

Opportunistic Pricing: A New Scourge, A New Call for Action

The introduction of Highly Active Antiretroviral Therapy (HAART) has greatly diminished the incidence of opportunistic infections (OI's) which threaten the health of HIV-infected people. However, it has also brought a new scourge threatening the viability of health care and treatment access for people with HIV. This new scourge might best be called opportunistic pricing.

Opportunistic pricing is a practice wherein some companies set prices for new drugs not based on any relationship to development and manufacturing costs, as in most industries, but rather based on ever escalating perceptions of "what the market will bear." In other words, some companies have begun to charge whatever they think they can get away with. In the short-term, such pricing practices threaten the ability of State AIDS Drug Assistance Programs (ADAPs), whose budgets are fixed by federal and state contributions, to deliver treatments to those who need them. If the practice becomes widespread, it will eventually lead to an escalation in the total federal expenditures for AIDS treatment by its impact on the prices paid for drugs by Medicaid and the Veterans Administration. Even though new drugs have reduced the cost of hospitalization and treatment for opportunistic infections, there is only so much reduction possible. There is little limitation, however, on how high the price for drugs can go. Over the longer-term, such unchecked increases further threaten to feed Congressional and public concerns over what some perceive as "too much spending on AIDS".

A Little History

Some might say that the practice of opportunistic pricing began with first drug approved for AIDS when AZT (zidovudine, Retrovir®) came to mar-

ket at a disturbingly high price. At the time, the sponsor—then known as Burroughs Wellcome—tried to justify its price on the hotly disputed grounds that the company had spent huge sums on developing the drug. More importantly, they claimed they expected only a relatively small number of people to use the drug since it was initially recommended only for people with CD4+ cell counts below 200. Perhaps the most realistic explanation for the initial price of AZT is that some form of treatment was so desperately needed that the company knew it could charge almost anything and get away with it. To its credit, as the market unfortunately expanded, the company engaged in two major price reductions. These, of course, were prompted by the loud public outcry against the price by patient advocates, health care workers, and people within government itself. Scientists at the National Cancer Institute argued that they—not Burroughs Wellcome—did most of the basic research on AZT and only licensed the drug to the company. They managed to drag the company into Congressional hearings to explain the price on what they felt amounted to a "government drug."

In more recent years, the new generation of drugs known as protease inhibitors pushed the pricing threshold skyward. The new drugs, while enthusiastically received, were priced at up to three times the cost of the older generation of

anti-HIV drugs. Also the new drugs had to be used in combination with two of the older drugs. Overnight, the annual price of basic therapy for HIV disease leapt from around \$3000 per person (for single drug therapy) to \$10,000 to \$12,000 (for 3-drug combination therapy), depending on which protease inhibitor was used. Manufacturers asserted, with some justification, that development and production costs were far higher than with previous drugs. For example, Merck, the manufacturer of indinavir (Crixivan®), asserted that making their new drug required a huge investment in factory refitting costs and a production process that require more than 20 separate steps. Indinavir's price, though still high, was still substantially lower than the other protease inhibitors, whose manufacturers made no claims about development costs. Perhaps more than anything else, the price escalation for protease inhibitors was accepted because the affected public was too weary from years of memorial services and burials to put up much of a fight. No one could dispute that the drugs brought about an immediate and dramatic reduction in death and suffering. Despite these justifications, a dangerous precedent was set in letting the high prices stand without challenge.

Perhaps due to the pressure of competition, and perhaps a bit of good citizenship, the next new generation of drugs, represented by the "non-nucleosides" nevirapine (Viramune®) and delavirdine (Rescriptor®), came to market at prices that were pleasantly more like those of the old nucleoside analogues such as ddI (Videx®) and d4T (Zerit®). In some cases, these were even less expensive than their less powerful and older competitors. This act of good civic behavior, however, was never heralded by the public and was perhaps the last act of its kind.

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December 1998

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Project Inform

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Opportunistic Pricing: A New Scourge, A New Call for Action

Company	Drug(s)	Good Citizenship Awards	Troubling Actions	Special Concerns
Abbott Labs	Ritonavir (Norvir®), ABT-378	No price increases, yet.	Highest priced protease inhibitor.	Price of new ritonavir and ABT-378? New price of nelfinavir was unexpected and will cause serious trouble in 1999.
Agouron	Nelfinavir (Viracept®)		High initial prices; plus recent price increases, despite high sales.	Will Dupont's actions trigger a price increase?
Boehringer Ingelheim	Nevirapine (Viramune®)	Relatively modest initial pricing; no increases; large study program.	Limited interest in AIDS research.	How will they price new anti-HIV drugs in development?
Bristol-Myers Squibb	ddl (Videx®), d4T (Zerit®)	Relatively modest initial prices.	Recent prices increases.	"Used car" sales tactics by top management; unwilling to negotiate; no concern for cost to government.
Dupont Pharma	Efavirenz (Sustiva®)	Large expanded access program; large study program.	Initial prices 60% above others in this class; over promotion of early data.	Will prices rise?
Glaxo Wellcome	AZT, 3TC, Combivir®	Lowered AZT price twice.	High initial prices. Recent price increases.	
Glaxo Wellcome	Abacavir (Ziagen®)	Ideal expanded access design; many studies; fair final price.		High or low end of protease-inhibitor pricing scale?
Glaxo Wellcome	Amprenavir	Ideal expanded access design.		Are they planning an increase in the price of saquinavir?
Hoffman LaRoche	(Agenerase®) ddC (Hivid®); Saquinavir (Invirase®)		High prices for all versions of saquinavir; 2-year promotion of a defective formulation (Invirase®).	Management may argue it was not rewarded for setting low prices, so why hold the line?
Merck	Fortovase® Indinavir (Crixivan®)	Lowest priced PI by a large margin; responded to community input on pricing; highly ethical.	Watching others, weighing possible price increase.	Will they hold the line on pricing in light of efavirenz price?
Pharmacia & Upjohn	Delavirdine (Rescriptor®)	Lowest price in class; continuing study program.	Slow in clarifying benefits of the drug.	

