

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

● Drug Pricing ... and What You Can Do about It

Over the last few years, a great deal of attention has been devoted to lowering the cost of HIV treatment in developing nations. Due to generic competition, activist and political pressure, and movement within the pharmaceutical industry itself, the cost of a typical three-drug anti-HIV combination has plummeted in some countries. Regimens that cost \$15,000–\$20,000 per person per year in the US are now being delivered in some places in Africa, Asia and South America for as little as a few hundred dollars per person per year. Some drugs from major pharmaceutical companies are delivered at their raw cost, while generic equivalents of others are sold at unheard of low prices. The crisis of AIDS in developing nations has done a great deal to show that good drugs needn't be prohibitively expensive.

The success in lowering the cost in some developing countries, however, has had no positive effect on prices in the US. In fact, prices for new drugs have skyrocketed in the US in recent years, while the prices of older drugs have been raised annually. It is appropriate and necessary for health care insurers in richer countries to bear more of the cost for drugs. However, the impact of rising costs on the US health care system can't be overstated. Higher drug prices are one of the primary drivers in skyrocketing health care costs, causing restriction of public programs, making private health care unaffordable, and increasing the already dramatic numbers of the uninsured. A significant portion of the increased (but still inadequate) funding provided by Congress to meet the growing number of people needing treatment has been consumed by the higher cost of drugs. This trend must stop and it must stop now.

When the first protease inhibitors (PIs) were released in 1995 and 1996, their price ranged from roughly \$4,500 per year for the lowest priced (Crixivan from Merck) to approximately \$7,000 year for the higher priced (Norvir from Abbott and Invirase from Hoffman-LaRoche). The two most recently approved PIs, Reyataz (Bristol-Myers Squibb) and Aptivus (Boehringer Ingelheim), each set new records for initial price. The basic price for Reyataz is \$10,862 per year when used alone, or \$14,774 when used with a small "booster" dose of Norvir (which is required for people who have used other protease inhibitors before). Roughly a year after Reyataz set a new price threshold, Aptivus leap-frogged it, selling for \$13,596 alone. As bad as that sounds, Aptivus must always be used with a large booster dose of Norvir, a booster dose that costs private insurance payers as much as \$15,654 per year, bringing the total cost of using Aptivus to \$29,240 per year. (The high cost of Norvir in both cases reflects a huge 400% increase in the price of Norvir that was implemented more than year ago. The increased price applies only to private insurers and individual buyers, while the price

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was not raised for the various government payers such as AIDS Drug Assistance Program [ADAP] and Medicaid. See the box on page 4 about how people using Aptivus can get free Norvir.)

As high as these prices sound, they are not the total cost of the regimen. Both Reyataz and Aptivus must also be accompanied by at least two other anti-HIV drugs, which typically add more than \$9,000 to the total cost of a treatment regimen, bringing the regimens somewhere in the range of \$24,000–\$38,000. But wait, we're still not done! The data available on the use of Aptivus further demonstrate that the drug really only works well in the patient population it is licensed for when combined with another very pricey drug, Fuzeon (Hoffman-La Roche), which adds an astounding \$27,000 to the cost the regimen. So now we're looking at regimen costs that could be as high as \$65,000 per year. With costs like these, plus future annual price increases, is it reasonable to expect our advocates to successfully petition Congress for the needed funding year after year, for the next 25 or 50 years?

To be fair, it must be acknowledged that these are all approximate "retail" prices. The majority of people with HIV get their medicines through government programs and the prices charged to these programs include substantial discounts of at least 25% or more. Still, even a 25% discount leaves a huge cost for these drugs.

Such prices represent a transfer of wealth from taxpayers and purchasers of health insurance directly to the pharmaceutical industry. Unlike many other expensive drugs that are used only during periods of acute illness, pharmaceutical products for treating HIV are envisioned to be a daily, lifelong requirement or, from the perspective of the drug companies, a lifelong revenue stream. In almost any other industry, long-term sale of a product results in gradually reduced prices since the development costs of the product have long since been recovered by the manufacturer. Not so for the pharmaceutical companies, which have somehow convinced the payers and patients that their products should increase in price with each passing year. It's true that the pharmaceutical industry must reinvest a portion of its profits into research and development of new products, but the percent spent this way is not very different from many other industries. In fact, it is lower than in a number of other industries. The pharmaceutical industry's hunger for profits must be challenged. The health and well-being of the sick and the needy, whether in the developing or developed worlds, must not be exploited.

What Can We Do about It?

This brings us to the question of what can be done. Though many think of price limits as an obvious solution, they are unlikely in the current political economic climate. This leaves public pressure and market competition as the primary levers of pricing. This issue is extremely timely because at least four new drugs for treating HIV are likely to be approved in the next 18 months, some as early as June 2006. Two are from a new company, Tibotec Therapeutics (owned by Johnson & Johnson). One is a new protease inhibitor, darunavir, that appears to work well even against protease inhibitor-resistant HIV. A second, TMC 125, may be the first non-nucleoside RT inhibitor (NNRTI) that works against virus that has become resistant to other drugs of this class. A third new drug, from Merck, is the first of a new class of drugs called *integrase inhibitors*. Every indication so far is that the drug will rank among the most potent yet seen, and unlike darunavir, it does not require using a booster dose of Norvir. The fourth new drug heading for approval is maraviroc from Pfizer, which represents another in the relatively new class of drug called *entry inhibitors*, which should work despite any prior form of resistance. The prices set for these four drugs will determine whether the juggernaut of higher and higher prices and ever higher profits will prevail, or whether the pharmaceutical industry will finally come to its senses and begin to play the role of good citizen in a time of worldwide health crisis.

You can help determine the outcome. A campaign is currently underway to petition the leadership of Tibotec Therapeutics to break ranks with its competitors and set a new standard of responsible corporate citizenship. They can price their important new drug substantially lower than the last two protease inhibitors and still make a very healthy profit. We know this because the best selling protease inhibitor, Kaletra (made by Abbott Laboratories), is priced far lower than its newer competitors. Perhaps even more importantly, darunavir will reach FDA approval based on some of the easiest and least expensive requirements the FDA has asked of any company in the last ten years. Early on, the FDA apparently recognized the promise and potency of the drug and invited the company to submit for approval on the basis of Phase II data, without waiting for completion of the normally required Phase III studies. This represents a large economic advantage for the company, one that should be compensated with a respectively lower price.

The case for demanding a lower price from Tibotec is spelled out in a Consensus Statement that is being circulated throughout the country by an ad hoc action called the Fair Pricing Coalition (for more information about the Fair Pricing Coalition, see www.champnetwork.org/index.php?name=tibotec-letter). The Fair Pricing Coalition Consensus Statement asks that Tibotec price its new drug no higher than Kaletra, which is still far from inexpensive (\$9,555 annually, ritonavir boost included). The Statement does not ask that they cut the price to the bone, but only that they reverse the incessant trend toward higher and higher prices. As always, we expect additional discounts for government payers and a rock bottom price when the drug enters the market in developing nations.

