



P.I. Perspective

Information, Inspiration and Advocacy for People Living with HIV/AIDS

● Lessons in Hope

Today, anyone who follows HIV treatment with a casual interest may get the impression that things are progressing wonderfully. A recent publication of the Pharmaceutical Manufacturers' Association asserts that 82 new medicines are in development for treating various aspects of HIV infection. Of these, 36 are antivirals, the kind of drugs that has made the most profound advances against HIV and AIDS. Surely, this sounds like good news, especially for those who have developed resistance to the current therapies.

We've been hearing for years of the likely wonders of a new class of drugs called entry inhibitors as well as hoping for better drugs in the existing classes. For people with HIV, this was expected to be a cheerful holiday season indeed. It wasn't. Instead, the last half of 2005 offered one of the most discouraging lessons in drug development in a long time. News came of the complete failure of one entry inhibitor candidate and the partial failure of two another, as well as discouraging results in some of the studies of new NRTIs.

Though one new protease inhibitor came to market promising to help people with highly resistant virus, it offered limited utility, significant toxicity and exorbitant cost. Shortly after 2006 began, the largest-ever study that tested whether people needed to be on constant therapy was abruptly halted. All in all, this was one heck of a discouraging period.

In the interests of keeping hope alive, it's important to remember that the media's coverage of HIV issues tends to exaggerate the truth, whether good or bad. That is once again the case. Though some setbacks have occurred, several striking successes have gotten little or no fanfare. It's appropriate then that we start the New Year by looking not only at the failures, but also at some of what's working ... and working well.

Woes upon Woes

For the last two years, researchers and industry reps couldn't say enough good things about entry inhibitors. This new class of drug blocks HIV from attaching to receptors on T cells. If the virus can't attach to cells and insert its genetic material, there is no infection of the cell ... at least in theory. Several companies have had entry inhibitors in studies for up to two years already. The high hopes associated with entry inhibitors stemmed from two ideas. First, any new way of treating HIV is welcome, especially for people who are running out of treatment options. Second, the fact that these new drugs worked outside of the cell was hoped to mean that they would have fewer side effects. Many hinted that these drugs would open a whole new era in HIV treatment. Actual study results, however, have proved sobering.

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First, GlaxoSmithKlein (GSK), one of the giants of HIV medicine, announced that it was ending studies of its entry inhibitor, *aplaviroc*, in people who had used it as first-time therapy. This was due to the appearance of liver disease in a few volunteers. Soon, they stopped all study of the drug when similar problems appeared in people with more advanced disease.

Another company, Schering Plough, was one of the first to develop an entry inhibitor. It began with two different compounds and eventually settled on developing one of them, *vicriviroc*. To everyone's surprise, in the fall they suddenly announced that they were ending its development as first line therapy because of its weak activity compared to a Sustiva. Studies using it as an add-on to proven therapy combinations will continue, but it's already evident that the drug isn't going to have the kind of powerful effect once hoped for.

The other hope among this type of entry inhibitors is the Pfizer drug, *maraviroc*. It too has run into some problems. In a study looking at two different doses of maraviroc (once a day and twice a day) versus Sustiva, the once-a-day arm was stopped due to poor results. Right now it looks like the drug fails to produce the large and rapid decline in viral load seen with Sustiva and protease inhibitors. Years of data clearly show that the durability of treatment depends mostly upon how quickly and thoroughly it reduces viral load (in addition to patient adherence, of course). On this score, the Pfizer drug has so far scored no better than average.

Whatever the fate of oral entry inhibitors, the bloom is off the rose. However, hope remains that they will still be useful in the HIV tool kit. For more in-depth information, see the article *Entry Inhibitors: A Race to the Finish Line*.

The bad news isn't limited to entry inhibitors though. A once promising NRTI, Reverset, also lost ground when the FDA was less than satisfied with study results and ordered its manufacturer, In-Cyte, to conduct another study. The company was already running thin on cash reserves and hasn't yet found a large pharmaceutical company willing to partner with it. At the least, the drug will be delayed in the pipeline; at worst, it won't survive the approval process.

Last and not least, hope took a bit of a beating this year even in the approval of a new protease inhibitor, Aptivus (tipranavir), that was expected to offer renewed anti-HIV activity for people with resistance to most other protease inhibitors. The drug had a long and difficult history as it moved through the FDA approval process. Still, people were surprised at how modest the supporting data were when it went before an FDA review. In the end it was approved, but only with the apparent reluctance of the FDA and its committee.

The drug could indeed work against protease-resistant virus, but it only showed significant and lasting results when paired with a second drug, Fuzeon (enfuvirtide, T20), being used for the first time. Fuzeon is the most expensive antiviral available, and unfortunately, Aptivus carried the highest price ever asked for a protease inhibitor. Consequently, the combination is only available with special prior approval in many state ADAPs. To further complicate the situation, using Aptivus also requires using Norvir (ritonavir) as a booster. While it is common for protease inhibitors to require the Norvir booster, Aptivus requires a double dose of it, which increases the side effects of Norvir as well as the cost. Abbott Labs, manufacturer of Norvir, is willing to provide Norvir free for anyone who needs it as a booster for Aptivus, but getting the free drug requires filing additional paperwork and getting the Norvir from a separate program. Aptivus may indeed work against resistant virus, but making it work well is far from easy.

Hopefully Hype-less Hope

Despite the discouraging events of the last year, there is still plenty of hope. The last year has still been one of the most productive in the history of the epidemic. The good news just didn't get the attention it deserved.

At the top of the list of hopeful developments was Merck's announcement that their long-awaited integrase inhibitor had successfully passed Phase II studies and is now recruiting people for Phase III studies that should lead to FDA approval. Though the integrase step in HIV reproduction has been known as a potential target for drugs since the earliest days of HIV research, creating a drug that would safely block the "integration" step of viral reproduction has been daunting.

