



UPDATE

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AIDS COMMUNITY RESEARCH INITIATIVE OF AMERICA

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Drugs in Development: New Promise

Even with sixteen antiretrovirals approved in the United States for the treatment of HIV, new drugs and combinations are urgently needed. Most current regimens involve difficult dosing schedules, lots of pills, and short- and long-term side effects. Over time, HIV can become resistant to all of the approved drugs, no matter the degree of adherence. People who started treatment years ago, who were infected with drug-resistant virus, or who have had trouble with adherence for whatever reason, are experiencing treatment failure and have few, if any, treatment options left.

This issue of *ACRIA Update* focuses on antiretrovirals that are being developed to deal with some of these problems – new formulations of old

drugs, second generation drugs in existing classes, drugs like entry inhibitors that target HIV at different points in its life cycle, and drugs that are in very early stages of development. We may never hear of some of these drugs again; the promise that some have shown in test tube and animal studies won't achieve similar results in people. Others may be discontinued as pharmaceutical companies merge and corporate priorities change. Knowing about drugs in the pipeline can spur us to take action when development stalls. It's equally important to understand that new drug development is ongoing and that the pipeline is filled with candidates that offer promise.

J Daniel Stricker, Editor in Chief

The HIV Life Cycle

written & illustrated by David Pieribone

Understanding how the human immunodeficiency virus (HIV) works inside the human cell gives scientists important clues about how to attack it at its most vulnerable points. Knowing the secrets of how the virus functions and reproduces itself – a process called its life cycle – can help scientists design new drugs that are more effective at suppressing HIV and have fewer side effects. For people with HIV, knowing how HIV works can make it easier to understand the way the drugs work in the body.

Viruses cannot reproduce without the aid of a living cell. Although HIV can infect a number of cells in the body, the main target is an immune cell called a lymphocyte, more specifically a CD4 helper cell, a type of T-cell. T-cells are an important part of the immune system because they help facilitate the body's response to many common but potentially fatal infections. Without enough T-cells, the body's immune system is unable to defend itself against many infections. By ways that are not yet com-

pletely understood, HIV's life cycle directly or indirectly causes a reduction in the number of T-cells in the body, eventually resulting in an increased risk of infections.

After HIV enters the body – through unsafe sex, contaminated needles, blood transfusions or from mother to child (vertical or perinatal transmission) – it comes in contact with its favorite host cell – the T-cell. When this happens, HIV will hijack the host cell's cellular machinery to reproduce thousands of copies of itself. HIV has to complete many steps in order for this to happen. At each step of HIV's life cycle, it is theoretically possible to design a drug that will stop the virus. Designing drugs to interfere with specific steps in the viral life cycle is called rational drug design.

The following sections outline some of the better understood steps in the viral life cycle, along with the classes of drugs that inhibit these steps. Scientists are just now uncovering the ways

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ACRIA 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. ACRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of *ACRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information, call 212-924-3934 ext. 121.

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Standard of Care Treatment vs. ZEST Once-Daily Regimen

This study will determine whether HIV-positive individuals on an initial HAART regimen with a twice-daily or more frequent dosing schedule can successfully switch to a once-daily regimen.

The drugs being studied are Zerit XR, Epivir and Sustiva (ZEST) once a day. Those qualified will either remain on their current medications, or switch to the once daily regimen ZEST. The study will last approximately 48 weeks, during which time participants will attend nine scheduled visits at ACRIA. All blood tests, study visits, and study medications (Zerit XR, Epivir & Sustiva), as well as medications from the Standard Of Care arm that are manufactured by the sponsor, will be provided at no charge to the participants. Prescriptions will be written for any other anti-HIV drug.

You are eligible if you are HIV-positive, age 18 or over, and on an initial HAART regimen (one or more NRTIs, at least one agent must have a twice-daily dosing schedule, and no NNRTI in the past or in current regimen) and have two consecutive viral loads of less than 50 copies/mL. The first viral load result must be at least 90 days before the screening visit.

Study participants will be reimbursed \$25 for each of nine visits to ACRIA.

For more information, contact Dr. Douglas Mendez at 212-924-3934 ext. 126 or Dr. Yuriy Akulov at 212-924-3934 ext. 124

RESIST 1: Randomized Evaluation of Strategic Intervention in Multi-Drug Resistant Patients with Tipranavir

This study will determine the safety and efficacy of tipranavir (a protease inhibitor) boosted with low-dose ritonavir in multiple antiretroviral drug-experienced patients.

This study can last approximately 48 weeks, with 10-12 visits to ACRIA. All blood tests, study visits, and study medications will be provided by the sponsor. All patients must have previously received treatment from each of the three antiretroviral classes, have received at least two protease inhibitor-based regimens, have a viral load great than 1000 copies/mL, and be on a protease inhibitor regimen at the time of study entry. To enter the study, patients must have at least one primary protease inhibitor mutation, but no more than two mutations on specific condons.

Study participants will be reimbursed \$25 for each visit.

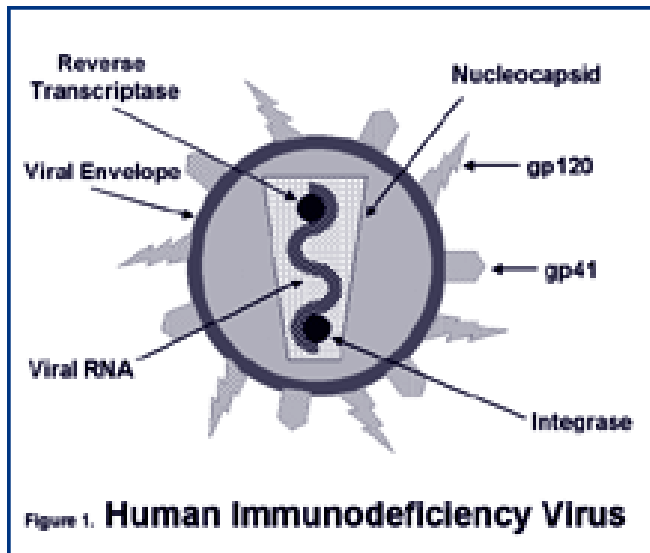
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Editor's Notes

- All material in *ACRIA Update* is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one's personal treatment and therapy choices should be made in consultation with a physician.
- *ACRIA Update* refers to all drugs by both their commercial and scientific names upon their first reference in an article. Thereafter in the article, they will be identified with the name by which we feel they are most commonly known, either commercial or scientific.

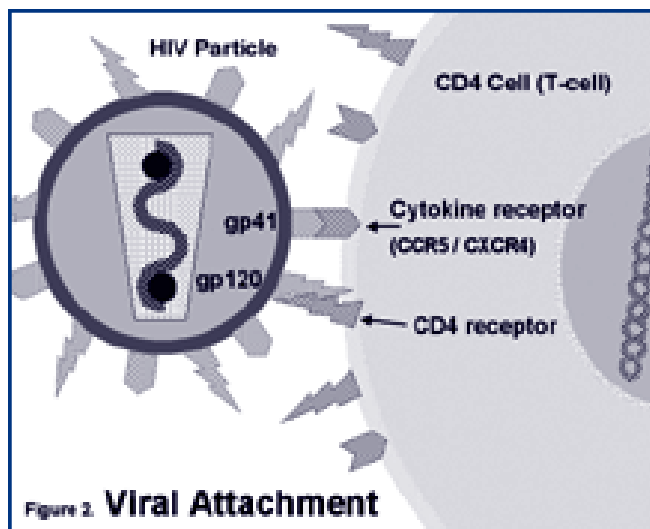
The HIV Life Cycle *(continued from first page)*

HIV manipulates the immune system to spread its infection throughout the body. This review will focus on events that take place when virus and cell are in close proximity. [Figure 1]



Viral Attachment

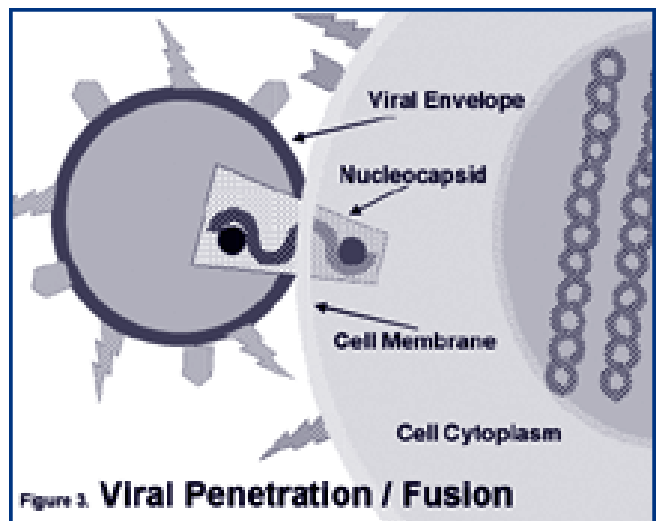
Once HIV comes into contact with a T-cell, it must attach itself to the cell so that it can fuse with the cell and inject its genetic material (a blueprint for making more HIV) into it. Attachment is a specific binding between proteins on the surface of the virus and proteins that serve as receptors on the surface of the T-cell. Normally, these receptors help the cell communicate with other cells. Two receptors in particular, CD4 and a beta-chemokine receptor (either CCR5 or CXCR4), are used by HIV to latch onto the cell. On the surface of the viral envelope, two sets of proteins (also known as antireceptors) called gp120 and gp41 attach to CD4 and CCR5/CXCR4. [Figure 2]



Drugs called attachment or entry inhibitors are currently being studied in clinical trials. These drugs block the interaction between the cellular receptors and the antireceptor on the virus by binding to or altering the receptor sites. Scientists have found that people who naturally lack these cellular receptors because of a genetic mutation, 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. Scientists are also examining vaccines that may help the body block these receptors.