The Consensus Statement can be read at this address: www.champnetwork.org/index.php?name=tibotec-letter. Hundreds of community organizations and individuals have already signed on and you can add your name, or your organizations name, via the earlier web address. Each week, an updated list of all those groups and people demanding a fair price is delivered to the Glenn R. Mattes, the President of Tibotec Therapeutics. If and when any indication is seen that Mr. Mattes is not taking the petition seriously, it will be redirected to the highest levels of Johnson & Johnson, owner of Tibotec Therapeutics.

If you really want to make a strong impression on Mr. Glenn R. Mattes, write him a personal letter: Mr. Glenn R. Mattes, President, Tibotec Therapeutics, 430 Route 22 East, Bridgewater, NJ 08807-0914. It needn't be long—just a few strong words about why you are fed up with excessive, unfair drug prices and encouragement for Tibotec to act as a responsible corporate citizen in the pricing of their new anti-HIV drug. The more such letters he gets, the more pressure the company will feel. Companies look forward to high praise and appreciation when they bring a new drug to market, and Tibotec's new drug appears to be a very good product that warrants praise. But not if the company takes advantage of the drugs benefits and sets an exorbitant price. Tibotec needs to know that such a decision on their part will result in a nationwide chorus of protest to the press on the very day they hope to hear applause.

This can only work if people support it. This is your chance to make an impact. Join the fight for fair drug pricing. Demand that Tibotec, which has thus far listened well to the communities affected by HIV, now listen to this cry for lower pricing.

And when Tibotec finishes with its protease inhibitor, we must raise the same cry about the pricing of their non-nucleoside RT inhibitor, and turn our attention to Merck and Pfizer as each brings an entirely new class of drug to market. This is just the beginning of a long fight. Your help is needed at every step.

Free Drugs—and How to Get Them

Drug companies typically make experimental new drugs available to patients in need prior to the completion of their approval by the FDA. This is done in the form of Expanded Access Programs (EAPs), one of the most important victories achieved by early AIDS activism. This is not, however, the only way to access free drugs. Additionally, most companies offer a Patient Assistance Program designed to provide treatment to people who “fall through the cracks” of all insurance and payer programs. Though Patient Assistance Programs usually include a requirement that a patient receives an income level that makes purchasing the drugs impossible, many companies supply the drugs free regardless of a patient’s income.

Here’s a list of currently available and soon-to-be available drugs through Expanded Access, along with a description of a special Patient Assistance Program that provides the drug Norvir free of charge under certain circumstances.

Expanded Access Programs

AVAILABLE NOW: TMC-114 (darunavir). This new protease inhibitor has shown great promise as a drug for “salvage therapy”—that is, for people who have failed most other protease inhibitors. To learn about the program and how to access it, go to www.tibotec.com/bgdisplay.jhtml?itemname=EAP2 or call 1-866-889-2074 in the US or, in other countries: earlyaccess@parexel.com.

“SORT OF” AVAILABLE NOW: TMC-125. This is a new “non-nucleoside reverse transcriptase inhibitor” (NNRTI, drugs similar to Sustiva or Viramune). It is designed to work when resistance has developed to the other drugs in this class. A regular expanded access program for this drug will open in the second half of 2006, but under some limited circumstances, patients may be able to access it now. For people who have lost all other options and start on TMC-114, it is unlikely that this or any other new drug will work very well by itself. Chances of success are greater if two new drugs can be started at the same time. Thus, Tibotec has been willing to make TMC-125 available to the most seriously advanced patients so they can get the chance to start two new drugs at the same time. To access this special, limited program, patients should have their doctor contact Lew Sibert at Tibotec at LSibert@tibus.jnj.com.

QUIETLY AVAILABLE NOW: Free Norvir. When the price of Norvir was suddenly increased dramatically last year, it made it particularly difficult for people using high doses of the drug to pay for it. Consequently, Abbott Labs started a program that supplies Norvir free of charge to anyone who uses or requires 400mg or more of the drug daily. This would apply to people who use “full dose” Norvir as a primary antiviral, and to people who use the new protease inhibitor Aptivus, which requires 400mg of Norvir daily. Access to free Norvir requires patients or their doctors to apply under the Abbott Patient Assistance program www.rxabbott.com/pdf/PAPbrochure.pdf. Doctors and patients should know that do not need to fill out the part of the form that asks for the patient’s income level or the part that asks about any other insurance a patient may have.

COMING SOON: Merck integrase inhibitor, MK-0518. This new class of drug will be available under an expanded access program in the early fall of 2006. Web site and contact information are not yet available. Patients must have failed other classes of drugs.

COMING SOON: Pfizer entry inhibitor, maraviroc. This is another new class of drug that will be available through expanded access in the last quarter of 2006. Web site and contact information are not yet available. Entry criteria not yet determined.

Anti-HIV Therapy Update

Prediction is, at best, an imprecise exercise. This is certainly true of anti-HIV drug development. Many factors affect the pace of drug development and research. Drugs do not move through these processes at an even or entirely predictable pace. Economic, scientific and human factors can have a profound affect on the speed with which a drug or other product moves from the laboratory shelf (or increasingly a computer model) to a product available in pharmacies or drug stores. Nonetheless, it's important for people to know what is coming through the development pipeline—as the treatment decisions made today may affect one's options available later and can, in turn, be affected by what we *think* will become available. This article looks at some of the developments we expect over the next year or so, knowing that these are only our best guesses based on the information we have at this time.

The next new anti-HIV drug to be approved by the Food and Drug Administration (FDA) is likely to be darunavir (previously known as TMC-114 and soon to have the trade name Prezista). This protease inhibitor (PI), developed by Tibotec Therapeutics, is designed to work for people whose virus has developed resistance to any of the currently approved PIs. Tibotec has submitted data from phase II studies to the FDA, which is expected to rule on it in late June 2006.

Based on promising results of earlier studies (called POWER 1 and 2), there is little doubt that the FDA will approve this drug. The drug will initially be approved only for people with PI resistance, like another PI called Aptivus (tipranavir). The manufacturer is expected to quickly complete other studies in people just beginning therapy, thus widening the drug's approval.

Based on its high potency, its strong barrier against development of resistance, and its low level of toxicity seen so far, there seems little doubt that the drug will succeed as first line therapy. This might make it one of the most important drugs in the anti-HIV arsenal. Although completing studies to prove its value in first line therapy will take at least another year, once it's approved for any group of patients, doctors are free to prescribe it for anyone they wish.

It is less clear, though, whether insurance companies and other payers will be as quick to offer reimbursement until these other studies are completed. However, if darunavir offers all the advantages people are hoping for, even payers may see it as a real advance and move quickly to offer reimbursement. The price charged for the drug may play an important role in how supportive payers will be. (For more information, read the article "Drug Pricing ... and What You Can Do about It" in this issue of *PI Perspective*.)

Another new drug from Tibotec should enter expanded access in late 2006 or early 2007. Etravirine (TMC-125) is an experimental non-nucleoside reverse transcriptase inhibitor (NNRTI). It is designed to work on viruses that are resistant to other NNRTIs, like Sustiva (efavirenz) and Viramune (nevirapine). This is a potentially important development, as all of the current drugs in this class are highly cross-resistant—meaning that HIV that develops resistance to one is likely to be resistant to the others. Between etravirine and a second and possibly more potent NNRTI in development at Tibotec (TMC-278), the curse of cross resistance may be conquered for this class of drugs.

