PROJECT inform

PERSPECTIVE

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

The Crisis in Drug Pricing

The price of drugs is a major factor contributing to the escalating cost of healthcare in America. Within HIV disease, the advent of effective but expensive treatment illustrates the problem. People with adequate access to healthcare routinely live 20 years or longer with HIV. Yet the net cost of the drugs needed over such a long period has become a huge burden. Programs that assist people with purchasing drugs, such as the AIDS Drug Assistance Program (ADAP), are failing to meet the need, due to a mix of excessive prices and increasing demand. More and more people in the US are finding themselves without access to treatment.

Many living with HIV appreciate the contributions that the pharmaceutical industry (hereafter called "pharma") has had on their lives and health, at least if they have access to the drugs. In a relatively short time, it developed more than 20 anti-HIV drugs. The success of basic and clinical research funded by the National Institutes of Health (NIH) combined with the drug development expertise of pharma gave new hope and new life to people afflicted by one of the worst diseases ever known. Activists must balance this against the high prices of the drugs and harm such prices do in the battle for universal access to treatment.

Drug prices have long been a problem, now further complicated by the ballooning federal deficit. The US government will spend at least $500 billion more than it collects in 2004. The budget resolution, now in debate, could contain provisions that would further damage essential domestic programs for many for years to come. State governments face their own budget crises. Consequently, many ADAP programs are reducing the lists of drugs covered and/or the number of people served. More than 1,600 people are already on ADAP waiting lists because of inadequate resources and high drug prices.

Another issue is the recent passage of a partial Medicare prescription drug benefit for the elderly and disabled, who are deeply affected by drug prices. The program helps only some people and doesn't guarantee access to drugs, yet it will cost taxpayers at least $534 billion over the next 10 years. Some estimate that a comprehensive drug benefit for senior citizens, at current prices, would cost close to two trillion dollars. Every new increase in drug prices will make things worse.

Pharma's justification for high US drug prices is that they are necessary to finance research and development (R&D) into new drugs. They argue that the lower prices charged in almost all other countries (typically forced by local regulations) allow little margin for new research. Thus, US taxpayers must subsidize the costs for everyone. No one wishes to force prices so low as to discourage R&D, but there's considerable dispute whether lowering prices would harm future research. It is not clear that European prices, for example, are insufficient to contribute to R&D, and there are many other ways to reduce industry spending, as described later.

A few companies have attempted to keep prices down. For example, Merck originally priced its protease inhibitor indinavir thousands of dollars lower annually than competitive drugs. Others have been less responsible citizens, setting ever higher prices for new drugs and repeatedly raising the price of older drugs for higher profits. Abbott Labs recently raised the price of its protease inhibitor ritonavir several hundred percent in a single step, setting off a storm of criticism and legal action. Most companies prefer a lower profile, quietly making 5–10% increases one or more times a year. Over time, this adds up to major increases. In contrast, we almost never hear that a drug's price has been lowered after its development costs have been recovered.

Unless this trend of escalating prices is not stopped but reversed, it will hasten the collapse of the American healthcare system. The system is already overburdened by rising hospital costs, ballooning malpractice insurance costs, and a rapidly increasing number of uninsured and underinsured people. Pharma, which as a whole is the most profitable industry in America, must understand the part it plays in this time of crisis. While people and institutions suffer greatly, it has come to look greedy and insensitive. It is failing to convince the public and policy makers that its high prices are needed to

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sustain R&D. Something must be done. The only question is whether it will be voluntary change or forced.

Possible solutions are routinely discussed, and some have been tried. To date, there's no national consensus on any of these and views are sharply polarized. The most commonly discussed solutions include:

1. Federal price controls;
2. Purchasing drugs at lower prices through other countries;
3. Changes in patent laws to widen the use of generic drugs;
4. Other methods of drug research, development and manufacturing; and
5. Government action to break patent protection on unfairly priced drugs and other forms of government pressure.

Federal price controls

Federal price controls have been tried as a general way to stabilize prices, but they've not been selectively used in the US to fight prices of individual industries. Economists debate whether controls have helped or hurt. The last imposition of controls occurred in the Nixon era. While they sound attractive, they also carry risks. At best, they temporarily block against runaway inflation. Once lifted, prices quickly rise again.

The core of the problem is that pharma has often been pushed and molded more by Wall Street than the Hippocratic Oath.

Some forms of price control are already used in the US, like forced discounts for ADAP and Medicaid as well as negotiated prices for the Veterans Administration. In Europe, several different approaches help contain prices. European type controls (ranging from cost-effectiveness evaluations, to price comparisons with similar countries, to industry/government negotiations) offer promise, but only when there is a political consensus about their use. It's hard to get a political consensus on anything in Washington. The fact that the US would be the last major industrial country to widely use such controls would bring more burdens to the negotiating table, particularly in terms of how they would affect investment in pharma—and thus the effect on future drug development.

Although price controls are intensely opposed by the present Administration, the mere discussion of them is important and might influence the leadership of pharma. This debate must be encouraged. If industry leaders really believe that price controls would be disastrous to their business, they can easily avoid them by offering their own plan to reduce prices and begin acting more responsibly.

Purchasing drugs at lower prices through other countries

Purchasing drugs through other countries at lower prices (re-importation) is a popular notion, with many in state legislatures and Congress discussing ways to make it legal. It sounds great—like buying drugs at a discount pharmacy rather than a small retail store. It is not that simple, however.

Drugs are cheaper in Canada because its government negotiates prices under the Canadian national healthcare plan. But if large numbers of US citizens, or even whole states, take advantage of Canadian pricing, a huge problem can develop—Canadians may soon be pitted against US buyers. The vast majority of these lower priced Canadian drugs are made by the same companies that sell them in the US at higher prices. Those companies are not going to start shipping greater quantities of their drugs to Canada so that they may be re-imported to the US at lower prices.

Several major drug companies have announced that unless the practice stops, they will stop or greatly curtail shipments to Canada. In addition, advocacy groups in other countries are likely to protest. Already, several of Canada's advocacy groups have petitioned its government to stop sales to the US through internet pharmacies. Another option for industry would simply be to increase prices to all countries, thus undermining the value of re-importation to the US while also harming the interests of citizens of other countries. Such a response could undermine all the progress that has been made in securing lower drug prices for developing nations.

Industry supporters argue that re-importation is, at its core, a way to import price controls into the US. Well-meaning efforts to buy lower-cost drugs this way amount to the US fighting its drug-pricing war on another country's soil, potentially at the expense of their citizens and healthcare systems. There's also growing pressure from the US on the World Trade Organization to establish trade barriers to these practices. Like price controls, however, discussion of re-importation schemes may help stimulate public debate. Whether compromise is possible depends on the scale of re-importation.

Changes in patent laws

Changes in patent laws are sometimes proposed to increase the use of generic drugs. It is only when generic versions of popular drugs become available that market pressures can work to lower prices. Without generic competition, treatment would still be out of reach for most people with HIV in developing nations. However, the competitive power of generics within the US and other developed nations is limited by patent laws. Patent laws create incentives for people or companies to form a steady stream of new and better products. Under current international trade agreements, patent owners get exclusive rights to sell their inventions for 20 years (except in certain healthcare emergencies).

Drugs, however, almost never get the full 20 years of protection due to the long lag time between getting a patent and when a drug comes to market. If it takes 10 years to bring a drug to market, it would only have 10 years of protection left in the marketplace. Drugs are allowed to get back an extra year of patent protection for every two years spent in the FDA approval process, up to a maxi-

mum of 5 years of patent extension. But they are limited to no more than a total of 14 years of exclusive marketing after FDA approval. There are, of course, ways that companies get around this, such as making slight changes in their products and calling them "new" drugs when the patents run out.

