PROJECT inform

PERSPECTIVE

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

28

The Fine Line Between Education and Marketing

Though much of the American media continues to believe that AIDS has become a non-issue nationally, it has at least recognized the growing severity of the problem in the developing world. But whether speaking from the perspective of women, gay men, children, injection drug users, people with hemophilia, or any community in the "changing face of AIDS," unresolved problems continue to threaten the lives and well-being of HIV-positive people nationwide.

There has been considerable discussion recently of problems of treatment access and the inadequacy of currently available treatments, but precious little public discussion of the growing role that the pharmaceutical industry is playing in treatment education for HIV-positive people. Under the well-intentioned banner of education and treatment advocacy, the pharmaceutical industry has begun to spread its tentacles in unprecedented ways. Treatment education is indeed an important need at this stage of the epidemic, but there are profound questions about where that information comes from and whose interests it promotes.

A Little History

The pharmaceutical industry has a legitimate, long-term stake in issues regarding HIV therapy. There would be no protease inhibitors and other advanced therapies without industry. Government's work generally focuses on basic science, primarily learning how HIV causes disease, but it lacks the capacity for actual drug development.

Putting aside the critical topic of drug pricing, it is reasonable for industry to expect to see a fair return on their investment. Like it or not, it is the way our economic system works. Therefore, it would be naïve not to expect industry to competitively and aggressively market its products.

The question is just what constitutes legitimate marketing and what is, instead, an inappropriate intrusion into public efforts to educate HIV-positive people, caregivers and the many case managers and treatment advocates hired by AIDS service agencies. Left unchecked, industry's growing influence in this area threatens to upset the balance of control over the practice of medicine. In short, we need to ask where the line is drawn between marketing and education. The pervasiveness of industry support makes it a difficult issue to raise—few if any major agencies can afford to utterly reject industry funding—and Project Inform is not interested in criticizing the choices made by others. But the issue must be addressed.

Pharmaceutical companies have always wined and dined doctors and cluttered their offices with sales materials, but these efforts go far beyond their brochures. At best, they help inform physicians of advances in medicine and how best to use new drugs. At worst, they are biased marketing efforts designed to sway doctors' opinions with vacation trips, gifts, expensive dinners, free samples and (hopefully) everything short of outright bribes. To be fair, it is reasonable to assume that doctors have adequate training to objectively evaluate what they hear and sufficient integrity to act in their patients' interests. Whether they listen to their inner wisdom or the drug company pitch is a matter of conscience. Historically, though, efforts to influence the consumer's choice of therapy ended at the doctor's door.

A major change in the law took place a few years ago which permitted drug companies to engage in "direct-to-consumer" marketing, resulting in aggressive ad campaigns in televised and print media. The companies argued that this would help educate consumers on medical matters. The physician, they argued, was still the gatekeeper.

The pharmaceutical industry also has a history of meeting with AIDS activists to review medical data and get input on drug development and patient assistance strategies. At such meetings, activists often had a chance to ask more questions than was possible at scientific conferences. Surely, industry often saw these meetings as an opportunity to influence activists' points of view, but to the extent that the meetings in-

September 1999

In This Issue

cluded people from many different groups, there was little opportunity for industry to corrupt individuals.

Some may have taken industry's bait, but most did not. And where people were seen as becoming too closely tied to industry, they were watched more carefully by their peers and their roles as "representatives" were called into question. Over the years most treatment activists became highly knowledgeable about AIDS research and were typically the first to challenge the views and behavior of drug companies.

Training a New Population

Industry is now trying to extend its span of influence directly to almost anyone working in the field of AIDS who might be in a position to impact the treatment choices of HIV-positive individuals. Prime new targets include:

- Casual contributors to newsletters, newspapers and magazines (as opposed to writers specializing in treatment information)
- Hotline operators
- Case managers
- Treatment advocates/educators
- General AIDS agency personnel with access to particular communities

Industry is especially interested in case managers and treatment advocates who help coordinate patient's relationships with medical and social care systems. To industry, people in these jobs represent new gateways to a largely untapped "market" made up of the harder to reach populations. While everyone agrees on the need for wider treatment education services, several companies have taken advantage of this opportunity and are now directly running or hosting educational programs aimed at people in these gateway jobs. The programs claim to be balanced and fair, but there is little question that many, if not most, are designed to deliver either subtle or obvious messages about the companies' products.

Treatment education is indeed an important need at this stage of the epidemic, but there are profound questions about where that information comes from and whose interests it promotes.

These programs for "intermediaries" take multiple forms. Some are simply "community meetings" hosted by pharmaceutical companies in major cities. People in the targeted jobs are carefully identified and individually invited by industry to attend these meetings. Another approach arranges broad-based meetings with specific agencies, hoping to catch in the net everyone who might have direct access to the patient population or the messages delivered to it. Such meetings often come with the hint of being some kind of agency inspection tour for potential grants and funding. Administrative and development personnel, as well as program managers, are asked to attend.

But whether the meeting is held for individuals, agencies or local groups, the outcome is largely the same: a company's pitch about the importance and competitive value of its products, along with the implication that the company might do something for the agency or groups involved. Very often the companies view their roles as being responsive because, indeed, community groups look for help and support in providing treatment education. Whether this requires letting the fox in the hen house, however, is another matter.

Historically, scientific data have always been presented primarily to medical and scientific peers for review. That way, challenges to the analyses of data was guaranteed and overt product promotion was quickly called to task. Not so in these new programs, as the only medical or scientific personnel present are usually those working for the company. No one should expect a company presentation to be objective or unbiased. It is their job to present their products in the best light possible. To say that such efforts sometimes stretch the truth is an understatement.

Through just these two vehicles, activists case managers, administrators, program managers and treatment advocates are being exposed to slick, carefully targeted sales pitches, thinly disguised as "treatment education," while a carrot of implied funding potential whispers in the background. Such presentations to agency workers are but the first step.

Taking the Message to the Consumer

From the very beginning of the treatment era of the AIDS epidemic, companies jumped in (with varying degrees of integrity) to support development of educational materials on a number of topics, such as prevention, HIV 101, etc. Some have done a fine job while keeping their own interests at bay. Others have not.

Industry has today moved lock, stock and barrel into the AIDS field industry, supporting the total existence of a number of newsletters through advertising or targeted support. While advertising doesn't necessarily corrupt the writers or the content, it does use the relationship between the patient community and nonprofit agencies as a conduit for sending industry information directly into patients' homes. And if the newsletter source allows itself to become primarily dependent upon such ads for support, it exerts a subtle but powerful pressure to avoid displeasing the funders, since the alternative may be to go out of business.

Most companies offer a variety of support and grant programs to help AIDS agencies. There is nothing inherently wrong with this, and like most groups, Project Inform seeks industry grants. When well managed, such relationships stop far short of letting the companies influence what agencies do or how they do it. A new expansion of this is that industry now often pays for the creation of treatment education programs. Well enough, if the writers are allowed to maintain their independence and editorial distance. But not every agency is in the position of strength needed to negotiate such murky waters.

Of greater concern is that industry goes beyond providing financial support and sometimes simply writes the programs for some agencies. The appeal is obvious, especially for groups that lack staff support and time to develop their own materials. Industry comes along and delivers a slick, packaged product, ready for immediate use. Sometimes, at least a semblance of community input is allowed into the program, but the end product is still primarily the work of the company, not the community group.

Many feel this is an improper intrusion into community affairs, but more importantly, a dangerous precedent. The offer to provide training packages is often accompanied by significant levels of financial support to the agencies involved, intended to help defray the cost of presenting the programs. For groups trying to serve their communities on a limited budget, it is an offer

In Memory Of . . .

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

Eunice Clegg
Michael Eisman
Will Pretty
Bill Thorne
Jerry Weaver

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

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Project Inform
205 13th Street, Suite 2001
San Francisco, CA. 94103
PHONE **415-558-8669** FAX **415-558-0684**
EMAIL **INFO@projinf.org** WEBSITE **www.projectinform.org**

that is hard to refuse.

Examples of industry programs present a varied picture. Some seem reasonably well balanced. But others include misinformation and distortions, either by intent or accident. Others contain what seem to be images calculated to provoke culturally rooted emotional responses in targeted communities. Though these programs don't necessarily pitch a specific product by name, none seem to acknowledge that one of the reasonable choices available to people is to choose NOT to use treatment for some period of time. Nor do they address the strategy and drug resistance questions so key to wise treatment choices. And many contain product-specific messages or implications by describing strategies that can only be engaged by using the sponsor's drugs. The message, even when it is not directly competitive against other company's products, is simple and clear:

- Everyone should be on treatment, regardless of the stage of HIV disease.
- Everyone needs to take the drugs for the rest of their lives.
- Effective treatment strategies require the use of one or more of the sponsors' drugs.
- People who don't use treatment and adhere to the regimens are irresponsible.

Just whose interests are served by such messages and how do they help people make wise treatment choices?

Looking for Balance

There is an important need for educational outreach to hard-hit populations, and treatment is one of the things that must be talked about. Many agencies are struggling to find the money to provide such services. Many do not have the staff or the time to develop professional programs of their own. So when industry comes knocking, it looks like the answer to many problems, especially if the company says all the right things about community input, objectivity, etc. And at least some of the companies are reasonably fair and balanced in their approach.

No one faults agencies for their participation. They are trying to meet a real need, and many if not most know how to inject a sufficient degree of skepticism into the process to counter the drug company pitch. But not always. Even with the best intentions, it is hard to avoid the influence of the pharmaceutical industry.

If industry is sincere about wanting to provide support for community education, it must learn to do it in ways that separate proprietary interests from generic treatment messages. If the marketing departments can't live with that, they should take their money elsewhere and community agencies must be prepared to reject the offer. Ideally, industry should not produce or write the educational programs, but instead only provide resources—no strings attached—to agencies or groups developing the material. Though still fraught with difficulties, having a strong and diverse community input process into anything produced by industry makes a "second best" approach.

Perhaps a few good, culturally relevant programs may be all that are needed. By keeping the number small, the potential for catching any abuses would be greatly enhanced. There is perhaps no need for multiple companies to write or support different programs at all. If the message is truly generic and noncompetitive, maybe all of industry should contribute to a single fund for the development of a limited number of independently reviewed programs.

AIDS communities must begin to debate and challenge the role of industry influence. This doesn't mean agencies need to reject industry funding. On the contrary, as the one most profiting from the epidemic, the pharmaceutical industry indeed should be offering support back to the community. Support must come with the fewest possible strings, and should completely detach itself from the direct creation of educational materials by industry. If we fail to draw a line in the sand over these rapidly evolving practices, real damage will be done to the independence of our nonprofit sector as well as to the welfare of our constituents.

Industry control of treatment education materials is but the tip of the iceberg. Just below the waterline is a large cadre of new industry employees hired right out of the AIDS and activism communities. Whether such people represent an infiltration of industry by the community—or the other way around—remains to be seen. In a number of other diseases, the pharmaceutical industry is the primary source of support for services like education, hotlines, even support groups. Unless this sounds like an acceptable future for the AIDS community, a large and critical debate must begin, right now. ■

New Anti-HIV Drugs in Development

Compared to previous years, advances in the field of HIV antiviral research today are few and far between. Only a handful of new drugs in development block HIV reproduction by new mechanisms. Most experimental anti-HIV drugs are simply improved versions of existing therapies or new variations of those currently available. Such therapies are likely to offer only incremental benefits in potency, simplified dosing and reduced side effects. Some will claim to be effective against anti-HIV drug resistant viruses based on laboratory tests, but it remains to be seen whether they will help people with highly resistant virus.

This article reviews the new anti-HIV drugs currently, or soon to be, in studies. We also note any attributes about each drug that may make it different (or not) from those currently available.

New Protease Inhibitors

ABT- 378: Abbott Laboratories' ABT-378 is furthest along in development of all the new protease inhibitors. This drug will be packaged with a small amount (100 to 200mg twice a day) of ritonavir (Norvir®), which significantly boosts and stabilizes ABT-378 levels in blood. Studies show that ABT-378 is very potent and well tolerated. Preliminary results show that people who had viral load increases after their first protease inhibitor-containing regimen experienced good responses to a combination of ABT-378 and nevirapine (Viramune®).

Laboratory studies show that ABT-378 has resistance patterns similar to those of currently available protease inhibitors. However, it is hoped that people will achieve such high levels of ABT-378 in the blood without toxicity that it will be able to overcome some of these protease inhibitor resistant viruses.

Preliminary results of using ABT-378 as part of a second line regimen (people who have failed only a single previous protease inhibitor regimen) were recently released and appeared quite positive. Seventy people with an average viral load of 10,000 copies HIV RNA and CD4+ cells counts of about participated in this study. While participants had not previously used a non-nucleoside reverse transcriptase inhibitor, most had previously used indinavir (Crixivan®) or nelfinavir (Viracept®) in combination with either AZT (zidovudine, Retrovir®) + 3TC (lamivudine, Epivir®) or d4T (stavudine, Zerit®) + 3TC. Almost everyone had developed resistance to 3TC and approximately half to AZT. Participants received 400mg of ABT-378 taken twice a day in combination with either 100mg or 200mg of ritonavir also taken twice a day for 14 days. At day 15, everyone added nevirapine (Viramune®) and at least one new nucleoside analogue reverse transcriptase inhibitor. See Drug ID Chart on page 11 for a list of drug names and classes.

After 24 weeks, 77% of the participants had viral loads below 400 copies HIV RNA. There was also an average CD4+ cell count increase of 93 cells. More research is needed to determine if these results persist over time and whether the combination will be as successful when measured by the more demanding ultra-sensitive viral load test, which measures down to 50 copies of HIV RNA. Moreover, it is unknown if participants of the third line regimen studies will respond similarly to ABT-378.