Tibotec is also responsible for a unique advance in HIV research beginning in the spring 2006. It is the first study that combines two experimental anti-HIV drugs at the same time. The trial, called DUET, will study darunavir + etravirine vs. darunavir alone in people with resistant virus—with both groups taking optimized background therapy in addition to the experimental therapy. This study is enrolling now, and data should start coming out in 2007. Tibotec deserves recognition for this innovative approach. For years researchers and companies have urged patients with resistant

virus always to start two new drugs at the same time, but this is the first time a company has made it possible for those with the most serious resistance problems.

2006 will see two important milestones for an entirely new class of drugs called *integrase inhibitors*, represented by Merck's MK-0518. Large, pivotal Phase III trials of MK-0518 began enrolling in spring 2006 and the company will open an expanded access program no later than fall 2006. (Expanded access programs provide some people early access to experimental drugs prior to approval.) For a more detailed discussion of MK-0518, read the article "Drug Pipeline Offers Diverse New Therapies and Hope". Early indications are very positive for this class of drugs and for MK-0518 in particular, which is the farthest advanced in development. FDA approval is likely in 2007.

Two other major advancements expected in the near future aren't new drugs, but hopefully better ways to use existing drugs. The first is a needleless injection system for the entry inhibitor (EI) Fuzeon (enfuvirtide, T20). The device, called a *Biojector*, uses high pressure carbon dioxide to inject the drug under the skin, rather than through a metal needle. The hope is that this new system will result in fewer injection site reactions and be easier to use. There is no firm timetable on this, but it looks possible to make it on to the market by the end of 2006.

The final and some think most impactful, anticipated development is the first one-pill-a-day full anti-HIV drug regimen. This new pill will combine three elements of one of the most highly recommended combinations—Sustiva (efavirenz), Viread (tenofovir) and Emtriva (emtricitabine, FTC). While another pill on the market, Trizivir, contains three drugs—Retrovir (AZT, zidovudine), Epivir (3TC, lamivudine) and Ziagen (abacavir), —it is not considered sufficiently potent to serve as a full treatment regimen. It also requires two daily doses. The new combination is a single pill that is taken just once a day.

This achievement required the cooperation of two companies, Gilead Sciences and Bristol-Myers-Squibb, each of which will sell the drug. This level of cooperation, unprecedented in HIV, is good for patients, good for payers (if it's priced fairly) and good for business. The new three-drug combination has been submitted to the FDA for approval and it should be in drug stores by the end of 2006. Because of its advantages, it's likely to be approved faster than this. Let's hope that this will inspire greater cooperation between other pharmaceutical companies.

Looking a bit further into the future, 2007 may see the approval of another type of EI, called a CCR5 inhibitor. Though some experimental drugs of this type have failed in clinical studies, at least one (from Pfizer) continues to show strong performance and another (from Schering) is being studied in treatment-experienced people.

A closing note of caution: While we have hopes for all of the new drugs and products mentioned above, the full story isn't known yet about any of them. Most of the drugs discussed here are experimental and haven't yet been fully proven to be effective. Even at their best, they will still require lifetime maintenance, which is not a cure for HIV disease. At Project Inform we will continue to work toward the goal of a cure, which must be the real goal of AIDS treatment research. Until then, we welcome all advances in HIV care and treatment.

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 |

Update on Structured Treatment Interruptions

Structured Treatment Interruptions, or STIs, were the subject of a lively session at this year's Conference on Retroviruses and Opportunistic Infections (CROI). Spurred in part by the early closure of enrollment for the SMART study (see below), interest in STIs is higher than in many years. This article reviews the studies presented at CROI and summarize the state of current understanding on this important subject.

In order to better understand the results of these studies, it is helpful to review the focus of STI research and what previous studies have shown. Interest in STI research is driven by four different and sometimes overlapping goals:

- Reinvigorating the immune response,
- Helping people with treatment fatigue,
- Helping reduce the costs of treatment, and
- Helping reduce long-term side effects of treatment.

The following is a brief overview of the rationale for each goal and what research to date has shown.

Reinvigorating the Immune Response

This strategy came from observations that HIV disease progression may be linked to the loss of a type of immune cell, called an HIV-specific cytotoxic lymphocyte (CTL). These cells seek out and destroy HIV-infected cells. Some, but not all, research indicates that some long-term non-progressors—those who stay well for many years despite HIV and without therapy—maintain robust levels of potent HIV-specific CTLs while people who progress more rapidly do not.

The goal of one STI approach is to preserve and enhance the body's natural immune responses against HIV infection. In theory, this would help a person's immune system better control HIV on its own for longer, perhaps indefinitely, without therapy. In this context, anti-HIV therapy curbs the destruction of cells by HIV while treatment interruptions are employed to modify the immune response. By starting and stopping therapy periodically, it was hoped that with each successive treatment interruption, the immune system would become more able to recognize and control HIV on its own. This is sometimes called *autoimmunization*, where it's hoped that enhancing a person's exposure to HIV in a controlled manner can create a more potent and effective response against it.

The results of this research, however, were exactly the opposite of what was hoped. People living with HIV the longest were actually more likely to have more potent CTL response. Those who had started therapy soon after being infected with HIV had a fairly weak CTL response that could be boosted somewhat during an STI, but then decreased again after restarting treatment. Similar results have been found in several other STI studies in people with long-term infection.

Several studies have combined STIs with immune therapies, like IL-2 (Interleukin-2, Proleukin) or therapeutic vaccines. The hope is that they may, when used with an STI, provide the needed lift to orchestrate a stronger immune response to HIV. Although several studies are still ongoing, the results so far have not been promising. As such, people who hope to “boost” their immune response to HIV should not look to STIs as a strategy.



For more
treatment
information, call
Project Inform's
toll-free National
HIV/AIDS
Treatment
Infoline at
1-800-822-7422.

Helping People with Treatment Fatigue

Simply put, treatment fatigue is when a person is “tired” of taking anti-HIV medicines. For people who wish to stop their therapy due to treatment fatigue, the data are conflicting. Results from the various STI studies show that some people can successfully take a break from treatment without developing drug resistance, treatment failure or symptoms of disease progression. For others, such interruptions can be harmful. Several factors have emerged that may help predict when a person may have a worse outcome during their time off treatment. These are:

- low CD4+ count (below 200) before starting anti-HIV therapy,
- high HIV level (above 55,000) before starting anti-HIV therapy,
- poorer control of virus while on therapy or other signs of drug resistance, and
- earlier opportunistic infection (OI).

In most studies, at least one-third of volunteers were able to stay off therapy for at least one year. The average time off therapy for the other participants ranged from 8-12 weeks. It should be noted, however, that people who interrupted their treatment had major drops in CD4+ cell counts (on average dropping 50%) compared to people who stayed on treatment. Without proper preventive medicine against OIs, these decreases could be dangerous for people whose counts drop below 200.

A recent and highly publicized study, called SMART, compared several thousand people who used constant therapy to others who stopped treatment whenever their CD4+ cell counts rose above 350. Those who took therapy “breaks” restarted treatment when their CD4+ cell counts fell to 250 or below. Overall, the study showed that people who used continuous treatment were less likely to experience death or disease progression.

