PROJECT inform

PERSPECTIVE

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

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A Tale of Two Tragedies

When the World Trade Center and the Pentagon were attacked on September 11, Americans were stunned by the tragedy unfolding before them on television. Thousands of lives were lost in the outcome, resulting in an unprecedented outpouring of sympathy, support and demands for action. Most people felt they had never seen or experienced anything like it before. To a smaller portion of the population, however, the shock of sudden and unforeseen disaster was strangely reminiscent of what we experienced in the onset of the AIDS epidemic. There were many similarities to what people were feeling then and now. Little more than a month after the terrorist attacks, however, it was clear that there were also some striking dissimilarities that added to the pain felt by all those who have lost someone to AIDS. Those dissimilarities became clearer with each passing month.

Certainly, no one expected to see commercial airliners hijacked and flown into crowded skyscrapers and government buildings. Likewise, in the early 1980s, no one expected the sudden appearance of a deadly new disease ravaging clusters of our friends and loved ones in cities across the nation. It was only a few years earlier that some prominent scientists declared that the fight against infectious disease was over and had been won.

The horrible damage caused by fuel-laden airliners exploding into buildings was all but beyond our imagination. Equally beyond our imagination was this new disease that appeared two decades ago, first called Gay-Related Immune Deficiency or GRID (and later, AIDS). It was a disease that appeared without warning and seemed to lead to a painful, agonizing death in just a few weeks for some, a few months for others. The depth and scope of human destruction was so unprecedented that only a very few people were quick to recognize the horror that was to come. Some, like Larry Kramer, were even ridiculed for sounding the alarm.

On September 11, while the image of jetliners exploding into the World Trade Center was still painfully fresh, we were further stunned to see these seemingly invincible structures collapse in upon themselves, crushing thousands of living human beings in a vast cloud of toxic dust, rubble and fire. A week earlier, no one would have believed that such pillars of steel and stone could collapse at all, let alone from the top down. In the tragedy that began to unfold in the early 1980s, scientists, doctors and ordinary citizens were perplexed to see a disease that led to the collapse of the greatest achievement of evolution, the human immune system. Working from the inside out, here was a diabolically clever virus that destroyed the very system that was otherwise designed to defeat it.

In2001, New York the city reeled in shock as it counted the dead for days on end after the terrorist attack. It seemed that almost everyone in this great city of 10 million plus had lost a co-worker, a friend, a son or daughter, a mother, father or loved one. Some, like the firemen and the city and Port Authority police died in great acts of heroism, struggling to save others. No doubt there were many other unsung heroes, regular office workers, who also lost their lives while trying to save those around them. Some of those trapped in the towers found their situation so hopeless that they cast themselves out windows from a thousand feet above ground. A sadly similar story had unfolded in the AIDS epidemic. From its first days to the present, people have agonized over the loss of friends, family members and loved ones. Within our own communities, each of us knew people who suffered and died. Fearless researchers and healthcare workers mingled with the sick, often without protection, initially without knowing how the disease was spread and whether they would become the next victims. Heroic people rose up in our communities to care for the sick and dying, while others orga-

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In This Issue

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nized to fight for the needs of those infected and help each other avoid the new plague. Many unsung heroes stayed quietly at home, nursing loved ones and acquaintances sometimes abandoned by their families. As in New York, some surrendered to the hopelessness of the early days of AIDS, taking their own lives rather than face the suffering and near certain death.

Indeed, any person who has lived with and has been affected by the AIDS epidemic likely has a special empathy for the people harmed by the terrorist attacks. We know what it's like. Albeit a cliché, we feel their pain. Nearly 3,000 died in the terrorist attacks on a single day. They and their loved ones deserve our greatest sympathies. So too do the families of people who have died of anthrax. Yet, more than ten times this many still die of AIDS every year, even today in this time of a greatly reduced death rate. At its peak, more than 50,000 per year died of AIDS in the US alone. Worldwide, the figure is in the millions and growing rapidly.

Nearly 3,000 died in the terrorist attacks… Yet, more than ten times this many still die of AIDS every year, even today in this time of a greatly reduced death rate.

While acknowledging the similarities of these two devastating events in human history, let us also look to the many disturbing differences in how the nation responded to each, differences that speak to our character as a people and a nation. Within days of the events of September 11, the country undertook a massive mobilization to help all those affected. Government didn't hesitate for a moment to commit its full resources to meeting the needs of New York and Washington. A blank check was given to ease the pain and begin undoing the damage. Eventually individual grants of $300,000 to one half million dollars were given to each family who lost a member. Whatever someone said was needed, government was quick to send even more. Private charities raised more than half a billion dollars in the first six weeks. Celebrities and entertainers were all but tripping over each other creating fund-raising events and appealing for donations. As the economic consequences set in, government almost overnight authorized close to $15 billion to bail out the airline industry, not all of whose financial woes began on September 11. In later weeks, as the scare of anthrax settled in on the nation, the Department of Health and Human Services received $1.6 billion more for vaccines, antibiotics and bio-terrorism planning efforts. The CIA was given an *extra* billion dollars to make sure it could assassinate Osama Bin Laden. The Post Office received commitments in the billions of dollars to update equipment and enhance safety. The Coast Guard was given the nod to receive the bulk of its request for $10 billion to modernize our coastal defenses. Ten billion more will be spent over the next four years to enhance airport security. At least 120 billion new dollars will be spent to meet expanded military requests over the next five years.

All in all, it was a rather impressive response for the first few months of a tragedy. Of course, this tragedy hit at the mainstream of American society, not just some marginalized groups.

Memory paints a rather different picture of how the country responded when AIDS came on the scene. For the first few years after the initial outbreak of AIDS, the federal budget for combating AIDS, researching the cause, and finding treatment was… zero. Not one thin dime. Researchers who chose to work on AIDS in the early 1980s did so only by raiding other budgets and existing grants left over from cancer research. Government didn't encourage them to work on the problem, and some scientists attempted to discourage those who sought to study the problem. The first commitments of funding for research were made by a few hard-hit cities and states. At the federal level, this was the heyday of the Reagan era, a time in which the president refused to acknowledge the existence of the disease (or even say its name). People who worked in the Reagan White House today tell stories of how the White House Staff joked about the "good fortune" of a disease that primarily seemed to affect homosexuals and people of color. They were in no hurry to see it curtailed, feeling that people were getting what they deserved for their supposedly promiscuous ways. It wasn't until the mid-1980s, by which time many thousands had died and vast numbers were infected, that the first significant funding efforts were made. Even then, the impetus came from Congress rather than the White House.

The entertainment industry didn't get seriously involved in raising funds until after the death of Rock Hudson in 1986, even though groups like the American Foundation for AIDS Research were beating on its doors long before that. While AIDS research eventually became reasonably well-funded, it really wasn't until the end of the decade. Even then, care and prevention programs lagged far behind. Prevention remains hopelessly under-funded to this day, and some of the support programs critical for access to HIV treatments, such as the AIDS Drug Assistance Program, lose ground every year as Congress loses interest in the epidemic. Most of the dollars needed to help those stricken in the early years came from individual donors from the affected communities. But on their own, these philanthropists could never hope to meet the depth of the needs presented. Consequently, HIV and AIDS raged through our

In Memory Of . . .

We dedicate this issue of the *PI Perspective* to:

Alfredo Armendariz
Jeff Gangale
Jonathan Pon

Their memory lives on in the work that lies ahead of us all.

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communities all but unchecked for the first several years. Even today, the needs of the poorest remain unmet.

Instead of being the subject of a massive national outpouring of concern and support, as we see today for the September 11 victims, people with AIDS were frequently treated as outcasts and pariahs. Politicians were more likely to call for quarantine than they were for funding programs. Children with AIDS were shunned, sometimes even physically assaulted, often driven from their schools by the angry, ill-informed and compassionless parents of "healthy, normal children." While many people had to hide their illness to avoid losing jobs and housing, women with AIDS had to hide their HIV status to avoid losing their children.