Viral Penetration/Fusion

After attachment is completed, viral penetration occurs. Penetration allows the nucleocapsid – the genetic core – of the virus to be injected directly into the cell's cytoplasm. gp120 actually contains three sugar-coated proteins (glycoproteins) and, once gp120 attaches itself to CD4, these three proteins spread apart. This allows the gp41 protein, which is normally hidden by the gp120 proteins, to become exposed and bind to the chemokine receptor. Once this has occurred, the viral envelope and the cell membrane are brought into direct contact and essentially melt into each other. [Figure 3]



Drugs called fusion inhibitors prevent the binding of gp41 and the chemokine receptor. T-20 (enfuvirtide, Fuzeon), an experimental fusion inhibitor that is nearing FDA approval, binds to a portion of gp41, preventing it from binding to the chemokine receptor.

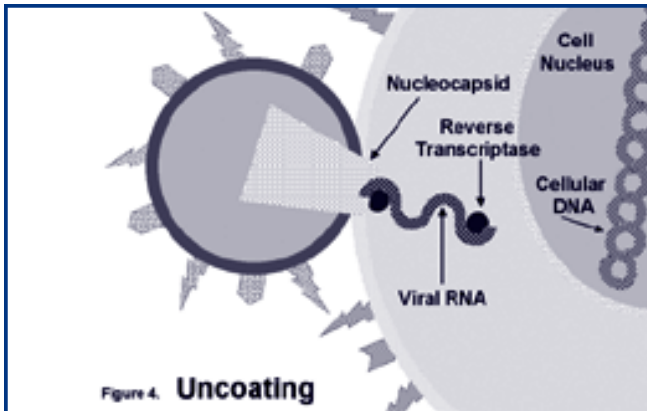
Uncoating

Once HIV has penetrated the cell membrane, it is ready to release its genetic information (RNA) into the cell. The viral RNA is protected in the nucleocapsid. The nucleocapsid needs to be partially dissolved so that the virus's RNA can be converted into DNA, a necessary step if

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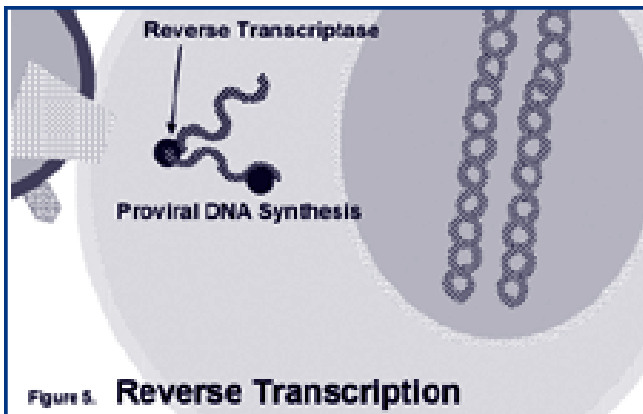
The HIV Life Cycle *(continued from page 3)*

HIV's genetic material is to be incorporated into the T-cell's genetic core. [Figure 4]



Reverse Transcription

The process by which HIV's RNA is converted to DNA is called reverse transcription. This transcription process happens in almost every human cell, but in the opposite direction – from DNA to RNA. DNA from the cell nucleus is transcribed into messenger RNA, which then directs the cell's various metabolic functions needed to do its job in the body. HIV uses an enzyme called *reverse transcriptase* to accomplish this transcription. The single-stranded viral RNA is transcribed into a double strand of DNA, which contains the instructions HIV needs to hijack a T-cell's genetic machinery in order to reproduce itself. Reverse transcriptase uses nucleotides – building blocks of DNA – from the cell cytoplasm to make this process possible. [Figure 5]

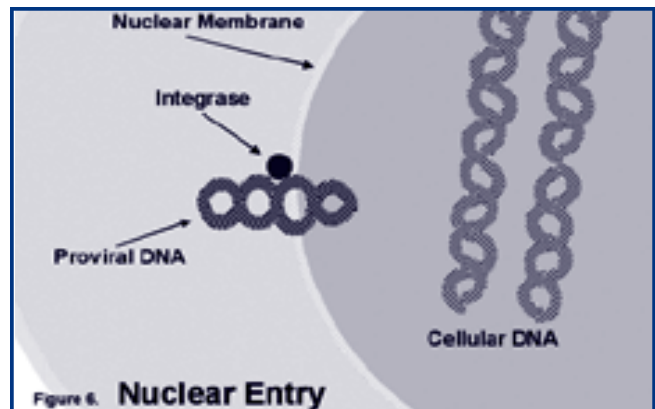


Drugs called reverse transcriptase inhibitors block HIV's reverse transcriptase from using these nucleotides. Nucleoside and nucleotide analog reverse transcriptase inhibitors (NRTIs) – such as Zerit, Epivir, and Viread – contain faulty imitations of the nucleotides found in a T-cell's cytoplasm. Instead of incorporating a nucleotide into the growing chain of DNA, the imitation building blocks in NRTIs are inserted, which prevents the double strand of DNA from becoming fully formed. Non-nucleoside

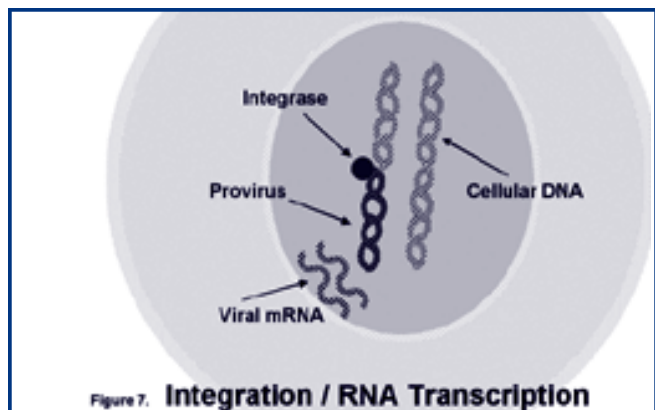
reverse transcriptase inhibitors (NNRTIs) – such as Viramune and Sustiva – block reverse transcription by attaching to the enzyme in a way that prevents it from functioning.

Integration

If HIV succeeds in translating its instructions from RNA to DNA, HIV must then insert its DNA (also called the preintegration complex) into the cell's DNA. This process is called integration. In most human cells, there is a structure called the cell nucleus, where the cell's DNA is stored. In order for integration to occur, the newly translated DNA must be transported across the nuclear membrane into the nucleus. [Figure 6]



Although the exact mechanism that HIV uses to transport its genetic cargo into the cell nucleus is still unclear, viral protein R (VPR), which is carried by HIV, may facilitate the movement of the preintegration complex to the nucleus. Once the viral RNA has successfully bridged the nuclear membrane and been escorted to the nucleus, HIV uses an enzyme called *integrase* to insert HIV's double-stranded DNA into the cell's existing DNA. [Figure 7]



Drugs that inhibit the HIV preintegration complex from traveling to the nucleus – integrase inhibitors – are currently in early clinical trials.

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Anti-HIV Candidates in the Pipeline

by Liz Highleyman

In the past year or so, the HIV drug pipeline seemed to slow to a trickle, with only one new approval, tenofovir (Viread). But the future is beginning to look brighter. Several agents that entered the pipeline years ago will soon emerge, including T-20 (Fuzeon) – the first in an entirely new class of fusion inhibitor drugs (see page 14). Further back in the development process are a slew of candidates in existing drug classes, along with many more that attack HIV by completely new mechanisms.

The drug development process is long and complex. Keeping track of agents as they make their way through the pipeline can be a challenge as drug names change, pharmaceutical companies merge, and studies are suspended and restarted. Candidates are frequently withdrawn due to toxicity or lack of effectiveness in early trials, and all too often, once-promising agents seem to stall in the pipeline or disappear with little or no explanation.

Existing Drug Classes

Despite growing concerns about resistance and side effects, research into the existing drug classes is far from dead.

Among the new protease inhibitors (PIs) in development is **TMC-114** from Tibotec-Virco that was designed to be active against HIV that is resistant to older PIs. This agent has shown good *in vitro* (test tube) activity against both wild-type and resistant HIV. Phase I/II studies are underway.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are well represented in the current crop of candidates, including **Capravirine** (formerly known as AG-1549 and S-1153, now owned by Pfizer), discussed on page 10. **Calanolide A**, produced by Sarawak MediChem, is derived from a rainforest plant. It is active against HIV in the laboratory and produced viral load reductions in early human trials. **Calanolide B** is in preclinical testing in conjunction with the National Cancer Institute. **MIV-150**, under joint development by Chiron and Sweden's Medivir, is

in Phase I studies. Roche and Medivir expect to begin Phase I trials of **MV026048** this year.

On the nucleoside analog (NRTI) front, **alovudine** (MIV-310 or FLT, being developed by Medivir) is actually an old drug making a comeback. Like AZT (which it resembles structurally), alovudine can cause low blood cell counts, but appears tolerable at low doses. Early Phase II trial results indicate that it's active against multidrug-resistant HIV. **Stampidine**, being developed by the Parker Hughes Institute, is a new and improved Zerit (d4T) derivative that looks stronger in laboratory studies. Toxicity was rare in rodent studies, but given the many side effects of Zerit, its sister bears close monitoring. Other NRTIs in the pipeline include **SPD-754** (a chemical cousin of the abandoned dOTC) and the new puridine analog **SPD-761 TP**, both under development by Shire Pharmaceuticals, as well as **GS-7340**, a prodrug of tenofovir being developed by Gilead. (A prodrug is a compound related to a drug that requires additional processing in the body before it becomes active.)

New Classes, New Mechanisms

While additional drugs in old classes continue to be developed, promise also lies with drugs that work in completely different ways. Each basic science discovery about how HIV infects cells and replicates opens doors for possible new treatments.

Entry Inhibitors

HIV entry inhibitors are receiving the most hype. The process of HIV entry into cells requires three steps – attachment, co-receptor binding, and fusion – and there are drug candidates that act at each step. Bristol-Myers Squibb's **BMS-806** inhibits the attachment step by binding to HIV's gp120 protein and preventing it from grabbing on to CD4 cells. Study results presented at recent conferences indicate that the drug has strong activity against HIV, including virus that is resistant to other classes of antiretrovirals. Animal studies to date have not aroused

safety concerns, and human studies are set to begin soon. Since BMS-806 is a small molecule, it probably can be taken orally rather than injected. **TNX-355**, produced by Tanox, is a monoclonal antibody (a genetically engineered antibody that recognizes a single protein) that inhibits HIV attachment by binding to host cell CD4 receptors; Phase I clinical trials are newly underway.