Additionally, the study did not show any reduction in drug side effects in the people who cycled on and off therapy as directed by CD4+ cell counts. While this seems to argue against the use of STIs, it is important not to overstate the findings of the SMART trial. What gets lost in the observation that people on continuous therapy did better overall, it is also a fact that a great majority of those taking therapy interruptions fared well too. The actual number of people suffering disease progression or death was quite small in both groups. Perhaps the biggest surprise of the study, though, is that neither CD4+ cell counts nor viral load were able to predict who would experience problems as a result of treatment interruption.

Another unfortunate aspect of the study was that it did not call for patient volunteers to use preventive therapy against the most common opportunistic infections when their CD4+ cell counts fell to levels considered risky. Consequently, the study doesn’t tell us anything about the possible role of preventive therapy as part of an STI strategy.

One important observation from SMART is that no matter what its conclusions, it will not stop people from using STIs in many situations. Treatment is still routinely interrupted when a person experiences certain major infections. It is interrupted because of drug side effects. And it will continue to be interrupted by people who suffer serious treatment fatigue. For such people, certain guidelines may be followed. Careful and increased monitoring by your doctor is critical due to the risks for disease progression and OIs. People should check their healthcare benefits (both private insurance or public assistance) to ensure that the cost of additional lab tests would be covered if needed.

for a complete list of drug names and classes, see the DRUG ID CHART on page 14

Helping reduce the costs of treatment

Interest in using STIs to reduce the cost of treatment has mostly focused on the developing world, where reducing the cost of treatment would increase the number of people who have access to it. Several studies have looked at a kind of STI, called Structured Intermittent Therapy (SIT), where people cycle on and off anti-HIV drugs for specific amounts of time. Most studies to date have shown this strategy to be safe, at least for people who start anti-HIV therapy with CD4 counts above 200.

Helping reduce the side effects of anti-HIV therapy

While there is still much to learn about the effects of long-term anti-HIV drug therapy, some consequences are well understood. Two important concerns are lipodystrophy and heart disease.

Lipodystrophy is an umbrella term for three conditions related to how the body regulates and stores fat (*lipids*). First is the accumulation of fat, usually in the abdomen, the breasts, and around or behind the neck. This is called *lipohypertrophy*. The second concern is the loss of fat, usually in the arms, legs, buttocks and face. This is called *lipoatrophy*. The third problem is elevations in two kinds of fats—called cholesterol and triglycerides—circulating in the blood. This is called *hyperlipidemia*.

Studies looking at the connection between anti-HIV drugs and all three kinds of lipodystrophy have yielded somewhat confusing results. While all three problems are more common in people who have taken anti-HIV drugs, they are all sometimes seen in people with HIV who have never taken anti-HIV drugs. To date there are no studies that have shown that STIs affect the risk of lipodystrophy.

A growing set of data show that people with HIV, especially those taking anti-HIV drugs, are at a slightly higher risk of heart disease. A particularly important study on this subject was the DAD study, which found an increased risk of coronary artery disease in people on all types of anti-HIV therapy. Importantly, the DAD study also found that some of the risk was lowered when people stopped taking their anti-HIV drugs.

STIs have been studied to reduce short-term side effects and improve quality of life as well. The studies have shown conflicting results. The first attempt, which had volunteers go on and off therapy every 14 days, resulted in several people developing drug-resistant virus and losing control of their HIV levels. Another small study of continuous cycles of seven days on and seven days off therapy resulted in fewer side effects and better quality of life for people on STIs than for people on continued therapy. HIV levels were well controlled as well. However, a similar study in Thailand had conflicting results, so it's impossible to state for certain whether STIs of this type will be safe.

The SMART trial also weighed in heavily on this issue with surprising and clear findings. Much to the surprise of many, people who interrupted therapy actually had a worse experience with drug side effects, much as they did with the occurrence of opportunistic infections. This is believed to be due to the way the immune system reacts when a person cycles on and off therapy. Whatever the reason, the SMART trial certainly didn't support the use of STIs as a way to reduce drug side effects.

STIs at CROI

Results from several new STI studies were presented at CROI or shortly thereafter. Here we focus on six studies—SMART, DART, TRIVICAN, PART, WINDOW and ACTG 5170.

SMART

The SMART study was the largest ever STI study, designed to enroll around 6,000 people. It was comparing two anti-HIV drug strategies—continuous therapy vs. CD4+ cell guided treatment interruptions. One-half of the study participants took anti-HIV drugs throughout the study. The

other half started anti-HIV drugs when their CD4+ cell counts fell to 250 and then stopped anti-HIV drugs when their counts rose to 350 (restarting therapy if/when counts again fell below 250).

The SMART study's Data Safety and Monitoring Board (DSMB)—a group of scientists not connected to the study and researchers charged with protecting the safety of study participants—halted enrollment due to a higher rate of disease progression, death and other serious health problems in the STI group compared to those on continuous therapy. Further, they advised that volunteers in the STI group switch to continuous therapy due to the safety concerns that emerged from interrupting therapy.

The first public presentation of the data that led to the DSMB's decision was at this year's CROI. The researchers found higher rates of disease progression or death (2.15 times), serious AIDS-related events (5.82 times), and non-HIV related events like heart attack, liver disease (1.6 times) and death (1.6 times) among those interrupting therapy. These results led the DSMB to decide that the STI strategy used was too risky. In addition to closing enrollment, the researchers recommended that everyone who had stopped taking anti-HIV drugs restart them.

It is important to remember, as stated above, that the actual incidence of disease progression and death remained low overall. An increase of 2.15 times might sound impressive, but if it is 2.15 times a low number, then the result is still a low number and a low percentage of people suffering progression. This aspect of the SMART data has been largely overlooked. We point it out here in hopes that people who are using STIs and doing well need not feel overly frightened by the reports from the SMART trial. The trial significantly adds to the data that people can use in making their decisions about STIs. It does not conclude that everyone taking an STI faces imminent danger of death or disease progression as some reports have seemed to imply.

While many expected there would be more disease progression and AIDS-related problems in people on STIs, the higher rates of non-HIV health problems—especially heart disease—surprised many. In fact the researchers who designed SMART believed they would see fewer such problems in the STI group.

There are two broad lines of thinking on the SMART findings. Some question the CD4+ parameters used to start and stop therapy in the STI group, arguing that 250 might be too low and 350 might be too close to 250. Others speculated on the role that HIV itself might be playing in heart and kidney disease. These doctors and scientists wondered what role inflammation due to unchecked HIV replication might play in the higher rates of these problems seen in the people on STIs.

DART

In March 2006, researchers from the DART trial, which is studying different anti-HIV drug strategies in Africa, announced a similar decision to stop an STI arm of their study. The STI strategy used in DART was different than the CD4+ guided strategy in SMART. DART used a Structured Intermittent Therapy (SIT) strategy that had people alternating between twelve-week cycles on and off anti-HIV meds. Researchers stopped the SIT part of the study because people in that group had about four times the risk of disease progression or death than those on continuous anti-HIV drug therapy. The trial will continue to study whether health monitoring plus lab tests vs. health monitoring alone is better for people taking anti-HIV drugs in Africa. Given there are many areas of Africa without access to lab tests, it will be important to know if health monitoring alone will result in improved outcomes and the safe use of therapy. If not, anti-HIV drugs might only be available in areas where lab tests are available—an important question for developing nations.