This is what we as a country did to our own citizens. The numbers of those who rose up in compassion to fight back and care for the sick were greatly outnumbered by those who responded with either hostility or indifference. It was "somebody else's" problem—a belief that was all too widely held until someone in one's own personal circle was affected.

The comparison to the September 11 response is even more disturbing when we consider the international situation. Tens of millions are infected in Africa and other developing nations, countries which often lack fundamental healthcare infrastructures and can barely dream of providing treatment and prevention programs. Prior to September 11, Secretary of State Colin Powell declared the international AIDS epidemic the "number one threat to our national security," a statement that has since disappeared from government's phrase book. This year, even before September 11, it took a major lobbying effort to get the US government to commit a mere $200 million to an international fund to fight the epidemic. This is spare change compared to tens of billions approved almost without discussion in response to the needs of September 11. The cost of the anti-terrorist war is currently estimated to be $1 billion per day. Hundreds of millions have been committed to rebuild the things we have blown up with our bombs in Afghanistan.

No one questions the need to confront international terrorism or the need to help the victims and surviving family members of the September 11 terrorist attacks. No one wishes to begrudge them the remarkable outpouring of concern and support they are receiving from their fellow citizens and the government. Nothing will ever bring back those they have lost. It is inspiring to see government and the nation as a whole rise fully to the task, with compassion and action. However, it cannot help but bring back a sad and perhaps bitter memory of how our nation, our institutions and even a large portion of our population responded to AIDS, both in the past and in looking to the future. The number killed by AIDS vastly outnumbers those killed on September 11, or for that matter, in all of America's wars put together. The total carnage of Americans in the Vietnam war is equaled almost every year by the AIDS death toll, even today when much of the public mistakenly thinks the battle against AIDS is already won. The lesson of September 11 is that when they care enough and when they want to, our government and our nation can be the most compassionate and generous on the planet. Yet this compassion and generosity can be highly selective, doled out quickly and without debate when the victims are somehow seen as "people like us," yet withheld or greatly delayed when they are a marginalized group in our society.

We are rightly reminded today that we are all Americans first and foremost, without regard for race or ethnicity, and that we should pull together and help all those who have been harmed or threatened by terrorism. A noble thought and one we should all embrace. But this vision somehow doesn't apply when tragedies affect only a less popular segment of our society. It is somehow inconsistent when we can't seem to recognize the huge tragedy of AIDS that is unfolding worldwide and taking far more lives than all the terrorist actions imaginable. AIDS is the ultimate terrorist.

We are one nation, one people, one planet. When will we begin to act like it? ■

Anti-HIV Therapy Update

Recently there have been good and bad news from the anti-HIV drug development front. First the good news, the Food and Drug Administration (FDA) recently approved tenofovir (Viread) for the treatment of HIV disease. This is welcome news for people who need a new drug to put together a second or third line regimen and may even be an important new choice for first line therapy. Additionally, a long awaited expanded access program for the fusion inhibitor T-20 (pentafuside) has been announced. The bad news is that the program is so small that it will provide drug to only 168 people in the United States, in the first stage of the program. This will be gradually increased as more drug becomes available but a wider expanded program is still a long way off.

More bad news comes in the form of a delay in the expanded access program for atazanavir (Zrivada), a protease inhibitor that is dosed once a day and which may offer important advantages in terms of reduced fat distribution effects. At this point it is not entirely clear why there is a delay in the program, although the likely reason is that in one study of the drug, there was an increased rate of elevated lactate levels (lactic acidosis), a side effect usually associated with nucleoside analogue drugs, which were also used in the study. Certain issues regarding the heart have also been raised as possible evidence of toxicity, though this too is unclear.

The following article will overview these issues. Also in the news is information on a new formulation of d4T (stavudine, Zerit), once daily dosing of indinavir (Crixivan), results from a study of a new non-nucleoside analogue drug called TMC 125 and surprising results from a structured treatment interruption (STI) study.

Tenofovir: New Kind of Anti-HIV Drug Gets Approved

Recently, the FDA approved tenofovir, which is taken just once a day, for treating HIV infection in combination with other anti-HIV therapy. The drug is a nucleo*tide* analogue, a class similar to but not exactly the same as nucleoside analogues. Tenofovir is the first nucleotide analogue approved for treatment of HIV. The approval was based primarily on the results from one study involving 550 people who were on anti-HIV therapy for at least eight weeks and had viral load of 400–10,000 copies.

Volunteers received either tenofovir or placebo in a 2-to-1 fashion, resulting in 368 people on tenofovir and 182 on placebo. All continued on their existing regimens in addition to the tenofovir or placebo. At the start the volunteers, on average, had been on anti-HIV therapy for 5.4 years, had viral load of about 2,300 copies and had CD4+ cell counts averaging 427. The average decrease in viral load between the start of the study and week 24 was 0.59 log among people taking tenofovir. Essentially no changes in viral load were noted among those on placebo. Additionally, about 45% and 22% of the participants had viral loads below 400 and 50 copies respectively compared to 13% and 1% of those taking the placebo respectively. Tenofovir was very well tolerated with no significant differences in moderate-to-severe side effects between the two groups.

Although the reduction in viral load levels may not sound like very much compared to what has been seen in many protease inhibitor studies, such a comparison is misleading. In the protease inhibitor studies, volunteers were just beginning treatment for the first time and were thus much more likely to have large decreases in viral load. In contrast, tenofovir was given to people who were already "failing" on their existing regimens, most likely due to the development of resistance against their current drugs.

Adding a single new drug to a failing regimen usually does very little, but in this case, the addition of tenofovir resulted in significant viral load reductions. This appears to confirm lab studies which showed that tenofovir remains active against many viruses that have developed resistance to older nucleoside analogue drugs. Thus, tenofovir appears able to make up for much of the failure of the older class of drugs.

An additional benefit of tenofovir is its apparently low level of toxicity. Though the data is limited and somewhat short-term, it so far appears to have the fewest side effects of any anti-HIV drug yet seen. Whether this will hold up in long term use is yet to be determined.

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Since the initial studies of tenofovir have focused on people who were failing other therapies—something the manufacturer, Gilead Sciences, should be congratulated for—the drug is currently recommended primarily for such people. This does not mean, however, that it has no role in people beginning treatment for the first time. Results from another tenofovir study, in people who have not taken anti-HIV therapies before, are expected in early 2002. If these data are positive and show

even more potent anti-HIV effects, as some researchers anticipate, it will raise questions about the ideal time to use the drug. Some doctors may prefer to use it initially, thanks to its delayed resistance, low toxicity, ease of dosing and high potency. Others may wish to hold it back for later use, if for no other reason than the fact they can do so without fear of losing its potency. Only time and experience will tell which, if either, is the best strategy.

Atazanavir: A New Protease Inhibitor

Results from a study comparing two doses of atazanavir (BMS-232632, Zrivada) to nelfinavir (Viracept) were recently presented. Both drugs are protease inhibitors. The study enrolled 467 people with a median viral load of about 50,000 copies HIV RNA and CD4+ cell count of about 275.

None of the volunteers had taken anti-HIV therapy before, and they all received nelfinavir (1,250mg twice a day) or atazanavir (400mg or 600mg once a day). In addition, all of them took d4T (stavudine, Zerit) and 3TC (lamivudine, Epivir). The results are found below.

Not surprisingly, people on nelfinavir were more likely to develop diarrhea, a well-known side effect of the drug. Those taking atazanavir were more likely to have headaches, abdominal pain and increases in bilirubin levels. People using the higher dose of atazanavir were more likely to stop taking it due to side effects.