Chemokine antagonists inhibit the middle step by preventing HIV from binding with one of two co-receptors – CCR5 or CXCR4 – which allow the virus to enter host cells. Several CCR5 antagonists are in the pipeline. **PRO-140**, under development by Progenics, is a monoclonal antibody that has been shown to block HIV infection of cells in the laboratory and to lower viral load in animal studies. Other CCR5 blocker candidates include Pfizer's **UK-427-857** and Schering-Plough's **SCH-D**, a reportedly more potent successor to SCH-

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Drug Name Confusion

Experimental drug candidates are usually designated by a combination of letters and numbers. The letters typically stand for the drug company that discovered or first began developing the agent; for instance, T-1249 is being developed by Trimeris. Mergers and sales make matters more confusing. For example, "DPC" agents are owned by Bristol-Myers Squibb, which acquired DuPont, and "AG" candidates were first developed by Agouron, which is now part of Pfizer. As a drug nears the end of the development pipeline, it is given a generic name and later a brand name for marketing. To confuse things further, some drugs – especially nucleoside analogs – also have chemical names such as FTC or FddA.

Anti-HIV Candidates in the Pipeline *(continued from previous page)*

C (see page 15). Development of the first CXCR4 inhibitor to gain widespread attention, AnorMED's **AMD-3100**, was halted in 2001 due to poor effectiveness and possible heart toxicity.

HIV that uses CXCR4 co-receptors was once widely thought to cause more rapid disease progression than virus that uses CCR5. Although this theory has recently been reevaluated, some researchers remain concerned that agents that block CCR5 might encourage more aggressive HIV that can still use CXCR4. On the other hand, CXCR4 antagonists may cause a shift toward the less aggressive strains that use CCR5. Combining CCR5 and CXCR4 blockers could prevent HIV from switching back and forth between targets. GlaxoSmithKline is even looking at an agent called **vMIP-II** that appears to block multiple co-receptors. Unfortunately, because chemokines have other functions in the body, agents that block their activity could potentially lead to serious side effects.

Finally, Lexigen's fusion inhibitor **FP-21399** appears to be well tolerated in Phase I studies, although many people developed a bluish skin and urine color. **SJ-3366**, being developed by South Korea's Samjin, inhibits entry after HIV attaches to CD4 cells, but its exact mechanism is unknown; this agent also acts as an NNRTI once HIV is inside a cell.

Integrase Inhibitors

After HIV enters a host cell, it must splice its genetic material into the human DNA in the cell nucleus in order to replicate. The HIV enzyme called integrase is required for this process. Several experimental integrase inhibitors are under study, but development of this class has been slow. Integrase is the last of HIV's three enzymes – after reverse transcriptase and protease – to be successfully targeted by a drug.

Diketobutanoic (diketo) acids interfere with the final step in the process of assembling and transferring HIV DNA

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The Drug Development Process

It usually takes ten or more years for a promising candidate to wind its way through the drug development process (although activists have succeeded in speeding up development of medications for HIV and other life-threatening diseases). According to the Food and Drug Administration (FDA), only one in 1,000 compounds makes it from the laboratory to clinical trials in humans, and only one in five that enters human trials is ever approved.

The earliest stage of drug development takes place in the laboratory. Traditionally, large numbers of candidate agents are screened by combining them with disease-causing organisms and cell cultures in a test tube or Petri dish to see how they interact. Such preclinical work is known as *in vitro* research (Latin for "in glass"). Today, drug companies increasingly use a process called rational drug design in which computers guide the construction of custom-made compounds that have a desired action.

If a candidate shows good activity in the lab, preclinical testing continues with animal studies (*in vivo* research, Latin for "in a living organism"). Different tests are done to see what side effects an agent causes and what doses are safe. It is not unusual to see specific toxicities in animals but not in humans, and vice versa.

If all goes well, the candidate then enters human clinical trials. Before a drug is approved for marketing, it is called an investigational new drug (IND).

Phase I trials are usually conducted in a small number of healthy HIV-negative volunteers (typically 10-100); sometimes testing in people with HIV may begin in Phase I. These early trials establish the pharmacokinetics of a drug (how it is absorbed, processed, and excreted by the body), its safety and tolerability, and the best doses.

Phase II trials involve a larger number of participants with the disease under study (typically 50-500). While researchers continue to look for toxicities, they also seek preliminary indications of effectiveness, or efficacy. Sometimes Phase I and II or Phase II and III trials are combined to speed the development process.

Phase III trials include the largest number of participants (typically hundreds or thousands). These trials are designed to determine whether a drug is effective. They also continue to monitor toxicity, especially longer-term side effects. Once Phase III trials are complete, a company may submit a New Drug Application (NDA) to the FDA. The agency uses results from these studies to determine whether a drug should be approved for marketing.

Phase IV trials are post-marketing studies conducted after an agent has been approved. They are intended to further confirm efficacy and safety under "real world" conditions, and are especially valuable for detecting long-term and uncommon side effects that do not show up in Phase III trials. Since many HIV drugs have been given accelerated approval, activists have complained that companies often neglect to do these follow-up studies.

Traditionally, drugs are tested against a placebo (an inactive substance such as a sugar pill), but this is now less common in HIV trials. However, randomized, double-blind trials – in which participants are assigned by chance to receive different treatments and neither the researchers nor the participants know who is getting what – remain the "gold standard." New agents are often compared to an existing standard of care, such as the best currently available drugs.

Once-A-Day Dosing: Balancing Convenience and Effectiveness

by Theo Smart

The era of once-a-day anti-HIV therapy is upon us with five antiretrovirals approved for once-a-day use and more on the way. It is now possible to construct a first- and even second-line once-a-day anti-HIV regimen. A number of surveys have reported that people with HIV want once-a-day therapy. Adherence would probably be better – clinical data from a number of different diseases suggest that adherence is better on once-a-day compared to twice-a-day medications, although not dramatically so. But are once-a-day regimens the best therapeutic option? We need to be certain that convenience does not come at the cost of effectiveness.

Study results support using some antiretrovirals as once-a-day drugs. Even so, there are reasons to carefully scrutinize the data:

- Most of the studies were conducted over only 48 weeks, although some have gone on longer.
- Most were in patients who had never taken any antiretrovirals before and tend to have wild-type virus, which has no mutations and is, therefore, most responsive to the drugs.
- Some of the studies were “switch” studies – in which people whose viral loads were suppressed by the drug when used twice a day, continued to respond when they switched to taking the drug once a day. This is not the same as demonstrating that taking the drug once a day to start with would have suppressed HIV as well.
- In the clinical trials designed to win once-a-day approval, the study drug is generally administered with other antivirals that are given twice daily. The effect of twice-daily drugs could mask slight weaknesses of the once-a-day drug. This is particularly worrisome if people want to try to take all their antiretrovirals once a day, because there is very little data to show that using all the drugs together once a day works. In fact, it will be years before there are results from large trials comparing each of these once-a-day regimens to today’s standard twice-a-day therapy.

It helps to understand the strengths and weaknesses of each individual drug’s pharmacokinetic (PK) profile – what happens to the drug in the body after it’s been absorbed. However, what is true about a drug in the bloodstream may not explain what’s happening inside an infected cell, and drug concentrations can differ from one cell type to another. For example, less frequent dosing could mean insufficient concentrations of drug in harder to reach “sanctuary” sites such as the brain and

“...The best solution is to tailor the combination, whether once or twice daily, to the individual.”

testes. Cells such as HIV-infected macrophages require more drug than CD4 cells to keep the virus in check. HIV in sanctuary sites and macrophages may develop resistance sooner on once-a-day than on twice-a-day therapy. Once-a-day dosing may look fine the first year or two on therapy, but not necessarily with longer follow-up.

Finally, what’s true for the majority may not be true for the individual. Even if trials demonstrate that most people can use these drugs successfully once a day, a sizable minority may not be able to. Pharmacokinetics may vary from person to person, and people with different genetic backgrounds, diets, co-infections, or more or less sensitive virus may respond very differently. Of course this is all true for twice-daily dosing, too, but these theoretical concerns deserve consideration and continued research.

Nucleoside/tide Analogs

The pharmacokinetics of nucleoside and nucleotide analogs differ from most other drugs. Cellular enzymes must change these drugs into their active form *inside* the cell. With the exception of Viread (tenofovir), they have very short half-lives in the bloodstream. The half-life is the amount of time that it takes the body to eliminate half of the absorbed drug. The nucleoside analogs’ half-life in the bloodstream is generally less than an hour – but their active forms have much longer half-lives within the cell (intracellularly). In some cases, the intracellular half-life appears to be long enough for once-a-day dosing.

Videx (ddI): Videx EC (enteric-coated) has an intracellular half-life ranging between 25-40 hours. Clinical trial data have demonstrated equivalence of once and twice-a-day dosing when given with other drugs taken twice a day. Videx is only absorbed in an empty stomach, which poses a problem for use in once-a-day combinations with drugs that have to be taken with food. When taken with Viread (even with a light meal), blood levels of Videx may be dangerously high in some patients – a case of pancreatitis and several cases of lactic acidemia have been reported. If the two drugs are used together, Bristol Myers-Squibb recommends that the Videx dose be reduced and patients be monitored closely.

Epivir (3TC): Epivir has an intracellular half-life of 16-19 hours. It has been approved for once-a-day use on the basis of clinical trials that demonstrated the equivalence of 300 mg once daily to 150 mg twice daily when used with other drugs taken twice-a-day. 300 mg tablets are now available.

Sustained release Zerit (d4T): A new once-a-day formulation of Zerit has been approved in the U.S. and is expected to be on the market early this year. Zerit’s intracellular half-life is only seven hours, so the pills had to be improved to make this drug once-a-day. The extended release

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Once-A-Day Dosing *(continued from previous page)*

formulation is absorbed as the pill passes through the colon. It continues to deliver drug to the bloodstream over the course of several hours. Clinical data to support use of this once-a-day formulation include a large study in 783 patients comparing the new formulation to the old twice-daily formulation. There were no statistically significant differences in activity or toxicity up to week 48. The once-a-day dose is 100 mg or 75 mg depending on body weight.