Integration is a step in the reproduction of HIV in which HIV inserts its newly formed viral DNA into the DNA of the cell it infects. Once HIV's DNA is inserted, it integrates into the cell's genetic machinery and uses it to make new copies of the virus. The enzyme, integrase, makes this integration of viral DNA into the cell possible. An integrase inhibitor is thus a drug that blocks this action.

Since the process takes place entirely inside a cell, it has been difficult to find compounds that could do the job without interfering with other essential cell activity. Several companies have searched for years for a useful compound. Most gave up over time and focused on other targets. A few, particularly Merck in the US, pursued the goal year after year. The first compound of this type the company tested in humans proved that inhibiting integrase would indeed reduce viral load, but animal studies warned of a possible serious toxicity.

Merck dropped that compound and proceeded to develop a second one. A phase II study showed evidence of strong anti-HIV activity, likely on the level of the best protease inhibitors. For a full report on the Phase II study of the Merck integrase inhibitor reported at the Conference on Retroviruses and Opportunistic Infections, see the report from the conference on Project Inform's website at www.projectinform.org/conference/croi.html. Although tested in only a relatively small number of people so far, the drug has shown few side effects. Phase III studies are beginning in March 2006 and some form of expanded access to the drug is likely in the last quarter of 2006.

Resistance to any previously used drugs should not affect an integrase inhibitor since it targets a completely different step in viral reproduction. Is the hope once assigned to the entry inhibitors on its way to becoming a reality with integrase inhibitors? Integrase inhibitors are simple oral drugs that will be taken once or twice a day. Based on what's known to date, the Merck drug can be combined with almost any other HIV therapy. More research is needed before we will know how this new drug will be used.

At least two other companies have also conducted human studies of an integrase inhibitor. GSK bought the rights to one from the Japanese firm Shinogi. Unfortunately, this compound failed to show the high levels of antiviral activity achieved by the Merck drug, so studies have halted. GSK remains committed to developing an integrase inhibitor and is currently screening additional compounds. A third firm, Gilead Sciences, maker of Viread, Emtriva and Truvada, has an integrase inhibitor in early phase II trials, perhaps a year behind Merck in the development process. The success of these two companies will undoubtedly spur competitive research at other firms.

Aside from the growing excitement over integrase inhibitors, two other types of compounds are in development that target the control of HIV in a different way. One is a *maturation inhibitor*. This refers to a step in viral reproduction that occurs just before new copies of virus burst out from the infected cell. An early study, from the company Panacos, showed evidence of significant viral sup-

pression from a single dose. Further studies will determine the ultimate hope of this target.

A second approach is using a monoclonal antibody that targets HIV. A monoclonal antibody is a cloned copy of one or more of the antibodies made by the immune system in its effort to control HIV. This has been tried before, and many such artificial antibodies are possible. Earlier efforts failed because of the high cost of making the antibodies combined with the high cost of delivering them to the body. These antibodies are given intravenously, a procedure normally typically done in a medical facility. One such antibody, made by Tanox, has shown evidence of viral suppression at levels similar to those of entry inhibitors. Tanox claims it will be able to make it cheaply enough for practical use, though the cost of the periodic IV infusions is still an obstacle.

Not all hope requires new classes of drugs. Many companies prefer to work with proven viral targets, such as protease and reverse transcriptase. Sometimes, a better version of an existing drug may be as significant as one aimed at a new target. Darunavir (TMC 114), a new protease inhibitor from Tibotec, shows evidence of great strength against viruses resistant to other protease inhibitors. The FDA was so impressed with their phase II data that they encouraged the company to submit an application for approval before they had even begun their phase III study. This is unprecedented in HIV and reflects the agency's apparent belief that the drug will offer a major advance for people who are resistant to all other protease inhibitors. The drug is now available in an expanded access program and will likely be approved in the second quarter of 2006.

Another area of hope comes from making therapy much easier to use. Gone are the days of taking handfuls of pills three times daily. A number of drugs are now available as two-drug combinations in a single pill. But an even greater advance has been achieved by the collaboration of two companies, Bristol-Myers Squibb and Gilead Sciences. They worked together to create a single pill that combines three highly potent drugs—Sustiva, Viread and Emtriva. Such efforts were inspired by generic drug makers who have been creating similar combinations for use in developing nations. The result is that an entire day's regimen is now reduced to taking a few pills, greatly simplifying adherence. The goal of such simplification is to help make it possible for people to use a regimen for a decade or longer without developing resistance due to adherence challenges.

Another avenue of genuine hope is research that challenges the once sacred rule requiring a combination of three drugs. Studies of Abbott Labs' highly potent protease inhibitor, Kaletra, have revisited the question of whether everyone needs to use at least three drugs all the time. An initial study comparing a typical three-drug combination to using Kaletra as a single drug produced surprisingly favorable results, with rapid and long-lasting viral suppression for both the combination and for Kaletra alone. This approach may initially be limited to use in people with low level viral activity beginning therapy for the first time. But over time, other experiments will test whether it is possible even in advanced disease to reduce the number of drugs used after several months of strong viral suppression. This concept was tested once in the early days of protease inhibitors and found unsuccessful, but today's drugs are more potent and may produce better results.

Beyond Maintenance Therapy

As emphasized in *PI Perspective #39*, we believe the ultimate goal of HIV research should not be limited to creating drugs good enough to be used for a lifetime. Rather, the goal must be an outright cure of the disease—the achievement of a state of wellness either despite or without HIV that can be sustained without constantly using drugs. This is perhaps the most controversial area of HIV research, as many scientists and activists question whether this is achievable. Many believe it is impossible. However, we remember that back in the early days of treatment research, many scientists believed that it would never be possible to treat the disease at all. Happily, others disagreed and took up the



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challenge.

Today the question is whether to believe in the outright cure of HIV. The answer to that question must be a resounding yes! Moreover, the pursuit of a cure must be a rallying cry of people with HIV and their advocates worldwide. A lifetime made possible by the constant use of expensive and sometimes toxic drugs may be far better than the death sentence once expected of HIV, but it is far from ideal. Medical science is making enormous strides with each passing year. We must make sure that one of them is the ultimate and complete cure of HIV disease.