SHADED ITEMS DEMAND IMMEDIATE ACTION

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Today's crisis in drug pricing has been triggered by the price set for the newest drug of the non-nucleoside class, efavirenz (Sustiva®) from Dupont Pharma. Development, manufacturing, and distribution costs apparently played little or no role in setting the price. Instead, the manufacturer has waged a powerful public relations campaign claiming the drug is superior to others of its type, or even to protease inhibitors, and thus it "deserves" its premium pricing. Despite the public relations campaign, there is little or no evidence as yet to support any claim of superiority on behalf of efavirenz. All three drugs in the non-nucleoside class are considered highly potent, easy-to-use agents which are hampered primarily by cross resistance between themselves and the tendency to develop resistance relatively easily. Despite these fundamental similarities, the cost of efavirenz was set nearly 60% higher than nevirapine and nearly 70% above delavirdine. Apparently, the public relations campaign has run up a large bill that must be paid.

In addition to its dubious claims of product superiority, Dupont Pharma argues that efavirenz lowers the cost of therapy since they recommend using it instead of a protease inhibitor for initial therapy. Whether this is the wisest use of the drug remains to be seen, but it takes only a

short memory to recall that nearly every one of the drugs approved in recent years has tried to position itself as the "right" drug to use in initial therapy. The company, like others, also argues that they need higher prices to be able to afford research and development costs for other new drugs for AIDS. This argument rings hollow since there is little evidence in the current market that high prices lead to any increase in the development of new and better drugs for HIV. They also cite the cost of expanded access programs in which the drug is given away free for many months prior to FDA approval. Critics point out that such programs are really a relatively inexpensive way to build market share (i.e. get more people taking their drug) and interest before the drug is launched, as well as collect additional information on their drug that is supplied to the FDA to support approval.

In the view of most advocates, all these rationalizations lack substance. Consider Dupont's claim that its drug is superior. Every company believes its drug is superior to its competitors. Dupont Pharma hopes to convince people that efavirenz is superior to nevirapine and delavirdine, yet it has not conducted a single study directly comparing the drugs. They rest their case on one study in which the drug was paired

successfully with AZT and 3TC in people just beginning therapy, thus acting as a substitute for a protease inhibitor in a typical three-drug combination. Although the data from that study seem impressive to the casual viewer, they have raised many unanswered questions, discussed in the article entitled "Strategy Update: Protease-Sparing Regimens" on page 14. Both nevirapine and delavirdine have also shown good performance when paired with AZT and 3TC and given to people just beginning therapy. All three drugs have also shown reasonably good performance in previously treated patients and all three may play an important role in "salvage" therapy. None of the three, however, has demonstrated long-term effectiveness comparable to protease inhibitors, probably due to the ease with which they develop resistance. No study has attempted to determine what, if any, differences there are between the three drugs in terms of efficacy or durability of response. Since the drugs differ widely in side effects and cost, a direct comparison could provide critically needed information.

Dupont Pharma has brought efavirenz to market with a flurry of confusing, some say obfuscating, claims about pricing. Different prices have been repeatedly quoted by the company,

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PI Perspective is published three times per year and is distributed free of charge. *PI Perspective* is a publication of.

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some being the "retail price," others the "average wholesale price" or the federal "ADAP" price or the "Average Manufacturers Price." Even competing pharmaceutical companies say they have had a very hard time figuring out the actual price of efavirenz. One point has been consistent in all manifestations of the price: it remains 55-60% higher than the equivalent price for nevirapine, 65% to 70% higher than delavirdine, and nearly as high as the price of a protease inhibitor. Despite the company's hope that everyone will "use their drug first" a fairly typical use of the drug will be to add it to a new protease inhibitor when patients have experienced failure with their first major combination regimen. In such use, it will add another \$3500 to \$5000 per year onto the current \$10,000 to \$12,000 cost of combination therapy. Bottom line: the cost of HIV therapy is creeping nearer and nearer to the \$20,000 per year mark.

What is a Fair Price?

It is virtually impossible to know what a truly fair price is in the pharmaceutical industry. In most other industries, production, materials, research and development, labor and overhead costs drive basic pricing decisions. Some additional price padding is based on market opportunities, prestige and brand position. There is no way to determine how much money is really spent directly on developing, testing and marketing any individual drug since almost anything can be construed as part of the "cost." Thus, manufacturers look to their competitor's prices and ask how much threat their new drug poses and how much the market might possibly bear. Consequently, prices move only in one direction: up. But if manufacturers are so inclined to look to competitor's prices as their frame of reference, so too must the public. Such a look cannot help but find a 60% increase relative to competitors to be anything but unfair.