Viread (tenofovir): Viread is distinguished by having a long half-life in the bloodstream (about 17 hours). Its intracellular half-life is between 10-50 hours. Every study of Viread has used it as a once-a-day drug. However, it needs to be taken *with* food.

Ziagen (abacavir): Early data suggested that the intracellular half-life of Ziagen was only 3.3 hours. Recently, however, more advanced lab techniques suggest that the half-life is much longer, perhaps long enough for once-a-day dosing. There is little clinical data as of yet, but studies are underway.

Nucleoside analogs in development with once-a-day potential include Coviracil (FTC, emtricitabine) and amdoxovir (DADP). A combined once-a-day formulation of Viread and Coviracil is also planned.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The case seems strong for using Sustiva (efavirenz) and Viramune (nevirapine) as once-daily drugs. Though only Sustiva is approved as a once-a-day drug, both of these NNRTIs have such long half-lives (over 24 hours) and consistently high blood concentrations that they can be given once a day, just by taking the pills all at once. These drugs offer more “forgiveness” than other antivirals – if you’re late taking your next dose, blood concentrations should remain above the levels needed to suppress viral replication.

Sustiva: Now available in a single 600 mg tablet, Sustiva’s half-life is 40-55 hours.

Food slightly increases absorption and thus possibly toxicity as well, so the label recommends taking the drug on an empty stomach. Also, higher than normal blood levels of Sustiva have been associated with more central nervous system toxicity – although it is not clear whether higher peak concentration of drug in the bloodstream after once-daily dosing increases the incidence of side effects.

Viramune: Although not yet approved for once-daily dosing, Viramune’s long half-life (30-40 hours) should allow for it. Several studies have used Viramune once a day – the first one that should be large enough to win approval from the Food and Drug Administration (FDA) is ongoing.

Protease Inhibitors (PIs)

Protease inhibitors have borderline pharmacokinetics. Even after swallowing many large pills, only a small amount of drug is absorbed into the bloodstream and this is usually rapidly broken down by the body. Although PIs are potent, there is a wealth of data demonstrating that they stop working when blood concentrations fall too low.

Norvir (ritonavir), however, was discovered to improve the pharmacokinetics of other PIs by slowing down their metabolism and, in some cases, improving their absorption. With the addition of low-doses of ritonavir – called ritonavir-boosting – Crixivan (indinavir) and Fortovase (saquinavir) can be comfortably taken twice a day. The pill count is lower, and there are no dietary restrictions. Total exposure to drug is higher, sometimes high enough to treat resistant HIV or virus in sanctuary sites in the body, with improved concentrations of drug persisting at the next dosing.

But can ritonavir-boosting make PIs once-a-day drugs? The data are mixed. Ritonavir-boosting of some PIs achieves adequate drug concentrations *for most people*. For others, drug levels in the blood fall below those necessary to suppress the virus. So it’s worth questioning whether this is the best way to take PIs.

Agenerase (amprenavir)/ritonavir:

Agenerase has the longest half-life of the approved PIs (around 7.1-9.5 hours) and is a twice-a-day drug without ritonavir. With Agenerase/ritonavir (1200 mg/200 mg) once daily, blood levels of Agenerase are six times higher 24 hours after dosing than seen with standard dosing after twelve hours. But there is at least one problem – ten pills. A high pill count can lead to adherence problems, especially when coupled with Agenerase-related nausea.

In one study, patients with undetectable viral loads on Agenerase were switched to Agenerase plus ritonavir taken either once or twice daily. Thirty-two weeks after the switch, three-quarters of the participants still had viral loads below 50 copies/mL; however, the CD4 cell rise was much higher in the *twice-a-day* arm – 314 vs. 100 cells.

The FDA has amended Agenerase’s package insert to include data on once-a-day usage. Once-a-day use is now an approved *option*, although not necessarily the best way to take the drug.

Kaletra (lopinavir/ritonavir): In initial once-a-day studies with Kaletra, Abbott found that long before a day had passed, the remaining levels of lopinavir were inadequate. However, another study has reported more promising results comparing twice-daily to once-daily (double-dosed) Kaletra in combination with Zerit and Epivir taken twice a day. Although blood concentrations of lopinavir just before the next dose were found to be 56% lower as well as more variable from patient to patient in the once-a-day arm, the antiviral effect in both arms was similar. This was a small study, however – only 17 patients took once-daily Kaletra. Abbott is conducting a larger follow-up study.

Saquinavir (Fortovase or Invirase)/ritonavir: On its own, saquinavir’s half-life is one to two hours. However, ritonavir dramatically improves the elimination (and

(continued on page 13)

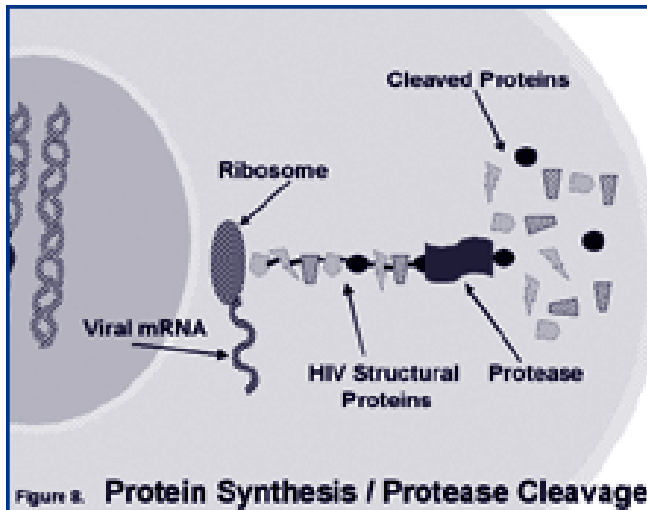
The HIV Life Cycle *(continued from page 4)*

Viral Latency and Protein Synthesis

After successful integration of the viral DNA, the host cell is now latently infected with HIV. This viral DNA is referred to as provirus. The HIV provirus now awaits activation. When the immune cell becomes activated, this latent provirus awakens and instructs the cellular machinery to produce the necessary components of HIV, like plastic pieces of a model airplane. From the viral DNA, two strands of RNA are constructed and transported out of the nucleus. One strand is translated into subunits of HIV such as protease, reverse transcriptase, integrase, and structural proteins. The other strand becomes the genetic material for the new viruses. Compounds that inhibit or alter viral RNA have been identified as potential antiviral agents.

Cleavage and Viral Assembly

Once the various viral subunits have been produced and processed, they must be separated for the final assembly into new virus. This separation, or cleavage, is accomplished by the viral *protease* enzyme. [Figure 8]



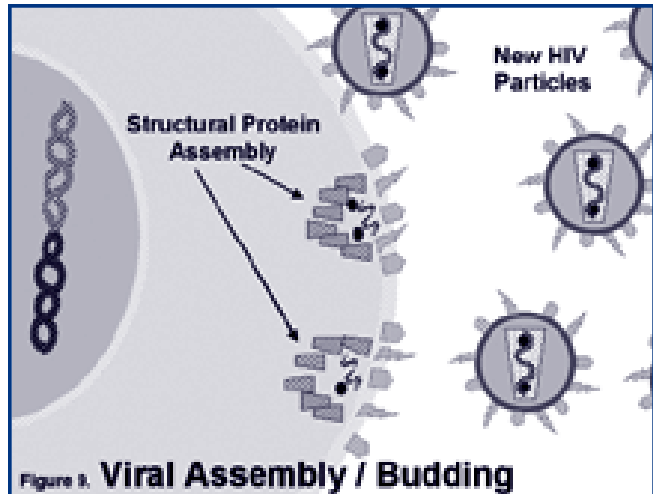
Drugs called protease inhibitors – such as Kaletra, Crixivan, and Viracept – bind to the protease enzyme and prevent it from separating, or cleaving, the subunits.

If cleavage is successfully completed, the HIV subunits combine to make up the content of the new virions. In the next step of the viral life cycle, the structural subunits of HIV mesh with the cell's membrane and begin to deform a section of the membrane. This allows the nucleocapsid to take shape and viral RNA is wound tightly to fit inside the nucleocapsid. Researchers are looking at drugs called zinc finger inhibitors, which interfere with the packaging of the viral RNA into the nucleocapsid.

Budding

The final step of the viral life cycle is called budding. In this process, the genetic material enclosed in the nucleocapsid merges with the deformed cell membrane to form the new viral envelope. With its

genetic material tucked away in its nucleocapsid and a new outer coat made from the host cell's membrane, the newly formed HIV pinches off and enters into circulation, ready to start the whole process again. [Figure 9]



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 come up with 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 – a self-destruct program intended to kill the cell with the hopes of killing the virus as well. A second possible mechanism for the death of the cell is that, as thousands of HIV particles bud or escape from the cell, they severely damage the cell's membrane, resulting in the loss of the cell. 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, a weakened immune system may be able to repair some of the damage over time.

There is still much that is not known about HIV's life cycle. More research will enable scientists to coax HIV into giving up more secrets of how it survives and spreads in the body. In turn, this will allow for the development of new drugs and vaccines designed to stop it.

David Pieribone is Associate Director of Education at AIDS Project Los Angeles.

New and Improved? Next Generation Drugs in Existing Classes

by Mark Milano

There's lots of talk these days about new targets for antiretrovirals – fusion, integrase, zinc fingers, and other approaches. Drugs using current targets (the reverse transcriptase and protease enzymes) have plenty of problems, including difficult dosing, short- and long-term side effects, resistance – the list goes on. The following are brief descriptions of some of the new drugs in development from currently approved classes.

As with all drugs in development, take everything you read here with a grain of salt. Today's "promising new treatment" is often tomorrow's forgotten footnote.

Nucleoside Analogs

Nucleoside analogs were the first type of drug approved to fight HIV. While there are already six approved nucleosides (and one nucleotide), many people have become resistant to some or all of them or can't take them due to side effects. So new drugs in this class that work against resistant virus with fewer side effects and easier dosing are being studied.