TRIVICAN

The TRIVICAN study compared three anti-HIV drug strategies: continuous treatment (CT), CD4+ guided treatment (with the same basic criteria used in the SMART trial), and intermittent therapy (with two-month interruptions alternating with four months on therapy). The researchers halted the CD4+ guided arm due to a marked increase in the risk of disease progression and death. The other two arms of the study continue. It's unclear why the SIT arm of this study didn't show the same negative results as was observed in the DART study. Perhaps twelve weeks off therapy is just too long to let HIV remain unchecked, whereas the eight weeks being studied in TRIVICAN is reasonable. Until more research is done on this strategy, with more consistent results, it is wise for people to be cautious.

PART

One last presentation at CROI held mixed news for STIs. The PART trial compared continuous treatment to cycles of intermittent treatment. Those in the intermittent arm would alternate between cycles of three months taking anti-HIV drugs and increasingly long interruptions, starting at one month and increasing to three months by the end of the study. People had an average CD4+ cell count of 700 at the beginning of the study. Researchers reported a high dropout rate in the STI group, due to large drops in CD4+ cell counts. People with lower pre-study CD4+ cell counts, people with lower CD4 nadir (or lowest ever CD4+ cell count), and those living with HIV for a long time were more likely to see major losses in CD4+ cell counts. Importantly, most people in the STI arm who restarted treatment were able to re-suppress HIV replication. There weren't significant differences in HIV drug resistance between the arms.

WINDOW

A couple of other studies drew different conclusions. The WINDOW trial compared continuous therapy vs. six cycles of eight weeks on, eight weeks off intermittent therapy. In contrast to the SMART, DART, TRIVACAN and PART studies, WINDOW researchers found that people in both arms of the trial had low rates of HIV-related illnesses. Researchers did report higher rates of thrush (oral candidiasis) and idiopathic thrombocytopenic purpura (ITP)—both signs of immune dysfunction—in the intermittent therapy group, but they considered the differences insignificant.

Perhaps the biggest difference between this trial and others like SMART was how the researchers chose to describe their results. Most trials focused on the rates of increased risk associated with treatment interruption. The reports from WINDOW instead focused on the overall levels of disease progression, rather than the difference between the treatment arms. Both points can be (and are) true of many of these studies.

ACTG 5170

Another study, ACTG 5170, examined what factors might predict the results from a single treatment interruption. The findings reported at CROI were consistent with many earlier studies. The researchers found that when people stopped taking their meds, they saw a rapid increase in viral load and decrease in CD4+ cell count followed by a plateau in both after a few weeks. Importantly, they also found a very low risk of disease progression. The factors in this study that helped predict the results from the single interruption were lowest ever CD4+ cell count (nadir) and starting the study with a detectable viral load.

What does this all mean?

How do these studies add to or change our understanding of STIs? There are several conclusions to be reached from these studies. The first is that the hope that STIs would reduce the risk of heart disease and other unintended effects of anti-HIV drug therapy was unsupported by these studies. It is important to caution that each of the studies that found negative results from STIs found them after a relatively short period of time and in an overall context of low net levels of disease progression. The question of the effects of STIs on long-term outcomes remained largely unanswered. However, people considering STIs need to be aware of these short-term risks.

Some of these results, especially those from WINDOW and ACTG 5170, support the idea that while STIs carry some known risks; they can be done safely for some people. A careful analysis of other studies, including SMART, shows the same thing, though it is not emphasized by the study investigators. It appears that STIs are safest for people who have never had very low (under 200) CD4+ cell counts and who were able to reduce viral load to undetectable levels while on anti-HIV therapy, though even this was questionable in the SMART study. None of these studies looked at the question of reinvigorating the immune response, nor have any yet examined the overall cost of therapy.

Taken together, many of these studies show that interrupting therapy carries with it some increased risk of disease progression. People considering an STI may discuss the relative risks with their doctors and develop a strategy for increased monitoring of their health while off anti-HIV treatment. Certainly no one is encouraging treatment interruption when CD4+ cell counts are below 200, whatsoever. Also, there is no support for discontinuation of OI preventive or maintenance therapy when those therapies are indicated. Also, while individuals might have interest, outside of studies, to experiment with STIs, the trade off for interrupting therapy is increased monitoring. Community experience has shown time and again those who wind up in the most troubling and dire health situation are those who stop therapy and don't increase monitoring of their health, CD4+ cell counts and HIV levels.

While the results of some STI studies have not been what many had hoped, a compelling need to continue studies on this subject remains. The prospect of non-stop, life-long anti-HIV therapy is daunting for many. The possibility that this long-term treatment can contribute to a higher risk of heart disease, diabetes and other troubling health consequences also supports the need for more research.

The high hopes for STIs may have indeed faded, but the questions are far from fully settled. Some people with HIV will still want to take time off their HIV meds. This might be to reduce exposure to the drugs and their toxicities, or just due to treatment fatigue. It is vital that doctors and scientists continue to study this important topic, to better understand the safest and most helpful ways for people with HIV to interrupt their treatment.

Drug Pipeline Offers Diverse New Therapies and Hope

Some of the most important research presented at the 2006 Conference on Retroviruses and Opportunistic Infections (CROI) suggest there is a change in the air. The next few years may see the introduction of several wholly new ways of treating HIV. Entirely new classes like integrase inhibitors,

monoclonal antibodies, covert nucleosides and maturation inhibitors give us a pipeline that is both robust and diverse. Together they offer the hope of significant advances for those people running short on treatment options. Some may prove equally important for all people with HIV.

For several years now, HIV drug development has seemed to be a series of incremental advances, with a noticeable lack of new approaches or major advancements. A quick review of the most recently approved anti-HIV drugs tells a story of ‘me-too’ drugs—Emtriva (emtricitibine, FTC), Lexiva (fosamprenavir)—and niche drugs, like Aptivus (tipranavir) and Fuzeon (enfuvirtide, T20). While these are real and important advances for people with limited treatment options (sometimes referred to as treatment experienced or ‘salvage’ patients) and for people seeking easier and more convenient treatment options, there has been little of anything truly new or different.

Currently there are four classes of anti-HIV drugs: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and entry inhibitors. While pharmaceutical companies continue to work on developing new drugs in these classes, this article focuses on drugs with new ways of working—or novel mechanisms of action.

Perhaps the most compelling story out of this year’s CROI was integrase inhibitors. Three companies—Merck, GlaxoSmithKline (GSK) and Gilead—presented data on their integrase inhibitors. Merck’s drug (MK-0518) is the furthest along and is now in the last stage of studies—Phase III. GSK and Gilead’s drugs are now entering Phase II testing and are at least two to three years away from approval. The data on MK-0518 were surprisingly good and generated quite a bit of excitement among conference attendees.

The results of research on another new type of anti-HIV drug, called CCR5 inhibitors, had decidedly mixed results as reported at CROI. Part of the larger class of drugs called entry inhibitors (EI) that includes Fuzeon, this type of drug attempts to stop HIV from entering immune system cells, by blocking the virus from attaching to receptors on the cell’s surface called CCR5. Data on two CCR5 inhibitors were presented at CROI.