Hope for this outcome is alive and well, burning like a series of small fires in the dark. In late 2005, Dr. David Margolis and his team conducted the next round of their experiments using *valproate* (valproic acid) in an effort to clear the body's reservoirs of HIV. Though they haven't yet succeeded, they clearly showed evidence of dramatic reduction of the reservoir. Many follow-up experiments are possible and in development. We salute this team and its leader for their courage and vision.

In another area, a small firm named Koronis is pursuing an unusual theory that turns most treatment research on its head. Almost all other research seeks to slow the rate at which HIV produces mutations because they are the mechanism that produces resistance to anti-HIV drugs. Instead, the theory under study at Koronis seeks to speed up the mutation rate of HIV. Lab studies suggest that just a small increase in the rate of mutations leads over time to a dysfunctional virus—an HIV that can no longer reproduce itself. It's a long way from doing this in a lab setting to making it happen to every copy of HIV in humans, but that doesn't make it impossible. We are watching and encouraging this work as it faces a series of difficult hurdles.

Lastly, our hopes were encouraged regarding a cure this past year when the American Foundation for AIDS Research (amfAR) held its first think tank meeting of researchers addressing the subject of emptying the reservoirs of HIV. In other words, it was a meeting about "the cure." Following the meeting, grant proposals are being sought for this kind of research. The Linda Grinberg FAIR Foundation, which funds leading edge research via grants channeled through Project Inform, has noted an interest in furthering amfAR's work in this area through additional funding for new research proposals. Combined with Project Inform's research advocacy efforts, this growing movement focusing on curative research cannot help but influence the National Institutes of Health to address this area.

Hope is still alive, despite setbacks, and a cure is possible. A cure will someday happen—because people who believe in it will make it possible.



Project Inform Analysis: Results of a "Cure" Study

The August 12, 2005 issue of *The Lancet* reported on the results of a study which attempted to reduce the reservoir of cells that are latently infected with HIV. In theory, a treatment that could achieve this perfectly might result in an outright cure of HIV disease since scientists believe it is the continued presence of this reservoir that makes HIV infection a permanent condition. This study was one of series of steps researchers have taken attempting to deal with the problem of the reservoir of HIV-infected cells. Unfortunately, the magazine splashed the word *cure* all over its

cover, raising inappropriate expectations about what the study was able to accomplish.

These latently infected cells are normally not affected by anti-HIV drugs because they are inactive and not producing virus. Thus, the anti-HIV drugs have no effect on them. Most anti-HIV drugs only work with cells that are active, HIV-infected and producing new copies of virus. Additionally, when HIV-infected cells are inactive, they are also not recognized by the immune system as a problem, again because they are not producing virus or doing anything the immune system recognizes as “wrong.” Thus, they “fly under the radar” of the immune system and remain a constant, unchecked threat. Any time the latently infected cell “wakes up” or is activated, it begins producing new copies of HIV. Thus, the body never rids itself of HIV. Some is always left in reserve.

This particular approach to reducing the reservoir described in *The Lancet* article was proposed and discussed in Project Inform’s Immune Restoration Think Tank several years ago. It was proposed at that time by Dr. David Margolis, whose lab managed the study mentioned in *The Lancet* article. The general model of attempting a “cure” in this fashion was in fact proposed by immunologist Max Cooper of Alabama at the very first meeting of the Think Tank back in 1991, when the meeting was hosted by the National Academy of Science’s Institute of Medicine. Project Inform has described this potential approach to a cure in a number of articles over the years. For those wanting more background, consider the following (available through Project Inform’s Infoline and website):

- *PI Perspective* #26, 1998—Interleukin-2: A Path Toward Functional Eradication?
- *PI Perspective* #24, 1998—HIV Eradication: Dead or Alive, or Even Necessary?
- *PI Perspective* #19, 1996—Eradication of HIV: Hope or Hype?
- *PI Perspective* #17, 1995—*Four New Concepts for Combating HIV Infection*

The basic idea of flushing the reservoir begins with providing maximum suppression of viral replication by whatever means available. This is to make sure that no new HIV is created in the body or allowed to infect cells while the effort to clear the reservoir takes place. In this case, the small study reported in *The Lancet* included four people whose HIV levels were already “undetectable” while on anti-HIV therapy. Their treatment was then intensified with the addition of a potent new drug, T20 (enfuvirtide, Fuzeon). Up to this point, Margolis’ approach was similar to earlier efforts to rid the body of HIV. But his approach differed in the next step. Earlier efforts by other researchers added another type of drug that was intended to “activate” the latently infected cells in the reservoirs. The hope was that this would make the cells visible to the immune system as they began to produce HIV, leading to their eventual death, while the standard anti-HIV drugs blocked any new virus from infecting other cells. These past approaches failed, either because the effort to activate the cells proved too toxic, or because it failed to activate all the latently infected cells.

Margolis’ team tried a different approach at this step. They added a well known and quite safe anti-convulsive drug, *valproic acid*, to the patients’ daily regimens. Recent research had shown that the drug seemed to interfere with the process that allowed some HIV-infected cells to become dormant in the first place. Those cells that were already dormant infected with HIV would just die off on their own over time. If no new dormant, infected cells were created, they theorized the chronic HIV infection would eventually be eliminated.

The challenge of this or any approach to truly “curing” the disease is that virtually every latently infected cell must eventually die without a single new copy of virus being allowed to infect another cell. That’s a pretty tall order and to date, no one has even come close to achieving it.

In the study reported in the August issue of *The Lancet*, a reduction of the number of latently infected cells, ranging from 68–85% in three of the four volunteers, was observed, while there was no

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complete
list of drug
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response in the fourth volunteer. Researchers concluded that that this could be proof of the concept that we might someday be able to cure the disease. Dr. Margolis said that he was concerned that people might over-interpret these results as meaning a cure had been found, but he defended the belief that this was a step in that direction. Some scientists and many people living with HIV applauded the effort, while others raised caution because of the great challenge of dealing with virtually every infected cell.