There was, on average, very little change in triglyceride or cholesterol levels among the people taking atazanavir while those on nelfinavir had significant increases in these laboratory markers. Changes in these markers have sometimes been associated with changes in body shape, called *lipodystrophy* For more information on lipodystrophy, call Project Inform's Hotline at 1-800-822-7422 or visit *www.projectinform.org*.

The lack of effect on triglyceride and cholesterol levels and the once a day dosing are clearly what makes atazanavir stand out from the existing protease inhibitors. Starting in spring of 2002 a large expanded access program will provide atazanavir free of charge to people who have failed other therapies. Stay in touch with the Project Inform Hotline and website to learn how and when to sign up.

Indinavir or Boosted Indinavir?

Results from the Danish BEST study suggest that taking indinavir (Crixivan) with low dose ritonavir (Norvir) may not be very well tolerated. This study enrolled 323 people. All were taking indinavir 800mg three times a day in addition to two other anti-HIV drugs at study entry and had viral load below 500 copies. Volunteers either continued taking indinavir three times a day or switched to indinavir/ritonavir (800mg/100mg both taken twice a day) in addition to their other anti-HIV therapies.

After 48 weeks, 74% of the people who continued taking indinavir had viral load below 500 copies compared to only 58% of those who switched to the indinavir/ritonavir combination. This difference is almost entirely due to an increase in side effects among those on indinavir/ritonavir. Over twice as many people had to stop therapy and/or switch therapies because of side effects compared to those on the thrice-daily indinavir regimen. Side effects included stomach distress, kidney stones, blood in the urine (hematuria) and elevations in lipid levels (lab markers for triglycerides and cholesterol).

Results from this study are somewhat different from many physicians' experience, where the indinavir/ritonavir combination has been generally well tolerated and in fact has become the preferred method of dosing indinavir for many.

Results after 48 weeks: Atazanavir

	% <400 copies HIV RNA	% <50 copies HIV RNA	HIV RNA drop
ATV (400mg) + d4T + 3TC	65	31	2.51 logs
ATV (600mg) + d4T + 3TC	62	36	2.58 logs
NFV + d4T + 3TC	59	38	2.31 logs

ATV = atazanavir; NFV = nelfinavir

If you are looking for HIV/AIDS treatment information, log onto Project Inform's HIV/AIDS Treatment Website at:

www.projectinform.org

TMC-125: A New NNRTI

Early results show that a new non-nucleoside reverse transcriptase inhibitor (NNRTI), TMC-125, has potent activity against HIV. We have previously reported on a related drug, TMC-120, which also showed potent activity and is still in development. Eighteen people, all of whom had not taken anti-HIV therapy before, participated in this study. Twelve received 900mg TMC-125 twice a day for seven days and six received a placebo. After seven days of therapy, people on TMC-125 had an average viral load decrease of about 2 logs (99%) and an average CD4+ cell count increase of 100.

Larger studies with TMC-125 are planned in early 2002, including a study for people who have been on all three classes of anti-HIV drugs [protease inhibitors, NNRTIs and nucleoside analogue drugs (NRTIs)]. Other drugs in the same NNRTI class include the approved drugs nevirapine (Viramune), delavirdine (Rescriptor) and efavirenz (Sustiva). For more information about these classes of drugs, call Project Inform or visit the website and look for *Anti-HIV Therapy Strategies.*

STI and Third Line Therapy

Results from a French study shows that a structured treatment interruption (STI) may benefit people with limited treatment options. Participants had to have previously taken at least two NRTIs, one NNRTI and

two protease inhibitors. As would be expected, the 68 people in the preliminary analysis had been on extensive anti-HIV therapies (on average eleven drugs each), had a high viral load (about 160,000 copies) and low CD4+ cell counts (about 30). Volunteers received:

- immediate *giga*HAART (three to four NRTIs, hydroxyurea, one NNRTI and ritonavir + amprenavir or ritonavir + lopinavir plus a third protease inhibitor), or
- an eight-week therapy interruption followed by *giga*HAART.

At the end of the eight-week STI, there was a small increase in viral load (0.2 log or 1.6 fold) and a decrease in CD4+ counts of 10 cells. Researchers looked at viral load responses after each group had completed 12 weeks of gigaHAART. For the immediate therapy group this was looked at after the first twelve weeks. For the STI group this was evaluated after 20 weeks of study, as the first eight weeks included a therapy interruption.

Somewhat surprisingly, the gigaHAART regimen was rather well tolerated in this study, although some participants stopped hydroxyurea and/or decreased the dose of ritonavir.

d4T (stavudine, Zerit): A New Formulation

Results have been presented for the first time of a new once-a-day formulation of d4T, known as d4T extended release or d4T XR. This study enrolled 150 people who had not taken anti-HIV therapy before with a viral load of about 50,000 copies and CD4+ cell counts of about 300. Participants used either d4T XR or regular d4T together with 3TC and efavirenz.

The dose of d4T XR used was 100mg once a day for people weighing over 60kg (about 130 pounds) and 75mg once a day for those weighing less than 60kg. d4T XR results in lower *peak* and higher *trough* concentrations of the drug compared to regular d4T.

Peak concentration is the highest amount of drug in the blood soon after taking a dose. *Trough concentration* is the lowest amount of drug in the blood after taking a dose. *Higher* peak concentrations are sometimes associated with a higher risk of side effects. *Lower* trough concentrations are associated with the development of anti-HIV drug resistance. It's assumed that *lower* peak concentrations of a drug will sometimes decrease side effects and *higher* troughs will decrease the risk of developing resistance to the drug.

The lack of effect on triglyceride and cholesterol levels and the once a day dosing are clearly what makes atazanavir stand out from the existing protease inhibitors.

At the end of the 48-week study, there was essentially no difference in response between the two groups, with about 50% of the participants having viral loads below 50 copies and an increase in CD4+ cell counts of about 200. There appeared to be slightly fewer people experiencing peripheral neuropathy (a tingling or numbness around the extremities, especially fingers and toes) among those on d4T XR, although they experienced slightly more headaches. Only a larger study will truly determine the safety profile and effectiveness of the new formulation. ■

Results after 12 weeks of gigaHAART

	% viral load drop of at least 1 log	% <400copies HIV RNA
GigaHAART only	26%	15%
STI + gigaHAART	59%	35%

T-20 Expanded Access

Starting November 27, 2001 at 3pm EST, a study allowing for access to the fusion inhibitor T-20 (Pentafuside) began. However, because there's a severe supply problem, this study was very limited and only provided drug to 168 people in the United States. All slots were filled within weeks. The study may be expanded later in 200, perhaps by summer. Interested physicians should call 1-888-722-6321 for more information.

The study is limited to individuals who need T-20 to put together a viable anti-HIV regimen, must have a viral load over 10,000 copies *and* have a CD4+ cell count below 50. Physicians are encouraged to give first preference to people who have had an AIDS-defining opportunistic infection within the last 90 days and have a CD4+ cell count below 50 while taking potent anti-HIV therapy. Secondary preference is encouraged for people with CD4+ cell counts below 50 for the last 90 days despite taking potent therapy. While the deadline has passed and the program full/closed to enrollment, as more drug becomes available the program might expand/increase in size. If or when the program expands and accepts new enrollees, the Project Inform hotline will have more information. Visit the website frequently or call the hotline for updates! ■

Lipodystrophy Update

Lipodystrophy is the term given to describe a series of changes in body composition [loss of fat in the legs, arms, or face, breast enlargement, central obesity (sometimes called *protease paunch*), dorsal fat pads (known as *buffalo hump*), etc.] as well as changes in laboratory markers associated with how the body processes fats and sugars (e.g. cholesterol and triglyceride changes, also called *lipids*). Several new findings were recently reported at the *3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. Although these results may help in making decisions about specific therapies, they offer little information on the cause of lipodystrophy syndromes. However, several studies to be presented at the Conference on Retroviruses and Opportunistic Infections in February 2002 may shed more light on the cause and will be reported on in the next *PI Perspective*.