Results of studies with ABT-378 for third line use (people who have lost sensitivity to two or more previous protease inhibitor regimens) have

Results of studies with ABT-378 for third line use have not yet been presented. Enrollment ... has been surprisingly slow and there are many available opportunities for people to access the drug.

Ritonavir and Menstruation

Women living with HIV often experience changes in their menstrual cycle, including the flow and frequency of menstruation. A recent study suggests that women using the drug ritonavir (Norvir®) as part of their anti-HIV combination therapy may be at a greater risk for anemia (a decrease in red blood cells) due to excessive menstrual bleeding, a condition known as hypermenorrhea.

The study followed a group of ten HIV+ women, all of whom had normal menstrual cycles and hemoglobin levels (a measurement of how much oxygen is being carried by the red blood cells from the lungs to other parts of the body) before starting anti-HIV therapy. Within two months of starting a combination containing ritonavir, however, four women developed hypermenorrhea. One required a transfusion because of severe anemia. Three of the four were switched to another protease inhibitor without any further complications. The remaining woman continued to use ritonavir, although her periods remained irregular.

While this study is too small to conclude that hypermenorrhea is caused by ritonavir, it does stress the need for more studies looking at menstruation in positive women. Since protease inhibitors in general are associated with several side effects, this study also underscores the need to consider whether menstrual irregularities and anemia occur with the use of other anti-HIV drugs, and whether these effects are long lasting or subside over time. In the meantime, positive women taking ritonavir should be aware of this possible effect on menstruation.

Commentary

Ritonavir has long been viewed as having the most side effects of the currently available protease inhibitors and consequently it is seldom used as the main protease inhibitor in a three-drug combination. This new information seems to support this view. The most common way to use ritonavir today is as part of a dual protease inhibitor strategy. In this approach, small doses of ritonavir are taken along with either saquinavir (Fortovase®) or indinavir (Crixivan®) to improve the activity of the second drug. There are no data yet available on whether these smaller ritonavir doses are as likely to contribute to anemia in women as the full doses used in this new report. ■

Ritonavir Capsules Available

After being withdrawn from the market for almost a year due to complications in the manufacturing process, ritonavir (Norvir®) is once again available. This eliminates the need to drink the unpleasant liquid form of the drug. The newly formulated soft gel capsules are already in pharmacies.

Abbott Laboratories, the manufacturer, recommends refrigeration of the new capsules but says it is not required if they are stored below 77°F (25°C) and used within 30 days. The new capsules are fairly large and contain 100mg of ritonavir. As with the old capsule formulation, ritonavir should be taken with food twice a day. Abbott believes that this new formulation behaves in the same manner as the old formulation. Therefore, the side effect profile and drug interactions should also be the same. For more information on drug interactions with ritonavir and other drugs, contact Project Inform's National HIV/AIDS Treatment Hotline and request the *Drug Interactions Fact Sheet*.

One of the great interests with ritonavir has been its ability to substantially raise and sustain the levels of other drugs in blood, especially other protease inhibitors. This often results in making it possible to take lower doses of both drugs and, in most cases, to reduce the number of times they must be taken each day. Because the drug levels are better sustained in the presence of ritonavir, it is unnecessary to take large initial doses of the drugs to get adequate long-term levels in the blood. Consequently, it is likely that some side effects may also be reduced by the use of such combinations.

One particular combination sparking a lot of interest is ritonavir and indinavir (Crixivan®). Results from several small studies suggest that this is a very potent combination, one that may 'overpower' some of the protease inhibitor resistant viruses because higher levels of indinavir can be achieved and sustained. Studies are now ongoing to determine the activity of this combination in people who have developed resistance to protease inhibitors.

Preliminary results in people starting therapy for the first time suggest very good anti-HIV activity, a reduction to twice daily dosing for indinavir, and the ability to take indinavir with food. There is even some suggestion that this combination may reduce a few kidney related side effects associated with indinavir. This may lessen the need to drink large amounts of water when taking the drug. These potentially important benefits, however, need to be confirmed in larger and longer studies.

Several dose combinations are currently being studied to determine the optimal dose. They include 100mg ritonavir/800mg indinavir, 200mg ritonavir/800mg indinavir and 400mg ritonavir/400mg indinavir, all of which are taken twice a day. ■

not yet been presented. Enrollment in these studies has been surprisingly slow and there are many available opportunities for people to access the drug through studies. For a list of study sites, call 1-800-TRIALSA. An expanded access program for ABT-378 began in early September. For more information on this program, see page 8.

Tipranavir: Results were recently released of a laboratory study showing that tipranavir (formerly PNU-140690) remained sensitive to almost all of the protease inhibitor resistant viruses tested. Pharmacia and Upjohn, the developers of the drug, are planning several large studies that will include people who have not previously taken anti-HIV therapies as well as those seeking a third line regimen. It has been difficult to develop resistance to this drug in laboratory studies. However, this has been true for many other drugs only to later find that resistance can be developed quite readily in real life applications.

The initial formulation of the drug, which required people to take ten large pills three times a day, had slowed down the development process. Most people in the early studies developed diarrhea because of the 'ingredients' in the pill as well as the number of pills that had to be taken. A new capsule formulation that allows for better drug absorption has recently been introduced. This new formulation should allow for twice a day dosing as well as a lower number of pills per day. Whether this solves the problem with diarrhea is unknown, but at least it makes the drug easier to use. Tipranavir is also being studied in combination with ritonavir, which significantly boosts tipranavir levels, and it is hoped that this combination will be useful for people who have developed resistance to the currently available protease inhibitors.

L-756,423: L-756,423 is Merck's new protease inhibitor. Laboratory studies suggest that the drug can be taken twice, or possibly once, a day with a reduced risk of developing kidney stones compared to Merck's other drug, Indinavir. This drug is being developed for use in a combination with indinavir (similar to ABT-378 and ritonavir). Laboratory studies show that the resistance pattern is similar other protease inhibitors so it's use in third line therapy is dubious.

DMP-450: DMP-450 is a protease inhibitor being developed by Triangle Pharmaceuticals. The drug is designed to be taken twice a day and has a similar resistance profile to other protease inhibitors. One possible advantage for this drug is that it is easier to manufacture and so, in theory may be less expensive.

BMS-232632: Bristol-Myers Squibb's first protease inhibitor, BMS-232632, is being studied in a once daily regimen. In some laboratory studies the drug develops the same resistance mutations as the currently available protease inhibitors, but in other experiments it appears to have a different resistance profile. Drugs which have shown similar conflicting results in the past have usually turned out to have problems with cross-resistance, like almost all other protease inhibitors.

Other New Protease Inhibitors: Parke Davis' PD 178390 and Agouron Pharmaceuticals' AG1776 appear to have different resistance profiles based on laboratory studies and the manufacturers claim they *may* be active against protease inhibitor resistant viruses. Both drugs are in early human studies. Again, past history with such claims suggests a cautious approach.

New Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Emivirine: The new NNRTI furthest along in development is Triangle Pharmaceuticals' emivirine (Coactinon®, formerly MKC-442). Triangle is expected to file for approval of this drug by the end of this year. Studies show that emivirine has the same resistance patterns as the other NNRTIs and most researchers believe that this drug will not offer any benefits for people who with NNRTI resistant virus. Emivirine is dosed twice a day and is quite well tolerated. Rash (perhaps at a much lower incidence than nevirapine) and gastrointestinal problems are the most commonly reported side effects.

Other New NNRTIs: There are many other NNRTIs in early development, most of which the developers claim to be at least somewhat active against viruses resistant to the currently approved

NNRTIs, based on laboratory studies. These include Agouron Pharmaceuticals' AG1549, Glaxo Wellcome's GX420867X, Pharmacia and Upjohn's PNU142721, MediChem Sarawak's Calanolide A and Dupont Pharmaceuticals' DPC961 and DPC963. Time will tell if such claims are realistic.

New Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (NARTIs and NtARTIs)

FTC: Almost all of the new NARTIs in development claim to be active against some viruses resistant to drugs of this class. The one exception is Triangle Pharmaceuticals' FTC (emtricitabine, Coviracil®). This drug is very similar to 3TC (lamivudine, Epivir®) and has the same resistance profile. FTC, however, does appear to be more potent than 3TC and only has to be dosed once a day. Like 3TC, FTC also has activity against hepatitis B virus.

Adefovir: Gilead Sciences recently applied for approval to the FDA for their NtARTI, adefovir (Preveon®). Study results show that the drug, which is dosed once a day, only has marginal anti-HIV activity but may play a role for people putting together a third line regimen. This drug appears to be especially active in the presence of 3TC resistance (and probably should be used in combination with 3TC even if someone has developed high level resistance to 3TC). Laboratory studies suggest that the drug is active against multi-NARTI resistant viruses. Despite this, the drug's activity level remains low.

Adefovir can seriously decrease L-carnitine levels, therefore supplemental L-carnitine should be taken with it. The side effects from this drug have been of great concern to many physicians. Increased serum creatinine levels (an indication of kidney dysfunction) and decreases in phosphate levels (an indication of decreased bone density) are of greatest concern. Furthermore, these side effects usually develop about 20 weeks after starting adefovir so people should be monitored more closely around that time.

Due to the increased risks of side effects and the minimal anti-HIV activity observed with adefovir, AIDS activists may not enthusiastically support FDA approval of this drug.

Because of its somewhat unique mix of low activity levels and high risk of a potentially dangerous side effect, there is serious question whether the FDA will grant approval for adefovir. Were a similar drug with a similar mix of properties offered much earlier in the epidemic when there were fewer choices, approval would have seemed likely. But in the context of the 14 anti-HIV drugs already on the market, and with more in the wings, the outcome for adefovir is uncertain. It is further complicated by the fact that the manufacturer has a related and much more potent compound, PMPA, right behind it in the pipeline.

Due to the increased risks of side effects and the minimal anti-HIV activity observed with adefovir, AIDS Activists may not enthusiastically support FDA approval of this drug.

Based on early study results, adefovir also appears to have potent activity against hepatitis B virus including activity against 3TC resistant hepatitis B.

PMPA: Gilead Sciences is also developing another NtARTI, PMPA (tenofovir). Studies show this drug is significantly more potent against HIV than adefovir. PMPA is also dosed once a day. It is still unclear whether people taking PMPA will encounter the same side effects as those seen in people taking adefovir. Several third line studies are planned with PMPA in combination with other new anti-HIV therapies. Gilead announced an expanded access program for PMPA starting in October. For more information, refer to the box on page 8.

Lodenosine: US Bioscience is developing lodenosine (formerly f-ddA). Laboratory studies suggest the drug may be effective against multi-NARTI resistant viruses. Lodenosine is being studied with twice a day dosing although it may be possible to take the drug once a day. Like ddI, adefovir and PMPA, lodenosine has a particularly potent interaction with hydroxyurea, an older cancer drug which is widely used in combination therapies.

Other NARTIs: Two other NARTIs—Bio-

Recent News About ddI

There has long been a love-hate relationship with ddI (didanosine, Videx®) in the HIV community. The drug has repeatedly demonstrated its potency and laboratory studies (with some confirmation from human studies) show that resistance to ddI develops very slowly. However, the current formulation of ddI contains an antacid buffer to help the drug survive its passage through the stomach (ddI breaks down quickly in the presence of stomach acid). Similarly, ddI must also be taken on an empty stomach (at least a half hour before a meal), when stomach acid levels are low. The antacid buffer further complicates the use of ddI in combination with some other drugs. For instance, a combination which includes ddI and indinavir (Crixivan®) is extremely difficult to take because both drugs need to be taken on an empty stomach but the buffer in ddI, which helps that drug, will reduce the amount of indinavir found in blood if they are taken at the same time. As a result the two drugs have to be taken at least an hour apart, which can make scheduling the drugs a challenge. In addition, the antacids are also associated with diarrhea and nausea, two side effects commonly reported by people taking ddI.

There is finally some good news on this subject. Bristol-Myers Squibb has developed a new formulation of ddI designed to solve these problems. It is currently being tested in studies. This new formulation eliminates the antacid buffer, simplifying the use of ddI in combination therapy. This should also reduce some of the diarrhea and nausea associated with the current formulation. People will be able to take the new ddI at the same time as indinavir, although the restrictions on taking both drugs on an empty stomach will still apply. Unfortunately, the Food and Drug Administration has requested that long-term studies be conducted to determine if the new formulation works as well as the old one. As a result, the new formulation ddI will not be available, outside of clinical trials, until the latter half of next year.

On another front, results from two studies suggest that ddI can be safely taken once a day rather than the currently recommended twice daily dosing. Both studies found that 400mg of ddI, taken once a day, was as effective in decreasing HIV levels and increasing CD4+ cell counts as 200mg of ddI taken twice a day. Participants in these studies also received d4T (stavudine, Zerit®) dosed twice a day. The incidence of side effects was similar between the two groups with elevations in liver enzymes being the most common. The once a day regimen makes ddI a little more user-friendly. ■

Chem Pharma's dOTC and Triangle Pharmaceuticals' DAPD—are in early stage studies. Both Triangle and BioChem Pharma claim to have the rights to develop DAPD, although Triangle is the one sponsoring the ongoing studies. Both of these drugs may be effective against multi-NARTI resistant viruses.