While Project Inform is a staunch believer in the possibility and eventuality of a cure for AIDS, it's not clear that it's going to happen through eradication schemes of this nature. Others have done similar experiments, such as Roger Pomerantz at Thomas Jefferson University. He had similar results and a few patients remained virus free afterwards, without treatment, for several months. But eventually virus levels returned to detectable, evidence that not all infected cells were destroyed. Another similar experiment, at the Aaron Diamond Research Center in New York, resulted in what may have been life-threatening complications in a patient due to the side effects of a high dose of the drug (OKT3) used for activating cells. Because the experiment failed and a patient was endangered, this experiment did not continue. Researchers in Dr. Anthony Fauci's lab at the National Institute of Allergy and Infectious Diseases also attempted eradication with a combination of anti-HIV drugs and IL-2 (interleukin-2, Proleukin), a potent immune stimulator. Although viral expression was completely suppressed in a number of people, without further treatment, for a number of months, HIV eventually reappeared. This proved that some latently infected cells had escaped the process.

It was refreshing in this new case that some scientists were able to see the results as a sign of progress rather than failure. Research of this type should definitely continue, even it has not yet been fully successful. It may be that multiple rounds of the process need to be repeated to achieve success or a longer period of treatment. Or perhaps we need to try a combination of activating the latently infected cells plus the new approach demonstrated by Dr. Margolis. One thing is clear though and it is that the mere use of standard anti-HIV drugs is unlikely to cure AIDS. One way or another, the problem of the reservoir of latently infected cells must be addressed. We applaud Dr. Margolis and his team for continuing this kind of research, even if we feel *The Lancet* may have engaged in a bit of unhelpful hype on the magazine's cover.



Entry Inhibitors: A Race to the Finish Line

As reported in *PI Perspective* #38, entry inhibitors are a promising new class of anti-HIV drugs. One of them, enfuvirtide, is already approved and two others (maraviroc and vicriviroc) are currently being studied. A third drug was close behind but its development was stopped in October 2005 due to serious side effects. Several others are in early stages of development.

People are hopeful about entry inhibitors for a couple of reasons. Most importantly, they suppress HIV in a completely different way than other classes of anti-HIV drugs, meaning they should be effective in people with resistance to the older drugs. Because entry inhibitors work without interfering with what's going on inside cells there's also hope that they will not have some of the trou-

bling side effects of other drugs, like body composition changes (*lipodystrophy*).

Recently, some of the excitement about these new drugs has been tempered by new concerns about unexpected side effects and somewhat disappointing effectiveness. Early articles hailed them as the leading edge of a new era in HIV therapy, yet the most recent experiences may suggest a more modest future for them. As the two most advanced drugs are studied, researchers should better understand their strengths and weaknesses and how best to use them.

New entry inhibitors in study

Several companies are rushing to bring entry inhibitors to market. Each believes it has come up with the best way to block HIV from entering cells. Currently, there are two frontrunners—drugs that are able to be taken by mouth in pill form. Each is being developed by a large company with substantial resources and expertise in drug development. The drugs are:

- maraviroc (UK-427857) by Pfizer, already in large studies.
- vicriviroc (Schering D and SCH-417690) by Schering-Plough, recently entered large studies.

GlaxoSmithKline's entry inhibitor was recently withdrawn from development due to indications of liver toxicity. Other entry inhibitors not covered in this article, but show some promise in early studies, include: AMD070, by Anormed; BMS-488043, by Bristol Myers Squibb; TNX-355, by Tanox; and PRO 542, by Progenics.

Co-receptor blocking drugs

Maraviroc and vicriviroc interfere with HIV's attempts to enter a CD4+ cell by binding to a cell receptor called R5 (CCR5). If HIV cannot bind to R5, it generally cannot fuse to the cell and enter

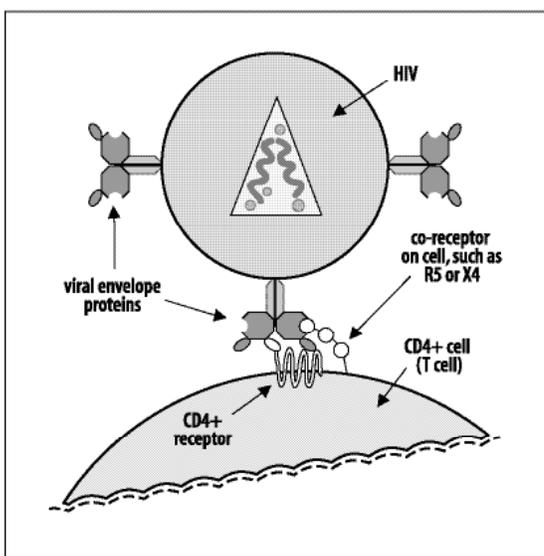
it. HIV can use several receptors on CD4+ cells, but X4 (CXCR4) is the only other one that it uses with any frequency. It is unclear whether HIV will eventually "learn" to use the other receptors after being blocked at R5. Because HIV must first bind to the CD4+ receptor on the cell, R5 and X4 are called *co-receptors*. These receptors have other functions for the cell—not all of which are understood—but HIV takes advantage of them in order to infect the cell.

All cells in a person's body produce R5. Some people make a damaged or non-functional form of it. Researchers began developing drugs to block R5 after it was found that people whose CD4+ cells do not make functional R5 rarely become infected with HIV.

For reasons that are not fully understood, HIV has a hard time establishing a foothold in a person whose cells have no functional R5. Also, some people have CD4+ cells that carry fewer functional R5 than normal. These people can still be infected with HIV, but they seem to carry greater protection against infection than people with normal amounts of functional R5. When they do get infected, the course of their disease is generally slower.