Some believe that patent protection may be working too well for prescription drugs, seen by pharma's extremely high prices and high profits compared to other industries. Thus, the threat of further reducing patent protection, or perhaps eliminating the 5-year extension might warrant discussion. But changing patent laws would be very difficult, as the basic patent laws apply to all inventions, not just drugs. It has taken decades to work out the mechanisms of patent protection for drugs, and there's a strong interest in keeping the rules consistent from one country to the next. Policymakers realize that shorter patents, which could hasten generic competition, would likely also result in higher, rather than lower, prices for branded drugs during their patent life.

Other methods of drug research

Other methods of research and production have been proposed as ways to lower the cost of drug development. One could try to put drug development into a public or non-profit environment. While this sounds logical because drugs are an essential health product, it may not be very practical. There are a few pioneering efforts of this type currently underway.

The tough questions are: Who will do the work? Who will fund it? Who has the infrastructure and experience? How would new discovery be fostered in a public setting? Right now, there are no clear answers, other than the existing pharmaceutical industry. Neither government nor anyone outside pharma has the infrastructure for large-scale drug development and manufacturing. Government funds a great deal of basic research, but it is only minimally involved, if at all, in "drug development."

While some may cite Brazil as a recent exception with its production of anti-HIV drugs, it has at best only performed the functions of a generic drug company. It did not create, develop or test any of the drugs it now manufactures. Even if society were to move in this direction, it would take decades to create a public sector process that could compete with industry.

It is time for us to make them be at least as responsible to their customers and the country as they have been to their stockholders.

Action to break patent protection

Public seizure of unfairly priced drugs is one method that has been in search of a test case for some time. Seizure is theoretically possible under a law called the Bayh-Dole Act. Recently, the 400% increase in the price of Abbott's ritonavir created a test case that's currently working its way through the legal process. The rationale is that if government funds were used to help create a drug, then government has a right to seize the product in the event that unfair pricing or failure to produce the product is harming access to a necessary drug.

What remains undefined though is just how much government involvement in a drug's history is needed to make a seizure legal. A large percent of new drugs will have some form of government grant in their history, simply because the NIH funds basic research that leads to new drugs and cures. Patent applications typically list such grants, but this doesn't prove that the government owns or has rights to the patent or product. Another uncertain factor is to what degree access to the drug is being harmed by the company's actions. In the case of the ritonavir pricing action, there are also efforts to test in court whether the company's actions have harmed patients or the drug's competitors. All these matters remain undecided for now.

Still, the threat of such action—successful or not—will cause companies to think hard before acting in the future.

The bottom line: will anything work?

To date, these methods all seem to present both challenges and opportunities. Most lack the necessary support to carry them through a strong counterattack by industry. But this doesn't mean the task of reducing prices is impossible. And we must always remember that drug prices alone are not the sole source of our crisis in healthcare.

The senior managers of pharma must balance many conflicting interests: people want better therapies as quickly and as cheaply as possible; stock owners want to see high profits; institutions that invest employee pensions in drug company stocks want to see their funds grow; regulators want the highest quality data and product; scientists seek investment in their area of expertise and interest; and a lot of ordinary folks who happen to work in the company, with families, needs and lives of their own want to feel good about what they're doing. It is too easy, and unfair, to see drug companies and their executives and employees simply as greedy monsters. But they are indeed people who need to face change.

High profits cannot be allowed to come at the cost of denying people access to medicine, crippling their financial security or undermining our healthcare system. More money should not be spent on marketing than research. The "me too" drugs in their portfolios should not outweigh innovative advances against disease.

The core of the problem is that pharma has often been pushed and molded more by Wall Street than the Hippocratic Oath. The people in this industry need to get serious about the crisis of drug pricing, from the Chief Executives and Clinical Researchers to the Community Relations Managers and heads of Marketing. The system is broken and must be fixed. No one could fix it more quickly than those who run the companies.

As prices have soared, the number of new drugs and devices being submitted for FDA approval has actually declined. In recent years, the industry has consolidated as a few large companies have bought up

more and more of the smaller ones. Yet these acquisitions seem to have done more to crush competition than to develop more and better products. *How is the public served by this?*

Pharma must rethink and restructure its business model. If they truly believe they can't sell drugs for substantially less without harming R&D, they need to ask, "What can we cut? What must we change?" At the same time, government must rethink its all too cozy relationship with the industry. A few suggestions for government and industry follow.

Change the law that allows Direct-To-Consumer (DTC) advertising by drug companies. Billions of dollars could be freed up over the next 5 years to permit lower drug prices, without spending a nickel less on R&D. Vast amounts of corporate cash now go into DTC advertising. This was banned until well into the 1990s, when Congress "gifted" the right to industry.

Although some surveys suggest that doctors and their patients benefit from advertising, these are simply *opinion* surveys. There is **no evidence** that people are medically served by such advertising. Continued bans on this advertising in most other developed nations don't seem to hurt anyone.

Moreover, there's no evidence that the extra sales it generates have resulted in greater revenues being spent on research. However, it does appear that drug prices have risen right along with advertising dollars. Fewer drugs and devices are being submitted to regulatory agencies worldwide each year, signifying that increased drug prices and marketing budgets have not led to new drugs.

Set limits on lobbying. Pharma spends more money on lobbying Congress, the Executive Branch, political parties, and state governments than any other industry. It may also spend more on lobbying than on R&D. (Because of complex accounting practices, it's difficult to know what they spend on anything.) The need to reduce spending in this area requires no explanation.

Remove any bans that prevent government payers, like Medicare, from negotiating prices with pharma. While some government purchasers do negotiate drug prices, a key provision of the new Medicare prescription drug benefit is a ban on negotiating prices with manufacturers. This makes no sense in a country, and under an Administration, that claims to believe in free market forces. The ability to negotiate prices is perhaps the most fundamental tool of a free market economy. Drug prices are negotiated in some way with industry in almost every other industrialized nation.

Use the "bully pulpit" of the presidency to encourage lower drug prices. Pharma currently spends hundreds of millions of dollars to gain the favor of the White House, and it seems to get what it pays for. The president has made it clear he would never consider price controls. So what is his solution then? Let the White House make use of it its friendly relations by telling industry what's needed for the good of the people and the country in these difficult economic times. Pharma can't "take its business elsewhere" because no place else in the world is willing to pay the high prices routinely accepted here.

Let the Boards of the major pharmaceuticals restructure executive compensation packages. This would reward competitive pricing strategies and better product development, rather than just short-term profits. Competitive pricing and better products are perhaps the best ways to increase sales and market share.

Spending on DTC advertising by pharma:

- 1997: 908 million
- 1998: 1.3 billion
- 1999: 1.8 billion
- 2000: 1.9 billion (Jan.–Sept.)
- 2005: estimated at 7.5 billion

Final Comment

However reasonable and self-evident these approaches might appear, none are things that pharma will do on its own. However, they are all things that can be accomplished through public or political pressure. If industry abhors such methods, fine—let them reduce prices some other way. The only option that can't be tolerated any longer is to continue the status quo. In the end, this will crush them as badly as it is already hurting people who need their drugs. It is time for us to make them be at least as responsible to their customers and the country as they have been to their stockholders.

Anti-HIV Therapy Update

New drugs similar to those already approved are in the research pipeline; yet only one, tipranavir (from Boerhinger Ingelheim), may get Food and Drug Administration (FDA) approval in 2004. Drugs of new classes and different modes of action are discussed elsewhere in this issue of *PI Perspective* but they will not be in wider use for two years or more.

New drugs that impact the virus in different ways are needed in order to make the next major advance in the treatment of HIV disease. However, progress is also needed on improving existing drugs and providing options for people who are failing current regimens. This article discusses the progress on new protease inhibitors (tipranavir and TMC-114) and reverse transcriptase inhibitors (capravirine and Reverset).