All of this comes at a time in the AIDS epidemic when it has actually become possible to drop the price of drugs without endangering company profits or ongoing research. Today's anti-HIV drugs are used by far more people, and now for vastly longer periods of time, than were drugs in the early years of the epidemic. In the 1980's and most of the 1990's, only a modest percentage of HIV-infected people actually took advantage of therapy. Far more were concerned about potential side effects than were convinced about the potential for long-term benefits. Moreover, a lack of support programs made it hard for many people to have access to the drugs. Even when the drugs were readily available, people were likely to use them only later in the disease process, and then for only a relatively short time

period before death or progression. Today, the benefits of therapy are much better understood and people who use treatments are likely to go on doing so for many years, if not an entire lifetime. Under these uses, the development costs of new drugs are quickly recovered and many long years of easy profitability set in. Were this any other industry, these conditions would lead to annual price reductions to keep older drugs competitive as newer ones come to market. A company truly interested in fairness, good citizenship and a reduction in suffering could easily set lower prices and still make healthy profits.

Why Does Pricing Matter?

Even though few individuals pay for drugs out of their pockets, the costs still affect everyone. Regardless of whether the prices are buried through Medicare, Medicaid, and the AIDS Drug Assistance Program (ADAP), in the taxes we pay, or through insurance premiums, we are all affected by drug pricing. Like the drugs themselves, unfair pricing produces long-term, cumulative side effects. Over time, those side effects begin to affect an ever-greater number of people and ultimately threaten a complete collapse of the hard-won system of health care and treatment access programs for people with HIV. A few ways in which this happens:

When one company pushes its price of a drug far beyond the accepted limits of its price class, other manufacturers watch closely. Today, one of the most critical factors influencing the price Glaxo Wellcome sets for abacavir (Ziagen) and its upcoming protease inhibitor amprenavir (Agenerase) is the price Dupont Pharma sets for efavirenz. Glaxo Wellcome senior management and their peers at other companies will carefully study the public reaction to Dupont's pricing action. If there is generally easy acceptance of Dupont's price by insurance companies, government programs, and other payers, and if AIDS activists fail to stir up a public outcry, the next drugs that come along will almost certainly be priced at the higher end of the range envisioned by management. If instead Dupont Pharma meets a wall of public and private criticism, forces will arise in other companies arguing for more modest pricing when their new drugs reach the market.

When one company sets an unexpectedly high price for a new drug, as was done with efavirenz, ADAPs have an increasingly difficult time delivering treatment to those who need it. For 1999, a national coalition of HIV/AIDS advocates, with considerable help from the pharmaceutical industry, sketched out the most accurate budget yet to cover the cost of the AIDS Drug Assistance Program for the coming year. People were able to go to Congress with what they thought was

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a clear picture of how much money would be needed for 1999. No one anticipated how much a high price for efavirenz might affect the upcoming price for abacavir. *If pricing trends continue some ADAPs will continue to have to close programs or limit access in other unacceptable ways.*

Continual, unchecked price increases allow industry to think of federal support programs as a form of entitlement, a belief that will surely need to be challenged politically. The pharmaceutical industry has struggled to form a coalition with AIDS advocates over securing money for programs like ADAP, but this effort is more than a little self-serving on industry's part. While this gave important political power to the ADAP effort—Congress listens well to big business—companies have come to assume that government will cough up the money no matter what they charge for their drugs. Not surprisingly, a federal backlash is very possible. Government does not set up special programs to pay for the drugs needed to treat every serious or life-threatening disease. It has done so for AIDS and for some other diseases because of the dramatic human need, the high cost of therapy, and the compassion of a small groups of highly

Make no mistake about it – AIDS activists alone cannot solve this problem. Only widescale public pressure, exerted directly and perhaps through the Congress, can influence these matters.

committed people in and outside of government who fought for the programs. But if industry takes advantage of these support programs by reckless opportunistic pricing, even the most caring people in Congress will have difficulty guaranteeing adequate future funding. In the current efavirenz situation, Dupont Pharma was shocked when it learned that the biggest state ADAP programs would delay putting its new drug on their formularies. They had bragged to analysts that state and federal program support was a given. Not so. And this is only the tip of the iceberg of what will happen in future years if pricing is not moderated. Unfortunately, no matter how the pricing fight is conducted, the danger is that patients in need will someday be hurt by it.

Pricing concerns are not limited to government programs, such as ADAP, Medicaid, and the Veterans Administration. Private insurers are being charged high prices for drugs, often even

higher than government programs. The kind of price increases seen in AIDS are also happening in other diseases, threatening to wipe out cost savings that may have been gained in the health care system through more widespread use of managed care. The increasing costs of health care, of which drug pricing is but one piece, have become a major political and economic issue. While it is true that drug prices are not the only cause of rising health care costs, they undoubtedly contribute to the problem. At a time when everyone else is struggling to contain the cost of health care, drug industry profits are setting new record highs. The United States is one of the only countries left that does not exercise price control over the pharmaceutical industry. As the industry becomes increasingly globalized, CEOs may look to the U.S. for the immediate profits they may not be able to reap in other countries. One example of the results of opportunist pricing is seen when senior citizens are forced to organize drug-purchasing collectives to purchase drugs at lower prices in Canada rather than in the US. Like HIV patients who organized similar collectives in the earliest days of the AIDS epidemic, the seniors do their purchasing over the border and take advantage of FDA rules which permit importation of "personal" quantities of medicine. Surely, the prices the companies are charging in Canada still permit a reasonable profit. Otherwise, the companies would simply stop selling there (as they have done in some countries where price controls are too strict for their tastes).

Cost and price problems are not limited to new drugs. Within days of Dupont Pharma's announcement of its prices for efavirenz, Agouron announced a range of price increases for its existing protease inhibitor nelfinavir (Viracept). Nelfinavir was already at the high range of prices for protease inhibitors. This in turn puts pressure on management at Merck, which currently offers the lowest and most fairly priced protease inhibitor. As one Merck spokesperson said to Project Inform, "How do we convince our management to hold the line on prices in this marketplace? They ask why should we be left behind?"