New Targets

Pentafuside and T-1249: One drug that has received a lot of attention in the past few months is pentafuside (also known as T-20), which is being developed by Trimeris. Pentafuside belongs to a class of drugs known as fusion inhibitors, which work by physically blocking the ability of HIV to attach to CD4+ cells. Studies show that this drug is effective as a third line therapy, even in people who have become resistant to all current protease inhibitors. Getting a durable response, however, requires the drug to be paired with at least one other anti-HIV drug to which the person still responds. Pentafuside has to be administered via a subcutaneous (under the skin) injection twice a day and it will never be available in an oral formulation. Trimeris has also recently started studies with a second fusion inhibitor, T-1249. Laboratory studies suggest that this drug will be effective against T-20 resistant virus.

Other fusion inhibitors in development include Progenics' PRO 542 and Lexigen Pharmaceuticals' FP-21399. Development prospects for this particular drug have dimmed somewhat since the company ran out of money.

AMD-3100: AnorMED recently started development of their CXCR4 blocker, AMD-3100. The chemokine CXCR4 is one of the 'pathways' that HIV uses to infect a new cell. This is the first chemokine blocker in development and if it proves successful, this drug may be particularly useful in people with advanced stage disease who have a particular type of HIV that reproduces very rapidly, known as syncitium inducing or SI type virus.

HE-2000: Hollis Eden recently started human studies with HE-2000. The exact way that this drug blocks HIV from reproducing has not been confirmed, although the company's current hypothesis is that it 'starves' HIV of the essential proteins that it needs. HE-2000 is given by injection directly into the muscle. In laboratory studies, this drug is also said to have activity against numerous other viruses. The drug's main claim to legitimacy rests on a small, uncontrolled study in chimpanzees, where chimps were given HE- 2000 were reported to live somewhat longer than expected due to their SIV infection.

Dose Adjustments When Using Amprenavir

Amprenavir (Agenerase®), the most recently approved protease inhibitor, is often used by people who have lost responsiveness to one or more of the previously available drugs of this class. It is considered wise in this situation to try to start two new drugs at the same time so many people combine amprenavir with efavirenz (Sustiva®). Unfortunately, few people seem aware that there are significant interactions between these two drugs which require adjusting their dosage.

Efavirenz decreases amprenavir levels in the blood by about 40%, making an increased dose of amprenavir necessary. The optimum dose of amprenavir in this combination is still not clearly established, but some researchers believe it should be increased to 1,200mg three times a day (compared to the standard dose of 1,200mg twice daily). However, early study results indicate that this change in dose is unnecessary if the combination also includes 100–200mg of ritonavir **or** 1,250mg of nelfinavir taken twice a day along with the amprenavir and efavirenz. Check the chart below for preliminary dosing recommendations. ■

Drug Combinations	Possible Dose Adjustments
APV	1,200mg, 2x (normal dose).
APV + EFV	APV 1,200mg, 3x; EFV 600mg 1x.
APV + EFV + RTV	APV 1,200mg, 2x; EFV 600mg 1x; RTV 100-200mg, 2x.
APV + EFV + NFV	APV 1,200mg, 2x; EFV 600mg 1x; NFV 1,250mg, 2x.

APV=amprenavir; EFV=efavirenz; RTV=ritonavir; NFV=nelfinavir.

On The Horizon

Several companies including Merck, Pfizer and Bristol-Myers Squibb are developing blockers against the CCR5 chemokine receptor. CCR5 is another 'pathway' that HIV uses to infect new cells. If this strategy proves successful, these CCR5 blockers may be useful in people with early stage HIV disease who have a type of virus known as non-syncitium inducing or NSI virus. Given that HIV can infect cells through many different pathways, it may be necessary to combine a CCR5 and CXCR4 blocker to prevent HIV from infecting new cells. Because this is a completely new field of drug development, it is likely to take a number of years before truly effective drug candidates will be found.

A few years ago there was a tremendous amount of interest in research around inhibitors of the integrase enzyme. Integrase is another one of the essential enzymes that HIV uses to make new infectious viruses. However, a lot of the enthusiasm has been dampened as companies have failed to come up with potent drugs against this target. One company that may be close to selecting a drug for development is Merck. They have reported on different integrase inhibitors that in laboratory studies are potent inhibitors of HIV. One barrier that they face is that the drugs bind to proteins found in the human body before they have a chance to become active against the virus. Though this probably effects most of the available protease inhibitors as well, Merck was able to overcome this problem with indinavir. Thus there is hope they will be able to do this again.

Commentary

While this may seem like a reasonable number of new drugs in the pipeline, their potential is limited by the fact that few if any are likely to be active against highly resistant virus, where the need is greatest. There are already many viable options for first line therapy, and reasonable, improving options for second line therapy. The new crop of drugs offers only incremental advances over these options, such as once-daily dosing. The greater challenge, finding drugs that will be highly potent despite multi-drug resistant virus, remains largely unmet, with the one proven exception of T-20. ■

Reporting Drug Side Effects?

Throughout the history of HIV disease, people have been making decisions about treatments with very little information about both the effectiveness and the side effects, particularly long-term side effects, associated with new medications. At the time the first anti-HIV drug, AZT (zidovudine, Retrovir®), was approved for wide-scale use, it had only been tested in few thousand people who were on the drug for six months or less. Little was even known about the proper dose of the drug. Most of what is currently known about the effectiveness, long-term side effects and optimal use of AZT was learned in later years after the drug was first approved. Since AZT and newer drugs for HIV were so desperately needed, waiting for the results of true long-term studies has never been feasible. This will undoubtedly continue to be true of most drugs used for the treatment of HIV disease as well as many drugs used to treat and manage opportunistic infections associated with HIV disease. Additionally, because women are often under-represented in studies of therapies, there is little known about serious side effects that may be unique to women when a drug is approved.

The only way that information on rare, unusual or long-term side effects of drugs can be gathered is if health care providers report information about such side effects to the Food and Drug Administration (FDA). To try to capture information on the rate of serious side effects associated with drugs, the FDA has a system in place called MedWatch. The success of the MedWatch system, however, is entirely dependent on physicians or other health care providers filling out the MedWatch form and sending it to the FDA. In cases where a doctor or health care provider is too busy to fill out the paperwork, or other circumstances prevent a doctor from doing so (e.g. you don't want the event reported by your doctor), you may file a report yourself.

Your doctor can obtain the MedWatch Voluntary Reporting Form by calling the MedWatch office at 1-800-332-1088. The one page form is simple and only takes a few moments to fill out. It can be submitted to the FDA by mail or through a toll-free fax number. Additionally, for those with access to the world wide web (internet), a form can be filled out online https://www.accessdata.fda.gov/medwatch/medwatch-online.htm

Online reporting can also be accessed by clicking the MedWatch button on the FDA's homepage http://www.fda.gov

Project Inform has sample copies of the MedWatch Voluntary Reporting Form available through the Project Inform hotline (1-800-822-7422). A link to online reporting to the FDA is being established from the Project Inform website http://www.projectinform.org ■

EXPANDED ACCESS

These new drugs are currently available free of charge while awaiting FDA approval.

Protease Inhibitors	
ABT-378 **888-711-7193**	Abbott Laboratories, the developers of a new protease inhibitor ABT-378, (see New Antivirals in Development on page 4), will start an early access program for the drug in September. This will initially be a very small program, allowing only 700 people worldwide, early access to the drug (about one-half in the US). This program will expand rapidly beginning in January, 2000. To qualify for the program, people must have all of the following: • Less than 50 CD4+ cells (within the past three months) and greater than 10,000 copies HIV RNA or an active opportunistic infection within the past three months • Intolerance to and/or failure (viral load increases) to at least two previously used protease inhibitors • Unable to construct a viable combination without ABT-378 To register patients in the program, physicians should call (888) 711-7193. In the US, the drug will be accessed through about 35 clinics, though people need not be receiving their medical care through those clinics to qualify for the program. For locations of these clinics, please call Project Inform's National HIV/AIDS Treatment Hotline.
NtARTIs (Nucleotide Analog Reverse Transcriptase Inhibitors)	
Adefovir **800-445-3235**	For anyone failing current therapy and requiring an additional new drug for treatment strategy.
Tenofovir (PMPA) **Phone number not available yet. Call Project Inform's Hotline for an update.**	Entry criteria same as for ABT-378. This will be a very small program limited to 300 people in the US. The program will begin in October, 1999, but unlike the ABT-378 program, it will not expand until after June, 2000.

Mycophenylate – A Potential New Option

Mycophenylate (CellCept®) is an available prescription drug that may enhance the anti-HIV activity of abacavir (Ziagen®). Most data so far come from lab studies published by David Margolis and Robert Redfield of the Institute for Human Virology (headed by Robert Gallo). The team also has started human studies.

Mycophenylate is normally used to prevent rejection of kidney transplants. Mycophenylate suppresses production of guanosine, a key building block of DNA critical to the reproduction of HIV. Researchers reasoned that the drug would be most effective if paired with an antiviral that produced "false building blocks" resembling guanosine. They realized this meant abacavir, which mimics guanosine.

This model is similar to what happens when combining hydroxyurea with ddI, though studies suggest the mycophenylate/abacavir combination may be more potent and less toxic. More importantly, lab studies show the combination is highly active when used against abacavir-resistant virus.

A key question is whether the combination adds unacceptable toxicity or immune suppression, sometimes a problem with hydroxyurea + ddI. Based on lab data, however, it appears mycophenlyate can be used at doses two to ten times lower than those employed in normal application and still achieve high level anti-HIV effects.

These observations need to be confirmed in human studies, and the first have already begun. The simple two-drug combination is being given to advanced-stage patients who have failed all other therapies. Dosing employs 250mg of mycophenylate twice daily with the standard abacavir dose. The current dose of mycophenylate was chosen largely for convenience and lower doses may be tried in the future.

It is too early to recommend this for common use, but it builds upon a proven model and offers hope of a better treatment than hydroxyurea + ddI. Mycophenylate also has activity against hepatitis C virus and should also combine well with ribavirin, which is currently used in the treatment of hepatitis C. Mycophenylate should not be used with AZT or d4T as it is likely to negatively effect the activity of those drugs. ■

Recent Lipodystrophy Findings

A lipodystrophy workshop, held in June in San Diego, CA, brought together top researchers to present data and exchange ideas. Groups from around the world presented information about ongoing studies to shed light on this emerging phenomenon, which includes changes in body composition and *sometimes* changes in laboratory parameters (cholesterol, insulin sensitivity, and triglycerides). The potential health risks for people with elevated lipid (cholesterol and triglyceride) levels were also discussed. Workshop attendees attempted to create an interim definition for lipodystrophy to improve the ability to diagnose and measure the syndrome(s).

Changes in Insulin Markers

Studies show that people with HIV experience a significant increase in insulin clearance along with a decrease in insulin sensitivity that may be due to anti-HIV therapy. Both changes in insulin maintenance may, in some circumstances, put people at increased risk for developing diabetes.

Working Definition of Lipodystrophy

Meeting participants spent a considerable amount of time trying to establish a case definition of lipodystrophy. They came up with the following "case definition" where any one of the symptoms listed below would be included:

- Sunken cheeks in the face
- Prominent veins in the legs
- Loss of contour in the buttocks
- Increase in abdominal girth
- Breast enlargement
- Buffalo humps (fat pad on back of neck)
- Lipomas (fatty growth)
- Accumulation of facial fat

Also noted was that there may be other changes in fat redistribution that have not yet been reported.

The class of anti-HIV drugs known as nucleoside analogue reverse transcriptase inhibitors (NARTIs, see Drug ID Chart on page 11) decreases insulin sensitivity somewhat, which may be associated with an increased risk of diabetes. Using NARTIs in combination with non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors, however, results in an even greater decrease in insulin sensitivity.

Several small studies have reported some success in combating insulin resistance. This includes instances where people discontinued protease inhibitors and switched to either abacavir (Ziagen®) or nevirapine (Viramune®) containing regimens. Among people who continued on protease inhibitors, the addition of troglitazone (Rezulin®) appeared to increase insulin sensitivity. Two recently approved therapies—rosiglitazone (Avandia®) and pioglitazone (Actos®)—are likely to have the same effect with perhaps a reduced risk of the serious liver side effects associated with troglitazone.

Much concern has been expressed about increased triglyceride and cholesterol levels and the potential for heart disease in people taking protease inhibitors. Dr. Grunfeld from the San Francisco Veterans Administration Medical Center compared these two levels in people with HIV taking protease inhibitors to a previous large study (Framingham Study) of HIV-negative individuals. Based on this model, the use of protease inhibitors would result in only a few additional cases of heart disease over ten years. It is important to remember that other factors, including genetics, may contribute to elevated cholesterol and triglyceride levels as well as increased risk for heart disease.

Dutch Group Findings

One provocative presentation from a Dutch group suggests using NARTIs may cause lipodystrophy syndrome, as they cause mitochondrial toxicities. Mitochondria are the site of production of a key source of energy in cells that is involved in the breaking down of fat.

NARTIs can cause mitochondrial dysfunction that can result in many different side effects including neuropathy (tingling and pain in the nerves especially in legs, feet and arms), myopathy (pain in the muscles) and lactic acidosis (accumulation of lactic acid in the blood, which can result in nausea, vomiting, abdominal pain and liver failure). Also, laboratory studies suggest that mitochondrial dysfunction may cause the abnormal function of fat cells during anti-HIV therapies. This Dutch group believes that NARTIs and protease inhibitors play a complementary role in causing lipodystrophy.

Australian Group Findings

The Australian group at the forefront of lipodystrophy research reported that people using NARTIs may risk developing lipodystrophy if their lactate levels (a measure of lactic acid) are above 2mmol/l. This again suggests that mitochondrial toxicity may be a factor.