Coviracil (emtricitabine, FTC) is a nucleoside analog that is chemically similar to Efavirenz (EFV). Both drugs stop working if HIV develops only one mutation (called M184V), so Coviracil won't work for people who are resistant to Efavirenz. And both drugs have a low incidence of side effects. So why develop this drug? Well, it's taken once a day, which we like, but Efavirenz was also approved for once-daily dosing back in June. Triangle Pharmaceuticals, the company behind Coviracil, was recently purchased by Gilead Sciences, so a pill combining Gilead's Viread (tenofovir) with Coviracil is a real possibility. That would be one pill, once a day – cool.

Trials have shown that people taking Efavirenz can successfully switch to Coviracil, and that Coviracil is superior to Zidovudine (ZDV) when used in combination with Didanosine (ddI) and Sustiva (efavirenz). The latter study was actually closed early due to the superiority of Coviracil (81% had viral loads below 50 after six months, compared to 70% of those on Zidovudine). But two things might have helped Coviracil in this situation. First, it was taken as part of a once-daily regimen, while Zidovudine was taken twice daily, so adherence might have been an issue. Second, people in the Zidovudine arm had a higher dropout rate due to side effects (possibly because they were taking it with Didanosine).

Coviracil is also being tested for hepatitis B, and initial trials have shown that it is quite effective. Triangle submitted their NDA (new drug application) to the Food and Drug Administration (FDA) in November. Since the FDA didn't see

an urgent clinical need for Coviracil, the company was granted only a standard, rather than an accelerated, approval, so the drug probably won't be on the market until the fall of this year.

Amdoxovir (DAPD) is a twice-daily nucleoside analog that has shown activity in the test tube against virus that is resistant to certain nucleosides *and* non-nucleosides. And some mutations actually make HIV more sensitive to amdoxovir (again in the test tube). Taken by itself for two weeks, it lowered viral load by 1.7 logs (a decrease of 98%) – a substantial antiviral effect. Triangle was ready to start a trial of this drug in combination with T-20 (Fuzeon), but it has been delayed while further safety tests are added in. Those kinds of trials – drug companies working together to offer people two new drugs instead of just one – are what people with HIV have been demanding for years. Let's hope it gets off the ground soon. Amdoxovir is also being studied in combination with CellCept, a drug used for organ transplant patients that may boost amdoxovir's effectiveness. Don't expect approval until 2004 at the earliest though.

ACH-126,443 is another once-daily nucleoside that should work against both HIV and hepatitis, and, in the test tube, is active against virus that is resistant to Efavirenz (3TC). Achillion Pharmaceuticals just started a Phase II trial to find out if this is also true in people, but the trial design may make it tough to enroll: you must be resistant to Efavirenz and have been taking it for the last four months, have a viral load within a very narrow range (1,000 to 30,000), and be willing to possibly be randomized to Efavirenz for another month, after which time you can get ACH-126. In the test tube, ACH-126 does not damage mitochondria like other nucleoside analogs can. If this is true in people – and that's a big "if" right now – it could mean that ACH-126 would be less likely to cause lipodystrophy than certain other nucleosides. Approval is a few years away at best.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

This class of drugs surprised everyone by being as effective as protease inhibitors when used as part of a three-drug combination. But a single mutation (K103N) can make the entire class useless. New drugs for people who are resistant to approved NNRTIs are badly needed.

Capravirine is a twice-daily NNRTI that is active in the test tube against HIV with the dreaded K103N mutation. Other mutations can make capravirine useless, however, such as Y181C, which also creates resistance to Virmune

(nevirapine). One Phase II study of capravirine taken with Viracept (nelfinavir) in people resistant to the NNRTIs found that half of them reached viral loads below 400, but was it the capravirine or Viracept that was responsible? And capravirine was no better than placebo in preventing viral load rebounds in this trial.

Research was moving along until the FDA put all capravirine trials on hold in January of 2001 due to reports of vasculitis (inflammation of blood vessels) in dogs. But Pfizer reported at the International AIDS Conference in Barcelona last July that this side effect has not been seen in people, so trials were recently re-started. Phase I trials suggested that capravirine is ten times stronger than the approved NNRTIs in people who have never taken them. Let's see if that translates into real-world use. So far, capravirine has not caused the rash that is often seen with the other NNRTIs.

DPC-083 (BMS-561390) is a Sustiva-like NNRTI that was originally developed by DuPont Pharmaceuticals. It stays in the body a very long time, so it could theoretically be taken every other day – but everyone seems to think that's too difficult for people to do, so it will most likely be given once a day. In one trial, people who were resistant to the available NNRTIs switched to DPC-083 and added one new nucleoside – 70% of them got their viral load below 400. But only

40% of those who did not add a new nucleoside got below 400, so you may need other new drugs available to get the full benefit of DPC-083.

Since taking over DuPont, Bristol-Myers Squibb (BMS) has put this drug on hold while they compare it to three other NNRTIs they have in the pipeline (DPC-082, DPC-961, and DPC-963). So we'll have to wait and see which drug they decide to pursue. In the past, BMS has put drugs on the back burner while they pursued a lead candidate (Zerit languished in Phase I trials for years while BMS studied Videx), so they might not study two non-nucleosides at the same time.

TMC-125 is a twice-daily NNRTI that also looks good against HIV that is resistant to currently available non-nucleosides. In one small study, sixteen people who were highly resistant to Sustiva or Viamune switched to TMC-125 for eight days and got a viral load drop of 0.9 log (a decrease of about 87%). More time on drug will hopefully lead to even greater drops – but will they be sustained? Some people who had never taken any antiretrovirals before had viral load drops of over 3 logs (99.9%) after a week on this drug, so it may turn out to be quite strong.

An interesting study compared viral load results in people
(continued on page 12)

FDA-Approved Antiretrovirals for the Treatment of HIV

Each of the anti-HIV drugs that are now available go by at least two names – a brand name (sort of like Coca-Cola®) and a generic/chemical name or names. Add to that pills like Combivir and Trizivir that combine medications, and it can be pretty confusing. The following medications are organized by class and listed by brand name first, followed by their generic names in parentheses.

Reverse Transcriptase Inhibitors (RTIs)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

(also called nucleoside analogs or nukes)

Ziagen (abacavir)
Videx (didanosine, ddI)
Epivir (lamivudine, 3TC)
Zerit (stavudine, d4T)
Hivid (zalcitabine, ddC)
Retrovir (zidovudine, AZT)

Combivir (AZT + 3TC combined in one pill)
Trizivir (AZT, 3TC + Ziagen combined in one pill)

Nucleotide Analog

Viread (tenofovir)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

(sometimes called non-nucleosides or non-nukes)

Rescriptor (delavirdine)
Sustiva (efavirenz)
Viamune (nevirapine)

Protease Inhibitors (PIs)

Agenerase (amprenavir)
Crixivan (indinavir)
Kaletra (lopinavir/ritonavir)
Viracept (nelfinavir)
Norvir (ritonavir)
Fortovase (saquinavir)

New and Improved? *(continued from previous page)*

who took TMC-125 alone for a week to earlier studies of people who took five-drug combinations, none of whom had ever taken antiretrovirals before. TMC-125 by itself produced better viral load drops (almost 2 logs, a decrease of 99%) than the five-drug combinations (1.5 logs, or 97%). What this means, no one knows. Could TMC-125 be used with just one other drug? We'll have to wait and see. The answer remains a long way off, as does approval, since trials are still being done to find the best dose. Johnson & Johnson recently acquired Tibotec-Virco, the company behind this drug. Hopefully, this won't slow down the drug's development.

Protease Inhibitors (PIs)

When protease inhibitors made their debut in 1995, they were hailed as "wonder drugs" that might even eradicate the virus from the body. That didn't happen, of course, and shortly after they were approved, side effects like lipodystrophy and elevated cholesterol and triglyceride levels began showing up. Once again, the need is for drugs that work for people who have become resistant to the approved PIs, with fewer side effects and easier dosing.

Atazanavir is a once-daily PI from Bristol Myers-Squibb with a unique quality – it doesn't seem to cause the kind of triglyceride and cholesterol increases seen with other PIs. It can, however, raise bilirubin levels, a substance produced by the liver. As with Crixivan, however, this increase in bilirubin levels doesn't seem to mean that the drug is damaging the liver. Atazanavir worked as well as Viracept in one study, but since Viracept may not be the strongest PI, that's not particularly impressive.

The real test was a head-to-head comparison of atazanavir to Sustiva. In this trial of people who had never taken anti-HIV drugs before, 32% of people taking atazanavir had viral loads below 50 copies after 48 weeks, compared to 37% of those on Sustiva. That's about the same, but the big question is: why did Sustiva perform so poorly in this study? Other trials have found rates of 80% or more reaching 50 copies while on Sustiva. It might have been the viral load test that was used, the way the data were analyzed, or the fact that the trial was done around the world, in people with many different subtypes of HIV. Still, atazanavir's low pill burden (two pills once a day) and the fact that it does not increase lipids may make it a good candidate for use as a first-line drug.

The \$64,000 question: will it work for people who are resistant to other PIs? BMS has shown that it's effective in the test tube against HIV that is resistant to other PIs, but whether that's true in people is still to be determined. The drug was submitted to the FDA for approval in December. If the FDA grants accelerated approval, it should be approved by June; if not, look to the end of the

year. Atazanavir is currently available through an expanded access program (877-726-7327).

Tipranavir is a twice-daily PI that has languished for years while various drug companies searched for the right dose. It appears that Boehringer Ingelheim (BI), the new owner, has finally decided on a dose. Unfortunately it includes 400 mg of Norvir (ritonavir) a day, which many people can't tolerate. BI is also testing a lower dose of Norvir (200 mg a day) in people who have never taken antiretrovirals. Tipranavir is important because early trials have shown that it may work in people who are resistant to other PIs. One trial found that people resistant to multiple HIV drugs were still responding to tipranavir after a year, with viral load drops of up to 99%. Large-scale trials to confirm this are scheduled to begin early this year, and Boehringer Ingelheim has agreed not to wait until those trials enroll before starting an expanded access program. Instead, people who don't qualify for the trials or who live too far from a trial site will be able to get the drug through an expanded access program if they meet other requirements. Those randomized to approved drugs in the trials will be able to take tipranavir after eight weeks if the other drugs don't work.