Cosmetic Surgery for Facial Wasting: New-Fill Injections

Results from a French study of New-Fill (polylactic acid) shows that it may help increase the thickness of the cheek fat pad and other places where fat loss is sometimes apparent. Some people have experienced *lipoatrophy* (fat loss), which is believed to be associated with anti-HIV therapy and in particular the nucleoside analogue (NRTI) drugs. This study involved four injections of New-Fill (3cc in each cheek) at days 0, 15, 30 and 45. A fifth injection was given at day 60 if there was inadequate response.

Fifty people participated and all began the study with a marked and visible reduction in fat tissue in the cheeks (sunken cheeks) as measured by *ultrasonography* (using ultrasound technology to produce an image). At the time of the report, four people had received three injections, 29 had four injections and 17 had five. All volunteers had a dramatic improvement, with the majority regaining fat tissue in the cheeks. Some participants experienced a slight swelling at the injection site.

The manufacturer claims that New-Fill does not directly fill the spaces left empty by lipoatrophy. Rather, the product is claimed to build or grow a matrix under the skin which is then filled in by the body's own production of collagen.

New-Fill is not currently approved by the FDA and is not commonly available to physicians. For a time, the product was being imported from France for personal use, but in recent months the FDA blocked bulk importation of the product, arguing that the product should be classified as a "device" rather than a drug or natural supplement. The agency feels it is thus not subject to the personal importation rules for drugs. Still some people are successfully bringing back personal supplies of New-Fill from Tijuana, Mexico.

Discussions with the FDA are ongoing, looking for a way to make the product available to people in need while further studies are designed. A major problem is that the supplier is a small company that does not have the resources to conduct clinical trials. Some dermatologists offer products they claim are similar, and a few clinics near the Mexican border treat patients with New-Fill or similar products.

Facial lipoatrophy many not be physically harmful, but it can add a serious psychological burden for people with HIV infection. Although New-Fill has not been proven to be effective, neither has it shown any serious toxicity to date. Project Inform supports the right of people with HIV to have access to this and similar products.

Human Growth Hormone and Lipodystrophy

A study of five people has shown that human growth hormone (Serostim) can decrease triglyceride and cholesterol levels (decrease in LDL or bad cholesterol and increase in HDL or good cholesterol). It was, however, associated with development of insulin resistance that led to increased glucose production (a condition associated with diabetes). The dose used in this study was 3mg/day. Similar to results from a previous study, participants experienced a loss in fat and gain in lean tissue. People considering using human growth hormone should also consider having a glucose tolerance test done before starting the drug. Future studies using lower doses are planned.

Do Some Therapies Pose More of a Threat?

Interim analysis of one study shows that different anti-HIV regimens may have different effects on cholesterol and triglyceride levels. This study enrolled 258 people (half were women), all of whom had not taken anti-HIV therapy before. The average viral load at study entry was about 30,000 copies and the average CD4+ cell count was about 350. Volunteers received abacavir/ Combivir (Combivir is AZT/ 3TC), nelfinavir/Combivir or d4T/3TC/nelfinavir.

After 24 weeks, there were no differences in anti-HIV activity among the three groups, with 49–59% of the participants experiencing viral load suppression to under 400 copies. However, there were major differences in triglyceride and cholesterol levels among them. People on the nelfinavir combinations saw their cholesterol levels substantially increase compared to those on abacavir who only had a slight increase. However, only people taking d4T/3TC/nelfinavir had substantial increases in triglyceride levels while the

other two groups only had minor increases. Cholesterol and triglyceride increases have been associated with lipodystrophy in some people. The study had not yet run long enough to know whether any particular regimen was more likely to result in fat loss or redistribution.

Amprenavir and Lipodystrophy

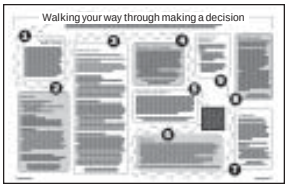
A small intensive monitoring study shows that amprenavir can greatly increase triglyceride and cholesterol levels, contrary to earlier reports that it does not affect these lipid markers. This study enrolled 16 people, all of whom had not previously taken a protease inhibitor, abacavir, d4T or 3TC. During the study, the volunteers received abacavir/3TC/amprenavir (two people used d4T instead of 3TC).

Overall there were no major changes in laboratory markers for diabetes, including fasting glucose and fasting insulin levels. There was, however, a decrease in insulin sensitivity after 48 weeks, but not before. People experienced a progressive increase in markers of fat processing, triglyceride levels and cholesterol levels. The good news is that HDL (*good*) cholesterol increased as well as LDL (*bad*) cholesterol resulting in no change in the overall ratio of HDL/LDL. The ratio of HDL to LDL may be even more important than the actual levels.

Additionally, participants saw an increase in weight, trunk fat and limb fat resulting in an overall increase in total body fat. There was also a trend towards an increase in lean tissue. One interesting observation is that insulin resistance developed *after* weight gain. This can potentially help in better understanding how the lipodystrophy syndromes occur. ■

Wise Words #9

When to use therapy: the decision is yours to make!



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Strategies for Third Line Therapy

One area of anti-HIV therapy research that has been inadequately addressed is strategies around third line therapy regimens. As a result, there is only a modest amount of data to guide physicians and patients in making treatment decisions in this setting. Third line therapy is usually defined as a regimen for an individual who has developed resistance to at least one drug in all three classes of anti-HIV therapies [nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors] or has failed two treatment regimens. In general, the nucleo*tide* analogue drug, tenofovir (Viread) can be considered an NRTI as it shares some of the same resistance patterns. However, just because someone has developed resistance to some drugs in all three classes of anti-HIV drugs does not mean that they have no further treatment options. This article will review some of the options available to people exploring third line regimen choices.

New Drugs and Expanded Access Programs

The most obvious option includes new drugs that are active against HIV that is resistant to most or all of the currently available anti-HIV therapies. There are several new drugs that may be active against multi-drug resistant HIV that are FDA approved or are still in early development. These include:

- Fusion inhibitors T-20 (pentafuside) and T-1249;
- Nucleotide analogue tenofovir;
- New protease inhibitors including atazanavir (Zrivada), tipranavir and TMC 114;
- Existing protease inhibitors enhanced by the addition of small doses of ritonavir, which increases their ability to overcome partially resistant virus;
- New NRTIs including DAPD, alovudine and ACH-126,443;
- New NNRTIs including capravirine, TMC125 and DPC 961;
- CCR5 inhibitors including Schering C (SCH 351125) and UK-427,857;
- Entry inhibitors including PRO 367;
- Attachment inhibitors including PRO 542; and
- Integrase inhibitors including S1360.

For most of these drugs, the only method of access is by participating in clinical trials, while some provide drug to people through expanded access programs. Currently there is a very limited expanded access program for T-20 and one planned for atazanavir by the end of the first quarter 2002. The Project Inform hotline will have information about these and other expanded access programs as they become available.

Mega-drug Regimens

Most third line regimens consist of four or more drugs. More traditional anti-HIV therapy regimens typically include only three drugs, or four anti-HIV drugs at the most. A third line regimen, however, often includes a minimum of four drugs and

it's not uncommon to see five, six, seven or more drugs used. Different groups have used different terms for these third line multi-drug regimens including mega-HAART, gigaHAART, salvage therapy and multi-drug rescue therapy. The theory behind using a larger number of drugs is that not all of the virus in a person's body is going to be resistant to all of the drugs. By using many drugs with different mechanisms of blocking HIV from reproducing, it may still be possible to achieve a potent anti-HIV effect.

