers in the Age of HAART**

*By Tim Horn*

Over the past ten years, an incredible amount of progress has been made in the management of cancers associated with HIV. Not surprisingly, highly active antiretroviral therapy (HAART) has had the most significant impact, not only in bringing down their rates of occurrence, but also in helping patients recover more fully. Unfortunately, HIV-infected patients are not out of the red just yet. HAART does not appear to have much of an effect on the incidence of non-Hodgkin's lymphoma (NHL), a potentially fatal form of cancer. And, while many patients are seeing improvements in their Kaposi's sarcoma (KS) lesions - along with fewer new lesions - these benefits are by no means universal and are often slow to develop. Needless to say, more effective treatments for both types of cancer are still very much needed.

In recent months, results from several studies looking at the number of new cases of HIV-associated cancers in the age of HAART were unveiled at conferences in the U.S. and elsewhere. For example, Dr. Susan Buchbinder of the San Francisco Department of Health presented data last April from a study suggesting that rates of KS have gone down in the age of HAART while the number of NHL cases have remained the same.

To reach this conclusion, Dr. Buchbinder and her colleagues reviewed the medical records of 6,704 gay or bisexual men (both living and dead) in the San Francisco area. According to Dr. Buchbinder, 3 of every 100 men were diagnosed with KS between the years 1993 and 1995, the years preceding HAART. After HAART was introduced in 1996, the rate of new KS reports fell to zero. In terms of NHL, approximately 2.2 of every 100 men were diagnosed with the cancer from 1993 to 1995. In 1996, the number of new cases only fell slightly, to 1.8 of every 100 men.

According to these data, Dr. Buchbinder concluded that, while the risk of KS has been significantly reduced in recent years, HAART appears to have little impact on the risk of developing NHL.

### **KAPOSI'S SARCOMA**

Concepts of Prevention One of the hottest concepts being talked about with greater frequency these days is the possibility of preventing KS using pharmaceutical compounds. This concept arrived on the heels of a discovery made a few years ago by a team of researchers at Columbia University: that a herpes virus-dubbed HHV-8 (or KSHV) - was thought to play a major role in the development and growth of KS lesions. While the role of HHV-8 is not yet entirely understood, numerous researchers have been relentlessly pursuing the idea that KS may become the PCP of the future: a completely preventable disease.

According to Dr. Steven Miles of UCLA, KS may become preventable if the following three criteria are met as research progresses:

1. That HHV-8, or another microorganism, is identified as the true cause of KS. Now some researchers are not entirely convinced that HHV-8 is the true cause, as it may be a "passenger" virus that plays very little role in the development of KS lesions.
2. The development of a test that can predict if or when disease might occur, such as a blood test that can measure the amount of HHV-8 in the blood.
3. The discovery of drugs that are effective against the microorganism and safe for use in humans. Candidates include lobucavir, adefovir dipivoxil (Preveon®), ganciclovir (Cytovene®), and foscarnet (Foscavir®), all of which have been shown to be active against HHV-8 in test tube studies and relatively safe for human use.

### **Past, Present ...**

Treatment options for KS have expanded over the last few years, such that there are now four FDA-approved drugs for the treatment of KS and several novel compounds in development.

Prior to 1995, the major modalities of treatment for KS included local treatments, such as radiation therapy, vinca alkaloids, and alfa interferon. Also used were standard chemotherapeutic drugs taken orally or intravenously, such as adriamycin, bleomycin and vincristine (ABV), and bleomycin and vincristine (BV). Unfortunately, these therapies were rarely associated with a complete remission of KS lesions and, at least with the latter group, often carried a number of serious side effects.

In 1996, two liposomal chemotherapeutics - liposomal daunorubicin (Daunoxome®) and liposomal doxorubicin (Doxil®) - were approved by the FDA, representing the first two drugs approved specifically for treatment of KS. The theory goes that, because the active compound is encapsulated in microscopic spheres of fat (liposomes), more of the drug would be available to attack the lesions without causing irreparable harm to healthy tissues and organs. In clinical trials and in practice, these drugs proved to be slightly more effective and caused fewer side effects than their chemical ancestors. Also approved over the past year were the drugs paclitaxel (Taxol®), a powerful intravenous chemotherapy, and altretinoin, a topical gel that seems to work best for patients with a small number of lesions.

### **... and Future**

All the above mentioned local and systemic chemotherapies are effective treatments, but none is a cure. Luckily, much has been learned about the pathogenesis of KS and, as a result, a number of new treatment concepts are currently being developed.