Tipranavir

Tipranavir has a different chemical structure than other currently available protease inhibitors, which may allow it to work against virus that is resistant to other

Atazanavir and side effects

Results from two studies confirm the benefits of the protease inhibitor atazanavir (Reyataz) with regard to side effects. Several studies show that other protease inhibitors can reduce insulin sensitivity in the body. Reduced insulin sensitivity can lead to diabetes. A study reported at the 11th Conference on Retroviruses and Opportunistic Infections (CROI) found that atazanavir had no effect on insulin sensitivity.

A second study reported at CROI found that Kaletra had more negative effects on cholesterol and triglycerides than atazanavir+ ritonavir. People entering the study had elevated triglycerides and cholesterol from previous regimens. Those receiving atazanavir had reductions in both total cholesterol and triglycerides over 48 weeks. Total cholesterol dropped by 8% and fasting triglycerides dropped by 4%. In contrast, participants taking Kaletra had a 6% increase in total cholesterol and a 30% increase in fasting triglycerides.

This is not to suggest that atazanavir has a lipid (fat) -lowering effect. Rather, an increasing number of studies have found that it simply does not have the negative effects on lipids that other drugs do. Though both studies presented here were rather small, they certainly suggest that atazanavir may be a reasonable alternative for people who have experienced lipid and insulin problems from other anti-HIV drugs.

drugs in this class. It is being studied in people who are taking anti-HIV drugs for the first time as well as in people who have been heavily treated and may have drug resistance.

The body clears tipranavir from the blood quickly, so each 500mg dose of tipranavir must be taken in combination with 200mg of ritonavir. The ritonavir helps keep tipranavir in the blood longer. Both drugs are taken twice daily.

Studies show the primary side effects of tipranavir so far are vomiting, diarrhea and nausea, none occurring in more than 5% of people. Most were able to be managed in studies by taking tipranavir with a light snack. The addition of ritonavir brings the potential for elevation in lipid markers (triglycerides) and liver related enzymes.

Preliminary results from large studies are expected by the end of summer. If favorable, the company is expected to apply for drug approval with the Food and Drug Administration (FDA). The company indicates that an expanded access program will open once the application for approval has been filed.

Tipranavir is available to a small number of people nationwide through an open label safety study (OLSS). The study is open to people living within 100 miles of a phase III study site and who need tipranavir to construct an active treatment regimen. It is currently limited to people with fewer than 100 CD4+ cells. The study hotline number is 800-632-2464.

TMC 114

Like tipranavir, TMC 114 (from Tibotec/Johnson & Johnson) is a protease inhibitor which may have activity against virus that has become resistant to other protease inhibitors. Recently, researchers reported on the completion of a small human study and a test tube (in vitro) resistance study. The goal of the small study was to assess safety and compare the anti-HIV activity of three different doses of TMC 114. Each dose (300mg twice daily, 600mg twice daily or 900mg once daily) was combined with a 100mg ritonavir booster.

The dosing schemes and viral load responses at the end of two weeks (14 days) follow:

- TMC114 300mg + ritonavir 100mg twice daily = 1.2 log reduction
- TMC114 600mg + ritonavir 100mg twice daily = 1.5 log reduction
- TMC114 900mg + ritonavir 100mg once daily = 1.3 log reduction

Viral load responses at the end of two weeks were similar among the three dose groups. Reductions in virus were comparable whether the person entered the study with resistance to only one other protease inhibitor or to all of the approved protease inhibitors. In test tube studies, TMC114 was active even against virus with six or more protease resistant mutations. If these results hold up in larger studies, this could prove to be a very hopeful candidate for people who have problems with drug resistance in need of new treatment options.

Capravirine

Capravirine (from Agouron/Pfizer) is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which belongs to the same class as efavirenz and nevirapine. Early data suggest that it may be active against virus that has become resistant to other NNRTI drugs. It was also found to be quite potent, producing up to 2 log drops in virus when dosed at 1,400mg twice daily. Development of capravirine was stalled when animal studies suggested that the drug might cause heart problems. A review of data from a small human study with close heart monitoring did not reveal heart-related side effects. Development is now proceeding.

In Europe, studies of capravirine are enrolling people who have never taken anti-HIV drugs. Studies in the U.S. and Canada are enrolling people who have been on failing regimens that included protease inhibitors and an NNRTI. The U.S. study will compare three different doses of capravirine + Kaletra + two NRTIs to Kaletra + two NRTIs. People interested in the study can call 1-800-323-4204 for more information.

D-D4FC

D-D4FC (Reverset, from Pharmaset) is a nucleoside analog reverse transcriptase inhibitor (NRTI). Results from a small short-term study of people who have not taken anti-HIV drugs before suggest it may have potent anti-HIV activity. Taken as a single agent therapy (monotherapy, not together with other anti-HIV drugs) over a ten-day period at three different doses, D-D4FC produced the following drops in viral load:

- an average 1.67 log reduction in people on the 50mg once daily dose,
- an average 1.74 log reduction in people on the 100mg once daily dose, and
- an average 1.77 log reduction for people on the 200mg daily dose.

While these viral load reductions are impressive, the study was very small and short-term. Other studies are needed to determine whether the drops in viral load can be sustained over time. Activists will also be pushing for drug interactions studies between D-D4FC and other existing drugs to ensure its usefulness as part of combination therapy.

The company developing the drug shared data from test tube studies showing that D-D4FC may be active against virus resistant to AZT, 3TC and other NRTIs. It is too early to draw conclusions about the resistance and cross-resistance patterns of D-D4FC, however. Nearly every new drug promises activity against drug resistant virus—only larger studies will tell if this holds true over time. A larger study will begin recruiting 180 treatment-experienced people later in 2004.

Conclusion

It is likely that the novel HIV treatment strategies discussed elsewhere in this publication will take at minimum several years before they are more widely available to people living with HIV. Some of those strategies are in their scientific infancy and will take even longer. In the meantime drugs like those discussed in this article offer promising alternatives to people who will need new drugs in the near future.

All four drugs (tipranavir, TMC-114, capravirine and D-D4FC) were developed with the goal of suppressing drug-resistant HIV. Together, they represent three of the four classes of approved drugs. Though not a revolutionary step forward, they nonetheless offer hope to people who will need them.

Genetics, race/ethnicity and efavirenz side effects

A study (ACTG5097) was designed to determine whether higher levels of efavirenz in the blood are related to side effects of the central nervous system (CNS). CNS side effects, including vivid nightmares, difficulty sleeping and mood changes have been reported in a number of efavirenz studies. Results of ACTG5097s were recently reported, finding a significant association between genetic factors, race and how quickly efavirenz is cleared from the bloodstream.

ACTG5097s found that people who identified as black or Hispanic maintained higher blood levels of efavirenz than their white non-Hispanic counterparts. As might be expected, people with higher blood levels of the drug were more likely to stop taking it due to side effects. The study also found that while people with higher efavirenz blood levels did not develop CNS side effects more rapidly than those with lower blood levels, they were more likely to stop taking efavirenz because of them. This suggests that while CNS effects aren't developing more rapidly among people with higher blood levels of drug, when they do occur they are more severe.

Upon closer examination, researchers found a genetic variation that explained the difference in how people's bodies processed efavirenz better than racial identification. This genetic variation, which affects how the liver functions, was found in 20% of black participants and only 3% of white participants. No data were presented regarding the percentage of Hispanic study participants who carry the gene. The genetic tests used in this study are unlikely to be available anytime soon. In the absence of access to these tests, Blacks and Hispanics who are taking efavirenz should be aware of a potential increased risk of side effects and continue careful monitoring.

Further confirmation of the genetic variation, its impact on liver function and the people most likely to carry it is needed to determine its impact on peoples' response to anti-HIV treatment.

Bottom Line on Anti-HIV Therapy Update

Tipranavir

- New protease inhibitor, likely to be approved in 2004.
- May be active against virus resistant to other PIs.
- Must be boosted with ritonavir.
- Low to moderate side effects so far.

TMC-114

- New protease inhibitor, currently in small studies.
- May be active against virus resistant to other PIs.
- Must be boosted with ritonavir.