The use of several drugs of multiple types, however, also increases the risk of side effects and makes it much more difficult to manage drug interactions. Another approach, the use of therapeutic drug monitoring (see below) may help to reduce side effects while ensuring optimal drug levels are maintained.

Structured Treatment Interruptions (STI)

There is still considerable debate and much research that needs to be done about the role of STIs as part of a third line regimen. The goal of an STI here is focused on the potential for at least partial reversal of drug resistance when all anti-HIV therapies are stopped for some period of time.

Several studies have shown that the majority of people in a third line situation who utilize an STI strategy do in fact see a reversion back to wild type virus (a reversal of resistance), when using the standard resistance tests, but when using a more sensitive test, drug resistant HIV can be detected. Still, there is often a period of renewed activity from drugs that had previously failed. It remains unclear how long the anti-HIV benefits will last once therapy is restarted after an STI.

One major concern with STIs in this scenario is that there is often a rapid drop in CD4+ cell counts and an increase in viral load, both of which can be very significant after stopping anti-HIV therapy. Furthermore, after restarting anti-HIV therapy there is a slow increase in CD4+ cells with some people never returning to their pre-STI CD4+ cell counts. On a more positive note, a small French third line study involving a STI shows promising results. The gigaHAART study results can be found on page 6.

Immune-Based Therapies

The use of immune-based therapies has not been adequately studied as part of third line regimens. There are some data suggesting that the use of GM-CSF (granulocyte colony stimulating factor, Leukine) may have some benefit. It remains to be seen what the role of immune-based therapies may be in third line regimens.

Participate in a Study

There have only been a few studies of third line regimen strategies. One reason is third line regimens require the use of different drugs from the various pharmaceutical companies and there has been a history of difficulty in getting them to collaborate in these types of studies. However, if a study is available it should be considered as an option.

Resistance Testing

It is probably advisable for people considering a third line regimen to get a resistance test. A phenotypic resistance test may be more useful in this situation than the genotypic test. Results from the resistance test will be useful in putting together a treatment regimen. For more information on HIV resistance tests, call the Project Inform hotline.

Therapeutic Drug Monitoring (TDM)

This is a new experimental diagnostic test that measures the amount of drug in blood. Given that most third line regimens involve many anti-HIV drugs, there are many potential drug interactions. Drug levels that are too low are associated with drug resistance while high drug levels are associated with excess side effects. Several studies have now shown that adequate drug levels are essential to achieve a potent and sustained anti-HIV response. Information from the TDM test can be used to change the dose of a particular drug to ensure that adequate drug levels are achieved. For more information on TDM, call the Project Inform hotline and ask for the publication *Pharmacology: Drug Level Monitoring and Beyond*.

Continued Benefit from "Failing" Drugs

A number of studies have reported that even after drug regimens appear to "fail"—defined as a return of measurable viral load despite treatment—there is usually still a lasting benefit for people who remain on treatment. It seems likely that simple viral load tests do not tell the whole story of how the body responds to anti-HIV drugs.

There is much research in this area looking at the "fitness" of the virus. Early results suggest that HIV is not able to replicate as well after it becomes resistant to certain drugs. Thus, for some people who might seem to lack options, one reasonable choice might simply be to stay on whatever regimen they have been using. As long as they remain clinically well and don't suffer a rapid further decline of CD4+ cells, it might not be wise to worry excessively about drug "failure."

Commentary

We are seeing increasing numbers of people in need of third line regimens or at least better therapy. There is a definite need to evaluate the optimal strategy in putting together a third line regimen and the various clinical trial networks and pharmaceutical companies need to make this issue a priority. ■

Highlights from the 2001 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

The following are highlights from ICAAC held in December in Chicago.

Comparison of Two Once Daily Regimens

Preliminary results were presented from the FOCUS study, which compares saquinavir (Fortovase) + ritonavir (Norvir) taken once a day to efavirenz (Sustiva), which is also taken once a day. FOCUS enrolled 161 people who received either 1,600mg of saquinavir + 100mg of ritonavir or 600mg of efavirenz. Both groups also received two nucleoside analogue drugs. Volunteers had not previously taken anti-HIV therapies and had an average viral load of about 56,000 copies HIV RNA and CD4+ cell counts averaging 350. After 24 weeks, the results were as follows:

	SQV + RTV	EFV
% <400 copies HIV RNA	71%	84%
% <50 copies HIV RNA	60%	81%

SQV = saquinavir; RTV = ritonavir
EFV = efavirenz

More people taking the saquinavir/ritonavir combination discontinued the study because of side effects than those taking efavirenz. The most common side effects included nausea, diarrhea and vomiting. Interestingly, there were no differences in total cholesterol, LDL (bad cholesterol), HDL (good cholesterol) or triglycerides between the two groups.

A previous study compared the two different versions of saquinavir (Invirase and Fortovase) in combination with ritonavir. Volunteers achieved similar drug levels of saquinavir in the blood that resulted in similar anti-HIV responses. However, people on the Invirase combination had fewer side effects. There are now plans to look at the Invirase + ritonavir combination as part of a once-a-day regimen.

Results from the Antiretroviral Pregnancy Registry

An analysis of the Antiretroviral Pregnancy Registry shows that there is no increased risk of birth defects among the children of women taking anti-HIV therapies during pregnancy. This international registry requires healthcare providers to report anti-HIV therapy use during pregnancy. The overall prevalence of birth defects was three per 100 live births, which is similar to the general population. There was also no difference in the risk of birth defects between taking anti-HIV therapies during the first trimester of pregnancy compared to the second or third trimester.

Most doctors encourage women to use caution in taking any therapy during the first trimester of pregnancy, as this is when the risk of side effects and resultant birth defects is of most concern, at least in theory. It is thus encouraging that anti-HIV therapy taken during this important time did not result in an increased risk of birth defects. Even still, there are therapies commonly used in the treatment of HIV disease that should not be used by pregnant women because of serious concerns about birth defects These include, but are not limited to, efavirenz (Sustiva) and all of the *azole* drugs, such as fluconazole (Diflucan), etc.

Second Line Therapy with Tipranavir

A small study shows that the new protease inhibitor tipranavir is active as part of a second line regimen. This study enrolled 63 people, all of whom were experiencing a viral load rebound on their current protease inhibitor-containing regimen. Participants with an average viral load of about 32,000 copies HIV RNA and CD4+ cell counts of about 300 received two different doses of tipranavir and ritonavir (500mg tipranavir + 100mg ritonavir or 1,250mg tipranavir + 100mg ritonavir, all taken twice a day) or ritonavir + saquinavir (both dosed 400mg twice a day). In addition, all participants added two new nucleoside analogue drugs (NRTIs). The results after 16 weeks, though not statistically significant, were as follows:

	500mg TPV	1,250mg TPV	SQV/RTV
% <400 copies HIV RNA	39%	55%	40%
% <50 copies HIV RNA	22%	35%	30%

TPV = tipranavir; SQV = saquinavir; RTV = ritonavir

Somewhat surprisingly, even though people were experiencing a viral load rebound, a large number of people did not have any protease inhibitor-related resistance mutations on entry into this study. This suggests that the reason for drug failure in those cases was probably resistance to the nucleoside analogues being used, not the protease inhibitor. Not surprisingly those with no protease inhibitor-related resistance mutations had better anti-HIV responses.

The higher dose of tipranavir is not going to be pursued in future studies because of excess side effects, including nausea, diarrhea and vomiting. Instead, lower doses of tipranavir (500mg and 750mg) will be studied in combination with either 100mg or 200mg of ritonavir.