These facts alone are reason enough to explore therapies that block HIV from using R5. However, another reason was learning that people without functional R5 appear to suffer no negative health effects. This is significant and hopeful, as studies have found that there may be severe consequences to blocking other co-receptors from

HIV must first bind to the CD4+ receptor and then to a co-receptor, such as CCR5 (R5) or CXCR4 (X4), before it can infect a cell



HIV.

Drugs that block R5—are there risks?

The immune system is complex and controlling it with drugs is tricky. Researchers simply don't know whether giving someone a drug to block R5 will provide the same protection from HIV as that seen in people who are genetically unable or less able of making functional R5. Also, using drugs to block R5 may be harmful in ways that are not apparent in people who naturally do not make functional R5.

One of the most serious, though theoretical, risks has to do with how changes in receptor use by HIV may hasten disease progression. At least half of all people with HIV eventually have measurable changes in the type of HIV found in their blood. Instead of using R5, HIV begins to use another receptor called X4. This change seems to correlate with a rapid decline of CD4+ cell counts and the onset of opportunistic infections. Other research suggests that nearly everyone with HIV, at some time during their disease, may experience this shift—but about half may revert back to R5 virus.

HIV primarily uses R5 along with the CD4+ receptor to enter cells. However, it can evolve to use X4. Some strains appear to use both (*dual tropic virus*). In test tubes, HIV that uses X4 has been found to cause CD4+ cells to clump together (*syncytia inducing*) and die in a way that R5 virus does not. This, along with the fact that X4 virus usually has been found in people when they begin to have rapid disease progression, has led many to label it as more aggressive and dangerous than R5 virus. However, others point to the fact that half of people who die from HIV disease mostly have R5 virus. This may be because the amount of X4 virus in blood can vary.

So, when researchers looked for X4 virus in these people, it may be that it simply wasn't measurable at that time, but was in fact present. Or, it may be that people with R5 virus are also in danger, whether or not they ever change over to X4 virus. Thus, the story may be too complex to simply label R5 virus as *moderately bad* and X4 virus as *really bad*. But given that some researchers may overstate the negative effects of X4 virus, there are some entirely new risks posed by the studies of R5-blocking drugs.

The greatest potential risk by blocking R5 on CD4+ cells is that it may give HIV that uses X4 a chance to take over and become the dominant strain. If X4 virus turns out to be more lethal than R5 virus, using these new entry inhibitors could actually harm people rather than helping them. This is most likely to happen in those who already have some measurable degree of X4 virus, are heavily

TESTING FOR THE R5/X4 VIRUS

Wise use of the newest entry inhibitors may hinge upon knowing whether a person has R5 or X4 virus. If there's one thing that has become clearer through these early studies, it is that the test used to determine the type of virus in a person's blood has major limitations. In fact, the test (by Monogram Bioscience, formerly Virologic) is reliable only 90% of the time. This means that out of every ten tests done on a sample of HIV, one will miss the X4 virus. Small labs can run similar tests, but none are currently any more effective than Monogram's. Also, none of these labs has anything near the resources or expertise that Monogram has to test thousands of samples.

Clearly, advocacy is needed to improve this test, and Project Inform is working with other groups on this issue. It is also possible that the results of the studies described here will show that the R5-blocking drugs will work (at least together with other anti-HIV drugs) whether or not X4 virus is present. Thus, the only way to know whether the risks outlined here will prove true is through the current studies or those about to begin. Anyone who wishes to enroll in these studies should be aware of both the potential risks and benefits.

treatment experienced, and have CD4+ cell counts below 200 (or lowest-ever counts, *nadirs*, below 200). This risk is theoretical and no one can say for sure that it will occur, but it still is a concern.

Evidence of R5 to X4 shift?

Because using drugs to block R5 might increase disease progression, the earliest studies did not allow people with any trace of X4 virus to participate. Several people who originally showed no X4 virus on the screening tests had X4 virus emerge after taking a short course of the new drugs. When this occurred, other tests were done on the blood that was originally collected. In most cases, these other tests found that X4 virus had been present all along but had been missed. In at least two cases, however, the presence of X4 virus before using the study drug could not be confirmed by using the standard screening tests.

Researchers followed these two people very closely in the months after the studies ended and sent samples of their virus for further evaluation. The results appeared to show that X4 virus had likely been present before they took the study drug, but that there was too little present for the standard tests to pick up. In one of the two, X4 virus disappeared within a few weeks after stopping the drug. In the other person, X4 virus has remained detectable more than a year after stopping the drug. So far, neither case has shown evidence that the shift in virus has caused harm.

Spotlight on the drugs in study

So far there's a striking similarity between the R5 inhibitors in terms of their effects on viral load and the degree to which they remain stuck to R5 receptors for hours (or days) after a person stops taking the drug. One main difference, so far is the degree to which the older anti-HIV drugs may increase or decrease the blood levels of each of the new drugs. Though further data are needed, scientists have developed virus in the lab that is resistant to each of the new drugs. Safety problems have already stopped one R5 drug, and potency problems are being seen in another.

Large studies of maraviroc started in December 2004 while large studies of vicriviroc started in the summer of 2005. Development of a third R5 drug, aplaviroc, has stopped due to several cases of liver-related side effects. AIDS Community Research Initiative of America (ACRIA) maintains one of the best resources for finding studies that may be recruiting near you. It can be found online at www.acria.org/clinical_trials/index.html. Another resource by the National Institutes of Health (NIH) is available online at www.aidsinfo.nih.gov/clinical_trials/ or by phone at 1-800-448-0440.

Maraviroc (UK-427857)

The first safety studies of maraviroc took place in healthy HIV-negative people. Various doses were tried, including single doses as high as 900mg per day and multiple doses of 300mg twice a day, for 28 days. The most frequent side effects were headache and upset stomach. A more serious side effect in those who took more than 600mg per day was a feeling of dizziness or faintness from quickly sitting up or standing (*postural hypotension*).

Animal studies showed that maraviroc could cause irregular heartbeats. So far, this has not been found in human studies. Studies also found that while maraviroc blood levels were reduced by almost half with food, there was very little difference in viral suppression between people taking it with or without food.