According to their study, risk factors for lipodystrophy include age (risk increases with age), d4T (stavudine, Zerit®) use and duration of NARTI use. Their findings suggest that people taking protease inhibitors are more likely to have elevated cholesterol and triglyceride levels as well as insulin resistance. People who have lipodystrophy and are taking only NARTIs are more likely to also have evidence of liver dysfunction.

French Study Findings

A French study of 196 people suggests that lipodystrophy syndrome is associated with the duration of anti-HIV therapy use. The syndrome appeared about 20 months after starting highly active antiretroviral therapy (HAART) and was associated with longer HIV diagnosis, longer use of anti-HIV therapy. People experienced increases in cholesterol and triglyceride levels when they started HAART regardless of whether or not they developed lipodystrophy syndrome.

Effects from d4T

Several studies presented suggest that people taking d4T may be at higher risk of developing lipodystrophy syndrome. However, most researchers believe it is premature to single out d4T as a risk factor due to so many confounding variables that have to be examined. These include: almost all people had previously taken AZT (zidovudine, Retrovir®); almost all participants were also receiving 3TC; and almost all participants were taking other anti-HIV therapies, including protease inhibitors and/or NNRTIs. Additionally, the current lipodystrophy phenomenon was rarely if ever seen in the early and middle 1990s, despite the fact that d4T was used extensively in studies, in a very large expanded access program, and eventually in clinical practice. Future studies should be able to determine whether taking d4T really does increase a person's risk for developing lipodystrophy. At this stage, similar cautions should be employed in drawing any conclusions about what does and doesn't contribute to lipodystrophy. The suspected causes have changed several times in just the last 24 months. ■

Body Composition Changes in Women

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Anecdotal reports suggest that women might experience body composition changes (e.g. breast enlargement, central obesity, "buffalo hump" and/or facial and limb wasting) at a slightly higher frequency than those observed in men. HIV disease itself, or possibly therapies to treat HIV, may contribute to these changes, as well as other changes in how the body processes fat, sugars and proteins (called metabolic processes). Some early studies are beginning to add weight to the reports of differences based on gender.

At the recent San Diego conference on body composition changes and metabolic processes (called lipodystrophy), Dr. Garg of the University of Texas Southwestern Medical Center presented an overview of non-HIV related lipodystrophy syndromes. He provided participants with a broader context for looking at inherited and acquired lipodystrophy, what is known about them and how they develop. Interestingly, while these conditions are very rare, acquired lipodystrophy in people who are not HIV-positive appears more common in women—affecting only one man for every three women. The reason for this gender difference is unknown.

What the Studies Show

In a large study, known as the SALSA study, which specifically looked at lipodystrophy, 55% of 140 men and 33% of 30 women reported changes in body composition after starting anti-HIV therapy. The kinds of changes differed between men and women. Men more frequently noted *only* loss of body fat, whereas women more commonly reported *only* gaining fat. Moreover, women maintained normal lipid levels (a laboratory marker of circulating fat) while men typically showed abnormal lipid levels. Another observation from this study was that only a few people on highly active antiretroviral therapy (HAART) for less than a year reported changes in body composition whereas about 50% of the participants who were on HAART for one to three years reported changes.

Another study from Milan, Italy included 92 men and 96 women, *none* of whom received a protease inhibitor or NNRTI. In this study 26% of women and about 7% of men experienced changes in body composition, demonstrating that these changes do not strictly relate to the use of protease inhibitors. Women had a five times higher risk of developing fat redistribution, with the largest differences being breast enlargement (14.6% women, 0% men) and loss of weight in legs.

A French study that included 624 people (84% men) also showed evidence of gender differences in body changes. All participants received triple-drug therapy (HAART). Breast enlargement was observed in 49% of women and only 15% of men, and central obesity was observed in 67% of women and 48% of men.

Commentary

These studies suggest that gender differences may exist in the incidence and prevalence of body composition changes associated with HIV disease and/or anti-HIV therapies. Moreover, the types of changes that occur may differ between men and women. Women may be more likely to experience breast enlargement, for example, while men may be more likely to experience fat loss and laboratory abnormalities (i.e. abnormal lipid levels). If fat accumulation proves more common among women, then risks associated with certain kinds of fat accumulation, such as diabetes, may also be more common among women. However, it very important to recognize that these studies, like all studies of lipodystrophy so far, may be hampered by imprecise definitions, inconsistent measurement methods and the relatively small number of women who were followed. There may indeed be real differences between men and women in this regard, but the current round of studies should not be seen as conclusive proof of this. Prospective, controlled studies with adequate numbers of men and women must be conducted under a single definition of lipodystrophy before hard conclusions can be reached. ■

A New Acronym, a New Threat: IRU

Eye doctors (ophthalmologists) have recently observed the appearance of eye inflammation in people who have experienced remission of cytomegalovirus (CMV) retinitis in response to highly active antiretroviral therapy (HAART). This eye inflammation is currently called *Immune Recovery Uveitis* (IRU). Uveitis is an inflammation inside the eye which can result in significant vision loss. IRU has only been observed in people who started HAART and had a significant increase in CD4+ cell counts and who have stopped their anti-CMV therapies. Additionally, IRU only occurs in eyes that were previously diagnosed with CMV retinitis.

One hypothesis for IRU is that there may still be low level CMV replication in the eye. The newly invigorated immune response may be attacking the CMV and causing inflammation. There are several unknowns at this point. It is not known if people who have the ganciclovir implants (Vitrasert®) to treat CMV are as likely to develop IRU because the implants are better able to control CMV replication. It is also not known if IRU will improve if someone resumes CMV therapies.

Ophthalmologists have tried a few different therapies to treat IRU with limited success, including systemic prednisone, periocular (around the eye) injections of prednisone and methylprednisolone (Depo-Medrol®). In most instances, when these medications were stopped, the IRU returned.

A large observational study has started at the Studies of Ocular Complications from AIDS (SOCA) sites and it is hoped that this study will be able to assess the incidence and prevalence of IRU, the cause of IRU and strategies to treat it. In the meantime, people who previously had CMV retinitis should consider the risk of IRU when thinking about stopping CMV maintenance therapy. ■

Drug Identification Chart

INITIALS	GENERIC NAME	TRADE NAME	MANUFACTURER
Protease Inhibitors			
APV	amprenavir	Agenerase®	Glaxo Wellcome
IDV	indinavir	Crixivan®	Merck
NFV	nelfinavir	Viracept®	Agouron
SQVhgc	saquinavir hard gel capsule	Invirase®	Hoffman-La Roche
SQVsgc	saquinavir soft gel capsule	Fortovase®	Hoffman-La Roche
RTV	ritonavir	Norvir®	Abbott Labs
NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)			
DLV	delavirdine	Rescriptor®	Pharmacia & Upjohn
EFV	efavirenz	Sustiva®	Dupont Pharma
NVP	nevirapine	Viramune®	Boehringer Ingelheim
NARTIs (Nucleoside Analog Reverse Transcriptase Inhibitors)			
ABC	abacavir	Ziagen®	Glaxo Wellcome
AZT	zidovudine	Retrovir®	Glaxo Wellcome
AZT+3TC	---	Combivir®	Glaxo Wellcome
ddC	zalcitabine	Hivid®	Hoffman-La Roche
ddI	didanosine	Videx®	Bristol-Myers Squibb
d4T	stavudine	Zerit®	Bristol-Myers Squibb
3TC	lamivudine	Epivir®	Glaxo Wellcome
NtARTI (Nucleotide Analog Reverse Transcriptase Inhibitors)			
ADV	adefovir	Preveon®	Gilead Sciences
Cellular Factor Inhibitors			
HU	hydroxyurea	Hydrea®	Bristol-Myers Squibb

Opportunistic Infections Update

The US Public Health Service and the Infectious Disease Society of America recently issued new guidelines for the prevention of opportunistic infections (OIs). The revised guidelines take into account the increasingly common practice of stopping preventive treatment (to reduce the risk of getting a particular infection) and maintenance therapies (to prevent relapse) when someone has sustained CD4+ cell count increases as a result of highly active anti-HIV therapy.

While there have been few new therapies for treating or preventing OIs, most advances in this field come from a developing knowledge of how best to use existing anti-OI therapies—in short, better strategies using current drugs. The revised guidelines include recommendations on when to start preventive therapy, recommendations for maintenance therapies and guidance for stopping preventive or maintenance therapies. The chart on pages 12-13 provides the guidelines for the prevention of opportunistic infections.

It is important to consider the potential for drug interactions when planning to use preventive and maintenance therapies. For more information on drug interactions, call Project Inform's National HIV/AIDS Treatment Hotline and ask for the *Drug Interactions Chart* or check our website at *www.projectinform.org.*

Candidiasis

A fungus (yeast) that can infect the mouth and throat (thrush) and/or vagina. May result in white patches, loss of appetite and/or vaginal itching, burning and discharge.

When to Start Preventive Therapy §
- Routine preventive therapy is not recommended because of the potential for developing untreatable, drug-resistant candida.

Recommended Preventive Therapies
- Although routine prevention is not recommended, studies have shown that fluconazole (Diflucan) reduces the risk of developing candidiasis.
- Pregnant women should not use preventive therapies, particularly "azole" drugs, due to risk of birth defects.

Stopping Preventive Therapy ‡
N/A.

Who Should Use Maintenance Therapy
- Many experts do not recommend maintenance therapy for the same reasons preventive therapy is not recommended. If recurrences are frequent or severe, then fluconazole or itraconazole solution (Sporanox) can be considered.
- Pregnant women should avoid "azole" drugs and opt for topical therapies or in severe cases, amphotericin B (Fungizone).

Stopping Maintenance Therapy ‡
N/A.

Cryptococcosis

A fungus that primarily infects the brain resulting in headaches, fevers and altered behavior.

When to Start Preventive Therapy §
- Many experts do not recommend prevention because of the low overall incidence of the disease and lack of proven benefit.
- If a need for prevention of other fungal infections exists then people with CD4+ cell counts below 50 should consider preventive therapies.

Recommended Preventive Therapies
- Fluconazole is the preferred therapy.
- Pregnant women should not use "azole" drugs for prevention because of possible birth defects. Also, women who become pregnant should stop any "azole" antifungal therapies.

Stopping Preventive Therapy ‡
N/A.

Who Should Use Maintenance Therapy
- Everyone who has had cryptococcal disease should be on maintenance therapy for life. Fluconazole is the preferred therapy for maintenance therapy.
- Pregnant women should avoid "azole" drugs.

Stopping Maintenance Therapy ‡
Based on the small numbers of people studied, stopping therapy is not currently recommended.

Cryptosporidiosis

A parasitic infection that can cause diarrhea.

When to Start Preventive Therapy §
- The greatest risk is for people with CD4+ cell counts below 100.

Recommended Preventive Therapies
No proven effective therapies against cryptosporidiosis exist. People should try to avoid exposure to the organism which sometimes has been found in public water supplies. §

Stopping Preventive Therapy ‡
N/A.

Who Should Use Maintenance Therapy
N/A.

Stopping Maintenance Therapy ‡
N/A.

Cytomegalovirus (CMV)

A virus that can infect the entire body. Left untreated, CMV can cause diarrhea, blindness, inflammation of the brain, among other things. Most common is infection of the eye (retina), CMV retinitis.

When to Start Preventive Therapy §
- People whose CD4+ cell counts stay consistently below 50 and who are CMV+ are at highest risk for CMV infection and should consider CMV prevention.

Recommended Preventive Therapies
- Oral ganciclovir (Cytovene) is the recommended preventive therapy.
- Pregnant women should not take preventive therapies. Also, women who become pregnant should stop oral ganciclovir preventive therapy because of possible birth defects.

Stopping Preventive Therapy ‡
It *may* be reasonable for people with a sustained (six months or longer) CD4+ cell count above 100-150 as a result of HAART to consider stopping CMV prevention.

Who Should Use Maintenance Therapy
- People with a history of active CMV disease should be on maintenance therapy for life. Oral or intravenous (IV) ganciclovir, IV cidofovir (Vistide), IV foscarnet (Foscavir), IV foscarnet + IV ganciclovir or ganciclovir implants (Vitrasert) (for retinitis only) are recommended.
- Pregnant women should receive maintenance therapy and the choice of therapy should be individualized.

Stopping Maintenance Therapy ‡
It may be reasonable for people with CD4+ cell counts sustained above 100-150 AND sustained suppression of viral load to consider stopping CMV main-tenance therapy. Immune recovery uveitis (IRU), a potentially sight-threatening inflammation, has been observed in some people who have stopped maintenance therapy. This should be monitored.

Histoplasmosis

A fungus that can cause fevers, fatigue and difficulty breathing. Common only in a few areas of the country, primarily midwestern river valleys.

When to Start Preventive Therapy §
- People whose CD4+ counts stay consistently below 100 and who live in an area where histoplasma is commonly found.

Recommended Preventive Therapies
- Itraconazole is the preferred therapy.
- Pregnant women should not receive prevention because of possible birth defects associated with "azole" drugs.

Stopping Preventive Therapy ‡
No recommendation at this time.

Who Should Use Maintenance Therapy
- Everyone who has had histoplasmosis should be on maintenance therapy for life. Itraconazole is the preferred maintenance therapy.
- For pregnant women, amphotericin B (Fungizone) is preferred, especially during the first trimester of pregnancy.

Stopping Maintenance Therapy ‡
Based on the small numbers of people studied, stopping therapy is not currently recommended.

‡ Before stopping any maintenance or preventive therapies it is important to discuss this with a doctor.

* Call the Project Inform Hotline for a PCP Prevention Fact Sheet for a desensitization regimen.