Capravirine

- New NNTRI, entering large studies this year.
- May be active against virus resistant to other NNRTIs.

D-D4FC

- New NRTI, still in small studies.
- May be active against virus resistant to other NRTIs.

Anti-HIV Pipeline: Spotlight on Integrase Inhibitors

Current anti-HIV drugs work at three points in HIV's life cycle. Entry inhibitors, like enfuvirtide, keep HIV from entering cells. Reverse transcriptase inhibitors—like AZT, tenofovir and efavirenz—keep HIV from changing its genetic structure. Protease inhibitors, like atazanavir and Kaletra, ensure that newly made viral particles aren't assembled into infectious virus. (For a list of these drugs and their classes, see page 13.)

After many years of research, drugs are nearing development that block another part of the viral life cycle. These are called *integrase inhibitors*. This article highlights both the challenges and the promise of integrase inhibitor development.

What are integrase inhibitors?

Viral integration is when newly made genetic material of the virus (called viral DNA) enters the nucleus of a cell and inserts itself into the cell's genetic material (DNA). Once this integration is complete, the cell is operating on the genetic instructions of the virus as opposed to the cell and the cell becomes a sort of HIV factory. Integrase inhibitors seek to block the integrase enzyme from allowing this integration process from happening.

Blocking integrase could offer much to the treatment of HIV disease. Because it would work at a different part in the viral life cycle than existing drugs, an integrase inhibitor would likely work against virus resistant to the current drugs. Also, the integrase enzyme doesn't occur naturally in the body, so blocking it might not cause some of the side effects common to the existing drugs.

Resistance to integrase inhibitors is likely to develop. However, researchers hope that integrase inhibitor resistant virus would be less able to infect other cells and make new virus. Such hopes have kept integrase inhibitor research alive despite the challenges involved in developing them.

Identifying and developing integrase inhibitors

Chemists must comb through millions of potential compounds when searching for drugs that may be active against HIV. In order to narrow the search, they must create tests that determine which candidates are most likely to be active. Creating tests that accurately mimic the integrase enzyme has been one of the biggest challenges. However, a number of private and government researchers have now developed tests for integrase, and two integrase inhibitor candidates have gone into human testing in the past two years.

The first, **L-870,810** by Merck, was last reported on in the spring of 2003. It performed well in test tubes and in animal studies. In both test tubes and monkeys, resistance to L-870,810 was slow to develop and when it did, the resistant virus was severely crippled in its ability to reproduce. Initial tests in HIV-negative volunteers found that the drug was well tolerated. A phase II study was planned for 2003. Merck has been undergoing significant restructuring, however, and their HIV research has been slowed down considerably for the past year. They've stated recently that they are still committed to integrase research and we hope to hear more in the coming year.

The second integrase inhibitor candidate, **S-1360**, is a joint venture between Shionogi Pharmaceuticals and GlaxoSmithKline. S-1360 showed anti-HIV activity in test tubes and safety in animals. In phase I studies, volunteers maintained adequate levels of S-1360 in blood. This had been a concern before the study started, because the drug binds easily with blood proteins, keeping much of it from entering the cells where it needs to go. Side effects were minimal in the study and development moved forward.

A phase II study of S-1360 was conducted in early 2003 in HIV-positive people. Unfortunately, S-1360 did not reduce HIV levels enough to warrant continued development. The companies have a back-up candidate, however, currently called RSC 1838. This compound is similar to S-1360 in its structure and function. RSC 1838 has not yet entered human testing and few details of studies in test tubes and animals are available.

While it has taken longer for integrase inhibitors to make it into human testing than the current classes of drugs, the failure and/or delay of these first two is no reason to write off the entire class. People living with HIV stand only to gain from having more options in treating the disease, and determined activism has helped a number of other drugs make it to the marketplace.

The future of integrase inhibitors

Test tube studies of more than a dozen integrase inhibitor candidates have appeared in scientific journal articles over the past two years. Nearly all are the work of academic scientists in the United States and Europe. While it is too early to tell whether any of these will make it into development, it is imperative that activists work with researchers to help them overcome hurdles to drug development.

Several approved anti-HIV drugs originated from research started at universities. Drugs like enfuvirtide and tenofovir may never have made it through development without the assistance of community activists. Helping add integrase inhibitors to the list of approved drugs is merely one more challenge, and we are equal to the task.

Project Inform's Research Advocacy Priorities

In the lead article of *PI Perspective #36*, "The Cure: We Get What We Demand," Project Inform announced changes in treatment and research advocacy priorities. Response to the issue was overwhelming and positive and many people wanted more information.

Project Inform's treatment and research advocacy goals are to 1) Facilitate research toward a cure for AIDS; 2) Focus research on issues facing people with advanced-stage HIV disease; 3) Address treatment access issues; 4) Address standard-of-care issues; and 5) Remain nimble and responsive to emerging information and issues.

Our strategies to meet these goals are varied and many. They include but are not limited to:

- **one-on-one meetings** with leadership in industry, academia and at the National Institutes of Health (NIH). These cross topic areas from design of drug access programs to pricing to defining research priorities and the mechanisms to serve them;
- **discussions with individual scientists** and/or companies regarding "cure-oriented" research; goal is to first make sure we understand the science involved, then to support and motivate as needed and possible for continued development;
- **hosting meetings of researchers** to focus dialog and strategic planning, as has been done through our Immune Restoration Think Tank (IRTT) and other meetings on structured therapy interruptions (STIs);
- **participating in committees**, such as:
  - fiscal year planning committees where the NIH's Office of AIDS Research (OAR) defines its funding priorities or study sections where grant applications are reviewed and ranked;
  - Federal Guidelines Committee where standard of care guidelines are set;
  - scientific review committees where programs are reviewed;
  - protocol review committees where specific studies are reviewed; and
  - Food and Drug Administration Advisory Committees where new drugs and technologies are evaluated and recommendations are made about their use and licensure;
- **speaking out in various venues**, including scientific conferences and forums on AIDS, FDA hearings, the press, etc. with the goal of keeping the concept of "curing" AIDS on the radar screen; and
- **referring high potential/high risk projects** to potential funding sources.

The following chart does not include all the issues that Project Inform is working on, but rather some representative examples of issues, how we address them and ways others can get involved.

Finally, another goal of this activist effort is to educate people about treatment activism and inspire people to become involved. To that end, in addition to periodic updates through Project Inform's Treatment Action Network (TAN) at *TAN@projectinform.org*, articles focusing on various aspects of our treatment advocacy work will appear in *PI Perspective* throughout the year. Your input and involvement in the fight for a cure is always encouraged and welcomed.

The issue	What we'll do about it
Potentially effective treatments and strategies often languish because researchers across disciplines rarely share data and ideas or think together strategically to solve problems.	Engage top HIV and other disease researchers in creating strategic plans for collaboration and the creation of new research studies.
	Identify funding mechanisms for new research coming out of the strategic plans. Influence funding mechanisms toward research of interest to the community.
	Share ideas generated by the IRTT with research institutes like the Institute of Human Virology (IHV), individual researchers, other activists and PI constituents.
Large networks that establish scientific priorities and conduct research on therapy, basic understandings of HIV and vaccine research are inefficient and hinder progress toward a cure.	In 2004 proposals will be developed to "re-compete" nearly all of the large networks that conduct HIV research. Project Inform will influence the "re-competition" to serve the needs of our constituents.
Potentially important therapies often face roadblocks in drug development.	Meet with pharmaceutical and biotech companies that have novel therapies to treat HIV to drug development plans and ensure they meet community needs and identify obstacles to progress and work to remove them.