Interactions are expected between maraviroc and other drugs. Ritonavir, even at low doses, and saquinavir greatly increase blood levels of maraviroc—by up to four times. On the other hand, drugs like efavirenz and rifampin can greatly lower its blood levels. Pfizer provides information on adjusting the dose of maraviroc when taking it with these drugs. Drug interaction studies are ongoing.

Studies examining the effect of maraviroc on viral load in people with HIV were reported in 2004. It was found that doses of 100mg to 300mg taken twice a day for ten days (without other anti-HIV drugs) resulted in viral load decreases of up to 1.6 logs.

Several studies (phase II/III) started in December 2004. One study of 1,071 people who had never taken anti-HIV therapy is comparing one of two doses (300mg once or twice daily) of maraviroc + 3TC + AZT to efavirenz + 3TC + AZT. All will be screened for X4 virus and anyone who has it will not participate.

A US study is recruiting people who are heavily treatment experienced. They plan to enroll 500 volunteers to determine whether one of two doses (150mg once or twice daily) of maraviroc added to an optimized regimen of approved drugs (based on resistance testing and treatment history) will suppress a person's HIV better than by using the optimized regimen alone.

Eligible volunteers must have known resistance to at least one drug in each of the three older classes of anti-HIV drugs. They will be screened for X4 virus. If it is found, these people will not be eligible but may be allowed to enroll in another study limited to those with X4 virus. Other studies are looking at maraviroc in people with X4-only virus and R5/X4 (*dual tropic*) virus.

Vicriviroc (Schering D)

Schering-Plough has presented data on a 14-day dose finding study of 48 people living with HIV. Volunteers had CD4+ cell counts above 200 and were off all anti-HIV drugs for at least eight weeks before starting the study. People were randomized to take one of three doses (10mg, 25mg or 50mg) of vicriviroc once a day or a placebo. All who took vicriviroc had a major reduction in viral load by day 14, at which point they were scheduled to stop taking the drug.

Viral load results from phase I dose-finding study			
Regimen 28 drug)	Viral load at day 14 (last day on drug)	Viral load at day 16 (2 days off drug)	Viral load at day (14 days off
vicriviroc 10mg	- 0.9 log	- 1.0 log	- 0.2 log
vicriviroc 25mg	- 1.5 log	- 1.4 log	+ 0.1 log
vicriviroc 50mg	- 1.6 log	- 1.5 log	- 0.3 log
placebo	+ 0.2 log	+ 0.3 log	+ 0.2 log

Of note, the decreased viral load was sustained for at least 48 hours after they stopped the drug, and it did not return to its original (baseline) level until two weeks after the drugs were stopped.

A larger ongoing study is comparing three different once-daily doses of vicriviroc given together with a ritonavir boost. To enter the study people must be failing on a ritonavir-boosted protease inhibitor regimen and have viral loads above 5,000. A total of 120 people will receive one of three doses (5mg, 10mg or 15mg) of vicriviroc or a placebo, added to their failing regimen for the first two weeks. The ritonavir dose will be the same as the one used in the failing regimen. Then, people will switch to a new optimized regimen (with input from drug resistance tests) and continue taking the original dose of vicriviroc or a placebo, together with the new regimen and a ritonavir boost, for 46 weeks. The study results will not likely be available until Spring 2006.

An ongoing phase II trial of vicriviroc was recently stopped because of treatment failure. It com-

pared vicriviroc plus AZT/3TC to efavirenz plus AZT/3TC in people who had never taken anti-HIV drugs. An independent group (called a Data and Safety Monitoring Board) evaluating results from the trial recommended that it be stopped when too many people taking vicriviroc were having increases in viral load. This was a somewhat surprising outcome as most people had expected a regimen using vicriviroc to work about as well as a standard three-drug combination. It did not. Studies of the drug in treatment-experienced patients, so far, will go ahead as planned. However, there's no reason to expect the drug to work better in experienced patients than those just starting treatment, so any further studies will be watched very carefully.

The similarity in the design of this study and the ongoing trial of maraviroc raises some concern. After all, the two drugs have shown similar strength in earlier trials and the two studies use the same additional drugs (AZT + 3TC). It is important to note that similar problems haven't been reported for maraviroc, though the study is far from complete.

A large study of vicriviroc in treatment-experienced patients is scheduled to begin in 2005. Those interested in learning more about it can call Project Inform's InfoLine or call or visit the ACRIA or NIH websites as noted earlier. Vicriviroc has not been used long enough to know what side effects it may have. However, some drug interactions are expected given the way that it is broken down by the body and because it must be used with ritonavir. Schering-Plough will provide recommendations for study doctors and volunteers about adjusting the dose of vicriviroc or the other drugs. Other drug interactions studies are ongoing.

Aplaviroc

GlaxoSmithKline's (GSK) R5 drug, aplaviroc, ran into problems and its development has been stopped. The first problems were seen in studies of people who had never taken anti-HIV drugs (*naïves*), when two volunteers developed serious liver problems. In both cases the problems got better when they stopped taking aplaviroc. This led GSK to halt all studies of aplaviroc in *naïve* people while researchers try to determine the cause and severity of the problems. Initially the company said it would proceed cautiously with studies of aplaviroc in people who have taken other anti-HIV drugs. However, the same problem was later seen in the study of people who *had* taken anti-HIV drugs before. This wasn't surprising as here has never been a side effect of an anti-HIV drug that only affected people starting therapy for the first time while not affecting people who have use treatment before. In general, people who have used treatment for longer periods tend to have more, not fewer, drug side effects.

Putting R5 blockers into place

After a year when only one new anti-HIV drug (tipranavir) came to market, it is gratifying and hopeful to have several drugs of an entirely new class making it into larger studies. Because these drugs work so differently than the older drugs and so little is known about how treatment-experienced people will respond to them, it is wise to proceed cautiously.