Perhaps most importantly of all, US pricing matters because it sets the stage for the prices that will be charged worldwide. By setting high initial US prices, manufacturers in effect make a statement that the drug is simply "too expensive" to ever be given away or sold at a marginal price in developing nations. Consequently, as far as treatment goes, it is still 1980 in those places of the world where 90% of HIV-infected people live. For Africa, Asia, and parts of South and Central America, there simply is no feasible treatment for HIV disease. And as long as new drugs continue to come to market at the multi-thousand dollar

In Memory Of . . .

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

Scott Calender

Mark Frey

Jonathan Kwitny

Andrew Pelletier

Mike "Pappy" Schmitz

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

per year cost level, there cannot even be a serious discussion of how to make treatment available to developing nations.

What Can YOU Do About It?

Make no mistake about it – AIDS activists alone cannot solve this problem. Only widescale public pressure, exerted directly and perhaps through the Congress, can influence these matters. Unfortunately, it is far too easy for most HIV infected people in the United States to be content with having their own access to the drugs. But if we hope to exert meaningful pressure, we must join together locally as well as internationally and say these prices are unacceptable.

One thing that could have an enormous and proven impact on this problem would be for every person—or even one in every ten persons—reading this article were to write a short but heartfelt letter expressing concern. Such letters must go to the President, Chairman of the Board, or CEO of the companies who are pushing the boundaries of pricing. Letters need not be threatening – ordinary pleas to their humanity will do. Individuals within these companies are not monsters. In fact, many of them feel the same way we do about the need for lower prices. A massive letter-writing campaign would give great strength to those factions in the companies who want to see prices come down. Issues that need immediate action in the form of letters, in their order of importance, are as follows:

- Letters to the Chief Executive Officer of Dupont Pharma protesting the company's pricing of efavirenz and the company's unwillingness to negotiate with either the community or the government about it.
- Letters to the CEO of Glaxo Wellcome urging the company to hold the line on pricing with amprenavir, and to resist the temptation to set new, higher pricing thresholds.

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- Letters to the President of Agouron Pharmaceuticals protesting the company's recent price increases.

Please take this request seriously. The future, long-term availability of government drug support programs, and the viability of managed health will at least partially depend on our ability to win this issue. ■

Opportunistic Infections Update

With the availability of highly active antiretroviral therapy (HAART), there has been a dramatic decrease in the incidence of many HIV-related infections (called Opportunistic Infections or OIs). While clearly this is great news, it has made studying new therapies to treat or prevent common OIs very difficult. This is a serious concern for people experiencing OIs and in need of more and better therapies.

While there are only a few studies looking at new therapies for OIs, many are examining when it might be safe to stop taking OI prevention or maintenance (to prevent relapse of the disease) therapies. Such studies test the value of improvements in immune status seen as a consequence of HAART. Preliminary results from these studies will not be available until sometime in 1999. In the upcoming years, we can probably expect to see further research on HIV-related conditions focusing on questions of stopping preventative and maintenance therapy, issues of treating hepatitis and metabolic consequences of HIV disease and therapy, including body composition changes (e.g. lipodystrophy) and wasting syndrome.

While HAART has decreased the incidence of most OIs (pneumocystis carinii pneumonia (PCP), cytomegalovirus (CMV), mycobacterium avium complex (MAC), etc.) it has not reduced the incidence of all HIV-related infections. One study conducted in Spain showed that advances in anti-HIV drug availability and effectiveness has not decreased the incidence of tuberculosis (TB). The study showed that the incidence of TB has remained constant between 1988-1998 despite improving standards of care for treating HIV. It is not clear whether effective antiviral therapy has affected the severity or treatability of tuberculosis. Another study conducted in France shows that HAART has only had modest effects in reducing the incidence of bacterial infections that require hospitalization. Somewhat surprisingly, about half of the cases were among people with CD4+ counts of over 200 cells.

Hepatitis C

There has been a new focus of research attention on studying hepatitis C virus (HCV) in people with HIV-disease. HCV has always been of concern to people living with HIV-disease, the majority of people with hemophilia and HIV also received HCV through contaminated blood products. HCV has become even more a concern as many of the new anti-HIV drugs greatly stress the liver, making management of HIV and HCV difficult. There are approximately 4 million Americans infected with hepatitis C

(HCV) and that number is increasing dramatically with about 150,000 newly infected people each year. A growing number of those people are co-infected with HCV and HIV. There are many similarities between HCV and HIV, one being that people with HCV experience high increases in liver enzymes (specifically ALTs or alanine aminotransferases) after initial infection with HCV. With the help of the immune system, the level of liver enzymes decreases, but gradually increases again over time. Antibodies against HCV take a while to develop, rendering HCV antibody testing during the acute phase unreliable. In most people with HCV, their HCV levels, without treatment, are in the 100,000 to 10,000,000 copies HCV RNA range. These numbers, however, should not be compared to the viral load numbers we are accustomed to seeing from HIV. Currently, there is little or no information about how specific viral load levels of HCV relate to clinical illness, and therefore, treatment decisions should not be made based on viral load levels alone. Unlike hepatitis B, in which only a small percentage of people develop chronic liver disease, a majority of people with hepatitis C develop chronic illness. Serious symptoms do not develop until someone reaches an advanced stage of disease but patients often suffer a series of relapses characterized by sometimes severe fatigue and other gastrointestinal symptoms. For some people, the disease can be mild and symptoms do not develop.