How we'll do it	What can others do?
Project Inform's IRTT is an internationally acclaimed think tank, including thought leaders inside and outside the field of HIV to brainstorm on ways to repair the immune system of people with advanced stage disease.	Support Project Inform and/or individual research institutes.
Foundation for AIDS and Immune Research (FAIR) has been instrumental in providing seed funding for many projects borne out of Project Inform-sponsored events on topics ranging from salvage therapy to STIs. Project Inform staff sits on the Board of Directors and the Scientific Advisory Board for FAIR as well as co-sponsors events with FAIR. The NIH funds the majority of HIV research worldwide. Most NIH research is conducted through the National Institutes of Allergy and Infectious Disease's (NIAID) Division of AIDS (DAIDS). Project Inform meets with OAR and DAIDS staff to discuss priorities and work to influence funding decisions and programs in accordance with the needs of people with HIV.	Donate to foundations that fund AIDS research, like FAIR. Supporting funding mechanisms like FAIR allows research to get off the ground quickly and move forward.
The IHV and the University of Baltimore is an integrated HIV research effort formed under the leadership of Dr. Robert Gallo. It is one example of the types of research efforts Project Inform engages in, through one-on-one interaction with researchers to providing input into scientific priorities of the institute. Creative, imaginative scientists working together hold the key to a cure. Maintaining relationships with the scientific community, fostering collaborations, providing community input into priorities and helping to remove barriers to moving innovative ideas forward are among the most important strategies activists can use to accelerate the pace of discovery toward a cure, outside of working to increase the resources for this effort.	Serve on local Institutional Review Boards (IRBs) that review the ethics of research and the adequacy of informed consent documents. Get involved in local Community Advisory Boards (CABs) for HIV research centers. Educate yourself about new research opportunities and volunteer for studies that are meaningful and of interest to you.
Project Inform and other organizations attended preliminary meetings, hosted by DAIDS, on the re-competition issue. Several groups are following its progress and providing comment. Project Inform attended an inter-institute meeting debuting re-competition issues at NIH. This provided opportunity for Project Inform staff to hear concerns of other institutes as we formulate strategy. Project Inform will continue meeting with DAIDS leadership over the next year. The scope of influence involves assessing the structural needs of networks to support research toward a cure and making sure these needs are addressed in funding applications.	Support Project Inform. Write or call your elected officials in Washington about the importance of funding biomedical research at the NIH and in particular the importance of HIV/AIDS research funding.
As new therapy ideas are developed, Project Inform meets with industry sponsors in order to: • learn about and provide input into drug development plans; • encourage research in HIV where plans don't include an HIV component; • provide consultative input and/or assistance on overcoming structural barriers to research (regulations, etc.); and • assure that companies provide early access programs that meet community needs as research progresses.	

Entry Inhibitors

Entry inhibitors are a new class of anti-HIV drugs that work by blocking the virus' ability to infect a cell. There are two general types of entry inhibitors: fusion inhibitors and attachment inhibitors. They may be joined by a third type in future years.

Enfuvirtide (T20, Fuzeon), a fusion inhibitor approved by the Food and Drug Administration in 2003, is the first of this new class available for wide scale use. While enfuvirtide has proven to be potent, its side effects, mostly associated with the fact that it has to be injected with a syringe, have discouraged many people from using it. Still, others have been denied access because of the extremely high cost of the drug, which prevents many states from including it in their AIDS Drug Assistance Programs (ADAP). For more information on enfuvirtide, call Project Inform's toll-free hotline at 1-800-822-7422.

Many believe the greater promise for entry inhibitors will be realized with small molecule drugs. When large molecule drugs, like enfuvirtide, are taken orally, the digestive process breaks them into smaller pieces, thus rendering them ineffective. Therefore, they must be taken by injection. Small molecules drugs, however, are unaltered by the digestive system and can be taken by mouth, avoiding the problems associated with injections. Several are in development, including six that are in human studies, which we report on here.

HIV viral entry involves four steps. First, the virus attaches to the CD4+ protein, a receptor that appears on certain cells of the immune system. Then, it binds to a second surface protein on these cells, called a co-receptor. The most common co-receptors for HIV are CCR5 and CXCR4. Once it's anchored to the two receptors, the virus fuses its outer coat to the coat of the cell. Lastly, HIV sheds its own coat and injects its genetic material from its core into the cell.

There are compounds in development that target each of these entry steps. Most are still in test tube studies. The six entry inhibitors currently in human studies can be divided into two categories—those that block the first step (virus attachment to the CD4+ protein) and those that block the second step (binding to a co-receptor).

BMS-488043 is an oral attachment inhibitor drug that binds to CD4+ receptors. By binding, it blocks the virus from attaching to the cell. It is currently being studied at two doses, 800mg and 1,800mg, twice a day. Preliminary data show that among the 12 people who were given the lower dose (800mg twice daily), viral load decreased an average of .73 logs compared to .02 log decrease among the three people who received a placebo. Information was not presented on the higher dose group, but will be forthcoming. Further studies are being planned.

While enfuvirtide has proven to be potent, its side effects, mostly associated with the fact that it has to be injected with a syringe, have discouraged many people from using it. Still others have been denied access because of its extremely high cost.

TNX-355 is a *monoclonal antibody* of CD4+. It's a man-made antibody, binding to CD4+ cells in hopes of blocking the first step in the viral entry process—attachment to the CD4+ receptor. In a small study, 22 people were given TNX-355 by injection either weekly or every two weeks in addition to their standard anti-HIV regimen for nine weeks. Viral load reductions of approximately 1 log were observed within 2 weeks of initiating TNX-355. However, viral load returned to pre-study levels by the end of nine weeks, with evidence of resistance. CD4+ cell counts fluctuated during the study, and maximum increases ranged between 103 and 257, with greatest increases being seen among those receiving weekly injections. One inherent limitation of many monoclonal antibodies is that the human body sometimes makes antibodies against the antibody, diminishing their effectiveness. An additional concern is that monoclonal antibodies are very expensive to make in the large quantities needed for chronic treatment.

PRO 542, from Progenics, mimics CD4+ cell receptors, causing HIV to bind to PRO 542 instead of CD4+ cells. In one study of heavily pre-treated people whose drug regimens were failing, viral load reductions of 60–80% were seen after a single dose of PRO 542. The results are promising and follow-up studies are planned. However, the drug must be given by subcutaneous injection, a clear liability.

Schering D is a small molecule oral drug that binds to the CCR5 receptor and thus prevents HIV from binding to this co-receptor. Recent data from a small dose finding study were encouraging. A total of 36 people, who were not on other anti-HIV drugs, received one of 3 doses (10mg, 25mg and 50mg) of Schering D every 12 hours for two weeks. An additional 12 people received a placebo. Viral load decreases were reported in all groups receiving Schering D, with the largest decrease seen at the highest doses (-1.08 log, -1.56 log and -1.62 log respectively). No significant changes in viral load were seen in the placebo group.

UK-427,857 is another oral CCR5 blocker. Data presented last year from a small dose finding study, show it to be potent and well tolerated. A total of 16 people were given UK-427,857 at two dose levels and were compared to eight people given a placebo. At the higher dose, 100mg two

times a day, seven out of eight people had a 1 log reduction in HIV viral load. Half the people taking the lower dose of 25mg two times a day had viral load decreases of greater than .5 log. No serious side effects were reported in the study. As is the case with the Schering D drug, it is not clear whether the optimal dose has yet been determined for this drug.

GW-873140 is also an oral CCR5 blocker. In a small safety and dose finding study, the drug was found to be safe, with no serious side effects reported. The most common side effects were nausea, diarrhea and abdominal cramping. No data on anti-HIV effects were reported. Follow-up studies are planned.

Commentary

The promise of entry inhibitors, especially small molecules, has many companies working on their own novel drugs. Many are still in pre-clinical development, and are years away from being available. However there are a number of promising candidates already in human studies. If these continue to show promise, some might reach wider human use within two or two and a half years.

People living with HIV need drugs that address new targets, that are easier to take and have fewer side effects. Entry inhibitors hold promise in these ways, but as always, the proof will come from clinical studies.