So if you missed last year's tiny T-20 early access program (which filled up within a week), tipranavir is an option to explore. The best-case scenario for a tipranavir early access program is early this year. Since T-20's approval is expected around the same time, people in need of treatment options may be able to combine tipranavir with T-20 for the best antiviral effect. Look for approval sometime in 2004.

Fosamprenavir (GW433908) is an old drug in a new suit. One of the biggest drawbacks to Agenerase (amprenavir) has always been the pill count – eight huge pills twice a day! Taking it with low-dose Norvir can lower that to eight pills once a day, but that's still a lot of pills. With some antiretrovirals now being dosed at one pill once a day, GlaxoSmithKline understands that Agenerase can't compete, so they've come up with this pro-drug of Agenerase. Fosamprenavir turns into Agenerase once the body absorbs it. It will probably be dosed at just two pills once a day when taken with low-dose Norvir. Efficacy so far appears similar to Agenerase, and side effects are also about the same, perhaps less. The main decision now for Glaxo is what dosing regimen to recommend – twice daily without Norvir is still possible. Of course, if you are resistant to Agenerase, fosamprenavir won't work for you either. Application for FDA approval will most likely happen this year.

Mark Milano is a longtime AIDS treatment activist and a treatment educator at ACRIA.

Once-A-Day Dosing *(continued from page 8)*

absorption) of saquinavir. Studies in patients who had never taken any antiretrovirals before have used Fortovase (saquinavir soft gel capsules) (1600 mg) plus low-dose ritonavir (100 mg) given once daily for a total of nine pills. The blood levels of saquinavir were within targeted levels in most subjects but not in all.

The high pill count and gastrointestinal side effects are also a problem for Fortovase/ritonavir. One study of once-daily Fortovase/ritonavir (in combination with nucleoside analogs) reported a high discontinuation rate: 25 out of 81 patients. Tolerance may be improved by using the old Invirase formulation (saquinavir hard gel capsules), which, when given with ritonavir, achieves similar saquinavir concentrations without the gastrointestinal side effects.

Crixivan (indinavir)/ritonavir: Ritonavir slows the metabolism of Crixivan but does not improve its absorption. Thus the dose of ritonavir given with Crixivan is sometimes higher than with the other PIs, which may make it harder to tolerate. A trial of Crixivan (1200 mg) plus ritonavir (400 mg), in combination with Videx and Epivir, all given once daily, reported successful responses out to week 24 in seven of nine patients. Two patients had blood in the urine (associated with kidney problems), and one was diagnosed with kidney stones. Another study of Crixivan (1200 mg) plus ritonavir (200 mg), given once daily in combination with Zerit and Epivir both given twice daily, has reported success out to week 24. The small size and short length of these studies is worrisome. Like saquinavir, minimum blood concentrations of Crixivan fall below targeted levels in a percentage of patients.

Once-Daily Combination Regimens

Even if a drug is effective once a day when given with other antivirals taken twice a day, it may not perform adequately as part of an *all* once-a-day regimen. The antiretroviral coverage with an all once-daily regimen might be weak at hour 24, and, if the next dose is delayed or

missed, virtually non-existent. These regimens haven't been compared to standard therapy in any large study.

A couple of studies have evaluated a once-a-day combination of Sustiva/Videx EC/Epivir. One enrolled 75 patients with an average CD4 cell count of 251 and an average viral load of 123,000 copies/mL. After 48 weeks, 77% of those who started treatment had a viral load below 50 copies/mL. There was no difference in response between patients with higher or lower viral loads at study entry. The regimen was well tolerated, but Videx was given at a 300 mg dose to all patients regardless of weight. [300 mg is only recommended for adults who weigh less than 132 pounds; heavier patients are given 400 mg.]

Another study used the same combination in 40 patients in Senegal, with Videx EC weight adjusted. At the end of 24 weeks, 78% had viral loads below 50 copies/mL and the average increase in CD4 cell count was 153 cells. Similar responses have been reported with Sustiva and Videx in combination with Coviracil (FTC).

The controversial combination of Sustiva plus Viramune (plus Videx), all once-a-day, was successful in one study, both in people who had taken antiretrovirals before and those who hadn't. Viramune anchored the once-a-day regimen in a few small studies where dosing was directly observed by a nurse or social worker. One reported comparable responses whether using once-a-day (mainly Viramune-based plus Epivir/Videx) or twice-a-day antiretroviral regimens (mainly protease inhibitor-based) in 54 people enrolled at a methadone clinic. 65% of the participants achieved viral loads less than 400 copies/mL at 24 months. This is despite a high viral load at study entry of 210,000 copies/mL and despite the fact that all patients were on methadone. [Viramune reduces methadone blood levels, so the methadone dose must be increased by about 45% to avoid withdrawal.]

Once-a-day Agenerase (1200 mg), ritonavir (200 mg), plus Videx (400 mg) and Epivir

(300 mg) worked well in adherent patients from a similar population, although the researchers excluded many patients for skipping doses.

The Variable Patient

Drug pharmacokinetics vary from person to person due to differences in metabolism (sometimes inherited), diet, smoking, alcohol or recreational drug use, gender, other medications, and infections such as viral hepatitis. The best solution is to tailor the combination, whether once or twice daily, to the individual.

For most patients, plasma and intracellular concentrations of drug and therapeutic efficacy might be similar on a once-a-day or twice-a-day regimen. But a minority can represent many people and could possibly include you. For the time being, there are many theoretical concerns about starting with or switching to a once-a-day regimen, particularly the protease inhibitor-based combinations, and little reassuring clinical data to guide individual treatment decisions. Two types of laboratory tests that aren't yet used in clinical practice – therapeutic drug level monitoring and gene screening – could someday help determine whether a person has adequate levels of drug on a regimen.

In the meantime, it makes sense to choose regimens that are tried and tested, or at least those drugs with pharmacokinetic profiles that aren't stretched thin by once-a-day usage. Or stick with a twice-a-day regimen. Either way, staying on treatment requires commitment, hard work and a support network. Even if an all-in-one, once-daily small pill is developed, people will still have to take it every day. The struggle to do that consistently should not be underestimated.

Theo Smart works with SAFE-T, the Southern African Fund to Enable Treatment, in Cape Town, South Africa.

Entry Inhibitors: The Bouncers at the Door

by Donna M. Kaminski

There is good news on the horizon for people whose HIV is resistant to many currently approved antiretrovirals – the development of a new class of anti-HIV drugs called entry inhibitors. Entry inhibitors have shown promising results for people with few treatment options. The first of these drugs, T-20, may work when other drugs no longer do and is likely to be approved for use as early as March of this year.

Entry inhibitors work at HIV's first point of contact with a T-cell. They keep HIV from entering the T-cell by interfering with one of the steps involved in the entry process. Theoretically, at least, a drug could target any one of the proteins on the outside surface of HIV (gp120 or gp41, for example) or one of the receptors on the outside surface of the T-cell (CD4, CXCR4 or CCR5). To date, the most promising entry inhibitors work by targeting HIV's gp120 or gp41 proteins, or the T-cell's CCR5 receptor. These drugs work somewhat like nightclub bouncers, checking HIV's ID as the virus tries to enter the T-cell and not letting it inside. If the drug is effective, HIV is unable to use the T-cell to make copies of itself.

T-20

T-20 (enfuvirtide), also called Fuzeon, is the entry inhibitor furthest along in clinical trials. This drug, developed by Roche and Trimeris, is specifically called a fusion inhibitor. It sticks to HIV's gp41 protein, which HIV uses to bind to the T-cell. With its gp41 occupied by the drug, HIV is unable to fuse with the T-cell and send its genes inside.

T-20 is a molecule, like insulin, that can only be taken as an injection. It needs to be available to the body immediately and isn't stable as a pill. It comes in powdered form. In order to prepare an injection, a tube of sterile water is added to the powder and the solution is mixed. The solution is self-injected sub-

cutaneously (under the skin) twice a day. The solution can foam while it's being injected and therefore needs to be injected carefully. The drug's greatest value will be to people whose HIV is resistant to many current anti-HIV medications.

Results from two critical Phase III studies presented at the 2002 International AIDS Conference in Barcelona in July show that T-20 has comparable strength to current antiretrovirals. The two studies, called TORO (T-20 vs. **Optimized Regimen Only**), are similar in design. Each study is following about 500 HIV-positive individuals for one year to compare the effects of T-20 plus other

“...Studies have indicated that there may be a synergy between T-20 and T-1249.”

antiretrovirals to an antiretroviral combination without T-20 (the control group). The participants had previously used an average of twelve anti-HIV medications, and 80-90% had five or more primary mutations to all current classes of antiretrovirals. Not surprisingly, the trial participants had high viral loads and low CD4 counts. Based on the results of resistance testing, each individual was assigned a combination of three or more current or experimental anti-HIV medications. Two-thirds of the participants also used T-20. While the trials have not been completed, preliminary six-month results were presented at the conference and provide the most data on T-20 to date.

TORO-1 enrolled 491 people in the

U.S., Canada, Mexico and Brazil. The average viral load was 158,489 copies/mL, and the average CD4 count was 80. After six months, the viral loads of those in the T-20 group dropped by 98%. The viral loads of those not on T-20 dropped by 82%. 20% of individuals on T-20 had undetectable viral loads (less than 50 copies/mL), compared to 7% in the control group. In addition, there was an average increase in CD4 count of 76 in the T-20 group, compared to 32 in the control group. There was no significant difference in study withdrawal rates between the T-20 and non-T-20 groups. 98% of people using T-20 experienced injection-site reactions (pain, swelling and/or redness around the injection area) and most reported these reactions to be hard to tolerate. While very few stopped using T-20 due to the reactions, the difficulty of using this drug should not be underestimated. Other side effects experienced by those on T-20 included fatigue, insomnia, and peripheral neuropathy.

TORO-2 enrolled 504 individuals in Europe and Australia. After six months, the individuals in the T-20 group found their viral loads to drop by 96%, as compared to the control group whose viral loads dropped by 78%. Of the individuals on T-20, 12% reached undetectable viral loads (less than 50 copies/mL) compared to 5% in the control group. CD4 counts increased by an average of 65 in the T-20 group, versus 38 in the control group. More individuals who were on T-20 withdrew from the study (17%) compared to the control group (5%), which is significantly different from TORO-1. Similar to TORO-1, 98% of individuals on T-20 had injection-site reactions, but only 3% withdrew due to these reactions. Less than 10% of those on T-20 experienced headaches, fever, and fatigue.