The current recommendation for treating HCV is a 12 month course of interferon-alfa (Intron-A[®], 3 million units three times a week) which results in a long-term response (no detectable HCV RNA levels) in about 20% of people treated. However, for the other 80% of people, HCV RNA levels and liver enzymes increase. The recommendation to use interferon-alfa for only 12 months is because the drug can cause flu-like side effects and has to be administered by injection under the skin (subcutaneous). It is believed that many people are unwilling to use this drug for a longer period. Recently, the combination of ribavirin and interferon-alfa (sold together as

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Marketing Scam Spoils Hep C Treatment

Recent research has shown that treating hepatitis C (HCV) with a combination of interferon-alfa and ribavirin is more effective than using interferon-alfa alone. Ribavirin is a nucleoside analogue antiviral drug that is active against a number of viral diseases. Because the two drugs have been bundled together by their sponsor, Schering-Plough, under the brand name Rebetron[®], people can only purchase ribavirin (Rebetol[®]) if they also buy interferon-alfa (Intron A[®]).

Ribavirin was originally developed by ICN Pharmaceuticals but has been licensed to Schering Plough for use against HCV. People who might prefer to use a different brand of interferon-alfa product (such as Roferon-A[®], Alferon N[®] or Infergen[®]) with ribavirin must also buy Schering-Plough's version of interferon-alfa in order to get the ribavirin.

Although the different versions of interferon-alfa are similar, they have slightly different side effects as well as different anti-HCV activity and one version of the drug may be better suited for an individual than another. Due to this forced "bundling" of the two drugs, many third party payors will not reimburse people who chose to use another interferon-alfa product because they feel that they are paying for the same product twice.

This aggressive and anti-competitive marketing tactic prohibits most people from mixing ribavirin with other interferon-alfa products. Another prohibitive feature of the drug is its price, which Schering-Plough has dramatically increased. Even if an individual were able to purchase ribavirin alone, it would cost over \$1,000 a month. Compare this to the \$3,000 or so for a years supply of the nucleoside analogue drugs used to treat HIV disease. Back in the days when ribavirin was experimentally used to treat HIV disease, it could be purchased for less than half that amount. Schering Plough's bundling tactics present a dramatic example of what happens when business interests take precedence over patient needs.

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Rebetron[®]) has increased the long-term response rate to between 35–40%.

People who are co-infected with HIV and HCV tend to have higher HCV levels which usually leads to a more rapid progressive disease. The recommendation for treatment and reports of effectiveness do not include people co-infected with HCV and HIV. Results from a small study in Spain showed that co-infected people had similar responses to those only infected with HCV when treated with interferon-alfa. People with HCV levels below 10 million copies and a CD4+ cell count above 500 were most likely to respond.

There has been a lot of controversy in the past few years whether people co-infected with HIV and HCV can safely use protease inhibitors. A study conducted at Johns Hopkins University showed that people receiving the protease inhibitor ritonavir (Norvir[®]) were significantly more at risk for severe liver toxicity compared to people receiving other anti-HIV therapy regimens. This study involved 381 people, approximately two-thirds were receiving a protease inhibitor and one third were on a two-drug nucleoside analogue reverse transcriptase inhibitor (NARTI) regimen. People receiving ritonavir or ritonavir + saquinavir (Invirase[®] or Fortovase[®]) were about five times more likely to develop severe liver toxicity than people receiving the other protease inhibitors or the NARTI regimen. Interestingly there were no differences in serious liver toxic-

ity in people with or without chronic HCV and/ or hepatitis B infection who received ritonavir. However, people with viral hepatitis who received saquinavir, nelfinavir (Viracept[®]) or indinavir (Crixivan[®]) were at greater risk for developing liver toxicity compared to people on a two-drug NARTI combination. The good news from this study is that about 90% of people with HCV were able to safely use a protease inhibitor-containing regimen without serious side effects. Results from this study suggest that people who are co-infected can safely use the protease inhibitors while moni-

People who are most likely to respond to interferon-alfa therapy are likely to be younger, do not have cirrhosis, have low HCV levels and have HCV types 2 or 3. In clinical studies, approximately 65% of people with HCV type 2 or 3 responded to interferon-alfa and ribavirin compared to about 30% in people with HCV type 1.

toring their liver enzymes closely.

Hepatitis B

Most people with HIV have been or are still on a 3TC (lamivudine, Epivir[®]) containing regi-

men. 3TC also has potent activity against hepatitis B virus (HBV), although it is generally used at a lower dose than is recommended for HIV when used to treat HBV. However, HBV can become resistant to 3TC when a dose of 50-100mg/day is used. A study in France followed 19 people who were HBV and HIV co-infected who started 3TC (150mg twice a day for a total daily dose of 300mg) as part of their anti-HIV regimen. Study participants also received another NARTI and most also received a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. About a third of the participants had failed interferon-alfa for treating their HBV infection. All of the participants were men with a mean CD4+ cell count of about 200 and HIV levels of 50,000 copies HIV RNA. Almost all of the participants had good anti-HIV and anti-HBV responses with 14 people having HBV levels below the limits of detection with the currently available HBV tests. However, four people developed 3TC resistant HBV even with the higher 3TC dose. People who developed 3TC resistant HBV generally had lower CD4+ cell counts (about 30) and have been on anti-HIV therapies longer. Interestingly, HBV levels were not predictive of HBV resistance to 3TC. There were cases of increases in HBV levels when 3TC was stopped in people whose HBV was still sensitive to 3TC. People who are co-infected with HIV and HBV may want to consider continuing on 3TC even if their HIV is resistant to the drug, as it may still be active against HBV.