§ Call the Project Inform Hotline and ask for WISE Words #4 for ways to prevent exposure to common infections.

Mycobacterium Avium Complex (MAC)

A bacterial infection that can cause fever, night sweats, fatigue, anemia and diarrhea.

When to Start Preventive Therapy §
- People whose CD4+ count stays consistently below 50.
- Pregnant women may want to consider delaying prevention until after the first trimester of pregnancy.

Recommended Preventive Therapies
- Clarithromycin (Biaxin) or azithromycin (Zithromax) are the preferred preventive therapies. If someone cannot tolerate either drug, then rifabutin is the recommended alternative.
- For pregnant women, azithromycin is the drug of choice. Clarithromycin should be used with caution in pregnant women because of birth defects in animal studies.

Stopping Preventive Therapy ‡

It *may* be reasonable for people with CD4+ cell counts sustained above 100 for 3-6 months AND sustained viral load suppression to consider stopping MAC preventive therapy.

Who Should Use Maintenance Therapy

Everyone who has had MAC should be on maintenance therapy for life with either clarithromycin or azithromycin (only if it has been proven that there is no resistance to either of these drugs) in combination with ethambutol (Myambutol) with or without rifabutin.

Stopping Maintenance Therapy ‡

It *may* be reasonable for people with CD4+ cell counts sustained above 100 for 6-12 months as a result of HAART to consider stopping MAC maintenance therapy.

Pneumocystis carinii Pneumonia (PCP)

An infection that can cause fever, dry cough, difficulty breathing, weight loss and night sweats.

When to Start Preventive Therapy §
- People who have CD4+ cell counts below 200 or a history of thrush (candidiasis) in the mouth and throat should receive PCP preventive therapy.
- People with CD4+ percentages below 14% or a prior AIDS-defining illness should consider starting preventive therapy.
- If it is not possible to monitor CD4+ cell counts every three months, then people with counts below 250 should consider starting prevention.
- Pregnant women may want to consider delaying prevention until after the first trimester of pregnancy.

Recommended Preventive Therapies
- One double-strength TMP-SMX (Bactrim, Septra) per day is recommended, although one double-strength tablet three times a week or one single-strength tablet a day is also effective.
- People with allergic reactions (fever and/or rash) may be able to desensitize to the drug.* If someone cannot tolerate TMP-SMX, then dapsone; dapsone + pyrimethamine (Daraprim) + leucovorin; aerosolized pentamidine (Pentam); or atovaquone (Mepron) are alternatives.

Stopping Preventive Therapy ‡

It may be safe for people with sustained (six months or longer) CD4+ cell counts above 200, as a result of HAART, to consider stopping preventive therapy.

Who Should Use Maintenance Therapy

People with a history of PCP should use the same therapies as those recommended for prevention.

Stopping Maintenance Therapy ‡

It *may* be possible for people to stop maintenance therapy if CD4+ cell counts increase and stay over 200. However, based on the small numbers of people studied, this is not currently recommended.

Toxoplasmosis

A parasite that primarily infects the brain resulting in confusion and delusional behavior.

When to Start Preventive Therapy §
- People with CD4+ cell counts below 100 if toxoplasma antibody positive.
- Pregnant women may want to consider delaying a pyrimethamine-containing regimen until after pregnancy.

Recommended Preventive Therapies
- Daily doses of TMP-SMX is the preferred therapy. If someone cannot tolerate TMP-SMX, then dapsone + pyrimethamine or atovaquone +/- pyrimethamine are alternatives.

Stopping Preventive Therapy ‡

It *may* be possible to stop prevention if CD4+ counts remain above 100 as a result of HAART for six months or longer. Based on the small numbers studied, this is not yet recommended.

Who Should Use Maintenance Therapy

People with a history of toxoplasmosis should use a combination of sulfadiazine + pyrimethamine For people intolerant to sulfa drugs (e.g. TMP-SMX or sulfadiazine), a combination of pyrimethamine + clindamycin is an alternative.

Based on the small numbers of people studied, stopping maintenance therapy is not currently recommended.

Tuberculosis (TB)

A bacterium that primarily infects the lungs and can cause cough, weight loss and fatigue. TB is easily spread to others.

When to Start Preventive Therapy §
- Everyone with HIV may be at increased risk and should be tested for exposure to tuberculosis, generally with a tuberculin skin test (TST).
- When TST is positive but there is no active disease, a preventive course of therapy should be started.
- Pregnant women with no active disease may consider delaying preventive therapy until after the first trimester.
- When TST positive and active disease is present, start anti-TB treatment.

When to Start Preventive Therapy §
- TST positive people without signs of active TB, should receive nine months of isoniazid (INH) once daily or twice weekly or two months of pyrazinamide with either rifampin (Rifadin) or rifabutin (Mycobutin). If someone comes into close contact with a person with active TB, they should also receive the above mentioned regimen.
- Pyrazinamide should be avoided during the first trimester of pregnancy due to known risks to the developing baby.

Stopping Preventive Therapy ‡

Not recommended.

Who Should Use Maintenance Therapy

Maintenance therapy is not required for people successfully completing a TB treatment regimen.

Stopping Maintenance Therapy ‡

Not applicable.

‡ Before stopping any maintenance or preventive therapies it is important to discuss this with a doctor.

* Call the Project Inform Hotline for a PCP Prevention Fact Sheet for a desensitization regimen.

§ Call the Project Inform Hotline and ask for WISE Words #4 for ways to prevent exposure to common infections.

HIV Resistance Testing Proves Its Value

HIV resistance testing measures the degree to which HIV in a person has become resistant or less sensitive to anti-HIV drugs. Two major studies show that people who use resistance testing results to help make treatment decisions experience a better and more sustained reduction in HIV levels than those who make decisions based only on previous treatment history and viral load. As resistance testing becomes more widely available, it becomes important that HIV-positive people and their health care providers learn to accurately interpret the results—and limitations—of these tests.

Genotypic resistance tests determine what changes have taken place in HIV's structure that may alter the way it makes key proteins (like protease and reverse transcriptase). These changes are called mutations. The other approach—*phenotypic* testing—presents a more direct measure of resistance. It examines the amount of drug needed to stop the replication of the virus—grown from a person's blood—in a laboratory setting.

Resistant HIV requires higher levels of the same drug to get a level of suppression equal to that of a non-resistant virus. When the amount of drug needed is roughly four or more times the amount needed to suppress the original form of the virus, treatment with most drugs become impractical. Doses high enough to suppress the virus at that point may be too toxic.

The Viradapt Study

Results from two studies illustrate the benefits of genotypic resistance testing. First, the French Viradapt study followed 108 people, all of whom previously used anti-HIV therapies and had viral loads over 10,000 copies HIV RNA. Upon entering the study, half of the participants received the best available therapy as estimated by their previous treatment history. The other half received the best available therapy as determined by considering the results from a resistance test.

At six months, those whose treatment assignments were based on resistance tests experienced a 1.15 log (14-times) reduction in viral load. Those not getting the same guidance only experienced a 0.67 log (4.7-times) reduction in viral load. Moreover, 32% of the participants who had resistance testing guidance achieved viral load suppression to below 200 copies HIV RNA, compared to only 14% of those who did not. This clearly suggests that using resistance tests to guide treatment decisions results in a more useful regimen.

After six months, everyone in the study received a resistance test and accompanying results. Some certainly altered their anti-HIV regimen based on the test results. The benefits of resistance testing further emerged at the end of one year, where viral load results were nearly indistinguishable between the two groups. In the group with initial resistance testing, pre-study viral load reduction remained 1.15 logs (14-times). The other group realized improved viral suppression to 0.98 log (9.5-times).

The GART Study

The second study, known as the GART study, showed very similar results. The GART study included 153 people with a median viral load of about 28,000 copies and median CD4+ cell counts of 230. All volunteers experienced a return of measurable viral load while on three-drug (a protease inhibitor and two nucleoside analogues) regimens prior to enrollment. At study entry, half received therapy based on resistance test results, with expert interpretation. The other half received therapy based on previous anti-HIV therapy history.

After twelve weeks, there was about a half log (2.8-times) difference in viral load between the two groups, with the group which received resistance test results having the better anti-HIV response. One interesting observation found an average 0.37 log (2.3 times) reduction occurred in viral load for each drug that a person used and was not previously resistant to. For each drug used in a combination that a person was resistant to, a 0.17 log (1.5 times) reduction still occurred in viral load. This suggests that even when genotypic resistance testing detects some measurable level of resistance to a given drug, it does not mean that the drug is rendered completely useless.

Commentary

Resistance testing will play a major role in guiding anti-HIV therapy treatment decisions. Such tests will also likely be used to determine if someone was initially infected with a drug-resistant virus and to select anti-HIV therapies for use in a combination regimen.

The success reported in these initial studies may be somewhat dependent upon finding a number of drugs to which each person was not yet resistant. Whether similar results can be expected in people who show resistance to all currently available therapies remains to be seen.

This suggests that even when genotypic resistance testing detects some measurable level of resistance to a given drug, it does not mean that the drug is rendered completely useless.

Resistance tests are becoming more widely available as some third party payers begin to reimburse for them. Because of this, and study results showing the benefits of resistance testing, many laboratories now perform genotypic and/or phenotypic resistance tests. It is important to select a reputable laboratory as not all labs or all tests are the same. They differ in quality control, quality assurance, test sensitivity, test accuracy and the interpretation of the results. *For more information on resistance testing, call Project Inform's National HIV/AIDS Treatment Hotline and ask for the Geno-/Phenotypic Resistance Test Quick Sheet.* ■

Project Inform Website

If you have an internet connection to the world wide web and are looking for HIV/AIDS treatment information, log onto Project Inform's HIV/AIDS Treatment Website at:

www.projectinform.org

Structured Treatment Interruption Workshop

The Foundation for AIDS and Immune Research (FAIR), in partnership with Project Inform and Treatment Action Group (TAG), co-sponsored a workshop in Boston at the end of July on structured therapy interruptions. Researchers from around the world attended to discuss preliminary data and plan future studies. People living with HIV/AIDS and representatives from industry and government also attended.

The goals of the meeting were to:

- identify gaps in the research agenda for testing the safety and effectiveness of structured treatment interruptions which meet a minimum of three known objectives across the spectrum of HIV infection;
- develop new study concepts and/or specific studies to fill identified gaps to coordinate a comprehensive research agenda; and
- encourage collaboration to enhance current, planned and future studies to learn as much as possible about the risks and benefits of therapy interruption.

In general, the current goals behind structured treatment interruptions (STI) focus around three basic theories:

- STIs may make it possible to *preserve or strengthen immune responses against HIV*; this is primarily being studied in people with very early infection.
- STIs might *restore a useful degree of sensitivity to anti-HIV therapies* in people who are resistant to several available therapies.
- STIs might give people who are experiencing *treatment fatigue* or severe side effects a break from therapy long enough to permit some degree of healing, both physically and psychologically—if it can be done without creating long-term harm in a person's fight against HIV.

Research and interest in the area of STIs, however, *should not* indicate that stopping therapy, in any of these settings, is so far known to be either safe or beneficial. To the contrary, it could be found that STIs cause undue harm in some or all people. The goal of this research is to identify who (if anyone) might benefit from this approach and to shed light on potential harms of stopping therapy.

Most data presented at the Boston meeting were considered very preliminary and not ready for public distribution. Everyone carefully avoided drawing premature conclusions. Researchers agreed to present these early data only with the understanding that the forum was closed to the press. Major themes, however, came out of the workshop.

First and foremost, everyone agreed that people living with HIV and their providers should be aware that the benefit of STI has not been established in any setting and that stopping therapy involves numerous potential risks. People considering a therapy interruption are strongly encouraged to do so in the context of a planned study, where intensive monitoring of the immune system and virus is available to minimize risks.

There was at least one anecdote of a patient on effective anti-HIV therapy with full viral suppression who, upon stopping therapy, experienced increases in HIV levels and decreases in CD4+ cell counts. Upon re-starting therapy, this individual never again achieved optimal viral suppression with a potent anti-HIV therapy regimen. While no broad conclusions can be drawn from this single case, it underscores the potential risks of stopping therapy.

Secondly, workshop participants agreed that clear messages of what an STI is and is not should be clearly conveyed to people living with HIV and their health care providers. Stopping therapy for one or two days (what is commonly meant by a *drug holiday*) every now and then is neither strategic nor structured and will almost certainly increase the risk of developing anti-HIV drug resistance.

People considering a therapy interruption are strongly encouraged to do so in the context of one of the planned studies, where intensive monitoring of the immune system and virus is available to minimize risks.

A Structured Treatment Interruption will include stopping therapy for some extended and defined period of time (usually at least a month or more). Depending on the goals of the STI, re-starting therapy may sometimes be done according to a specific time frame (e.g. start after one month) or be based on certain viral load or CD4+ cell count changes.

Finally, based on preliminary data from observations and studies, even if therapy interruptions prove useful in some settings, they will not be useful for all people. In every setting, observations have been made of possible harm from therapy interruptions. These include:

- CD4+ cell count losses that might not be regained after re-initiating therapy;
- viral load increases that might not be brought back under control;
- the risk of resistant virus emerging and taking hold after stopping therapy; and,
- for those with resistant virus, lack of a shift toward a predominant drug-sensitive (wild type) form of virus.

For a few people, preliminary evidence suggests improved immune responses against HIV after an STI. Among people with multi-drug resistant virus, some seem to show a shift toward drug sensitive virus after stopping therapy. For people who can't fathom a lifetime of anti-HIV therapy, at the very least some information on long-term consequences is necessary to enable informed decision-making. With all these considerations, STI research proceeds with caution.