Second Line Therapy with Atazanavir

Results from a small study shows that the protease inhibitor atazanavir (Zrivada) also has activity when used as part of a second line regimen. Eighty-five people with an average viral load of about 16,000 copies

HIV RNA and CD4+ cell counts of about 300 and who were experiencing a rebound in viral load participated in this study. Almost all had previously taken a protease inhibitor [most were on either nelfinavir (Viracept) or indinavir (Crixivan)]. Volunteers received either two different doses of atazanavir and saquinavir (400mg atazanavir + 1,200mg saquinavir or 600mg atazanavir + 1,200mg saquinavir all taken once a day) or ritonavir/saquinavir (both dosed 400mg twice a day). The saquinavir formulation used in this study was Fortovase. Laboratory studies show that there is good synergy when atazanavir is used in combination with saquinavir. The results after 24 weeks were as follows:

	400mg ATV + 1,200mg SQV	600mg ATV + 1,200mg SQV	SQV/RTV
% <400 copies HIV RNA	53%	40%	38%

ATV = atazanavir; SQV = saquinavir; RTV = ritonavir

More people had to discontinue taking saquinavir/ritonavir because of side effects. Additionally, people on that regimen had significant increases in triglyceride and cholesterol levels whereas people on either atazanavir doses had either no change or a slight decrease in those laboratory markers.

HIV Drug Resistance in the United States

Blood samples from the HIV Cost and Service Utilization Study (HCSUS) were used to try to estimate the prevalence of HIV drug resistance in the United States. This study collected 1,906 samples of which 36.6% had HIV RNA levels below 500 copies and were assumed not to have any drug resistance. Resistance testing was performed on almost 1,100 blood samples. Seventy-eight percent of these samples were found to contain resistance to at least one drug, with the most common being 3TC (lamivudine, Epivir). This translates to an overall prevalence rate of 50%, when all of the samples are included.

Of the samples that had resistance performed, 70% were resistant to one or more of the nucleoside analogue drugs, 42% to one or more of the protease inhibitors and 31% to one or more of the non-nucleoside drugs. Of greater concern is the finding that 51% of the samples were resistant to drugs in two or more classes of anti-HIV drugs and 14% were resistant to at least one drug in all three classes of anti-HIV drugs. Additionally, 20% of the people who said that they have not previously taken anti-HIV therapies had detectable resistance to at least one drug.

Anti-HIV drug resistance was significantly associated with more advanced disease and the lowest CD4+ cell count but not current CD4+ cell count. Additionally, the prevalence of HIV drug resistance was associated with greater access to healthcare and anti-HIV therapies. (Men were more likely to have HIV drug resistance compared to women; as were gay men compared to other risk groups; and people with private insurance and people with higher educational status OR more formal education compared to people with lower educational status OR less formal education.) This should be expected since to a certain degree, resistance is related to the length of time a person uses therapy. Groups that have been on therapy longer, or who have traditionally had better access to therapy, are also more likely to develop resistance with time.

While this study raises important warnings about the frequency with which resistance is developing, many media reports have exaggerated its findings. Most reports failed to acknowledge that with more than 15 drugs now on the market to fight HIV, it is often possible to find combinations that will work for most patients, despite resistance to some of the drugs. Obviously, the more drugs a person is resistant to, the harder it gets to find a fully active combination. Nonetheless, even combinations that fail to fully suppress HIV have still been shown to produce a clinical benefit. Thus, resistance is a growing concern, but it does not mean people are beyond the reach of treatment.

Additionally, new treatments are now becoming available which seem to work despite resistance to previously used drugs. Drugs that overcome prior resistance at least to some degree include tenofovir (Viread), lopinavir (Kaletra) and other protease inhibitors boosted by ritonavir as well as several drugs likely to be approved in the next 18 months, including T-20, tipranavir and perhaps atazanavir. ■

Honoring Dr. Nava Sarver

Dr. Nava Sarver of the National Institute of Allergy and Infectious Diseases (NIAID), a member of the Project Inform National Board of Governors and a dear friend of many of our staff, died from complications of severe rheumatoid arthritis on August 3, 2001.

Nava was a long-time and key member of Project Inform's Immune Restoration Think Tank and involved and supportive of many of our research advocacy activities. She fundamentally challenged our stereotypes of a government bureaucracy and by the very gestures of her life demonstrated that AIDS activism could happen within government. In her work at NIAID, Nava helped to create and administer many of the most innovative programs aimed at finding new solutions and eliminating the barriers to faster and more effective AIDS research.

To recognize her contributions, Project Inform honored her work at our annual Evening of Hope awards dinner in 2000. Dr. Sarver is one of the great unsung heroes in the fight against AIDS. And though unknown to many, her work and dedication affected all. ■

Pulmonary Hypertension and HIV

People living with HIV have long had enough to worry about from the most common opportunistic infections and HIV-related conditions. There are, however, a number of less well-known illnesses for which HIV is considered a risk factor. When people afflicted with these conditions turn to general sources of HIV information, they often find little or no recognition of the connection with HIV. Consequently, they often feel isolated and alone in facing their new problem and can't get much help from their usual support mechanisms.

One such illness that recently came to Project Inform's attention in a dramatic and personal way is called PH, short for Pulmonary Hypertension. Though hypertension (high blood pressure throughout the circulatory system) is a common illness, PH is a relatively rare condition. It is distinguished by high blood pressure in the pulmonary artery, the main blood vessel that carries blood from the lungs to the right ventricle (chamber) of the heart. It is typically a progressive disease that ends in death if untreated.

The general cause of this increased blood pressure is a thickening or constriction of the pulmonary artery and the smaller blood vessels in the lungs that branch out from it. In a person with pulmonary hypertension, the branches begin to close off as the blood vessels thicken, starting with the smallest vessels first. As more and more branches close down, the lungs produce less oxygenated blood and the body becomes starved for oxygen. This causes the right ventricle of the heart to work furiously, trying to force more blood through the lungs to get more oxygen to the body. It is not designed for such high pressure work and the muscle soon stretches and eventually leads to congestive right heart failure, a type of heart of attack and potential cause of death.

Symptoms of PH

The most obvious symptoms of PH are shortness of breath, dizziness, fatigue, swollen ankles, poor lung capacity and sudden fainting or loss of consciousness due to inadequate intake of oxygen for the brain. The process begins slowly and most people have the disease for a few years before getting a correct diagnosis because the early symptoms are similar to those of many other diseases. The diagnosis is made *differentially*—that is, by ruling out other causes. The disease is progressive for two reasons. (1) The underlying cause remains present despite treatment; and (2) the rising blood pressure in the lungs increases the speed at which blood must flow through the remaining open blood vessels, causing friction on the cells of the inner lining of the vessels, further thickening them, resulting in ever more constriction.

The symptoms of PH somewhat resemble those of asthma, a common lung disease that also results in poor oxygenation through the lungs (though by a different mechanism). A person with PH, however, does not experience the "wheezing" typical of asthma, since the problem is due to a lack of oxygenated blood, not a problem getting air into the lungs. Many types of heart disease can also produce symptoms that resemble PH as well.

One prominent PH specialist has likened PH to "a slow death by drowning." The progressive inability of the lungs to supply oxygen can greatly restrict a person's activity levels and lead to increased isolation. Although a person with PH might feel fine while sitting, a simple climb up out of a chair or a short walk can trigger shortness of breath, dizziness or even a blackout. Patients quickly lose confidence in their ability to cope with even the most basic daily activities. Without treatment, many people become housebound and in need of oxygen tanks and masks. Doctors discourage air travel due to the reduced cabin air pressure and lower oxygen levels maintained on commercial airliners, which further exacerbate the problem.

PH must be diagnosed by an experienced cardiologist (heart specialist), pulmonologist or a PH specialist. A similar level of experience is needed to treat the disease.