Pfizer’s drug, called maraviroc (UK-427857) is the furthest along in development. Little new was reported about it at CROI. Two small studies were discussed: one looking at how long the drug stayed attached to the CCR5 receptor and another one looking at how HIV develops resistance to maraviroc.

Shortly before the conference, the discontinuation of one study of maraviroc was announced. In this study, maraviroc was taken once a day in people who had never taken anti-HIV drugs. When the researchers looked at the first 200 people enrolled, they found that those taking maraviroc once a day together with Combivir (Retrovir [AZT, zidovudine] + Efavir [3TC, lamivudine]) didn’t do as well as people taking Sustiva (efavirenz) + Combivir. Ongoing research is looking at maraviroc twice a day in people new to anti-HIV drugs and both once a day and twice a day in people who have taken anti-HIV drugs before.

Schering-Plough presented data on their CCR5 inhibitor vicriviroc (Schering-D). The main study of vicriviroc discussed at CROI was on the closure of a study comparing vicriviroc + Combivir to Sustiva + Combivir in people taking anti-HIV drugs for the first time. The study was stopped early because of unacceptably high viral breakthrough in the group on the vicriviroc combination. Vicriviroc is still being studied in people with heavy experience taking anti-HIV drugs.

While the development of the CCR5 inhibitors has hit some speed bumps in the past year, development of three other kinds of entry inhibitors continues. Trimeris and Roche Pharmaceuticals—makers of the fusion inhibitor Fuzeon—presented early data on two new fusion inhibitors, called

TR-290999 and TR-291144. The most notable feature of these two drugs is that they are being developed for possible *once a week*—with some quiet suggestion of even less frequent dosage. Both of these fusion inhibitors have been studied in laboratories (called *in vitro* studies) against HIV and shown to be effective. Neither has been studied in humans yet.

Another new approach to try and keep HIV from entering cells is really not new at all. The Houston-based company Tanox is developing an immune therapy, called a *monoclonal antibody* targeting CD4, called TNX-355. This therapy is given through an intravenous infusion given either once a week or once every other week. It blocks the very first step in HIV's entry process, where the virus attaches to the CD4 molecule. Early data suggest this therapy may be useful for people who have dwindling anti-HIV drug options. Another company, Progenics, has monoclonal CD4 antibodies called PRO-542 and PRO-140, which seek to block the CCR5 receptor—much like the CCR5 antagonists discussed above.

Another new entry inhibitor is AMD-070, Anormed's CXCR4 inhibitor. While most HIV uses CCR5 as its way into cells, in some cases the virus uses another co-receptor, called CXCR4 (or X4). This most often happens in advanced HIV disease. This drug is still in the earliest phase of development and not much is known about it yet.

In addition to the integrase inhibitors and the various entry inhibitors, several other novel targets or strategies are being developed. While each is very early in the development process, they represent new and innovative ways of stopping HIV and merit some attention.

Two such approaches try to interfere with the *reverse transcription* process in new ways. The first is called a *covert nucleoside* and is an especially different approach. While one of the goals of all anti-HIV drugs is to prevent or delay the development of resistance, this approach actually seeks to *accelerate* the evolution of resistant virus. Ultimately, this process seeks to force HIV to mutate into a crippled state where it can't infect cells and can't reproduce—something scientists call *terminal mutagenesis*. One such experimental drug, being developed by Koronis, uses this approach. While this idea is quite fascinating and theoretically sound, it raises some interesting issues for both the company and the Food and Drug Administration (FDA)—particularly how to evaluate its effectiveness. The traditional measure of anti-HIV activity is a reduction in viral load. For a covert nucleoside, such a measure won't make sense—at least not at first. The company will have to get the FDA to evaluate this drug in a whole new way if they are to succeed.

In order to explain the next new approach, it is helpful to describe the process of *reverse transcription*. HIV stores its genetic code in the form of RNA. In order to replicate inside an immune cell, HIV must use its RNA to make a DNA copy of itself. This process is called *reverse transcription*. The DNA copy is made with the help of an enzyme called *reverse transcriptase* (RT). The RT enzyme works by reading the instructions written into the RNA, and assembling the DNA using the cell's own building blocks—called *nucleotides*.

There are currently two classes, or types, of drugs that interfere with reverse transcription. The first, NRTIs, are analogs, or 'look-a-likes' of the nucleotides. The RT enzyme is tricked into using these non-functional building blocks, and the resulting DNA chain is non-functional. The other type of RT inhibitors is called NNRTIs. They work by physically attaching to RT, which harms its ability to build the HIV DNA chain.

A new class of drugs, called *nucleotide competitor reverse transcriptase inhibitors* (NcRTIs), can be seen as a mix of the two older approaches. They resemble the NRTIs chemically, appearing to the RT enzyme as the real DNA building block. But unlike the NRTIs, these drugs won't be incorporated into the DNA chain. Instead they will stick to the RT enzyme in the area that the

building blocks are put together and physically block the process. This differs slightly from the NNRTIs, which stick to the enzyme in a different place. Tibotec has one such drug, called simply 'Compound X', which is being studied in laboratories now.

Another new approach works at the latest stage of the HIV replication cycle. These drugs are called *maturation inhibitors*. Maturation is when HIV accumulates its inner protein coat called its *capsid*. Several maturation inhibitors are in laboratory studies and one, called PA-457 being developed by Panacos, is in small human studies.

Project Inform recognizes that the advances in HIV medicine in the past 20 years are truly remarkable, but are still not enough. Our ultimate goal remains the same today as it always has been ... a true cure. While we will never be fully satisfied with incremental improvements of existing types of drugs, we nonetheless welcome all advances in the treatment of HIV—whether being simplification (fewer pills, fewer doses), increased potency, decreased side effects and toxicity, or novel targets.

Since the introduction of the NNRTIs in 1998, the only truly new approach to treating HIV has been Fuzeon (enfuvirtide, T20), which has seen limited use in part because of cost and injection site reactions. As we look at the pipeline today, we see many new and hopeful approaches—attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, monoclonal antibodies, integrase inhibitors, covert nucleosides, nucleotide competitors and maturation inhibitors. While it remains to be seen how effective any of these new drugs are, it is undeniable that the anti-HIV drug pipeline has more diversity than ever before. Novel targets are important for two reasons. First they offer hope to people who aren't fully benefiting from the older kinds of drugs, due to resistance or tolerability. Second, they offer the hope of better, or at least more anti-HIV drugs to all people with HIV.

Three Novel Approaches to Treating HIV

Much progress has been made in AIDS treatment research, resulting in more than twenty anti-HIV drugs now available, with new combinations and easier to use formulations coming to market. Potent anti-HIV therapy has posed an ever growing list of questions about how best to use the therapies and how to manage side effects. Increasingly the concerns of availability and use of the current drugs in developing nations captures growing attention as well. In the midst of the all this, however, it's important not to lose site of the need for wholly innovative approaches to treating HIV—whether that be with the currently approved drugs or with entirely new types of therapies. This article highlights three such approaches. The first is an attempt to flush the reservoir of HIV in resting cells. The second forces drug resistance as a strategy for late-stage treatment. The third combines multiple targets for gene therapy.