Commentary

Hepatitis C deserves research attention as there are only a few therapeutic options, most of which have quite a few side effects. Additionally, we do not know how well these therapies work in people who are co-infected with HIV and HCV, if they will experience more side effects and how these therapies might affect the course of HIV disease. Furthermore, there is some potentially dangerous drug interactions between therapies for HCV and commonly used HIV therapies. For instance, people receiving ribavirin (Rebetol[®] or Rebetron[®]) should not take AZT (zidovudine, Retrovir[®]) as ribavirin significantly decreases the anti-HIV activity of AZT. More studies need to be conducted to determine which anti-HIV and anti-HCV drugs can be safely used together. ■

Advances in CMV Management: Fomivirsen (Vitravene®) Approved

The Food and Drug Administration recently approved a new treatment for cytomegalovirus (CMV) retinitis, an opportunistic infection affecting people with advanced HIV disease. Left untreated, CMV can lead to blindness.

Fomivirsen (Vitravene®, formerly ISIS 2922) is given by injection directly into the eye by an ophthalmologist (eye specialist) every 2 or 4 weeks. The recommended dose is 330µg on days 1 and 15 during the initial phase of treatment (when CMV is still spreading). It is then given once monthly during the maintenance phase (when CMV is not actively spreading but requires therapy to prevent it from reactivating). Studies show fomivirsen works equally well in people with newly diagnosed CMV retinitis as in those receiving other CMV therapies.

Since fomivirsen blocks CMV from replicating through a different mechanism than that of other approved CMV retinitis therapies, people who have developed resistance to other therapies may still benefit from this drug. Because fomivirsen is administered directly into the eye, it does not cause any systemic (throughout the body) side effects. However, in some studies, some people had retinal detachments. In one study that employed a higher dose in people with newly diagnosed CMV retinitis, some developed retinal stippling (spots in the retina) which resulted in some loss of peripheral vision. The fact that it works only locally in the eye also prevents the drug from suppressing CMV infections elsewhere in the body, a limitation not shared by most other treatments for CMV retinitis.

Though there have been no results directly comparing fomivirsen with other approved therapies, the results from studies so far suggest it is comparable in effectiveness to intravenous

ganciclovir (Cytovene®), foscarnet (Foscavir®) and cidofovir (Vistide®) in suppressing and preventing the recurrence of active CMV retinitis. However, the ganciclovir implant (Vitrasert®), which is surgically implanted into the eye and slowly releases ganciclovir, has demonstrated much longer lasting anti-CMV retinitis effects. Nonetheless, fomivirsen is a welcome addition to the arsenal of anti-CMV therapies, especially because of its

Since fomivirsen blocks CMV from replicating through a different mechanism than that of other approved CMV retinitis therapies, people who have developed resistance to other therapies may still benefit from this drug.

ability to work after resistance develops to other CMV therapies.

500mg Ganciclovir Capsule

A new 500mg capsule of ganciclovir (Cytovene®) is now available for use in the prevention and maintenance treatment of CMV disease. Previously, oral ganciclovir was only available in 250mg capsules, and when used for prevention or maintenance of CMV disease, required 12 capsules a day (1,000mg three times a day). This new 500mg capsule will reduce by half the number of pills needed daily.

Oral ganciclovir is poorly absorbed into the body and therefore is considered second-line therapy for the maintenance of CMV disease. However, because all other systemic therapies for CMV are administered intravenously (directly into the vein), many people opt for oral ganciclovir because it does not require a surgically implanted catheter, which is accompanied by a risk of serious bacterial infections.

Oral ganciclovir is also sometimes used for prevention of CMV disease in people with severely compromised immune systems, but this use of the drug remains controversial because of conflict-

Nevirapine in Children

Nevirapine (Viramune®), a non-nucleoside reverse transcriptase inhibitor, has recently been approved for use in children. Like other antivirals, the optimal use of this drug is as part of a three-drug combination. Nevirapine should never be used alone, and its use even in two-drug combinations is discouraged because of the risk of rapid development of drug resistance.

In adult studies, nevirapine has been combined with two nucleoside analogues, such as AZT and ddI, and AZT and 3TC, in a "protease sparing" regimen. Presumably, it can also be combined with d4T and 3TC or ddI and d4T, though it has not been formally studied in this fashion. Other common adult uses include salvage therapy, in which nevirapine is added along with other new drugs after a protease inhibitor combination has failed.

The recommended dose of nevirapine for children aged 2 months to 8 years is 4mg/kg once a day for the first 14 days followed by 7mg/kg given twice a day thereafter. For children 8 years or older, the recommended dose is 4mg/kg once a day for fourteen days followed by 4mg/kg given twice a day thereafter. Children generally experience the same side effects seen in the adult studies. Rash, usually mild to moderate in severity, is the most common. Other possible side effects include fever, nausea, headache and abnormal liver function tests. One side effect only seen in children was an anemia called granulocytopenia (a reduction in granulocytes, a type of white blood cell).

ing study results. More importantly, the success of HAART today in partially restoring immune function has diminished the need for preventive use.

A new formulation of oral ganciclovir, sometimes known as pro-ganciclovir or valganciclovir, is currently in studies. This new formulation is so much better absorbed by the body that the sponsor hopes it may eventually eliminate the need for intravenous therapy altogether. ■

National HIV/AIDS Treatment Hotline



For more specific information on issues to consider for prevention, treatment or maintenance of any of these HIV-related infections, call the Project Inform Hotline at:

1-800-822-7422

Antivirals Update

Several new anti-HIV drugs are likely to be available in the near future. The Glaxo Wellcome drug abacavir (Ziagen[®]) will reach the pharmacies by the end of 1998 or early 1999. Glaxo has also requested approval for its new protease inhibitor amprenavir (Agenerase[®]) and there is every reason to expect it to become available by early 1999.