For instance, people who wish to volunteer for any of these studies should fully understand the potential risks and benefits. As Project Inform has stated since its inception, it is vital to make informed treatment decisions. This is particularly true when a person considers volunteering for a study. The newest experimental drug is not always the best choice for one's treatment, especially when there are so many proven therapies already available.

It may also be that wide-scale access to these drugs may be slow to arrive or may be limited, compared to most drugs that have been approved in the past several years. This is because of safety concerns and the other studies that may be needed. Fortunately, as promising as these drugs are, they are by no means the only or even the best drugs currently being studied in HIV. At least two

other anti-HIV drugs have shown viral load results superior to all three R5 blockers discussed above. Most are covered in more detail on page XXX. With so many new anti-HIV drugs in development, there are an equal number of reasons to be hopeful that they will result in the next major advance in treating HIV.

Anti-HIV Drugs Update: In Brief

Once-a-day Kaletra

The FDA has approved once-a-day Kaletra (lopinavir/ritonavir) for people taking anti-HIV drugs for the first time. This requires taking six Kaletra capsules every 24 hours, with a small amount of food. This dosing scheme is not recommended for people who have taken other anti-HIV drug combinations in the past.

For more information on Kaletra—including side effects and drug interactions—read the publication, *Kaletra*, available at 1-800-822-7422 and www.projectinform.org.

New protease inhibitor approved by FDA: tipranavir

On June 22, 2005 the Food and Drug Administration approved the protease inhibitor (PI) tipranavir for people with extensive anti-HIV drug experience and detectable viral loads. Tipranavir, manufactured by Boeringer Ingelheim, must be taken with a low dose of ritonavir. It is taken as two 250mg capsules twice a day (total daily dose 1,000mg), along with 200mg of ritonavir twice a day.

Tipranavir's chemical structure is different from other protease inhibitors, and it has been shown to work for people whose virus has developed resistance to other PIs. It is approved only for use by people who have PI resistance and detectable viral loads despite taking anti-HIV drug therapy. The greatest benefits from tipranavir were seen when the drug was combined with enfuvirtide in people using both drugs for the first time. Without the addition of enfuvirtide, or perhaps some other potent drug a person is still sensitive to, the benefits of tipranavir are quite limited. The combined costs of tipranavir (around \$13,000 per year) and enfuvirtide (over \$25,000 per year) make for an extremely expensive form of treatment which may not be covered by all payers.

For more information on this new treatment option—including drug interactions and side effects—read the publication, *Tipranavir*, available at 1-800-822-7422 and www.projectinform.org.

No extended release d4T after all

Bristol-Myers Squibb (BMS) announced that it will not be moving forward with an extended release version of d4T, although the Food and Drug Administration (FDA) approved it more than a year ago. The drug is in the same class as abacavir, AZT, 3TC, Combivir, Epzicom, Trizivir and ddI. It is commonly prescribed as a single 40mg pill taken twice a day. The extended release version was a 100mg pill that could be taken once daily. It is likely that the decision not to produce the extended release version of d4T was heavily influenced by a decision by the committee that develops the guidelines for anti-HIV treatment to add strong warning language about the use of d4T to the guidelines and move it from the list of preferred anti-HIV drugs to the optional category.

New form of saquinavir and no more ddC

Hoffmann-La Roche has changed the original version of saquinavir (Invirase), which was the first protease inhibitor approved by the FDA. Until recently it had been available only as 200mg hard gel capsules. The new formulation will be sold as a 500mg film-coated tablet. The recommended dose of Invirase is 1,000mg, for use with a small dose (100mg) of ritonavir, taken twice a day. Thus, the new formulation reduces the number of saquinavir (Invirase) pills from a total of ten per day to just four. The company will no longer sell the soft gel capsule version of the drug. A different formulation of saquinavir, known as Fortovase, has been discontinued by its manufacturer.

The company also announced that it will discontinue the anti-HIV drug ddC. This drug is an NRTI in the same class as 3TC, abacavir, AZT, Combivir, Trizivir, ddI and d4T. Because of problems with potency, side effects, cross-resistance and drug interactions, ddC is rarely if ever prescribed as part of an anti-HIV treatment regimen.

drug i.d. chart

GENERIC NAME	TRADE NAME
Protease inhibitor	
amprenavir	Agenerase
atazanavir	Reyataz
fosamprenavir	Lexiva
indinavir	Crixivan
lopinavir+ritonavir	Kaletra
nelfinavir	Viracept
ritonavir	Norvir
saquinavir	Invirase
tipranavir	Aptivus
Nucleoside (NRTI) and nucleotide (NtRTI) analog reverse transcriptase inhibitor	
abacavir	Ziagen
didanosine (ddI)	Videx
didanosine enteric-coated (ddI EC)	Videx EC
emtricitabine (FTC)	Emtriva
FTC+tenofovir	Truvada
lamivudine (3TC)	Epivir
stavudine (d4T)	Zerit
tenofovir	Viread
zidovudine (AZT)	Retrovir
3TC+abacavir	Epzicom
3TC+AZT	Combivir
3TC+AZT+abacavir	Trizivir
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	
delavirdine	Rescriptor
efavirenz	Sustiva
nevirapine	Viramune
Entry inhibitor	
enfuvirtide (T20)	Fuzeon

Caution and dose adjustments for ddI + tenofovir

In late 2004, the companies that make ddI and tenofovir issued a letter to doctors regarding the combined use of the drugs. The letter urged doctors to use a great deal of caution before prescribing ddI and tenofovir together with either nevirapine or efavirenz in people with very high viral loads.

The basis of this caution were data showing a poor treatment response in some people who started or switched to a new three-drug combination that included these two drugs. Specifically, it was found that people who started therapy with the ddI + tenofovir combination in addition to either nevirapine or efavirenz were more likely to have viral failure than people who started therapy with two other NRTIs in addition to nevirapine or efavirenz. This was particularly true for people who started therapy with a high viral load (above 100,000), a lower CD4+ cell count (below 200) and/or history of an AIDS-defining infection.