Flushing the Reservoir

Despite current potent anti-HIV regimens' ability to reduce plasma HIV levels to undetectable levels for prolonged periods, they do not result in eradicating HIV from the body or a cure for AIDS. It's believed that currently available anti-HIV drugs don't wholly eliminate HIV from the body because the drugs primarily act on actively reproducing virus. In addition to virus that is actively replicating, HIV can also infect a cell and the cell can go dormant or quiet. As long as the cell is quiet, the HIV inside it is also quiet—and undetectable from both the immune system and the effects of anti-HIV

drugs. If or when that cell becomes active, the HIV inside of it becomes active and can rekindle HIV infection in the absence of anti-HIV drugs. These quiet or resting HIV-infected cells act as a reservoir for HIV.

Some researchers believe that a cure for AIDS requires completely eliminating or eradicating HIV from the body, including destroying the reservoir of HIV-infected cells. It has been proposed that one way to do this could be to activate resting cells in the reservoir while a person is taking potent anti-HIV drugs for an extended period of time. If all of the HIV-infected cells are activated, those cells would be blocked from effectively producing virus and would be destroyed. For this to work though requires reaching every single resting infected cell, a rather high hurdle.

Several experiments have attempted this activation strategy. Some have included the immune stimulator, interleukin-2 (IL-2, Proleukin). Others combined IL-2 with a very potent immune activator called OKT3. The OKT3 side effects overwhelmed any benefits, however, and studies were stopped. More recently, late in 2005, an article appeared in the medical journal *The Lancet* reporting encouraging results with the use of valproic acid. Project Inform reported on that study in *PI Perspective #40*.

There are different mechanisms by which HIV remains quiet/latent. Dean Hamer of the National Cancer Institute proposes that it may be possible to flush more of the reservoir by using activation strategies that activate through different mechanisms, called CIS and TRANS. Valproic acid works through CIS activation. Another researcher, David Margolis, has conducted initial studies using valproic acid (see *PI Perspective #40*). Another class of compounds called DAG lactones work through TRANS activation. Using a combination of CIS and TRANS activators (valproic acid + a DAG lactone compound, either LMC03 or LMC07), Hamer notes excellent success in activating quiet cells, at relatively low doses, with few side effects. Hamer proposes another study of CIS and TRANS activation approaches (valproic acid with a DAG lactone compound) along with an immunotoxin (to target and destroy activated cells) in combination with potent anti-HIV therapy. This is the type of research that may bring the field several steps forward.

Recently the American Foundation for AIDS Research (amfAR) hosted a roundtable on HIV eradication/activation that led to a new amfAR funding mechanism for this type of research. More is needed to explore the potential of HIV eradication strategies. Volunteers who participate in studies are true warriors of progress in the field, but not everyone can, wants to or should participate in studies of this nature. Another way to support innovative studies is by donating to the Foundation for AIDS and Immune Research (www.foundationFAIR.org) and specifically encouraging studies attempting to eradicate the reservoir of infected cells. For more information on eradication strategies, see:

- *PI Perspective #40*, “Results of a “Cure” Study”
- *PI Perspective #27*, “IL-2: Flushing the Reservoir?”
- *PI Perspective #26*, “IL-2: Path Toward Eradication”
- *PI Perspective #24*, “HIV Eradication: Dead, Alive or Even Necessary?”

Drug Resistance Strategy

As noted in the article “*Drug Pipeline Offers Diverse New Therapies and Hope*”, there are a variety of new entry inhibitors in development. Currently, there are three major classes of entry inhibitors including 1) CD4 inhibitors, 2) co-receptor inhibitors and 3) fusion inhibitors. On the next page is a grid outlining the products in development.

| CD4 Binding Inhibitors | Co-receptor Inhibitors | Fusion Inhibitors |
|--|--|-------------------------------------|
| Mab 2F5 Mab 2615 Pro-542 BMS-806 TNX-355 | Maraviroc Aplaviroc (terminated) vicriviroc AMD 070 | Fuzeon (enfuvirtide, T20) T-1249 |

The only entry inhibitor currently available through prescription at pharmacies is Fuzeon (enfuvirtide, T-20). Resistance to entry inhibitors is just beginning to be understood. It seems that minor changes in the virus might render co-receptor inhibitor therapies useless. This represents additional challenges to this field of research, which has thus far been fraught with set backs.

There have been a few interesting observations about entry inhibitor resistance—particularly as it relates to the drug Fuzeon. The development of resistance to Fuzeon does not result in resistance to co-receptor inhibitors. In general people whose virus develops resistance to Fuzeon appear to remain fully sensitive to co-receptor inhibitors. Even more interesting is that as people develop resistance to Fuzeon, changes appear in the virus population—forcing diverse virus to become more similar or homogenous with regard to co-receptor use.

There are two commonly discussed co-receptors, CCR5 (R5) and CXCR4 (X4). HIV that uses R5 to infect cells is generally considered less aggressive than HIV that uses X4. Most people have a mixed population of virus, with some percentage using the R5 to infect cells and other virus using the X4. A challenge for entry inhibitor research is that an R5 inhibitor has no impact on X4 using and vice versa. A fear of R5 inhibitor research is that it may give the more aggressive X4-using virus an advantage, resulting in worse outcomes. This might speak to the need to combine approaches, which would target both R5- and X4-using virus. This may ultimately be the best use of these types of entry inhibitors.

The observation that virus rebounding while a person is on Fuzeon becomes more homogenous, opens up a new possibility and potential for the co-receptor inhibitors. When someone develops resistance to Fuzeon, they may indeed be more susceptible to the beneficial effects of co-receptor inhibitors.

While the most potent effect of Fuzeon will undoubtedly always be its anti-HIV activity, it might also be that resistance to Fuzeon may have some benefit in increasing the potency and effectiveness of these other therapies. This is not the only time where the development of resistance to anti-HIV drugs has been observed to have some possible beneficial effects. Virus resistant to Efavir (lamivudine, 3TC) may be more susceptible to the anti-HIV effects of other drugs. Also, protease inhibitor resistant virus may be less fit, or less capable of causing damage to the immune system. In none of these cases is resistance considered a good thing. However, the information suggests that in some cases when resistance does develop it can be used to one's advantage rather than wholly being viewed as a loss of the use of drugs or classes of drugs. This opens the door for entirely new kinds of research, especially beneficial for people who have developed resistance to many anti-HIV drugs.

Ongoing studies of co-receptor inhibitors include people taking Fuzeon as well as folks who have developed resistance to Fuzeon. Emerging data from these studies will allow researchers to have some indication as to the benefit of using Fuzeon in combination with co-receptor inhibitors

and using these inhibitors sequentially, following Fuzeon failure. Results from current studies will point the direction for future research on this strategy. For more information, see:

- *PI Perspective #40*, “Entry Inhibitors”
- *PI Perspective #39*, “HIV Replication Capacity and Treatment”
- *PI perspective #38*, “Entry Inhibitors”

Gene Therapy for HIV

Research on gene therapy for HIV infection is moving from its infancy to adolescence. The *PI Perspective #41* article “A Very Different Approach to HIV Treatment” refers to a Johnson & Johnson sponsored study of ribozyme-modified stem cells, which was highlighted in newspapers across the country. Other innovative gene therapy research continues. Southern California is a hub of activity in this field, with world renowned experts at the City of Hope and long-standing collaborations with the University of California, Los Angeles (UCLA), particularly the Children’s Hospital.