In a nutshell, researchers tend to view KS as a disease of immune activation, beginning with HIV-infected lymphocytes and monocytes (two kinds of white blood cells) and their production of hormone-like proteins called cytokines. These cytokines include interleukins 1 and 6 (IL-1; IL-6), tumor necrosis factor (TNF), oncostatin M and gamma interferon. These cytokines have been shown to aid in the proliferation of vascular endothelial cells, a group of cells responsible for the protection and growth of blood vessels (called angiogenesis); it has also been suggested that HHV-8 plays a large role in the activity of these particular cells. To promote angiogenesis, vascular endothelial cells produce two of their own proteins, dubbed basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). For the most part, KS lesions are characterized by overgrowth of blood vessels, which ultimately lead to the appearance of KS lesions.

As confusing as this process sounds, it represents a golden opportunity for researchers attempting to develop better treatments for KS. For example, interferons, particularly alpha interferon, have been shown to inhibit the cytokines responsible for angiogenesis (e.g., basic fibroblast growth factor). In hepatitis studies, interferon has been found to stimulate the production of IL-1. Interferon also inhibits herpesvirus activity, making it a suitable candidate to combat the effects of HHV-8.

Other compounds being developed that appear to inhibit angiogenesis, at least in test tube studies, include IL-2, TNP-470; IM-862, col-3, SU-5416, and thalidomide. Another drug in development is human chorionic gonadotropin (hCG). In the test tube, hCG causes KS cells to die. In humans, when the drug was injected directly into lesions or administered through an IV, KS lesions often shrank or became less noticeable; only the systemic formulation, however, has been shown to delay the development of new lesions.

Also in development for the treatment of KS are some of the drugs listed in the above discussion of prophylaxis. One antiviral in particular, cidofovir, has been shown to inhibit IL-6 production by HHV-8-infected cells and to prevent the development of KS tumors in mice.

### **Non-Hodgkin's Lymphoma (NHL)**

Without a doubt, the most significant change in the treatment landscape for NHL has been the effects of HAART. In the years before HAART, NHL in the setting of HIV was associated with a 4 to 6 month survival rate. Now, when patients are treated with both HAART and chemotherapy, the survival rate often exceeds two years. While this is certainly good news, it is also true that HIV-infected patients do not seem to be any less likely to develop NHL while on HAART; just as many patients are developing this life-threatening form of cancer now as they were in the years before HAART.

Today's NHL patients are often treated with the same chemotherapeutic drugs that have been in use for years. While this may not seem like progress, researchers have learned a great deal in the past few years about how best to use these drugs more effectively and safely. After all, NHL can kill the patients. But so can the chemotherapy. For example, researchers have learned that two standard chemotherapeutic combinations for NHL-CHOP (cyclophosphamide, adriamycin, vincristine (Oncovin®), and prednisone) and mBACOD (methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, and dexamethasone) - can be administered at lower doses to achieve response rates that are similar to those associated with standard doses, often with fewer side effects. Moreover, researchers have learned that by starting G-CSF (Neupogen®) early on in the course of chemo, neutropenia (a decrease in bacteria-fighting white blood cells) can be delayed.

But these successes are clearly not enough. New cases of NHL do not appear to be going away in the era of HAART. Moreover, only 50% of people diagnosed with HIV-related NHL are successfully treated with these two chemotherapeutic combinations. And of those who do experience a complete remission, 50% will see their NHL return. Clearly, new treatments are desperately needed to aggressively fight this horrible HIV-related manifestation.

New chemotherapeutic regimens in development include CDE, a combination of cyclophosphamide, doxorubicin, and etoposide. In clinical trials, complete remission was reported in 6237; of patients who took CDE; a percentage that appears higher than both CHOP and mBACOD. Patients enrolled in the CDE study also seemed to have fewer side effects than those enrolled in similar studies of CHOP and mBACOD. Only head-to-head comparisons will enable us to tell whether or not this combination is superior to today's standard ones.

Like KS research, much has been learned about the pathogenesis of NHL. In turn, a crop of potential compounds has entered the research arena. For starters, there are immunotoxin therapies, including anti-CD22 and anti-CD19 (anti-B4-blocked ricin). Simply put, both compounds are antibodies from mice that attack and kill B-cells. Because the hyperactivity of B cells has been found to play a role in the development of HIV-related NHL, therapies that directly target B-cells without damaging other immune system cells are of particular interest to researchers.

Also in development are compounds known as topoisomerase-1 inhibitors (also known as camptothecins). One compound in particular is topotecan, a drug also being developed for the treatment of HIV-related progressive multifocal leukoencephalopathy (PML). Because topotecan and other camptothecins inhibit DNA function, cancer cells-particularly those involved in NHL-cannot replicate. SmithKline Beecham, who makes topotecan, is currently studying the safety and efficacy of the drug in clinical trials.