Commentary

The meeting in Boston culminated with a review of ongoing efforts and a list of recommendations by the scientists for modifying current studies, initiating specific studies and exploring existing data sets to gather more information on STIs. This would include developing an STI *case definition* and then applying that definition to large observational studies.

In addition to examining the experiences of people who may have already stopped therapy, the *case definition* can be applied and additional monitoring and data collection could take place. To achieve this goal, a Task Force is being created, including representatives from large studies around Europe and North America.

Project Inform has previously written on structured therapy interruption. For additional information, call Project Inform's National HIV/AIDS Treatment Hotline. ■

Advances in Research: Second and Third Line Therapy

The benefits of highly active antiretroviral therapy (HAART) have been confirmed in numerous studies, and reports have shown encouraging reductions in hospitalizations due to HIV-related complications and deaths. For some people, however, these benefits may be starting to wane as their viral loads increase and/or their CD4+ cell counts decrease due to the development of drug resistance. They are now in search of second and third line anti-HIV therapy regimens. The "Second International Workshop on Salvage Therapy," held in Toronto, focused on how to treat people in these situations.

Second Line Therapy

AIDS Clinical Trials Group (ACTG) study 359 followed 277 people using a second line anti-HIV regimen. Volunteers had an average viral load of about 32,000 copies HIV RNA and an average CD4+ cell count of about 229. All had previously received at least six months of indinavir (Crixivan®) but were now experiencing detectable viral load. None had previously taken non-nucleoside reverse transcriptase inhibitors (NNRTIs). Also, none had taken other protease inhibitors. Participants were selected to receive one of six different regimens:

1. **RTV** (400mg bid) + **SQV** (400mg bid) + **DLV** (600mg bid);
2. **RTV** (400mg bid) + **SQV** (400mg bid) + **ADV** (120mg qd);
3. **RTV** (400mg bid) + **SQV** (400mg bid) + **DLV** (600mg bid) + **ADV** (120mg qd);
4. **NFV** (750mg tid) + **SQV** (800mg tid) + **DLV** (600mg bid);
5. **NFV** (750mg tid) + **SQV** (800mg tid) + **ADV** (120mg qd); or
6. **NFV** (750mg tid) + **SQV** (800mg tid) + **DLV** (600mg bid) + **ADV** (120mg qd).

After 16 weeks of the study, only 30% of the participants had viral load reductions to below 500 copies HIV RNA and only 19% had CD4+ cell count increases. People taking delavirdine in addition to their new protease inhibitor assignments experienced significantly better anti-HIV responses than people taking adefovir, possibly because delavirdine improves the level of some of the other drugs in the blood. There were no noted differences, overall, in responses between those receiving ritonavir- or nelfinavir-containing regimens. The results after 16 weeks are listed in **Table 1**.

This study begs for cautious analysis for a number of reasons. First, the relatively small size and short duration of the study made it unlikely to find statistically significant differences among the six separate drug combinations. Much of the outcome may be due to chance. The overall results are disheartening with, at best, about 50% of the participants sustaining anti-HIV responses. Adding adefovir as a fourth drug did not result in increased anti-HIV effects, although this may be due to unexpected multiple drug interactions. It was observed that combining delavirdine and adefovir resulted in adefovir decreasing delavirdine levels by 50% in blood, which resulted in a 50% decrease of saquinavir levels.

Table I

Combination Regimen	% <500 copies HIV RNA
RTV + SQV + DLV	33
RTV + SQV + ADV	20
RTV + SQV + DLV + ADV	31
NFV + SQV + DLV	48
NFV + SQV + ADV	16

Furthermore, studies conducted by Gilead Sciences, the developers of adefovir, suggest that the potency of adefovir increases when used with 3TC (and possibly abacavir). People in this study did not receive 3TC and, as a result, may have reduced any anti-HIV effects that adefovir might have contributed as part of a second line regimen.

Third-Line Regimens

No standard of care exists for people considering a third line regimen, but many researchers use an approach now commonly referred to as megaHAART. MegaHAART essentially involves combining as many anti-HIV drugs as possible without causing severe side effects. Researchers in Vancouver have used this approach with some degree of success. Results from two separate observational studies were presented. (In an "observational study" people are not assigned to any rigid protocol and are allowed to take whatever seems appropriate, perhaps under some general guidelines. This type of study then simply collects data on what happened to volunteers. Such studies are not considered very precise or accurate but sometimes provide useful information that is used to guide future study design).

The first group involved 98 people with a median viral load of about 62,000 copies HIV RNA and CD4+ cell counts of 175. The second involved 79 people with a median viral load of about 55,000 copies HIV RNA and CD4+ cell counts of 200. All had previously taken about seven anti-HIV drugs before starting megaHAART regimens.

In the first group, people had used anti-HIV drugs for about 40 months compared to about 30 months in the second group. During the observation period of the study, participants typically received up to nine anti-HIV drugs including two protease inhibitors, four nucleoside analogue reverse transcriptase inhibitors (NARTIs), two NNRTIs and hydroxy-urea. Where possible, people used therapies they had not previously taken.

Results from the first group show that about 40% of the participants had viral loads below 400 copies HIV RNA after 52 weeks of treatment. Those in the second group were not followed as long, but after 20 weeks of megaHAART, 48% achieved viral suppression below 400 copies HIV RNA. In an analysis looking at predictors of anti-HIV response, viral load at study entry (the lower your viral load the more likely you would sustain an anti-HIV response) and phenotypic resistance at study entry (the more drugs you are sensitive to the more likely you would sustain response) were correlated with anti-HIV response.

Third Line Therapy Commentary

These results suggest that it is possible for people who have been on multiple anti-HIV regimens to sustain an anti-HIV response by employing a megaHAART strategy. However, it is very difficult and costly to take up to nine different drugs every day, and many people cannot tolerate such an aggressive regimen. Although physicians associated with studies employing megaHAART suggest that people tolerate these complex combinations well, the patient volunteers tend to be much more critical

of the difficulties involved.

On the surface, these results seem somewhat better than those reported in the ACTG 359 study, even though the patient volunteers had more severe problems with drug resistance. However, it is all but impossible to compare the outcomes of the studies because they were conducted in such completely different ways. While the ACTG 359 was perhaps too small and had too many controlled options to reach any clear conclusions, the Canadian observational study lacked controls of any kind, making it also difficult to interpret and analyze.

Treatment Interruptions

One of the most provocative subjects brought up at this meeting concerned treatment interruptions. The study that triggered the most discussion was reported by researchers from Frankfurt, Germany. This study followed 85 people who had an average viral load of 160,000 copies HIV RNA and CD4+ cell counts of 108. All had previously taken an average of six anti-HIV drugs. All of the participants received six to nine drugs as part of a megaHAART regimen.

The most intriguing part of this study included the responses noted among people who took a treatment interruption of more than two months before starting their megaHAART regimen. Among 50 people who did this, 39 had resistance tests performed before stopping their current regimen and again before starting their megaHAART regimen.

These results suggest that it is possible for people who have been on multiple anti-HIV regimens to sustain an anti-HIV response by employing a mega-HAART strategy.

Twenty-six people showed evidence of a shift from a multi-drug resistant virus to a wild type virus (not resistant to HIV drugs, as measured by the currently available resistance tests). These 26 people showed evidence of resistance to about eight different anti-HIV drugs upon entering the study. As would be expected, those who interrupted therapy experienced a significant rise in viral load (0.7 log or five-times increase) while off treatment. No apparent predictors determined who was more likely to shift to wild type virus from those who continued to have multi-drug resistant virus. People who shifted to wild type virus had significantly better anti-HIV responses when they started their megaHAART regimen and sustained it better compared to those who continued to show evidence of multi-drug resistant virus. Seventy-two percent of people with the shift had viral loads below 500 copies HIV RNA after 24 weeks of megaHAART compared to only 17% of those who evidenced persistent multi-drug resistant virus.

A somewhat more ominous decline in CD4+ cell counts (almost 90 cell drop) was also noted. The people most likely to experience this decline in CD4+ cells were found to have earlier experienced a significant increase while on their first HAART regimens. Those who did not have an initial increase were also unlikely to have a decrease when going off therapy.

While these results of treatment interruptions are encouraging, they should be viewed with some caution:

- Not everyone who interrupted therapy showed evidence of reverting to drug-sensitive virus (wild type virus);
- People who interrupted therapy had a significant increase in HIV levels as well as significant decreases in CD4+ cell counts, possibly putting them at risk for developing opportunistic infections.
- It is unclear if people experiencing CD4+ cell count declines during a treatment interruption fully regain lost CD4+ cells after starting a megaHAART regimen.

More information on treatment interruptions can be found on page 15.

Another third line regimen study also involved treatment interruptions. In this study only about 15% of the participants had previously used a NNRTI, leaving them with more options for employing a new class of drug in their megaHAART regimen compared to the German group discussed above. This study enrolled 63 people with a viral load of about 63,000 copies and CD4+ cell counts of about 128. About 85% interrupted therapy for over four weeks before starting a megaHAART regimen, which primarily consisted of efavirenz, ddI, hydroxyurea, ritonavir and indinavir.

After 28 weeks of megaHAART, 85% showed viral loads below 500 copies with about 100 CD4+ cell count increases. Unfortunately, thirteen people stopped all anti-HIV therapies either because of side effects (mostly because of neurological side effects) or personal choice. People with higher viral loads before starting their treatment interruption were less likely to have sustained anti-HIV responses. People who took a treatment interruption were more likely to sustain a response.

Commentary

Clearly the most interesting aspect of this meeting were reports of success among people who took treatment interruptions before starting a third line megaHAART regimen. As a result, studies are now planned to look at treatment interruptions more carefully and to try to identify who may benefit from such an approach. For now, people facing a third line therapy decision and considering a treatment interruption are generally discouraged from doing so outside the context of studies.

For now, people facing a third line therapy decision and considering a treatment interruption are generally discouraged from doing so outside the context of studies.

One of the most critical aspects for people on third-line regimens is the lack of a standard of care. It is difficult to design studies to determine whether one approach is superior to another if there is no standard of care. Project Inform, along with Forum for Collaborative HIV Research, Treatment Action Group and Division of AIDS of the National Institutes of Health sponsored a meeting immediately following the "Second International Workshop on Salvage Therapy." The goal of *The Challenges of the Clinical Trial Design in Evaluating HIV Antiretroviral Use in Heavily Pre-Treated Patients* workshop was to determine what may be considered a standard of care for thirdline therapy; to define what can be considered a treatment *success* or *failure*; to define methods to determine the contribution of a single drug in a multi-drug regimen; methods to access multiple new drugs for third-line therapy studies; and to develop new protocols for evaluating third line regimens. A report of the meeting will be available shortly and can be obtained by calling Project Inform's National HIV/AIDS Treatment Hotline. ■

Principles for Optimal Care During Pregnancy

A recent study in the Journal of the American Medical Association reported a 67% decline in the rate of mother-to-child HIV transmission between 1993 and the present. While this is welcome news, the understandable zeal to prevent mother-to-child HIV transmission (vertical transmission) has too often overshadowed the long-term goal of providing optimal HIV care to women during and after pregnancy. Recent advances in the management of HIV disease during pregnancy have centered on the short-term use of anti-HIV therapy and method of delivery (Cesarean-section, natural child birth, etc.).

While these factors play a significant role in preventing vertical transmission, they are not exhaustive, nor do they provide long-term HIV treatment plans for expectant mothers.

Maternal Factors

The mother's immune health may be one of the most important factors influencing the risk of HIV transmission. Some studies show that transmission more likely occurs in women with more advanced HIV disease, high viral loads and/or lower CD4+ cell counts (especially below 200). However, no exact threshold accurately predicts whether or not transmission will occur. Thus, it's probably more useful to look at the viral load and CD4+ cell count to determine the health of the mother.

Many women with HIV also live with other infections, such as hepatitis C or herpes. Infection with these and other viruses may increase risk of HIV transmission. For example, HIV-positive pregnant women with genital herpes are more likely than HIV-negative women with genital herpes to have a herpes outbreak during labor. Genital sores associated with herpes outbreaks shed high levels of HIV, even when viral load in blood (measured by a viral load test) is below the limit of detection. An infant of an HIV-positive mother with recurrent genital herpes faces the risk of exposure to herpes and an increased risk of exposure to HIV. Thus, anti-herpes drugs may prevent a herpes outbreak during labor and may lower transmission risk.

Prenatal Care

Access to and use of prenatal care increases the likelihood that a woman will experience a healthier pregnancy and deliver a healthy, HIV-uninfected baby. In addition to traditional prenatal concerns of nutrition, exercise and lifestyle, prenatal care for positive women should consider the HIV issues of both mother and unborn baby. These include charting viral load and CD4+ cell counts, performing other routine tests and balancing the risks and benefits of anti-HIV therapy during pregnancy.

Aside from considering anti-HIV therapy, positive women should largely expect their pregnancy and labor to proceed as if they were HIV-negative. However, certain tests and procedures that are a routine part of prenatal care for HIV-negative women should be avoided if possible.

Substance Abuse and Domestic Violence

Pregnancy is a time of change in body, mind and lifestyle. Good prenatal care should also include appropriate education, counseling and referrals to services which offer help with these changes and encourage making choices to ensure a healthy pregnancy. For example, street drugs adversely affect women's health, their pregnancies and their developing babies. Babies exposed to street drugs *in utero* often have abnormalities in their development, low birth weight or premature delivery.

Regardless of a woman's decision about the use of anti-HIV therapy, good prenatal care and addressing surrounding health issues are key to a prevention strategy.