Although these therapies do not represent major advances beyond currently available therapies for treatment-experienced patients, they will be a welcome addition as they give people more therapeutic options and offer simplified dosing regimens. Several new anti-HIV drugs are likely to be available in the near future. These include abacavir (Ziagen[®]) which is likely to be available in pharmacies by the end of 1998 or early 1999 and amprenavir (Agenerase[®]) which is likely to be available in early 1999. Although these therapies may not offer a major advance in comparison to the currently available therapies, they will be a welcome addition as they will give people more therapeutic options and will offer simplified dosing regimens. The greatest benefit from these therapies will come for people who are just beginning treatment. Both drugs' potency can be diminished or eliminated altogether when patients have developed resistance to other similar drugs. Cross-resistance, however, is not absolute but rather it depends on how many and which drugs of the same type the patient has previously developed resistance to. More encouraging and perhaps more relevant information has been reported recently from a study of nevirapine (Viramune[®]), which raises the level of enthusiasm over the potency of this drug in a protease-inhibitor sparing regimen. The following article provides an overview of these and other new findings in research on anti-HIV drug therapy regimens.

Amprenavir

Results from the first large study of the protease inhibitor amprenavir (Agenerase[®]) shows that the drug has potent anti-HIV activity. Three hundred and thirty-two people with an average CD4+ cell count of about 400 and an average viral load of about 45,000 copies HIV RNA participated in the study. None of the participants have received previous anti-HIV therapy. Participants received AZT (zidovudine, Retrovir[®]) + 3TC (lamivudine, Epivir[®]) or AZT + 3TC + amprenavir. The dose of amprenavir was 1200mg twice a day (total daily dose of 2400mg). The results after 16 weeks of the study, using the most conservative analysis, show that about 60% of people on the 3-drug combination had HIV RNA levels below 400 copies compared to only 17% of people receiving

AZT + 3TC. People with high HIV RNA levels (more than 100,000 copies) had similar anti-HIV responses compared to people with lower viral loads. These results are similar to those seen in short-term studies with other protease inhibitors and it remains to be seen how durable the anti-HIV response will be with amprenavir. There is, however, no particular reason to suspect that it will be any less durable than other drugs of this type. The most common side effects among people receiving amprenavir included rash, nausea, vomiting and oral paresthesia (a numbing around the mouth).

One of the major concerns with this study was that people risked receiving AZT + 3TC, which is, and was when this study was started, considered suboptimal therapy for people with HIV. Despite the best efforts by community advocates to change the study design so that everybody would receive optimal therapy, Glaxo Wellcome, the developers of amprenavir, refused, citing the fact that more conservative countries, like the

In the midst of the "big spin" campaign on behalf of efavirenz, the new information on the other non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine (Viramune[®]) and delavirdine (Rescriptor[®]), have been overlooked and overshadowed.

United Kingdom, the sponsor's home county, still recommend the use of two-drug therapy. Glaxo Wellcome recently submitted results of this and other studies to the Food and Drug Administration (FDA) in order to receive approval for amprenavir, which is expected in the spring of 1999.

Small studies of amprenavir in complex multi-drug "salvage therapy" regimens have not been encouraging but there remains some hope that the drug may still be active in at least some

people who have developed resistance to other protease inhibitors. Amprenavir has a somewhat, but not completely, different pattern of drug resistance than other protease inhibitors. Thus, some people who have failed one or more protease inhibitors still demonstrate sensitivity to the drug on typical tests used to determine drug resistance. Whether and how often this will result in good effectiveness in such cases remains to be seen.

Nevirapine and Delavirdine

With all the hype and promotion over efavirenz (Sustiva[®]), the HIV-interested public has been fed the impression that this drug is demonstrably more potent than other drugs of its type. The simple fact is that there little or no evidence to support this view. The drugs have not been directly compared, nor have then been tested in sufficiently similar studies to make a fair comparison. In the midst of the "big spin" campaign on behalf of efavirenz, the new information on the other non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine (Viramune[®]) and delavirdine (Rescriptor[®]), have been overlooked and overshadowed. However, results from a recent French study of nevirapine were very encouraging and suggest that the drug should be considered when deciding on a protease-sparing regimen. Sixty people with an average CD4+ cell count of about 400 and a viral load of about 40,000 copies HIV RNA participated in the study. None of the participants have received previous anti-HIV therapy. All of the participants received ddI (didanosine, Videx[®]) + d4T (stavudine, Zerit[®]) + nevirapine, all of which were dosed twice a day. Of the 48 people who remained in the study after 6 months, 88% had HIV RNA levels below 400 copies and 64% had HIV RNA levels below 50 copies. There was an average CD4+ increase of 162 cells. An additional 40 people are now participating in this study, however they are receiving nevirapine and ddI only once a day while still taking d4T twice a day. No data are available on the anti-HIV activity for this revised regimen as of yet.

Similarly, a study of delavirdine (Rescriptor[®]) in 369 people compared two different two-drug regimens (delavirdine plus AZT and AZT plus 3TC) to a three drug regimen of delavirdine plus AZT plus 3TC. As expected, the three-drug regimen was superior to either two-drug regimen at all data points. Perhaps most importantly, the three-drug regimen with delavirdine (122 people) showed excellent and durable results in suppressing viral load below the limit of detection on both standard and the most sensitive PCR test (less than 400 and less than 40 copies of HIV RNA).