## **ACRIA NEWS**

### **Treatment Education Program Expands**

ACRIA's Treatment Education Program was recently awarded two grants to further its mission of reaching underserved communities affected by HIV. The [New York State AIDS Institute](#) and Glaxo Wellcome have given awards that will promote our treatment education efforts focusing on substance users and the homeless. Individuals from these groups have traditionally encountered many obstacles to receiving medical care. With the growing rate of HIV infection in these groups, ACRIA's education program aims at providing the critical information they need to access medical care and understand the complexities of HIV treatments. ACRIA will be working with a number of AIDS service organizations to educate their staff and clients about HIV healthcare advances. Interested organizations that serve substance users, whether active, in recovery or in a

methadone maintenance program, and those who provide services to the homeless are encouraged to contact ACRIA's education department to receive our free services. For more information please call 212-924-3934.

### **ACRIA's New Home**

ACRIA moved to a new home on November 26th, Thanksgiving eve. We have much to be thankful for. For the first time in our agency's history, ACRIA has a clinic which has been designed specifically to promote our clinical research and HIV treatment education mission. This move, which was precipitated by the unexpected loss of our lease at the previous Chelsea location, has given our researchers and educators a unique opportunity to work in an environment that will best contribute to improving HIV healthcare. Our new facility in the Garment District of Manhattan is centrally located between New York City's two largest transportation hubs at 42nd Street/Times Square and 34th Street/Pennsylvania Station, making it easily accessible to the PLWA community throughout the New York Metropolitan region. Most importantly, we have been able to secure a 10 year lease at a rental rate substantially lower than what we were paying at our old site, giving us a greater degree of operating stability over a sustained period than we have had at anytime in our past. Although construction of the new space is not finished, and will likely continue through January, we are proud of the fact that our major relocation has been accomplished without disruption to any ongoing study. We look forward to welcoming the community of PLWAs and our many supporters to a housewarming at the new clinic shortly after construction is completed.

### **Staff Member Receives Mayoral Appointment**

ACRIA is proud to announce that David Pieribone, our Director of Treatment Education, has been appointed as a full member to the HIV Health and Human Services Planning Council of New York by Mayor Giuliani. The council is responsible for determining the priorities and allocations for use of Federal funds received under Title I of the Ryan White CARE Act, and recommends a comprehensive plan for the delivery of HIV-related services.

### **We Need Your Help**

ACRIA's important mission depends on volunteer support. In addition to individuals to help out at our reception desk, we are also looking for new members to join our Community Advisory Board (CAB). This group is composed of people living with HIV/AIDS who provide guidance for our many education initiatives. If you are interested in volunteering at ACRIA, please call 212-924-3934.

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## **ACRIA Trials**

### **Weekly Procrit® for Anemia**

Procrit® is a synthetic form of a natural hormone (erythropoietin) involved in red blood cell production which is approved for treatment of anemia in HIV-infected persons on AZT who have low blood levels of the hormone. This 16-week study will look at whether weekly injections of Procrit® can improve quality of life and effectively treat anemia in HIV-infected persons receiving antiretroviral therapy. To be eligible, you must have a hemoglobin of 11 g/dL or below, a low erythropoietin level, and be on stable antiretroviral therapy for at least 4 weeks. Study visits are weekly and participants will be reimbursed \$15 at the week 2, 4, 8, 12 and 16 visits.

### **Ultrase® for Diarrhea**

ACRIA is participating in a study of Ultrase® (pancreatic enzymes) for diarrhea due to the protease inhibitor nelfinavir (Viracept®). The 12-week study, which is being conducted along with CRI New England and CRI South Florida, is open to HIV-infected persons who have been taking nelfinavir at a dose of 1250 mg twice a day for at least two weeks and who have three or more

stools per day not due to any other cause. Participants will be reimbursed \$20 per 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. ACRIA is participating in a multicenter study 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-positive with unintentional weight loss of 10-20% of their usual body weight. Participants will be reimbursed \$15 per scheduled study visit after enrollment.

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

ACRIA 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 for the final visit.

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

ACRIA 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.

#### **Testosterone and MET-Rx™**

ACRIA 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-positive 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 at 212-543-5762.

#### **SALSA™ Questionnaire for Lipodystrophy**

ACRIA is participating in a multicenter information-gathering study sponsored by Serono Laboratories with the goal of better defining the features of lipodystrophy syndrome. Persons who think they have features of the syndrome, which include thinning of the arms and legs, fat redistribution to the abdomen, and buffalo hump are encouraged to schedule a one-time visit to complete the questionnaire. Eligible participants will be reimbursed \$10 for their time.

*For more information on any of these studies, please call Dr. Avinash Desai or Dr. Douglas Mendez at (212) 924-3934.*

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#### **Generous Contributors**

The following persons, corporations and organizations made major donations between September 16 and December 15, 1998, to support ACRIA's search for effective AIDS treatments:

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