Street drugs, particularly injection drug use and crack-cocaine, are also associated with increased vertical transmission rates. The risk of vertical transmission and complications associated with using street drugs can be significantly decreased when pregnant women get into early prenatal care and drug abuse programs during pregnancy. Prenatal care providers should discuss the enormous adverse health effects that street drugs (as well as alcohol use and cigarette smoking) hold during pregnancy. They should also provide referrals to resources dedicated to helping women to kick addictions.

Similarly, it is important to consider one's home life when developing an optimal pregnancy care plan. A regrettably common example of this includes domestic violence. About one quarter of women seeking prenatal care report abuse by their partners. Domestic violence specialists estimate the rate of abuse among HIV-positive pregnant women may be even higher, particularly among young women.

Women who are abused during pregnancy suffer greatly, as do their babies. Battered women are at increased risk for poor weight gain, infection, bleeding, anemia and substance abuse during pregnancy. Babies born to abused women are more likely to be underweight and premature. All of these outcomes are associated with increased risk of vertical transmission. Help is available for women who are victims of domestic violence.

Breast Feeding

HIV is present in breast milk. Researchers estimate a 29% transmission rate from HIV+ mothers who consistently breast-feed their children. It is unclear whether and to what degree anti-HIV treatment changes this rate. Women with safe alternatives to breast milk are urged to avoid breast-feeding to decrease the risk of transmission.

Commentary

Advances in managing HIV disease have offered many benefits in maternal and child health, most notably in terms of the reduction in rates of vertical transmission. Yet, anti-HIV therapy is only one part of a vertical transmission prevention strategy. Regardless of a woman's decision around the use of anti-HIV therapy, good prenatal care and addressing surrounding health issues are key to a prevention strategy. Such a comprehensive care strategy will no doubt translate into a healthier pregnancy, decreased transmission rate and a healthier mother and child.

For more information on this topic, call Project Inform's National HIV/AIDS Treatment Hotline and request the *Mother-to-Child HIV Transmission Prevention Discussion Paper.*

For victims of domestic violence, call the National Domestic Violence Hotline: 800-799-SAFE (7233). ■

Mother-to-Child HIV Prevention: Is Elective C-section Necessary?

Studies suggest that the majority of mother-to-child HIV transmission (vertical transmission) occurs during labor and delivery, thereby fueling a debate about the safest route of child birth. This debate centers around the risks and benefits of Cesarean-section (abdominal surgical delivery) performed before the onset of labor (called *elective C-section*) versus natural, vaginal delivery.

Results from three recent studies suggest that elective C-section and the use of anti-HIV drug AZT (Retrovir®) may further reduce the risk of vertical transmission compared to what has been achieved by using AZT alone.* Results also suggest that elective C-section reduces the risk of vertical transmission independent of the effects of AZT. This procedure protects the baby from direct contact with the mother's HIV-containing genital tract secretions and blood. One study showed that elective C-section was associated with a lower vertical transmission rate compared to natural vaginal delivery among women receiving AZT (O.8% versus 6.6%, respectively)

While these studies appear to make a strong case for recommending elective C-section for HIV-positive women, none have looked at anti-HIV regimens other than the AZT regimen. These studies also did not measure HIV levels.

Studies in progress are testing whether combination therapy reduces vertical transmission rates more than the widely used AZT regimen. The same benefits offered by elective C-section and AZT therapy are likely reached with combination therapy, a regimen that results in more complete suppression of the mother's viral load. In this context, surgical delivery may be unnecessary.

Moreover, the risk of vertical transmission must be weighed against the dangers surgical delivery poses for the mother. Compared to vaginal delivery, elective C-sections have much higher rates of complications, including increased risk of hemorrhage (uncontrolled bleeding), infection and death. One study found HIV-positive women have post-operative complications three times as often as HIV-negative women. In immune compromised women, these complications are particularly dangerous.

At this time, it is unclear which route of delivery is best for both mother and baby. More studies are needed to determine the effect of triple-drug therapy on reducing vertical transmission; if viral load predicts the benefit of elective C-section; and if postoperative complications are associated with HIV infection. In the meantime, the decision to deliver vaginally or via C-section remains a matter of carefully considered medical opinion and personal choice.

**Note: In one major study, vertical transmission rates were 25% among women who did not receive anti-HIV treatment compared to 8% among women who received AZT. The study provided AZT (or placebo) to the mother after week 14 of pregnancy; to the mother through intravenous (in the vein) injection during labor; and finally to the newborn for six weeks after birth.* ■

WISE Words is the three-times yearly publication of **Project WISE**, Project Inform's program focused on HIV/AIDS treatment information and advocacy for women. Each issue provides women with important tools for making HIV treatment decisions, covering topics such as anti-HIV therapy, prevention and treatment of opportunistic infections, gynecological health and more.

Sample articles include:

- Sex and Transmission, a Continued Concern for Positive Women
- Gender Difference in Viral Load?
- GYN Issues for Women with HIV.

If you would like to be added to the mailing list for WISE Words, call Project Inform's National HIV/AIDS Treatment Hotline at 800-822-7422 or email WISE@projinf.org.

Prevention of Fungal Infections During Pregnancy

The revised Guidelines for the Prevention of Opportunistic Infections include new recommendations regarding the use of antifungal drugs during pregnancy. In short, the Guidelines recommend that the oral "azole" antifungals [including fluconazole (Diflucan®), itraconazole (Sporanox®) and ketoconazole (Nizoral®)] not be started during pregnancy. The Guidelines further state that these drugs be discontinued in HIV-positive women who become pregnant and that women receiving these drugs take effective birth control.

In animal studies, use of itraconazole and/or ketoconazole during pregnancy caused birth defects. In addition, there have been four reported cases of infants born with severe skeletal abnormalities to women who used fluconazole for an extended period of time while pregnant. It is presumed that these same potential risks apply to other oral azole antifungals.

For the treatment or prevention of oral or vaginal candidiasis, topical antifungal therapies such as nystatin (Mycostatin®, Pedi-Dri®) may be preferable for pregnant women. For the treatment or prevention of other fungal infections, such as cryptococcosis or histoplasmosis, the Guidelines suggest amphotericin B (Fungizone®), especially in the first trimester. Amphotericin B is also approved for the treatment of oral candida. Although no formal studies have been performed, amphotericin B has been used by pregnant women without apparent harm to their unborn children. While amphotericin B may be preferable to azole therapy in pregnant women, it is not without potentially severe side effects, including kidney toxicity and anemia. In addition, the intravenous (in the vein) suspension of the drug may not be feasible for some women. ■

Simpler Regimens for Preventing Mother-to-Child HIV Transmission

New methods to prevent the transmission of HIV from pregnant women to their unborn babies have gained much attention recently. Indeed, while the effort to reduce mother-to-child HIV transmission (vertical transmission) is important worldwide, it is particularly so in many developing nations where transmission rates remain alarming high due to complex social and economic complex factors.

In much of the developed world, reductions in vertical transmission rates have been seen with advances in anti-HIV treatment. However, these advances have not been shared in developing nations or in poorer communities in the developed world because they are too expensive and complex to allow widespread use. This imbalance may be shifting somewhat as the result of new research.

Previous study results showed that mother-to-child HIV transmission (vertical transmission) can be significantly reduced by a three-step AZT (zidovudine, Retrovir®) regimen. The regimen includes giving AZT after 14 weeks of pregnancy, intravenously (into the vein) during labor and to the newborn for the first six weeks of life. By using this regimen, vertical transmission rates dropped from 25% to 8%.

. . . even these simpler and less expensive regimens should not be viewed as a panacea for the problem of mother-to-child HIV transmission in the developing world.

While this remains one of the few proven regimens for preventing vertical transmission, its use is decreasing in most of the developed world. AZT as a single therapy has long been shown to be less effective than combination therapy in treating HIV disease itself. Consequently, the standard protocol for reducing vertical transmission is seen as inadequate for the mother's health. Thus, pregnant women are commonly encouraged to consider combination anti-HIV strategies that best benefit their own health, while refraining from certain drugs like efavirenz (Sustiva®), which may harm the developing baby.

Ongoing research continues to evaluate the benefits of using AZT in different ways, primarily to make vertical transmission prevention more accessible and affordable in developing nations.

Two Short-Course AZT Studies

Results from a New York study indicate that, when given during labor or within 48 hours of birth, shortened courses of AZT reduce HIV transmission similar to the longer regimen described above (10% and 9.3% rates respectively). Also, a Thailand study evaluated AZT given twice daily in the 36th week of pregnancy until the onset of labor and then every three hours from the onset of labor until delivery. It yielded similar results, with transmission rates dropping more than 50% (9.2% transmission rate).

These studies show that shorter AZT courses appear to be roughly as effective in preventing vertical transmission as the longer course of treatment. But while the cost of shortened AZT courses is less than the three-part regimen, it still remains prohibitive for people in many countries. Moreover, this approach assumes a significant level of prenatal care and clinic support during birth. These may not be realistic expectations in much of the developing world.

A Simpler Approach Using Nevirapine

Preliminary results from a Uganda study, funded by the manufacturer of nevirapine (Viramune®), suggest that a simple, two-dose regimen of nevirapine can reduce vertical transmission rates more than a short course of AZT. In the group treated with nevirapine, women received a single dose of the drug at the onset of labor and their newborns were given a single dose sometime during the first three days of life. In the control group given a short course of AZT, women received that drug at the onset of labor until delivery and the infants were then given AZT twice daily for the first week of life.

At 14–16 weeks of age, 13.1% of children given nevirapine were HIV-positive compared to 25.1% of those given AZT. In other words, women receiving nevirapine were only half as likely to transmit HIV as those receiving AZT. While these results might still seem less effective than those achieved in longer term AZT treatment for the mother and newborn, other factors may contribute to the difference. In any case, the results still are quite an improvement compared to no treatment.

The babies in this study will be followed until they turn 18 months old. Since HIV passes through breast milk, it's possible that over time the benefits of either preventive course may diminish. Indeed, 95% of the mothers in the study breast-feed. Finally, it remains unknown if these regimens offer long-term risks or benefits to the mother's or child's health.

Commentary

While these results are preliminary, they represent a hopeful advance in developing a low cost preventive regimen. The cost of the two-dose nevirapine treatment totals about US $4, a price many believe could be affordable for the developing world. Nevertheless, even these simpler and less expensive regimens should not be viewed as a panacea for the problem of mother-to-child HIV transmission in the developing world. Indeed, they require a certain level of medical infrastructure to implement. In some areas, this simply may not exist.

Finally, longer-term solutions to the challenge of vertical transmission must go beyond preventing the transmission of HIV from mother-to-child. Coupled with this effort must be the assurance of healthy mothers, families and communities who can care for and nurture children affected by HIV worldwide.

For more information on this topic, call Project Inform's National HIV/AIDS Treatment Hotline and ask for the *Mother-to-Child HIV Transmission Prevention Discussion Paper*. ■

Is AIDS Getting Its Second Wind?

From the fall of 1996 through the first half of 1998, the Centers for Disease Control and Prevention reported encouraging reductions in the death toll from HIV/AIDS. At least some of the reduction has been attributed to the effectiveness of the new three-drug combinations using protease inhibitors in prolonging life. There are now some indications—perhaps misunderstood—that the situation may be beginning to change.

In a new report issued in August of 1999, the CDC raised concerns that the decline in death rates may be leveling off. The figures cited were that while the death rate declined 42% from 1996 to 1997, the decline from 1997 to 1998 was only 20%. While there is general agreement that things may be changing, there was a great deal of misunderstanding about the CDC figures. News writers and commentators seemed to assume that a stable level of improvement would require the reduction in the death rate to stay the same from year to year. This is simply bad mathematics, however. The only way the reduction in death rates could remain constant from year to year would be if each year brought an improvement in therapy over the previous year—in other words, continually improving therapy. Obviously this is not the case, as the major improvement in therapy happened in a single year—1996—and there have been only marginal changes since then. Until another major improvement in therapy occurs, the decline in the death rate can only go down with each passing year. That's simply the way the math works.

Despite the popular misunderstanding of these figures, it is still true that many people are dying from AIDS today. A significant number of people who "came back from the brink" in response to the new therapies a few years ago have now developed drug resistance or unacceptable side effects and are succumbing to the disease. The number of obituaries due to AIDS reported in community newspapers seems to have increased, and memorials are once again a fairly regular weekend event.

Another indicator of change is the number of people entering hospitals with serious opportunistic infections (OIs). Many medical practices in major cities report that the number of OIs is once again on the rise after having declined for two or more years.

A related indicator is the number of people signing up to enter studies of drugs for opportunistic infections. For nearly two years, the incidence of new CMV infection was so low that studies of anti-CMV drugs were greatly delayed. Today, that seems reversed again with study sites for CMV, MAC and other major infections reporting renewed enrollment.

As Project Inform and others have cautioned all along, the new therapies of 1996 were no cure and surely had their limitations. If anything, they have worked better and longer than many of us would have predicted. But we must all recognize that at most people have experienced a brief respite, not a cure.

The availability of today's therapies, as well as the current dynamics of the epidemic, make it unlikely the US will ever again see the catastrophic death rates experienced in the late 1980s and early 1990s. But it seems increasingly unlikely that major infections and death can be held off forever. Moreover, many of the communities more recently ravaged by HIV infection are just beginning to move into the critical time period when death rates begin to rise.

What's needed—another breakthrough with new classes of drugs unaffected by resistance and failure of previous therapies—will require the committed voices and demands of people living with HIV/AIDS. For now, no such breakthrough is on the horizon although several new drugs, a few with different mechanisms of suppressing HIV replication, are in early stages of studies.