Gene Therapy for HIV

Manipulating the body's cells and genes to treat disease holds great potential, but it is a field of research in its infancy. It will likely not yield results for years or perhaps decades as it takes baby steps towards progress. And although dramatic advances in treating HIV are not expected to come soon, its by-products—such as information about the immune system and HIV infection—may contribute to short-term advances. This article provides an overview of the reasons for and challenges of gene therapy research.

Why gene therapy?

Your immune system includes many parts: thymus, lymph nodes, bone marrow, etc. The cells in your body are made from cells found in your bone marrow. One special cell found in bone marrow, called a *stem cell*, is sometimes called the *mother of all cells*. If your immune system is intact and working well, then a single stem cell could divide and populate the full range of cells in your body.

Imagine there's a gene that makes a cell resistant to HIV infection. In theory, if that gene was inserted into a stem cell, all of the offspring of that cell would carry the gene and be resistant to HIV infection.

Again, in theory, as HIV destroys a person's CD4+ and other immune cells, the new cells resistant to HIV would replace them and thrive. Eventually these newer cells would take over and HIV could no longer weaken the immune system. Although a person may still have HIV, it could do no harm. The HIV may just die out because there are no cells for it to infect; or, it might persist but couldn't harm the immune system to any great degree.

The challenges

The success of using gene therapy to treat HIV rests on some important assumptions. The first is that all parts of the immune system must be intact in order to support the stem cells in repopulating the system. However, some researchers suspect that HIV may damage the thymus. So, at some point in a person's HIV disease the thymus may not help develop new healthy CD4+ cells. Other therapies may need to be used to improve or enhance damaged immune environments (such as the thymus or bone marrow) in order for gene therapy to be successful.

Assuming that the thymus, bone marrow and other immune environments are functioning well, the next challenge is finding a gene that makes a cell resistant to HIV infection. Once it has been identified, it's necessary to get that gene into a cell. Some researchers are experimenting with injecting these genes directly into muscle, called *direct DNA injection*. However, most researchers believe that the most effective way to get a gene into a cell is by "packaging" it into a virus. Viruses that scientists use to deliver genes, called *vectors*, include the Adeno-associated Virus (AAV) and maybe even crippled versions of HIV.

Getting a gene into a cell is no small feat. Not only must it be passed into the cell, but it must be done without harming it. It must also get into the gene without causing disease itself (and/or without combining with another virus, like HIV, and then causing disease).

In other gene therapy experiments for HIV, researchers have removed and genetically changed stem cells. However, when the new cells were infused back into the body, other immune cells detected that they had been altered and destroyed them. Therefore, it's not merely a matter of getting the gene into cells but doing it in a way that doesn't let the other cells target and destroy the new cells.

Once a stem cell is changed with a protective gene, and it remains functional and not targeted for destruction, the next challenge is making sure the stem cells begin dividing and that their offspring carry and use the protective gene. Of course, it's key

that the new cells aren't also targeted and destroyed. While the ideal target for gene therapy may be stem cells, researchers are also looking at altering their offspring CD4+ cells. This would help rid at least one of the challenges in stem cell research.

The challenge of getting genes into cells occurs in all gene research, from HIV to cancer to genetic deficiencies. The solutions will probably come from combining the findings from these fields of research. However, there are still many concerns about safety, and they must be addressed carefully.

The Basic Message

- Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!
- If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.
- Learn about your healthcare options and local support services.
- Get a complete physical and blood tests for CD4+ cell count and HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.
- Work with a doctor to develop a long-term strategy for managing HIV disease.
- If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.
- If anti-HIV therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.
- If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.
- If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.
- If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps monthly. Consider therapies for preventing MAC/MAI and CMV.
- Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.

Work in progress

Carl June at the University of Pennsylvania has reproduced CD4+ cells (not stem cells) that are resistant to HIV. His group has altered these cells with an HIV-based *lentiviral vector* that carries a gene targeting HIV, called *HIV antisense*. Together with ViRxSys, his group changed a large number of cells (above 90%) in the lab.

One small study is focusing on collecting safety information on five volunteers who have failed at least two anti-HIV regimens and have HIV levels above 5,000. They each will get one dose of these altered CD4+ cells. Their HIV levels and CD4+ cell counts will be checked along with the number of days that these cells persist.

Jan Van Luzen, through the Universities of Frankfurt and Hamburg in Germany, is developing a small study of gene therapy aimed at blocking HIV's entry into cells. (This is similar to the anti-HIV drug, T20.) The gene is called M87oRRE and the vector being used is called *myloproliferative sarcoma virus*. Van Luzen will alter CD4+ cells using Carl June's methods. The study will enroll ten people who are resistant to all classes of anti-HIV therapy and have CD4+ cell counts below 200. The first volunteer was treated by injection in January 2004. So far, no data are available.

Researchers in the US and Australia have developed a mid-sized study of gene therapy that targets the *tat gene*. The gene, called Rz2, is a hammerhead ribozyme and can potentially stop HIV at five places in its replication cycle. It is passed into stem cells using a retroviral vector, one that has already been evaluated for safety in over 50 studies.

This study will enroll over 70 people. Volunteers must have CD4+ cell counts above 300, and have been on anti-HIV therapy with HIV levels below 50 for at least six months. The study will include an interruption in anti-HIV therapy in order to assess the anti-HIV activity of the gene.

Data from a ten-person phase I study of this approach suggest that it's safe. (There were no safety concerns, and some volunteers have been followed for three years.) The Rz2 gene was found in the new cells in all volunteers. The study is enrolling at UC Los Angeles (Dr. Ron Mitsuyasu), UC Stanford (Dr. Tom Merigan), San Francisco (Dr. Steven Becker), and St. Vincent's in Sydney (Drs. Cooper and Carr).

Conclusion

Several studies using gene therapy to treat HIV have started over the past few years. Over the past decade, however, gene therapy research in general has been a rollercoaster of enthusiasm and disappointment. The darkest period struck just a few years ago when a volunteer in one experiment died due to complications from the procedure.

All human gene therapy research was stopped for nearly two years until the cause of death was evaluated and safety concerns were addressed. More recently there has been a renewed enthusiasm as gene therapy has successfully treated some other conditions. Advances in technology are also overcoming other challenges in the field.

Gene therapy research still faces many challenges, in addition to those outlined in this article. They include the need for increased public funding for biomedical research and the short-sightedness of biotech and drug companies investing in the future. It also includes the hurdles faced by independent researchers struggling to turn novel ideas into useful therapy for the patient.

Several years ago there was much enthusiasm for the RevM10 gene being researched in partnership with Systemix Corporation. Systemix was then bought by a larger drug company, and both gene therapy and HIV didn't fit into their development plan. The studies were stopped and the program was shut down.

Although gene therapy research won't offer a quick cure for AIDS, it is becoming an increasingly important part in the future of HIV treatment. It offers a new frontier for a cure, with great hope for promising new treatments.

Anti-HIV Drug ID Chart

GENERIC NAME	TRADE NAME
Protease inhibitors	
amprenavir	Agenerase
atazanavir	Reyataz
fosamprenavir	Lexiva
indinavir	Crixivan
lopinavir+ritonavir	Kaletra
nelfinavir	Viracept
ritonavir	Norvir
saquinavir hard gel	Invirase
saquinavir soft gel	Fortovase
NRTI (nucleoside analogue reverse transcriptase inhibitor)	
abacavir	Ziagen
didanosine (ddI)	Videx
didanosine enteric-coated (ddI EC)	Videx EC
emtricitabine (FTC)	Emtriva
lamivudine (3TC)	Epivir
stavudine (d4T)	Zerit
stavudine extended release (d4T XR)	Zerit XR
zalcitabine (ddC)	Hivid
zidovudine (AZT)	Retrovir
3TC + AZT	Combivir
3TC + AZT + abacavir	Trizivir
NtRTI (nucleotide analogue reverse transcriptase inhibitor)	
tenofovir	Viread
NNRTI (non-nucleoside reverse transcriptase inhibitor)	
delavirdine	Rescriptor
efavirenz	Sustiva
nevirapine	Viramune
Fusion inhibitor	
enfuvirtide (T20)	Fuzeon

Drug Delivery Strategies

The promise of drug delivery strategies is in their potential to improve current treatments and create opportunities for experimental therapy. Drugs that are absorbed through the skin or the nose instead of taken as a pill could help people reduce side effects and improve adherence. Drugs that are injected daily could instead be given through an implant once a year or through skin patches. Time release technology might allow for drugs now taken three or more times a day to be taken once a day or even once a week.