Additionally, data were presented in 2004 showing that people who start or switch to a combination including ddI and tenofovir actually had drops in their CD4+ cell count rather than an increase. Though the reasons for poor responses to this combination are not yet clear, it has been found that when people reduce the dose of ddI from 400mg per day to 250mg per day, they do not experience the CD4+ cell count decrease when using the combination. However, even when the dose of ddI is reduced to 250mg per day and combined with tenofovir, the combination should only be used by people whose viral load is under 100,000.

The bottom line on dose adjustments for ddI + tenofovir

- People who have never taken anti-HIV therapy, and whose viral load is over 100,000, should not start a regimen containing a combination of ddI and tenofovir.



- People who are thinking of starting or switching to a regimen that includes ddI and tenofovir should reduce the dose of ddI to 250mg per day.
- People who are currently on a regimen containing both ddI and tenofovir should speak with their doctor about this information and make an informed choice about whether or not to continue using the combination, to reduce the dose of ddI, or to switch to a different regimen.

Understanding Medicare Part D

Getting started: the standard Medicare benefit

Everyone who gets Medicare is eligible for prescription drug coverage through the standard benefit. Under the standard benefit, you are responsible for a plan premium (the amount you pay to keep your plan benefits). The average premium nationwide is \$32.20 per month for 2006. Some plans will have higher premiums, some lower. Once the premium is paid, you are responsible for a \$250 deductible before you start getting coverage for your drugs.

From \$251 to \$2,250 in total drug cost, Medicare will pay 75% of the cost; you will pay 25%. At \$2,251 in total drug cost, you reach the coverage gap, or *donut hole*. You are responsible for all of your drug costs until you reach \$5,100 (including your deductible). At that point, you reach the catastrophic coverage level and Medicare pays about 95% of your drug costs. You will then be responsible for the greater of 5% of your drugs or \$2 for generic and preferred brand name drugs that are multi-sourced and \$5 for all others.

Medicare also offers *extra help* or a low-income subsidy to all who qualify. People who have both Medicaid and Medicare and some others automatically qualify for *extra help*. Others must apply. People who have incomes at or below \$15,000 for an individual and \$20,000 for a married couple may qualify and should apply. *Extra help* is based on both income and financial assets. It will get rid of the donut hole or coverage gap and make a significant difference in how much you have to pay for your drugs. It is very important that you apply if you think you might qualify.

Enrolling in the Medicare prescription drug benefit

If you have Medicare and get your prescription drugs through Medicaid (known as Medi-Cal in California), your drug coverage will automatically change from Medicaid to Medicare on January 1, 2006. You will no longer have Medicaid coverage for most of your prescription drugs. You will be automatically assigned to a Medicare plan in October, 2005 and if you don't make changes, you will be enrolled in that plan in late December 2005.

If you have only Medicare and get your drugs from the AIDS Drug Assistance Program (ADAP) or pay for them yourself, you have until May 15, 2006 to sign up for the new benefit. After May 15, you will pay 1% more for your coverage for each month you delay signing up. However, if you need assistance from ADAP to cover costs associated with Medicare, you will have to sign up for a Medicare plan before you can continue to get ADAP benefits.

If you have Medicare and another type of insurance that pays for your prescription drugs, you may sign up for Medicare Part D or keep your other insurance. To avoid the late sign-up penalty, be sure that your plan is similar to the Medicare benefit. You should receive a letter from your plan

outlining your options but if you have not been contacted, the only way to be sure that your plan qualifies as similar is to check directly with the plan.

If you receive your healthcare through the Veteran's Administration, this new benefit should not change the way you get your prescription drugs.

Choosing a Medicare drug plan

The Medicare benefit allows you to get drugs through either private plans that will provide just your prescription drugs (known as prescription drug plans—PDPs) or private managed care plans that offer you healthcare and prescription drugs (known as Medicare Advantage Plans with Prescription Drug coverage—MA-PDs).

Everyone will have at least two plans to choose from; but depending on where you live, you could have more than 40. Each plan will have a different list of drugs (*formulary*). All anti-HIV drugs will be included on all formularies. However, other drugs you need may not be. Plans will also have different costs, including different premiums and different co-pays for individual drugs. If you qualify for *extra help*, some of these costs will be paid for you. In most places, you will also have to decide if you will use a stand alone prescription drug plan or a managed care plan that also offers prescription drugs. If keeping your doctor is important to you, you should discuss choices with your doctor as well.

Information about plans will be available at www.medicare.gov in October 2005. As well, a *Medicare and You 2006* handbook with information on plans in your area will be mailed to you. The handbook does not have enough information to make a good plan choice but will be a starting point for your decision-making process. Additionally, the handbook has a mistake in it regarding extra help. It states that if you qualify for *extra help*, it will pay the entire premium in all plans. In fact, it will cover only some premiums completely. The website will have the correct information. You can also call 1-800-MEDICARE for information.

If you have Medicaid and Medicare, you will be automatically assigned to a plan in October. If you don't make any changes, you will be enrolled in that plan in December. If that plan doesn't meet your needs, you can choose a plan that works for you starting November 15, 2005. You may change your plan as often as you need to.

If you have Medicare only or Medicare and ADAP, you can sign up for a plan starting November 15, 2005. However, once you make your decision, you have to stay in that plan for the entire year, so it is important to make a careful and informed decision.

How ADAPs will work with Medicare Part D

ADAP is allowed by law to cover premiums, deductibles, co-insurance and co-pays. However, not all ADAP have the money or the set up to pay all these cost-sharing obligations. Each state ADAP will make a decision about what assistance it can provide to Medicare beneficiaries. The requirements for receiving assistance will also differ by state. To find out how your state ADAP will work with Medicare, call your ADAP and ask for their policy. Be aware that the policy may not be in place yet, and ask how you can find out when it will be.

Getting help

You will need much more information about this important and complex benefit in order to make good decisions. HIV-specific information on Medicare Part D can be found at www.taepusa.org. General information can be found at www.medicare.gov, www.medicareadvocacy.org and www.cms.gov.