Overall, the results of these studies are promising. This drug seems to benefit the very people most in need of new

options, people who have gone through most of the available drugs and developed resistance to them. While having to inject the drug twice a day poses a significant disadvantage, this did not seem to stop people from using T-20 (see *Personal Perspective* on page 16). The data provided from the TORO studies suggest that the drug is tolerable through six months. Completion of these studies will provide more information on T-20, and other T-20 clinical trials are ongoing. One positive early finding is that T-20 does not share mutations with current antiviral drugs, although mutations to T-20 have been identified and can develop.

T-1249

Another fusion inhibitor being studied is T-1249. T-1249 also binds to HIV's gp41 protein, but it binds to a different part of the protein than T-20 does. If T-20 is the bouncer at the left side of the door, T-1249 stands at the right side of the same door. Both keep HIV from entering the T-cell. Like T-20, T-1249 is being developed by Roche and Trimeris, would be available only as a subcutaneous injection, and will be of greatest use to individuals with highly-resistant HIV. The information about T-1249 is still very preliminary. If T-1249 is approved, it will be available no sooner than 2007.

Data from several Phase I/II trials of T-1249 have been presented at recent conferences. At the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy last September, a Phase I/II study was presented that looked at the drug's safety, antiviral activity, and how the drug works in the blood. This study enrolled 115 HIV-positive individuals who had never used an entry inhibitor before (i.e. T-20) but had been on HIV treatment for several years. Participants stopped antiretroviral therapy two weeks before beginning the study, then took T-1249 alone, with no other antiretrovirals, for two weeks. At the start of the study, most individuals had a viral load of around 204,000 copies/mL. Most people had a CD4

count of 64. The study looked at various doses of T-1249, from 6.25 mg/day to 200 mg/day. The drug is currently made in quantities no larger than 50 mg, so the 200 mg dose required four injections a day. All but two of the participants completed the study. Decreases in viral load were observed – the higher the dose, the greater the decrease. The greatest drop was seen in those who took the highest dose; those on the 200 mg/day dose found their viral loads to drop by 99%. The maximum increase in CD4 count was 70 at the 150 mg/day dose. Fewer individuals (57%) experienced injection-site reactions than in the T-20 studies. The reactions were more common with higher doses. Other side effects included headache, fever, candidiasis (thrush), and diarrhea. Another study of T-1249 showed similar results.

T-1249 could be particularly useful for people with multi-drug resistant virus. In test tube studies, it doesn't seem to cause the same mutations as other current antiretrovirals – or as T-20. This suggests that T-1249 could work when other medications, including T-20, do not. There is an on-going study looking at T-1249 in individuals for whom T-20 didn't work. Studies have also indicated that there may be a synergy between T-20 and T-1249. In other words, when used together, there seems to be an even greater antiviral effect than when either drug is used separately. If these results hold true in larger trials, this could be very good news for people with HIV. Further studies are being done to evaluate how T-1249 works in larger numbers of people.

SCH-C

SCH-C is an entry inhibitor that targets a different part of the entry process than T-20 and T-1249. This compound binds to the CCR5 receptor on the T-cell. Normally, HIV's gp120 protein binds to CCR5. With SCH-C there, gp120 is unable to attach to CCR5 and enter the T-cell. SCH-C is specifically called an attachment inhibitor and is being developed by Schering-Plough. Unlike other

entry inhibitors, SCH-C can be taken as a pill. In test tube studies, it has shown activity against virus from a number of different HIV patients. This drug has a long way to go before possible approval.

In a Phase I/II study, twelve HIV-positive individuals with CD4 counts above 250 took SCH-C by itself every twelve hours for ten days with no other antivirals. Viral load was measured every six hours for the first three days, then every 24 hours for the remaining seven days. Participants also had phenotype testing performed before and after the study to check for new HIV mutations that might have developed. At the end of the study, ten of the twelve individuals had their viral loads drop by 68%; four of the twelve individuals had viral loads that dropped by 90%. Very few side effects were reported, the most common being headaches and unpleasant taste. However, several early studies of SCH-C have shown potential cardiac toxicity (premature heartbeats) in some patients, which may be associated with the drug. Careful monitoring is necessary in all ongoing trials. If SCH-C proves to be effective at lowering viral load and increasing CD4 counts in larger studies, its few side effects and potential availability in pill form are real advantages.

PRO 542

PRO 542, from Progenics, works somewhat like a decoy. It mimics the CD4 receptor found on the surface of T-cells. PRO 542 occupies HIV's gp120 protein, which would normally bind to the CD4 receptor. HIV is fooled into thinking that PRO 542 is the T-cell. As a result, it can't free itself to bind to a T-cell. Like most other entry inhibitors, PRO 542 has a difficult route of administration – it is currently being tested as an intravenous infusion.

In a Phase I/II clinical trial, 22 HIV-positive adults who had been on treatment before were given a single intravenous infusion of PRO 542. They had viral loads greater than 3,000 copies/mL and CD4 counts greater than

(continued on page 17)

The Constant Survival Battle and T-20

by Matt Sharp

Staying alive with HIV has been a thirteen-year battle for me. My story is one of survival in an imperfect, yet encouraging era that has produced some powerful drugs that have kept thousands alive.

In 1988 I tested HIV positive at an anonymous clinic in Oklahoma City. One year later, in the turbulent and desperate years of the AIDS epidemic when street demonstrations were as common as the funerals of many of my friends, I first began taking anti-HIV drugs. I knew I had to begin treatment or else end up like my friends. With only one drug available at the time, I began AZT at the 600 mg a day dose.

Along with other AIDS activists, I was constantly fighting for more and better HIV drugs in order to buy time until the cure. As AZT showed that it wasn't the panacea everyone had hoped and my T-cells reflected its ineffectiveness, I added new drugs as they became accessible either through clinical trials or the underground buyers' clubs. I rarely started a new drug that was *not* some kind of experiment. I used up every individual drug and combination possible. I spent lots of money on vitamins and the latest alternative therapies. The antivirals I chose were at least slowing the devastating progression of HIV, but my T-cells were falling. Fortunately, I never got sick with an opportunistic infection but was severely wasted by 1994.

In those early days, few people understood how much HIV could mutate, changing itself so that the drugs wouldn't work. Few knew how important adherence was. We learned the hard way –

through experience – that combination therapy was the best way to slow the virus. Adding a new drug to another previously used one would prove not to be the best road to take. We learned from our mistakes, and some people paid the ultimate price.

I continued to fight for the latest treatments and watched my viral load spiral out of control and my T-cells slowly inch towards single digits. But today, even though I have technically failed almost every approved drug, I'm a long-term survivor. Nobody is sure why I'm so lucky given that my drug resistance pattern is off the map, except that I have truly fought for access to every HIV drug I have taken. For years, AIDS activists pushed for ethical and quick research and development, and then made sure the drugs got into the hands of thousands who desperately needed them in order to slow the ravage of HIV.

In 2000 I moved to Chicago to be with my boyfriend. Twelve years into my HIV disease, I once again found myself scrambling for the next drug. My T-cells were perilously close to zero! I knew I needed a powerful new drug capable of controlling my viral load, which was climbing again. I was following the development of T-20, or Fuzeon, the first drug in a new class, fusion inhibitors. I attended numerous meetings with the T-20 working group that helped Trimeris, the company developing the drug, to make sure development went quickly and ethically. I didn't qualify for the early clinical trials of T-20 because I was a "salvage" patient and the studies had strict entry criteria that I didn't fit into. Finally, the working group got Trimeris to

design a new study that would benefit people like me. Again, I found myself fighting to stay one step ahead of the game.

One of the sites for the new trial was at Northwestern in Chicago, just up Lakeshore Drive from where I live. I had a hard time getting any study coordinators to return my calls. Due to excessive bureaucracy, it took a full year of harassment before the trial was ready to screen people. Meanwhile, my T-cells continued to drop and I was losing weight, having problems with my skin and having constant sinus infections. I was frightened again, remembering all my lost friends.

Finally the trial opened and I was screened. Then you guessed it – I was randomized to be in the control arm, still not receiving T-20. But after twelve weeks, I was rolled into the T-20 arm, taking it along with new drugs, including other experimental ones. The study required me to construct the most powerful regimen to add to T-20. Believe me, I needed all the help I could get! I managed a mega-HAART regimen with seven antivirals, including T-20, and for the first time in my years of living with HIV, I reached undetectable!...for one week.

It was no picnic injecting T-20 twice a day. I had experience with needles, having used human growth hormone and testosterone replacement for years. And I had probably been stuck a thousand times giving blood for research and while monitoring my health. But I didn't expect the painful injection site reactions from the drug, sometimes resulting in lumps the size of golf balls that were so painful that I couldn't lie

down. As with many issues living with HIV, however, I've learned to deal with problems that arise. Talking to other people in T-20 studies has helped me rectify

some of the issues with injection site reactions, learning where on my body to inject and techniques on the best way to do it. The injections are no longer as bad as they once were.

After that first week of being undetectable, my viral load slowly started climbing up again. Having been on T-20 for ten months now, I'm considered a T-20 *failure*. But I'm in a balancing act of sorts. My virus level is around 40,000, about what it was before I started the decline a year before I began T-20, and my T-cells are hovering at 120 where they were in the late nineties. But, all in all, things aren't so bad. My clinical health is excellent, I feel good, and my weight is back up to normal and stable.

If anything, I believe T-20 is adding to a moderate virus control, keeping me stable as the other drugs I take are probably no longer effective. Without T-20, I believe my HIV levels would jump to the sky. Despite the twice-daily injections, I've decided that the benefit of using T-20 outweighs the risk. So once again, I'm coping with yet another new drug in a clinical trial, maintaining, and still waiting for a cure.

Matt Sharp lives in Chicago. He is an AIDS treatment activist with the Coalition for Salvage Therapy and AIDS Treatment Activist Coalition (ATAC).