These methods are already being used to treat other conditions. Many companies probably feel that it's cheaper and safer to spend money on developing drugs that don't rely on experimental drug delivery. However, the next leap in treating HIV disease will likely require that researchers and drug makers think beyond the status quo.

HIV is not the only disease where people must take medicines exactly as prescribed for long periods of time. Diabetes and tuberculosis are two other conditions where strict drug schedules often present challenges. Until recently, however, drug makers basically offered only two ways to take most medicines—as a pill or a shot.

Recent advances in technology offer exciting alternatives to the handfuls of pills that many people now take.

Because most people prefer taking a pill over an injection, research in HIV and most other diseases has focused almost solely on developing drugs that are taken by mouth, usually as a pill. Only when a compound can not make it through the digestive system have companies considered making drugs that need a direct route to the bloodstream. Often, such drugs weren't developed at all as companies feared patients wouldn't use them.

People living with HIV are all too familiar with the shortcomings of current anti-HIV drugs. All of them demand near perfect adherence. Some cause hard-to-manage side effects like nausea, vomiting and diarrhea because of how they affect the digestive system. Also, the size of pills and the number that must be taken are a barrier for many, even those who do not find these strict pill schedules troublesome.

As is true with many drugs in pill form, most anti-HIV drugs require that people take a larger dose of the drug by mouth than is necessary by injection. This is because only a small percent of what starts out in the stomach makes it into the blood.

Recent advances offer exciting alternatives to the handfuls of pills that many people now take. One area of intense focus is the search for needle-free devices. More and more medicines are now delivered to the bloodstream less intrusively, through skin patches, gels and creams, inhaled products, nasal sprays and small patches that attach to the gums in the mouth. In the future, consumers may be given things that look like pens, or a sort of air gun. Both use air pressure to shoot a dose of medicine through the skin without a needle.

Getting drugs through the skin

Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include, among others, gels and creams for vaginal

yeast infections, topical creams for skin infections and creams to soothe arthritis pain.

New technologies now allow other drugs to be absorbed through the skin (transdermal). These can be used to treat not just the affected areas (for example, the skin) but the whole body (systemic). A growing number of medicines are now available as transdermal patches.

Patches usually have an adhesive rim that sticks to the skin, while the center is coated with a film of the active drug. The drug is slowly absorbed through the skin making its way into the bloodstream. Examples include patches that contain testosterone, estrogen, pain relievers and nicotine (to help people quit smoking). Other patches deliver anti-seizure medication like gabapentin (Neurontin).

Controlled release of the medicine is one of the greatest advantages of patches. In some cases, the active drug is mixed with another substance that controls how quickly it's absorbed through the skin. Also, a thin net-like layer of material can be placed between the drug and the skin to control absorption. This allows most patches to be worn continually for at least 24 hours. Some can be worn for several days.

Another form of transdermal drug delivery includes devices that use air pressure to inject a small stream of medicine through the top layers of the skin. Air pressure guns have been used for several years to give vaccines to children. Small, disposable pen-like devices are also available for diabetics who take insulin daily. Researchers working on HIV gene therapy have experimented with this technology to inject genetic material through the skin or into muscle.

Getting drugs through mucous membranes

Many drugs, when delivered to the lungs or inside the nose, are quickly absorbed into the bloodstream. Inhaled drugs now in development include a broad range, from pain relievers to an array of vaccines. In what could be a major advance in treating diabetes, an inhaled form of insulin is now being tested.

Also, expect to see other new products that are absorbed through mucus membranes (thin layers inside the nose, mouth, vagina and rectum). These include nasal sprays, buccal patches and suppositories. Butorphanol (Stadol), a pain reliever, is now available as a nasal spray. Several recent papers indicate nasal sprays may be an ideal way to deliver some peptide-based drugs that cannot be taken as pills.

Buccal patches are small patches that stick to the inside of the cheek. They slowly release medicine over time through the mucous membranes in the mouth. Buccal patches are now used to deliver antifungal and heart medicines. Buccal forms of anti-asthma and pain relief medicines are also being studied.

An ideal place to deliver drugs is through the rectum with suppositories. The lining of the rectum is porous and can absorb drugs quickly into the bloodstream. Drug makers have been slow to develop suppositories because they fear that most people are unwilling to use a drug that's put into the rectum.

However, nurses have long used them to care for infants and adults who are unable to take pills. Suppositories are used most often with anti-nausea and anti-asthma drugs, as well as hormones. Recently, researchers began to see their potential and are now developing new drugs to be given this way.

Drug delivery and HIV

There are currently limitations to the technologies described above, particularly with regard to current anti-HIV drugs. Most are made of molecules too large to pass easily through the skin or mucous membranes. For some drugs, the quantities that must be given for each dose are far too large to be made into patches or suppositories. However, these obstacles may not be insurmountable.

Researchers have already found chemicals that help larger molecules pass through the skin. Other chemicals cause drugs to stay in the body longer or to make it into cells more easily. The substantial improvements in treating hepatitis C with pegylated interferon is just one example of success in this area.

While much of this research is new, it demands our attention. It's not difficult to imagine the benefits of using anti-HIV drugs in small doses only once a day or even once a week by a patch or inhaler.

While these treatments do not exist today, the technology to create and test them does. Dozens of companies are developing and improving them. These are genuinely exciting developments. They have the potential to greatly ease the lives of people living with HIV, if not today then certainly in the future—as long as people living with HIV and their advocates push for them.

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Cytokine Therapies: Harnessing the Immune System

Immune cells communicate through chemical messages. For example, one chemical might direct cells to where they are needed to fight off an infection. Another may make cells reproduce, cloning themselves to build an army to combat a specific infection. These chemicals are called *cytokines*.

Scientists have been trying to decipher the chemical language of the immune system to learn how to harness it for use in the fight against AIDS. This article provides a general picture of cytokine therapy to date—approved therapies, those currently in large studies, those entering studies in HIV soon and a glimpse at tried and failed approaches.

Cytokines: the past or the future?

One of the great clichés of popular writings about medicine is the claim that some products "boost the immune system". This is far easier said than done, nor is it always clear that the goal, even in HIV disease, should be to "boost" any aspect of the system. Just as often, the real goal may be to suppress or modulate some aspect of the immune response.

Therapies designed to influence the immune system are called immune-based therapies. The field of immune-based therapies (IBTs) is still in its infancy, but not so new that the reality of IBTs is outside the grasp of day-to-day use in the practice of medicine. There are currently approved and proven cytokine therapies that are routinely used by people living with HIV. These include cytokines like interferon-alpha, granulocyte colony stimulating factor and erythropoietin-alpha.

Interferon-alpha (Infergen, Roferon, Intron-A, Peg-Intron) is a cytokine with broad antiviral properties. It has been researched and proven useful in treating viral hepatitis. It is also used in treating an AIDS-related cancer, Kaposi's Sarcoma (KS), which is triggered by human herpes virus 8 (HHV-8), also called KS Herpes Virus (KSHV).

Interferon-alpha is most known in the setting of HIV as a broad spectrum antiviral. While test tube studies show some anti-HIV activity of interferon-alpha, studies in people have been conflicting. Other facets of its impact on immune functions are also being explored. For example, studies are underway to see if its use can prevent diabetes. It has also been proven to be useful in treating non-viral cancers, such as malignant melanoma. It is available in standard and "PEG" (pegylated) forms. These forms combine it with PolyEthylene Glycol, which stabilizes the interferon and keeps it in the bloodstream longer, thus improving its effectiveness.