At a recent annual symposium on HIV/AIDS in Palm Springs, City of Hope’s Dr. John Rossi, a pioneer in gene therapy for HIV, presented the outline of a study which will be recruiting later this year. Like the Johnson & Johnson study mentioned previously, this study will also genetically modify stem cells. Stem cells are often called the mother of all cells, as a single stem cell can divide and differentiate into the entire spectrum of immune cells. By targeting this particular cell with anti-HIV genes, it’s theoretically possible to repopulate the entire spectrum of immune cells with cells that can resist HIV infection.

Dr. Rossi’s study is so innovative because it combines three anti-HIV gene therapy targets. Just like the combination of anti-HIV drugs, targeting steps in HIV’s lifecycle worked better than using single drugs, Dr. Rossi’s approach combines three approaches to targeting HIV—and this will be done in addition to the use of anti-HIV drugs. The study will be the first triple-construct approach tested in humans with HIV. The hope is that by combining different approaches resistance issues will be lessened and potency will be enhanced.

The three targets are TAT/REV, TAR and CCR5. TAT/REV and TAR are HIV genes, and CCR5 is a cell factor, which will be targeted to block the virus from entering the cell. This gene therapy approach will include an approach called RNAi, which we discussed in *PI Perspective #38*, in the article, “Interfering with RNA: Kill the Messenger”.

Preliminary data show that this approach does not appear to be toxic to the cells and in test tubes they were able to protect cells from infection for a long time. They have looked at these cells in test tubes after exposure to HIV and after 42 days they are not able to detect virus. This is considered a very long time in these experimental conditions. For more information, see:

- *PI Perspective #38*, “Gene Therapy”
- *PI Perspective #36*, “Interfering with RNA: Kill the Messenger”

Conclusion

While the advent of potent anti-HIV therapy has left a legacy of critical research questions to answer, there is also a need to get beyond highly active antiretroviral therapy (HAART)—to push HIV treatment to new frontiers, to a cure for AIDS. The three strategies highlighted above are but a few examples of this kind of research. Each represents a frontier of harnessing new information and testing to concepts and strategies. These kinds of studies promise to be the building blocks of progress. No one can predict their outcome but each, regardless of outcome, will help to shape progress in the field.

A Very Different Approach to HIV Treatment

On Friday, April 7, The *San Francisco Chronicle* published an article that raised hopes of people with HIV (“A Breakthrough AIDS Therapy in the Making?”). It focused on the experience of a single person in an ongoing study that combines gene therapy and stem cells for treating HIV. The person described in the article completed the process and has been able to stop using anti-HIV therapy for one year and counting, while remaining “undetectable” on tests that measure the level of HIV in his blood. This news is encouraging at first blush, but optimism should be tempered until more information is available. For example, did the study participant receive the protective anti-HIV gene or placebo? Are these encouraging results due to the intervention or some other factor?

While reports of the experience of this single person sound very encouraging, it is far too early to know what is really happening, either in this individual or in the study overall. Some people already have a natural ability to maintain extremely low or undetectable levels of virus without therapy. Some already have an inherited genetic characteristic that makes it very difficult for HIV to infect their cells or reproduce and make new copies of the virus. It is unclear whether this person’s good fortune is due to these or other factors or to the therapy used in the study. The study is “blinded,” which means that neither the volunteers nor the researchers know who got the new gene or placebo. Results will be unblinded after all volunteers complete their course of therapy, which is expected to be in February 2007.

The concept of this study has been in development for close to 15 years. The basic goal is to stimulate the growth of a new immune system in a person with HIV—one that is resistant to infection by HIV. This requires a source of cells that can grow in the patient and a way of altering them so they resist HIV infection. Gene therapy is one way of altering cells. A “gene” can be described as a set of instructions that tell a cell how to make a particular protein or group of proteins. Every cell in your body already contains a set of instructions that made it what it is and tells it what to do. Gene therapy attempts to insert a new gene with some additional instructions. The new gene must be delivered to cells in the body where it can begin to work.

In this study, the researchers chose to insert the new gene into adult stem cells. These cells exist in small numbers in the body and don’t yet have a specific purpose. They have the ability to grow into many possible kinds of cells and thus make a good target for this experiment—as one could theoretically repopulate an entire spectrum of gene-modified, protected cells from a single stem cell.

This phase II study compares stem cells modified with an anti-HIV gene to “placebo” or unmodified stem cells. Immune system cells containing the new anti-HIV gene can inhibit HIV at as many as five different steps in its reproduction cycle. The study includes 74 people with CD4+ cell counts above 300, who have been on stable and effective anti-HIV therapy for at least six months. Volunteers have stem cells (which reside in large numbers in the bone marrow) mobilized out of the bone marrow using a therapy called G-CSF (commonly known as Neupogen, which is normally used for treating low neutrophil counts, or neutropenia). Once the stem cells are encouraged to move out of the bone marrow, they are harvested through a somewhat elaborate blood draw (called pheresis). In a test tube environment, the cells will be modified with either the anti-HIV gene or a placebo. A harmless mouse virus that has had the anti-HIV gene inserted into it is used to infect the stem cells of half the patients, thus giving their stem cells the new anti-HIV gene. The modified cells are then re-infused into the patients. The other half of the patients simply gets their original, unmodified stem cells back.

Once back in the volunteer, these cells grow and differentiate (i.e. become other types of cells as they mature) over time, taking over for the cells that die as a result of HIV infection. Since these cells are now protected against HIV, they live on and in theory will become the dominant cells of the immune system. After a number of months, the volunteers are taken off anti-HIV therapy and closely followed to see what happens. The ideal response would be to see the volunteer continue to do well without therapy, hopefully remaining “undetectable” for HIV. This is what appears to be happening to the person in the article, but it is not possible yet to know if this is a result of the gene therapy or some other factor. (For more information on gene therapy, see the article “Gene Therapy for HIV” in *PI Perspective #38*.)

Many will be watching carefully when the study data are analyzed next spring. Everything about the study makes sense. It represents much of the best thinking of modern science, combining stem cells and gene therapy in a truly leading edge experiment. Certainly, much has yet to be determined about its practicality. Though some of the procedures involved are costly, the total costs will some day have to be compared to the cost of maintaining people on anti-HIV drugs for a lifetime. We salute the researchers in the US and Australia who are treating the patients, the scientists in Australia who developed the gene, and the volunteers themselves who have contributed a great deal of their time and hopes.

That said, though, it would be best to avoid speculation until the actual results are in hand. Little is ever gained by trying to guess what’s happening in a blinded study. Is this new study a “breakthrough” in the making? No one knows. It is, at the least, a bold and welcome experiment in seeking ways to either rid the body of HIV or minimize any future need for therapy. Even if it doesn’t succeed, it will almost certainly contribute important guidance for other similar studies.

Project Inform does not endorse or support specific studies, but we do, on occasion, provide contact information for studies of notable interest to the community like this one. Some sites for this study are fully enrolled, others are still recruiting in Los Angeles and San Francisco. Consider the risks and benefits before agreeing to participate in any study.

Location and contact information

ClinicalTrials.gov (identifier NCT00074997)

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