PH and HIV

No one knows for certain what the mechanism or link is that connects PH with HIV infection, even though inflammatory cytokines, which are common in people with HIV, are suspected as one of the possible causes. HIV been shown to be an independent risk factor for PH. Chronic hepatitis B and C, which are relatively common co-infections with HIV, are also risk factors for PH, but they explain only a small portion of the incidence of PH among HIV-positive people.

PH was originally believed to be a disease primarily affecting women but more recent findings seem to show a more widespread distribution among women and men. It is possible that the link to HIV is changing the makeup of the PH population. Other researchers simply believe that we are still in the early learning stages about PH and do not yet have a full picture of who gets it and why.

Two recent studies concluded that the incidence of PH in HIV-positive people is about 1 in 200, as compared to 1 to 2 cases per million yearly in the general population. This means the risk of PH is several thousand times greater for HIV-positive people than the general population. It is also likely that at least some HIV-positive people whose deaths have been attributed to heart disease, particularly congestive heart failure, were preceded or caused by PH. Several years ago,

Paul Corser, an early and well-respected AIDS activist who worked at amfAR until his death, struggled with PH in his final years. More recently, an HIV-positive Project Inform board member was diagnosed with PH. Her struggle led to this article's effort to better inform the HIV-positive community about this illness.

This means the risk of PH is several thousand times greater for HIV-positive people than the general population.

Treatment for PH

Until recently, the only treatment available for PH was a GlaxoSmithKline drug called epoprostenol (Flolan). It offers a mixed bag of benefits and drawbacks. It usually works quite well, reversing most symptoms for a considerable period. But it comes at a high price in terms of side effects, quality of life and cost. The drug must be directly delivered into a vein (intravenous infusion, IV) 24 hours per day. This means patients must have a surgically implanted IV (Hickman) line and carry a continuous infusion pump for the rest of their lives. Having an IV line carries risks of severe and life-threatening infections, notably sepsis. The drug is not a cure and works only as long as it is continued. It is extremely expensive, ranging from $50,000–$100,000 per year, depending on dosage, plus additional costs for the pump, IV lines, etc. As an "orphan drug" (a drug for a relatively rare disease that affects less than 200,000 people annually), these costs are not unusual.

In the fall of 2001, a new, simpler oral drug, bosentan (Tracleer) was approved by the FDA. Bosentan, a tiny pill taken orally twice daily, works by a different mechanism than epoprostenol. It is made by a Swiss company, Actelion, and distributed in the US by Genentech of northern California. While bosentan doesn't work in every case and may not be adequate in advanced disease, its greater simplicity and consequently better quality of life make it a godsend for many people with PH. It appears to at least halt disease progression within 30 days in most people and improves oxygen flow in many. Fortunately, the mechanism of action of bosentan is believed to be the most relevant mechanism for HIV-associated PH.

People using certain HIV antivirals, specifically ritonavir, need to exercise caution when using bosentan because of possible drug interactions. These interactions have not yet been tested, but it seems likely that ritonavir may increase the blood levels of bosentan, leading to an increased risk of liver-related side effects. Although studies combining bosentan and epoprostenol have not yet begun, there is interest in pursuing this because of their different mechanisms of action. Combination therapy, in this case, would eliminate the quality of life advantages offered by bosentan, but an oral formulation of epoprostenol is in development.

Project Inform encountered a slightly bumpy road in pursuing access to bosentan for HIV-positive people. Well before the drug was approved, it was available on an expanded access basis to people with PH, employing the regulatory mechanisms fought for and won by AIDS activists in earlier years. But in this case, the expanded access program excluded HIV-positive people, on the grounds that the new drug had not yet been specifically tested in HIV-positive people. HIV-positive people had also been excluded from the studies used to license the drug. There were also concerns about interaction with HIV antivirals.

Project Inform, which has played a fundamental role in creating earlier access programs for drugs, responded with a ferocious burst of activity. Through appearances at an FDA Advisory committee, pressure and support from the FDA, and hastily called meetings with company officials and clinical investigators, the ban on access for HIV-positive people was lifted just ten days after we first became aware of it.

For more information on support resources, or referral to PH research sites, call the Project Inform Hotline. ■

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.

A Potent Weapon in the Battle Against HIV: Your Own Immune System

The goal of HIV vaccines is to teach the immune system new and hopefully better ways to win the battle against the virus. There are different types of immune responses, those we were born with (*innate* immunity) and those we "learn" (*acquired* immunity). HIV vaccines exploit the side of the immune system that is learned (acquired) by providing information to cells in new ways in hopes of enhancing their learning and making them more effective fighters.

A Little Background

The first line of defense against nearly every new disease is our *innate* immune responses. It includes cells called dendritic cells (DCs) and natural killer cells (NK cells). These cells are out surveying the body looking for things that don't belong and trying to get rid of them. They're a bit like a neighborhood watch, looking for suspicious activity but not a specific perpetrator.

Our learned or *acquired* immune system is slower to respond at first, but it is highly specific in its activity and can respond fiercely and briskly once it has learned a task It includes specialized CD4+ T cells, CD8+ T cells and B cells. Unlike the innate immune response, these specialized cells will walk right past a group of neighborhood thugs (e.g. the flu virus, the fungal infection, etc.) to find a specific wrong-doer (e.g. HIV). If they're HIV-specific cells, they will seek out and destroy HIV-infected cells or if they are HIV-specific antibodies, they will seek out HIV floating in the blood.

HIV-specific cells learn by seeing. Other immune cells show CD4+ cells bits and particles of HIV that they have found while surveying the immune system for trouble. Once these other cells find a CD4+ cell that can learn about HIV (a *naïve* cell), the CD4+ cell communicates with other cells and provides instructions on how to respond. Depending on how HIV is shown or presented to the CD4+ cell, the cell will send out different chemical messages to activate a response.

One type of response is antibody (also called *humoral*) responses, which are generated by B cells. Generally these battle virus that is free floating in the blood (outside of cells). Another type of response is cellular responses, which are largely carried out by CD8+ cells. These destroy HIV-infected cells (eliminates virus that is inside of cells). Both *humoral* and *cellular* responses are believed to be important in controlling HIV replication, though some scientific debate remains about which, if either, is *more* important.

Vaccines and How They Work

The process of recognizing a new critter (i.e. an *antigen*, e.g. HIV) and responding takes awhile. If the way the particle of HIV was presented to the CD4+ cell wasn't done right, the entire process of *antigen* presentation, recognition and response could be crippled or ineffectual. Once a robust and effective response has been learned, however, the immune system marshals full force against the critter to specifically contain and hopefully control or eliminate it entirely. Vaccines teach these responses.

Preventive Vaccine – The goal of HIV *preventive* vaccines is to give people who are *not* infected with HIV specific memory responses that can act swiftly and effectively in controlling HIV if a person encounters the virus. Ideally, a vaccine might prevent the establishment of HIV infection altogether, although vaccines seldom achieve this goal. Instead, they prime the immune system to act quickly to prevent the infection from becoming serious or dangerous. Whether an effective vaccine will block the establishment of HIV infection altogether or merely alter the course of HIV disease in those who become infected is unknown. Currently there are no proven effective HIV preventive vaccines. If or when a vaccine is one day proven to have some benefit, it's highly likely that it will work best if combined with proven HIV prevention efforts (e.g. safer sex, etc.)

Therapeutic Vaccine – The goal of HIV *therapeutic* vaccines is to educate the immune system in hopes of shoring up a more potent and effective response against the virus in a person living with HIV. Whether or not it is possible to teach the immune system to better fight HIV remains to be seen. Some scientists believe that if continued production of HIV itself does not provoke an immune response sufficient to control the infection, no therapeutic vaccine is likely to do so either. Still, researchers are exploring strategies to improve HIV presentation and immune recognition and responses. Therapeutic vaccination is only one area of research aimed at trying to do this—others include gene therapy, cell therapy, structured treatment interruption approaches, passive immune therapy and cytokine therapy. Currently there are no proven effective HIV therapeutic vaccines.