Granulocyte colony stimulating factor (G-CSF, neupogen, Filgrastim) is used by people with low neutrophil cell counts (*neutropenia*). Neutrophils are important in fighting bacterial infections. When these counts are very low (below 750) people are at increased risk for severe and potentially life-threatening bacterial infections. Drugs to treat HIV and related conditions, particularly anti-CMV drugs, can cause neutropenia. It has also been associated with HIV disease progression. G-CSF mobilizes neutrophil cells and causes them to reproduce.

Erythropoetin-alpha (epoetin-alpha, Epogen) is used for treating mild-to-moderate AZT-associated anemia. *Anemia* is a decrease in red blood cell counts. Red blood cells carry oxygen throughout the body. Severe anemia is treated with blood transfusion. Symptoms of anemia may include fatigue, dizziness, difficulty concentrating, menstrual abnormalities and/or decreased sex drive. Anemia can be caused by HIV, HIV-related conditions and/or by drugs used to treat HIV.

The horizon

Interleukin-2 (IL-2, Proleukin) Of the cytokines being researched in the setting of HIV, IL-2 is the most widely studied and furthest along in development. Also known as *T cell Growth Factor*, IL-2 stimulates CD4+ cells to reproduce. An emerging body of research suggests that IL-2-stimulated cells thrive better in the face of HIV infection than other CD4+ cells. IL-2 induces increases in CD4+ cell count levels that far surpass those achieved by any other therapy researched for HIV. Two very large studies are underway to see if IL-2, in addition to anti-HIV therapy, reduces disease progression and prolongs life. For more information on IL-2, call Project Inform's Hotline.

IL-2 is also being evaluated for its potential to heighten responses to therapeutic HIV vaccines. A few small studies are including IL-2 as part of acute infection and early disease treatment and structured treatment interruption (STI).

The bleeding edge

Two cytokines are drawing increased interest from researchers for their potential in treating HIV infection. These are interleukin-7 (IL-7) and interleukin-15 (IL-15).

Interleukin-7. A healthy adult will maintain a CD4+ cell count generally from 500–1,500. What keeps cell counts from falling below 500 or from reproducing out of control remains something of a mystery. When CD4+ cell counts drop below normal ranges, other cells begin producing IL-7 (among other things), which in turn stimulates CD4+ cells to reproduce and causes the thymus (where new CD4+ cells come from) to produce more CD4+ cells. Low CD4+ cell counts have been correlated to increases in IL-7 levels in people with or without HIV (e.g. bone marrow transplant patients, etc.) It's theorized that the body produces more IL-7 as CD4+ cell counts fall as a way to prompt the regeneration of CD4+ cells to normal levels. For this reason it is believed to be a potentially important HIV therapy.

The first human study of IL-7 is recruiting volunteers in the setting of cancer. HIV researchers are watching this study and will learn about dose, schedule and side effects that will be further evaluated in

HIV studies. While there is increasing interest in using IL-7 for HIV, there are concerns about safety. IL-7 activates HIV and particularly a very aggressive form of HIV, called *syncitia inducing* (SI) or R4-dependent virus. It's possible that this concern could be lessened by giving IL-7 with anti-HIV medications. Some research in animals suggest that short-term activation of HIV by IL-7 might be a good thing as it may decrease the reservoir of HIV lurking in resting cells. The major barrier to moving this research forward is that no company committed to HIV research currently makes a form of quality controlled IL-7 suitable for large human studies.

Interleukin-15 (IL-15) appears to preferentially enhance CD8+ cell number, function and survival in animal and lab studies. These cells are important in cell-to-cell killing of virally infected cells. While IL-2 stimulates CD4+ cells to reproduce, IL-15 stimulates CD8+ cells. Also, IL-15 appears to inhibit cell death caused by activation. Immune activation and a cascade of activation-induced cell death are increasingly believed to be part of the immune dysfunction of HIV disease (the "sink and drain" notion that HIV simply kills billions of cells each day is no longer widely held). Increases in IL-15 levels have been associated with better control of HIV infection, though which is the cause and which is the effect have not been clearly determined. An IL-15 study for treating HIV has been in development for years and never materialized. The major barrier to moving this research forward is that the company who owns IL-15 (Amgen) is not committed to HIV research.

Tried and failed and tried again?

Several cytokines have been looked at in the context of HIV. **Interferon-gamma** enhances the function of cells that control mycobacterial infections, including tuberculosis and MAC. It has been studied together with anti-TB treatment in people with TB and HIV. It is also being looked at as an adjunctive therapy to enhance vaccine effects. Early studies suggest that low doses of interferon-gamma may control HIV whereas high doses may promote HIV replication. Interferon-gamma, however, is also associated with cell activation, which isn't necessarily a good thing. Over the years, increased interferon gamma levels have alternately been described as both a good thing and a bad thing.

This point is important when considering the challenges of researching cytokines. In the body, cells are producing these chemicals at very, very small—nanomolar—concentrations and together with other cytokines. The combination of cytokines, in varying concentrations, elicits different immune responses. At low doses IL-2 preferentially stimulates natural killer cells, while at higher doses, delivered intermittently, it stimulates CD4+ cells to reproduce. When IL-2 is given at high dose daily it produces no appreciable effect on CD4+ cell count. When it is given for five days every eight weeks, the effect is profound and pronounced The challenge with cytokine research is not merely to understand the various biologic functions of the cytokine, but also how best to give the therapy to achieve the desired responses.

Interleukin-12 (IL-12) was researched in the early 1990s because it's believed to enhance cellular immune responses (the type of responses associated with killing HIV-infected cells, as opposed to killing free virus in blood). Results from small studies suggest it had no effect on either HIV levels or CD4+ cell counts at doses that were tolerable. Dosing and schedules of doses may not have been fully explored to truly understand the potential of this therapy, however.

Granulocyte macrophage colony stimulation factor (GM-CSF) was evaluated in a large study to see if adding it to anti-HIV therapy would decrease risks for opportunistic infections among people with more advanced HIV disease. While there were some interesting observations of decreases of specific bacterial infections among those receiving GM-CSF compared to placebo, the differences were not significant overall.

Interleukin-10 is an immune suppressive cytokine that suppressed HIV replication in test tubes. One study in people showed no impact on HIV replication, positive or negative when IL-10 was given at 1, 4 or 8 microgram/kg daily compared to placebo. Another study suggested that IL-10 therapy may decrease HIV levels.

Interleukin-4 has been researched for activity against the AIDS-related cancer Kaposi's Sarcoma (KS) and its impact on HIV was monitored. At a dose of 1 mcg/kg daily IL-4 had no effect on HIV levels and little to no impact on KS.

These are a handful of cytokines that have been studied in the setting of HIV. While they failed to show benefit, it may be that at different doses, given intermittently as opposed to daily, or combined with other cytokines, they will one day be researched again and show promise.

Conclusion

As research advances and tools are improved to understand the immune system, more is being learned about cytokines. There is increased interest in harnessing the language of the immune system to direct its responses and improve health. This research holds great potential, though the road to realizing it will likely be riddled with failed experiments and confounding results. Cytokine therapy is not merely a tool of the future—years from the grasp of our medicine cabinets. To the contrary, several cytokine therapies are now routinely used by many people living with HIV.

Furthest along in the research pipeline is IL-2. Answers about the value of IL-2 in combination with anti-HIV therapy are expected within the next 2–3 years. The hottest new tickets in the cytokine town are IL-7 and IL-15. Although neither has made a debut in studies of people with HIV, there's not an immunology conference in HIV where they're not the buzz. Activist involvement is needed to ensure these two therapies are researched in HIV.

A handful of other cytokines have been tested in HIV, with either negative or confounding results. They may make comebacks as more is learned about the language of the immune system and how it acts.