Entry Inhibitors *(continued from page 15)*

50 when they started the study. The infusions were given at doses of 0.2–10 mg/kg based on individual body weight. No other antiretrovirals were given. PRO 542 was well tolerated and did not show toxicity at any of the doses tested. Participants' viral loads decreased to levels that were significantly lower. Most people's viral loads stayed at the same levels for up to one month after the study.

In another study, 18 HIV-positive children took various doses (0.2-10 mg/kg) of PRO 542 between one and four times a week for one month. After two weeks on the drug, some children had viral loads that dropped by 80%, and stayed at those lower levels for up to two weeks after they stopped the drug. Others' viral loads went down after the first infusion, but then continued to rise even while on drug. The greatest drop in viral load was seen in the children who received the highest dose, 10 mg/kg four times a week.

Preliminary results from a current Phase II study show that when people who had been on HIV treatment before took a single 25 mg/kg intravenous dose of PRO 542, their viral loads

decreased by 60-80%. While PRO 542 would not be the first HIV-associated treatment administered intravenously, this certainly isn't ideal. Progenics is exploring the possibility of administering PRO 542 as a subcutaneous injection.

In summary, entry inhibitors create an important advance in HIV treatment, particularly for people with few other treatment options. Although most agents in this new class of drugs will be harder to take than previous antiretrovirals, the approval of T-20 is long awaited and will fill a great need. While the drug has been shown to work well, it can't do its job alone. To get the most benefit, people will most likely need to use T-20 with at least one other drug to which their virus isn't resistant. A greater number of treatment options, such as T-1249, SCH-C, and PRO 542, are essential for the growing number of people facing multiple drug resistance.

Donna M. Kaminski is ACRIA's Associate Director of Treatment Education.



is looking for new COMMUNITY ADVISORY BOARD members.

ACRIA's Community Advisory Board (CAB) fosters partnership between the education staff and the local community impacted by HIV/AIDS. Involving community members in the development of our education programs ensures that community values and cultural differences are respected in ACRIA's educational work.

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For more information about the CAB or if you are interested in volunteering at ACRIA, please call Mark Milano at (212) 924-3934, ext. 123.

Anti-HIV Candidates in the Pipeline *(continued from page 6)*

into host cell DNA. **S-1360** (GW810781), under development by Japan's Shionogi and GlaxoSmithKline, is furthest along in clinical trials. Results from laboratory studies indicate that the agent is active against a variety of HIV strains (including multidrug-resistant strains) and works well with other classes of drugs. Early Phase I data reported at recent conferences suggest the drug can be taken orally and has low toxicity, but it may not work well in the body due to plasma binding (a process in which a drug attaches to proteins in the blood, making it unavailable where it's needed). Merck has also developed a series of diketo acid compounds. The earliest agents had poor pharmacokinetic properties (not enough drug was getting into cells), but later candidates appear more promising. Recent data show that **L-870,810** is active *in vitro* against multidrug-resistant HIV, and **L-870,812** lowered viral load in rhesus monkeys. Phase I human trials of L-870,810 are underway.

Other Targets

Before HIV can integrate its genetic material into a host cell, it must uncoat itself, or remove its envelope to release the proteins and enzymes inside. After integration, new viral components are produced and assembled, and then bud out through the host cell membrane to become complete virions (virus particles). All of these steps present potential drug targets.

HIV's nucleocapsid core, which contains its RNA (genetic material), is held together by protein structures called zinc fingers. **Zinc finger inhibitors** interfere with the packaging of RNA into new virions. Disruption of the nucleocapsid leads to the production of dysfunctional virus that cannot infect new cells. **Azodicarbonamide** (ADA), under development by Hubriphar in Belgium, is the most advanced zinc finger inhibitor. Results of Phase I/II trials showed moder-

ate activity against HIV. But while HIV may be unable to function without zinc fingers, the same might be true of the human body. Such agents may have serious side effects; kidney toxicity and glucose intolerance were seen in early studies. **GPG-NH2**, from Sweden's Tripep, also interferes with the assembly of HIV's p24 nucleocapsid protein. It has shown anti-HIV activity in laboratory studies and good absorption and safety in early clinical trials.

AXD-455, being developed by Germany's Axxima, works by blocking the action of an enzyme called eIF-5A that transports viral genetic material from the host cell nucleus to the main body of the cell for processing and assembly. *In vitro* studies showed anti-HIV activity, and the agent is undergoing early clinical trials in Europe. Panacos' PA-457, a betulinic acid derivative, appears to inhibit HIV assembly and budding. Laboratory studies show that it's effective against different strains of the virus. NeoR is a *Tat* inhibitor that interferes with one of

HIV's three regulatory proteins. Agents that target the other two regulatory proteins – *Nef* and *Rev* – are possible future drug development prospects.

Hope for the Future

New classes of anti-HIV drugs – and new drugs in existing classes – represent the best hope for people with HIV, especially those who have exhausted current therapies. Even people whose HIV is resistant to drugs in all three existing classes stand to benefit from new agents now in the pipeline. And drugs that work by different mechanisms may produce fewer side effects. But even with the best new agents, resistance remains a major concern. It will likely remain the case that the best treatment strategy involves use of multiple drugs that attack HIV from different angles.

Liz Highleyman is a San Francisco-based freelance medical writer, writing for the Bulletin of Experimental Treatments for AIDS (BETA), POZ and the Hepatitis C Support Project's HCV Advocate.

What Ever Happened To . . . ?

- dOTC (BCH-10652) — discontinued after deaths in monkey studies.
- DPC-681 and DPC-684 — halted due to toxicity in animal and human studies.
- DPC-961 — abandoned after study participants reported suicidal feelings.
- emivirine (Coactinon, MKC-442) — discontinued due to poor effectiveness.
- GW420867X — halted due to potential interactions with other anti-HIV drugs (powerful cytochrome P450 3A4 inducer).
- L-756,423 (MK-944) — discontinued due to kidney toxicity in animal studies.
- Iodenosine (FddA) — terminated due to life-threatening liver toxicity in some patients.
- mozenavir (DMP-450) — stopped due to disappointing effectiveness in early clinical trials.
- TMC-126 — dropped in favor of other agents in development.

National Online TrialSearch Service To Be Launched

ACRIA is assuming operation of TrialSearch, the national online database of enrolling HIV clinical trials. TrialSearch has been part of the University of California San Francisco's (UCSF) HIV InSite web site since 1997. Earlier this year, UCSF decided to reorient the focus of HIV InSite to primarily offer information on emerging HIV healthcare issues from an international perspective. TrialSearch has subsequently been removed from their service, and a new feature called TrialScope has taken its place to list HIV research sites worldwide.

UCSF did not want to abandon TrialSearch altogether. They've asked ACRIA to continue this service because our two organizations have collaborated on gathering HIV clinical trial information and because we already operate an online clinical trials directory for the New York State area. ACRIA agreed to develop the larger national database at www.acria.org within the next several months.

ACRIA would like to thank UCSF and Mike Donnelly for their past work with us on disseminating vital HIV clinical trials information and for their vote of confidence as we expand our efforts in this area.

ResPAC Report Available

ACRIA is pleased to announce the availability of the Research Policy Advisory Committee's (ResPAC) findings from their strategic planning meetings in 2002. The publication, *HIV/AIDS Research Priorities for New York State: Epidemiology, Behavioral Sciences and Clinical*, offers a unique perspective on the most urgent and high priority needs for studies within these various disciplines. ACRIA presented the ResPAC findings at the New York State Department of Health AIDS Institute in January. Copies of the ResPAC report can

be obtained by calling Salone Howard in ACRIA's Research Department at (212) 924-3934 x 105 or by downloading the document at www.acria.org.

Clinical Trials Community Education and Outreach

ACRIA has recently created a position to foster greater understanding of HIV clinical trials within underserved communities in New York City.

It is widely recognized that people of color and women are less likely than other populations to learn about the clinical trials process or about opportunities to access experimental therapies. The fact that underserved communities are largely absent from HIV clinical trials is particularly disturbing since it is these individuals who are now most directly affected by HIV and AIDS. ACRIA's new employee will address this problem by speaking to clients and staff of community-based organizations in all boroughs of New York City about the risks and benefits of participating in clinical research. Interestingly, the most responsive individuals at our presentations have so far been people living with HIV/AIDS, many of whom are not only learning for the first time that experimental therapies exist, but that they are not just accessible to those who are well connected to the healthcare establishment.

If you or your agency are interested in learning about the clinical trials process and new therapies, please call Philana Rowell in the Research Department at (212) 924-3934 x 125 to schedule an appointment.

ACRIA Provides Technical Assistance in Baltimore

ACRIA brought our national technical assistance (TA) service to Baltimore, Maryland in October. The four-day inten-

sive training helped over thirty community members and staff from seventeen area agencies develop the skills and knowledge to provide accurate and up-to-date HIV treatment information within their communities. ACRIA's TA program has grown tremendously since its inaugural trip to San Diego in 2000. The training in Baltimore represented our second new TA site in 2002, and we are pleased to report that this was our most successful endeavor of its kind to date. Virtually every participant enthusiastically embraced ACRIA's approach to health education for people living with HIV/AIDS.

Our next TA session will be held in Madison, Wisconsin during the Spring of 2003. ACRIA's goal in this area will again be to expand capacity of agencies to explain HIV treatment issues and to foster greater collaboration among local non-profits to support the health information needs of their clients. ACRIA would like to thank Ortho Biotech for its generous grants to help pay for the national TA program.

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generous contributions

Thoughtful donations were made in memory of the following individuals:

Cliff Adams	Michael Koenigsberg	Thomas Saporita
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Steve Cattano	Timothy Layton	Leslie Wasson
Jon Greenberg	Ezra David Litwak	Eric Weinmann
Robert Hull	Jeffrey L. Mitchell	Robert C. Woolley
Ken Kirschner	Carl Parisi	

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Jack Battaglia	Richard A. Jacobs	Frank Russo
Jerry Binkowitz	Adam Lippes	J Daniel Stricker
Neil Greenberg	Richard D. Piper	

The following persons, corporations and organizations made major donations between Sept 16, 2002 and Dec 31, 2002 to support ACRIA's research and education efforts:

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