Therapeutic HIV Vaccines: Things to Consider

Many HIV vaccines have already been tested in people living with HIV without compelling results. Studies conducted by the AIDS Clinical Trials Group compared several HIV therapeutic vaccines, including products developed by Genentech, Chiron Corporation, MicroGenSys and others. These studies showed that some products were more effective than others in inducing immune responses but it was wholly unclear if the responses had any impact in controlling HIV replication.

In the early 1990s, Genentech proceeded with a large study of its therapeutic HIV vaccine, rgp160. Results suggested that the vaccine made no impact on HIV disease progression and there was some

indication that people who received the vaccine did slightly worse than those on the placebo. Genentech stopped the study and abandoned efforts in this arena. (*Note: This vaccine was later sold to VaxGen, who modified it and is researching it as a preventive vaccine called AIDSVax*.)

Results of a large study of Immune Response Corp.'s (IRC) vaccine, the HIV-1 Immunogen (also known as Remune) suggested that the product had little to no impact on CD4+ cell counts or viral load. Unfortunately the study was not large enough to detect differences in the rate of HIV disease progression among those receiving the vaccine compared to the placebo. Pfizer Corporation, which was the principal investor in IRC, abandoned further development efforts of this product.

Many therapeutic vaccine products have been shown to elicit HIV antibody responses and some induce HIV-specific cellular responses in animal, test tube and human studies. Reports from complete and ongoing research will often highlight results from previous studies highlighting a product's *immunogenicity*. Immunogenicity is the degree to which the vaccine induces immune responses. Whether or not these responses will have any impact on HIV disease is unknown. Both the Genentech and the IRC vaccines were shown to induce at least transient and modest levels of HIV-specific immune responses but neither showed measurable benefits in people living with HIV. Whether larger and more lasting responses will make a difference remains to be seen. Ongoing studies should soon begin to provide answers to this question as some new vaccines, such as that from Merck, produce dramatically higher and longer lasting levels of these responses than any previous vaccine.

Some HIV vaccines have been shown to prevent infection in animal studies, including the Genentech vaccine referred to above. The new Merck DNA vaccine did not prevent infection, but it did appear to alter the course of the disease in animals that were later infected with an aggressive animal virus. Prior vaccination did not prevent the animals from developing disease, but it appeared to significantly slow disease progression. A few other vaccine products have shown similar results in animal studies. Humans do not react the same way to vaccines as animals. While results from animal studies may provide encouragement to vaccine developers to move forward into human studies, they may tell us very little about how the product will (or won't) work in humans. Also, not all animal models are the same—the types of animals used in a study are presumed to give better or worse information about what the human experience might be like. The kind of virus used to infect the animals in the studies might also make a difference in terms of how the information applies to the human setting.

One aspect of the excitement over animal study results of the Merck DNA vaccine may have to do with the kind of animal used in the studies. The animals used are known to develop a very aggressive form of AIDS following infection. That the product slowed disease in the animals was encouraging. Animals used in other studies do not develop disease following infection with HIV, so some researchers have been less enthused about results of studies where infection was blocked in those models. Of greater interest in the Merck studies is a compilation of new data showing that when the vaccine is used with the right adjuvant (a booster), it produces the strongest cellular immune responses yet seen from a vaccine. Still, researchers are not willing to predict whether it will work well enough to prevent infection altogether or provide therapeutic benefit to those infected already.

The way researchers report therapeutic vaccine study results can be a little misleading and generally this is not intentional or deliberate. The only way, truly, to report on initial findings of small studies of candidate vaccines is to discuss the *immunogenicity* of the product and any safety concerns. Generally speaking, when you hear or read that a vaccine product or a treatment strategy enhances HIV-specific immunity (either cellular or antibody) it's wise to remember that we've no idea if that is *functional* immunity or what level of this type of immunity is needed to make a clinical difference.

When considering therapeutic HIV vaccine *human* study results, look for:

- Was the study *controlled* (did some people receive vaccine and others receive placebo)? This will help you to sort out if any observed increases in CD4+ cell count or decreases in HIV levels were associated with the vaccine or merely the use of anti-HIV therapy. If the study was not controlled it may not be possible to sort out other factors that might be influencing the outcome.
- Did the report include information on *both* HIV-specific immune responses as well as viral load? Again, if the study was not *controlled* it is not really possible to say decreases in viral load were due to the vaccine product being researched. It's possible for the vaccine to be immunogenic (e.g. inducing HIV-specific immune responses) while anti-HIV therapy could be the factor controlling HIV replication.

Discussion

HIV vaccines are experimental. None have proven to be effective in preventing HIV infection or disease progression in humans. Several candidate vaccines are garnering interest from researchers and activists alike, including the Merck DNA vaccine and the GlaxoSmithKline HIV vaccine. Excitement for these products are due to the fact that they are moving forward into human studies and preliminary research suggests that they do something slightly different or novel compared to previously tested approaches. Whether or not these products will prove useful remains to be seen and is wholly unknown.

Generally speaking, HIV vaccines are believed to be relatively safe. Likely, vaccines will be given periodically, such as monthly, and side effects might predictably primarily be pain, redness and/or swelling at the site of injection and perhaps fever, fatigue and/or joint pain and stiff-

ness—as one might expect with any vaccine. In some HIV vaccine studies, more serious reactions have been observed (in a few rare cases there have been ulcerations at the injection site). It's quite possible that people with autoimmune diseases (e.g. lupus, arthritis, etc.) will be excluded from initial studies—as stimulating the immune system with vaccination has shown to worsen some of these conditions. It's even possible that stimulating the immune system with an HIV vaccine could worsen HIV disease progression. Results of previous studies don't suggest this is a major concern, but it is possible.

Initially, new therapeutic HIV vaccines will be researched in conjunction with anti-HIV therapy. Some proposed study designs includes the use of therapeutic vaccine or placebo in a structured anti-HIV therapy interruption model. The hope is that the HIV-specific immune responses induced by the vaccine will suppress HIV rebound following therapy discontinuation longer than what might be observed among people not receiving the vaccine. If you're considering participating in such a study it's important to understand the potential risks of structured treatment interruption.

When HIV mutates and becomes resistant to the effects of drugs, this is called *HIV drug resistance*. When HIV mutates and becomes resistant to the effects of the immune system this is called *immune escape*. At least one previous study suggests that the virus can mutate around the immune response. Theoretically, it's possible that HIV can become resistant to new, functional and potent HIV-specific immune responses. How much this will present a problem for therapeutic or preventive vaccines remains to be seen.

Finally, the potential of HIV vaccines is great. Despite years of research, however, this remains a field of study in its infancy. Many small studies have built the foundation for recent advances and researchers, activists and people living with HIV alike await the results of studies of new vaccine approaches to see where the next steps in this important area might lead. ■

Bottom Line

- There are currently no proven effective therapeutic or preventive HIV vaccines.
- Therapeutic HIV vaccine research is still in its infancy.
- Many studies have reported information that is not encouraging.
- We don't yet know if the ability of a vaccine to induce HIV-specific immune responses tells us, in and of itself, if the vaccine (or the immune responses) is useful in treating or preventing HIV.
- New vaccines, including the Merck DNA Vaccine, have garnered much interest among activists, researchers and people living with HIV. Only results of human study will tell us if this enthusiasm is warranted. Initial studies are underway.
- HIV vaccines researched to date have had minimal side effects, primarily pain, redness and swelling at the injection site and sometimes transient fever, fatigue and joint stiffness.
- In previous studies therapeutic vaccines were delivered monthly, by injection.
- In the short-term, it's likely anti-HIV therapy will be required in therapeutic HIV vaccine studies.