The best hope for the immediate future is for people to recommit to their strategies and make the best and longest possible use of the effectiveness of any therapies that are still working for them. Adherence is more critical than ever. Along with this must come rapid research into better strategies for using the treatments we already have.

We must recommit to the battles for better treatment and focused research that brought us the advances in the first place. Most importantly, we must help the public and the government recognize that AIDS is definitely "not over," and that it may even be getting a second wind. ■

The Basic Message

- **Get tested**, *anonymously*.
- **Learn your options** and line up your support.
- If positive: **maximize your health, get a complete physical, a full immune health workup** and **get *informed*!**
  (See Project Inform's discussion paper *"Day One"*).
- **Get baseline CD4+ and HIV RNA tests, repeat quarterly**. Chart the trends. Women should get "GYN" exams and "Pap" tests every six months.
- If the CD4+ trend is downward or already below 500, and HIV RNA above 5,000, **or** if HIV RNA is above 30,000-50,000, regardless of other factors, **optimize nutrition and consider combination ant-HIV treatment**.
- If viral measures do not decline below the limit of detection, **consider a more aggressive anti-HIV regimen.**
- If the CD4+ trend stays below 300, **consider preventive treatment against PCP** (oral drugs if possible). If the count continues to fall below 200, **consider a more aggressive anti-HIV regimen** if not already on one and **learn about preventive treatments** against other opportunistic infections. **Learn about drug interactions.**
- If you have begun preventive therapies and your CD4+ cell count rises as a result of anti-HIV therapy, **remain on any preventive treatments you have started for at least six months.**
- If CD4+ cell count stays below 75, **intensify monitoring,** con-sider prevention against MAC/MAI and CMV infections. **Learn about preventive therapies.**

Work Incentives Improvement Act

Legislation is making its way through Congress that could improve health care access for working people with disabilities. The Senate bill is called The Work Incentives Improvement Act, S. 331, and the companion bill in the House of Representatives is H.R. 1180. The legislation would provide opportunities for people with disabilities—including people living with HIV/AIDS—to enter, return to or stay in the workforce without losing their health care benefits.

Many people who had been disabled by HIV/AIDS are experiencing improved health and now struggle with whether or not to return to work or enter the workforce for the first time. They face a number of concerns including varying health, medication side effects, problems adhering to medication schedules during the workday, job-related stress and day care needs. Additionally, returning to work under the current system may cause them to lose previously gained health care benefits.

If the Work Incentives Improvement Act is signed into law, a lot of work will be necessary on the state level to ensure any new or expanded programs or benefits work for people living with HIV/AIDS. People with HIV/AIDS who are either working already or considering work will need to understand changes regarding health care coverage to make informed decisions about utilizing new programs. People living with HIV and their advocates need to be instrumental in implementing some of the bill's provisions so that support services meet the needs of all people with disabilities.

Several important state provisions are contained in the legislation, including some that individual states can choose to enact or not at their own discretion. Advocates and people living with HIV/AIDS and other disabilities must organize to encourage their states to make the choices that best meet their medical needs. The Work Incentives Improvement Act contains several important provisions as explained below.

Expanded Medicaid buy-in program for people with disabilities: This would allow some people who don't qualify for Medicaid to *purchase* Medicaid on a sliding scale basis. Monthly cost would depend on a person's income. Medicaid is the government insurance program for low-income individuals who qualify either by their connection to programs such as Supplemental Security Income (SSI) or Temporary Assistance to Needy Families, or by being *medically needy*, (e.g. very low income and disabled as defined by Social Security). Medicaid serves over 50% of people living with AIDS and 90% of children living with AIDS. The program differs from state to state, but in general it maintains strict criteria around how much money an individual can make and can save.

Under this bill, states would have the option to create a Medicaid buy-in program for working people with disabilities who do not normally qualify for Medicaid due to income and resources. Revising income and resource qualifications would allow many disabled people to earn a higher income and accumulate savings while still qualifying for Medicaid.

People who qualify for the buy-in program would be required to pay a monthly fee (called a *premium*—a payment to keep insurance intact) to receive services. Monthly fees would be set on a sliding scale; the more an individual earns, the higher the monthly rate. A *cap* or maximum monthly fee amount comparable to other insurance rates would be established. People currently employed because their disability has improved enough for them to work would be able to buy into the program as well.

This buy-in program could give many people living with HIV the fallback and flexibility they need to determine if they should work and at what type of job. Some people would like to work but, for a number of reasons, may not be able to commit to high-paying, high-stress or full-time jobs. Often part-time work does not provide the medical benefits that people must have to maintain their health. A buy-in program with a sliding scale could reassure many that they could work at a job that accommodates their health condition.

Extension of Medicare benefits for working individuals: This would extend the length of time an individual can access Medicare after re-entry into the workforce. Medicare offers insurance to older Americans and disabled people who have worked in the past and have completed the Medicare waiting period. Medicare delivers over $1.4 billion in AIDS care. Part A of the Medicare program covers hospitalization and Part B covers doctor's visits and routine health care.

Under this legislation, Medicare benefits would be extended for ten years for disabled people who return to work. Currently, people returning to work can continue receiving their Medicare benefits for a much shorter period of time (usually about three to four years). People could continue their Medicare benefits without paying a monthly fee for Part A coverage. They would likely pick up the monthly cost for Part B. Part B premiums would probably be comparable to the fee paid by people covered under a group insurance plan, about $150 per month.

Programs supporting working people with disabilities: Under this provision, the Department of Health and Human Services would create grants for eligible states to help establish programs that support working disabled people. There are often barriers for disabled people trying to return to work. In the case of people with HIV/AIDS, it may be difficult to adhere to a complex medical regimen, negotiate an appropriate amount of sick days with a prospective employer or have access to facilities to rest during the day. As support programs develop, it will be important for people to clarify their needs so that appropriate support services are designed and implemented. These grants could also fund outreach campaigns informing people about work incentive programs.

Demonstration projects for individuals with "potentially severe disabilities": This proposal could be a very important tenet for people living with HIV. It allows states to provide Medicaid to workers who do not qualify as disabled, under the social security definition, but who are at high risk of becoming disabled if appropriate health care is not available to them. A

potentially severe disability is defined as a condition that, without appropriate treatment, could be reasonably expected to lead to disability under the Medicaid definition.

People living with HIV could definitely be served under this type of program. Currently people living with HIV must progress to the Social Security definition of disability to qualify for Medicaid. In other words, people must wait until they become sick to access services under Medicaid. Under this type of program, eligible people could have access to health care services through Medicaid without progressing to disability.

Ticket to work and self-sufficiency program: States are mandated to provide work training and placement programs to people with disabilities who wish to enter the work force. Governmental vocational rehabilitation offices generally offer these services.

This ticket-to-work provision would allow disabled people seeking employment support services to present a *ticket* issued by the Social Security Administration (SSA) and obtain services at any approved *employment network*. The network could consist of community based organizations as well as government entities, allowing people to better tailor employment services to their individual needs. The tickets would be issued to disabled individuals who qualify to receive SSI or Social Security Disability Insurance (SSDI).

Work activity will no longer be the sole trigger a for disability review for some people: In order to remove barriers to people returning to work or entering the work force for the first time, this bill would change Social Security regulations so that work activity no longer serves as the only basis for review of an individual's disability status. Currently, if a person returns to work and completes a *trial work period*, it can trigger a continuing disability review (CDR). This could mean that people lose their health care coverage if they no longer qualify as disabled, since disability is a requirement for these healthcare programs. In the statute (the language that would become law) there is no income level attached to this provision. However, the Senate added report language (this is wording that does not carry the weight of law but indicates what Congress would like to see happen) that says that only people who make less than Substantial Gainful Activity (SGA - $700 a month) would be covered by this protection.

This provision would also allow for a quick reinstatement of benefits if a person could not continue to work for a generous time period after their benefits had stopped. Currently, once a person has completed any available trial work period, it can be difficult to reinstate benefits if s/he is forced onto disability again. This provision could be important for people who often fear losing benefits entirely if they enter, or re-enter, the workforce.

Work incentives planning, assistance and outreach: The SSA would establish an outreach program to help disabled people understand and apply their options, rights and responsibilities. It would also provide technical assistance to organizations assisting individuals returning to work.

Grants for advocacy services for people with disabilities who are going back to work: This provision would establish grants to states to provide advocacy services to assist disabled individuals in securing or returning to work.

The Work Incentives Improvement Act has been hailed by some as the most important measure since The Americans with Disabilities Act.

Demonstration projects and studies: The SSA would be authorized to set up several programs to determine the effectiveness of reducing SSDI payments by one dollar for every two dollars earned over an income level decided by the state for the purposes of the program. Currently, the SSDI program discontinues SSDI payment completely after a person has been back at work for at least nine months and is making more than SGA or $700 per month. For this reason, under current law, an individual is far better off earning $699 than earning $701, because the full SSDI payment can still be collected. In order to avoid falling off this income *cliff*, people who may be able to earn more may feel it necessary to stay under the $700 limit to avoid losing their SSDI income. This is a clear disincentive for people who want to return to or enter work. This provision would allow a careful evaluation of program that provides more of an incentive to return to work.

In addition, this provision would establish other studies looking broadly at current work incentives and disincentives which may result in recommended changes in the various systems.

Commentary

The Work Incentives Improvement Act has been hailed by some as the most important measure since The Americans with Disabilities Act. It will be critical for people with disabilities, including people living with HIV/AIDS, who consider working but fear losing their health care benefits.

Benefits counselors have noted that people living with HIV/AIDS who are ready to go to work are unwilling to take the chance that they might lose health care benefits, which—if they got sick again—could not be reinstated. Others are concerned that taking a job that allows them to earn slightly more than their current income could disqualify them for health care coverage. Other people are considering work but feel strongly that they need to seek a part-time job. They may also be deterred from working by the fact that part-time jobs often don't offer health care benefits.

The Work Incentives Improvement Act addresses many of these issues and has garnered strong support. It has been endorsed by the Senate with a 99-0 vote. It should soon pass the House of Representatives and the President has indicated that he will sign the bill if presented to him. It will be very important to support this act as it continues to move toward law. For more information on how you can support the legislation, contact Project Inform's Treatment Action Network at 415- 558-8669 x224 or tan@projinf.org. Once the bill is passed and signed, advocates are needed to work at the state level to ensure that states implement the provisions and enact some of the options, including the Medicaid expansion demonstration projects that could serve low income people with HIV.

You can play a role in this by educating yourself about the details of the law. You might want to identify HIV/AIDS and other disability advocates in your state you can work with to educate your legislators and administrative officials. Several organizations have followed this legislation closely and can be contacted for more information. They include AIDS Legal Referral Panel in San Francisco, CA; National Council on Independent Living in Oakland, CA; and AIDS Action Council and National Association of People With AIDS in Washington, DC.

Project Inform can help with this research and provide tips on state advocacy. For more information, contact the Public Policy Department at 415-558-8669 or tan@projinf.org ■

In Brief: Immune Based Therapies

HIV-1 Immunogen (Remune®) Study Closure

A Data Safety and Monitoring Board or DSMB (the group charged with monitoring the safety of a study) recommended the closure of a large study of HIV-1 Immunogen (Remune®). The study included thousands of volunteers and continued for a number of years. On a monthly basis, half of them received the injectable product, Remune®, and half received a placebo injection, monthly. All were permitted to use any other antiviral drugs or combinations of their choosing.

The DSMB reviewed the results of these 2,500 volunteers to date and observed no difference in HIV disease progression rates (opportunistic infections and deaths) between the two groups. Further, the DSMB did not believe that any notable differences would likely emerge if the study continued.

Confounding the study results was broader availability and wide-scale use of protease inhibitor therapy over the course of the study. Due to the effects of potent anti-HIV therapy, HIV progression rates (~1%) were so low that it was impossible to detect incremental benefits or harm the HIV-1 Immunogen may contribute. One interpretation is that whatever benefits Remune® might offer, they were largely insignificant against the background of more powerful therapies. The sponsor, however, says the people who receiving Remune® were more likely to see an improvement in a particular marker of immune function related to HIV. Whether or not this makes any difference to a patient's health, however, was not established by the study. The company has now begun a new study designed to determine if Remune® has a significant effect on viral load or durability of HAART regimens.

The bottom line, however, is that the jury is still out on this product after many years of research. To date, absolutely no claims can be made in terms of its benefits.

GM-CSF (Leukine®) Study Results Announced

A 309-person study of an immune based therapy called GM-CSF* (Leukine®) was completed with inconclusive results. GM-CSF is a naturally occurring immune chemical, which in laboratory tests enhances the ability of a kind of immune cell (macrophage) to fight and prevent opportunistic infections. The therapy is approved for preventing infections in immune compromised individuals who have undergone bone marrow transplantation.

In the recent study, which included people with low CD4+ cell counts, half received GM-CSF and half received placebo, by injection three times every week. No overall differences were observed with regard to developing new or recurrent opportunistic infections. However, volunteers receiving GM-CSF were more likely to experience more complete viral suppression (all volunteers were on standard anti-HIV therapy) than those who received the placebo. Whether this observation holds true over time, and whether it leads to improved survival, remains unknown.

**GM-CSF is granulocyte macrophage colony stimulating factor. G-CSF, granulocyte colony stimulating factor (filgrastim, Neupogen®) is commonly used to treat neutropenia (low neutrophil cell counts, associated with increased risk of bacterial infections) associated with HIV disease and some therapies to treat AIDS-related infections (e.g. anti-CMV therapies) and cancers.* ■