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Although study results are not yet complete, at the most recent report, roughly 70% of those who had reached the 52 week endpoint (29 people) remained undetectable on standard viral load tests, while approximately 60% were undetectable on the super sensitive assays. It remains somewhat difficult to compare these results to studies of efavirenz. For example, the delavirdine study included people with prior histories of AZT use while the efavirenz study was limited to people beginning therapy for the first time. Yet there is nothing in the data so far that even hints that delavirdine is any less successful or potent than efavirenz when used in combination with AZT and 3TC.

The need for studies that directly compare efavirenz, delavirdine, and nevirapine has been underscored by the skillful promotional campaign that has already characterized efavirenz as the superior drug. The need is further heightened by the fact that, based on this so far unproven assertion, efavirenz has been priced dramatically higher than the other two drugs.

Protease Inhibitor Studies

Although longer-term results from a recent study shows that twice daily dosing of indinavir (Crixivan[®]) was not as effective in keeping viral load fully suppressed as indinavir taken three times a day (see Indinavir Box on page 9), other twice daily dosing studies with protease inhibitors are continuing. Preliminary results from a study comparing saquinavir (Fortovase[®]) dosed twice versus three times a day in combination with 2 nucleoside analogue drugs (AZT, d4T, 3TC etc.) versus a combination of saquinavir + nelfinavir (Viracept[®]) + one nucleoside analogue drug (all dosed twice a day) shows that there are no differences in viral load or CD4+ cell count responses between the three groups after 24 weeks. Side effects were also comparable between the three groups with the exception of more diarrhea among people receiving the dual protease inhibitor containing regimen.

Another twice versus three times daily dosing study of nelfinavir shows that there are no differences in viral load or CD4+ cell levels between the two groups based on preliminary results. People received nelfinavir at 750mg three times a day or 1250mg twice a day in combination with d4T and 3TC. Approximately 65% of the participants had HIV RNA levels below 400 copies and 55% had HIV levels below 50 copies. There were also no differences in side effects between the two groups although there were slightly more cases of diarrhea among people receiving the twice daily dose of nelfinavir.

Nevertheless, the recent experience with indinavir suggest that people should cautiously

consider the wisdom of switching to a twice a day dosing regimen for a drug that is approved for three times a day dosing.

Several other new protease inhibitors are at various stages of development, but none are likely to be widely available any time soon. Abbott Labs' new drug, ABT-378, has shown promise initial trials but is a long way from FDA approval. New protease inhibitors from Pharmacia & Upjohn and Bristol-Myers Squibb both show initial promise and some hope of activity in people with

prior resistance to other protease inhibitors, but it is far too early to make any claims.

Salvage Therapy Studies

Salvage therapy refers to regimens that are used or being studied for people who have failed one or more protease inhibitor-containing regimens. This generally means that their treatment regimen was no longer able to suppress HIV replication to levels below the limits of detection with the viral load tests.

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Indinavir (Crixivan[®]) Twice a Day?

New information from a study of indinavir (Crixivan[®]) has shown that a twice daily dosing regimen is not as effective as the three times daily schedule in maintaining viral suppression. As a result, Merck, the manufacturer, is stopping the part of the study which uses twice daily dosing and has notified community groups, information providers and physicians of the new findings. Based on these findings, Merck is encouraging everyone using twice daily dosing to switch back to three times daily dosing schedules. The new findings are contrary to a previous, smaller study which suggested that twice daily dosing was at least equivalent to the standard three times daily dosing.

Percent of people with viral load below the limit of detection

Study group	at 16 weeks (287 patients)	at 24 weeks (87 patients)
3 times daily	78%	91%
2 times daily	72%	64%

The study included people who had never previously taken a protease inhibitor, or 3TC (lamivudine, EpiVir[®]) and the regimens used included twice or three times daily dosing of AZT (zidovudine, Retrovir[®]), 3TC and indinavir. After 24 weeks of study, 91% of those receiving three times daily dosing had reached or maintained HIV levels below the limit of detection, whereas only 64% on the twice daily regimen had experienced the same level of viral suppression. What's most important is that after only 16 weeks, the twice daily dosing schedule appeared equivalent. By 6 months, however, the superiority of three times daily dosing became very apparent.

Another regimen under study which might still permit twice daily indinavir dosing is the protease inhibitor combination of ritonavir (Norvir[®]) and indinavir (Crixivan[®]). Preliminary, short-term studies of this regimen appear to show indinavir quite suitable for twice daily dosing, while also eliminating the requirement that the drug not be taken with food. However, it's important to recognize this is based on early data, covering a short period in two small clinical trials. Another study using twice daily indinavir dosing is in combination with nelfinavir (Viracept[®]).

Caution about Regimen Changes

It's possible that more people than ever are currently using the indinavir twice-daily dosing regimen as news from the smaller study preceded the announcement of a shortage in supply of another protease inhibitor, ritonavir (Norvir[®]) capsules. When the supply problem was announced, some people may have begun rethinking their anti-HIV regimens and may have made regimen changes, possibly to an easier-to-use regimen using indinavir twice daily dosing.

The lesson learned here is something that Project Inform has been cautioning about for some time with regard to simpler and easier regimens using current available therapies. When these drugs were approved, the reason they were dosed according to schedules in their label instructions (e.g. three times daily) is because studies demonstrated these schedules were necessary to maintain optimal blood levels of drugs. While certainly people want, need and deserve simpler regimens, simply changing a regimen from three times to twice daily dosing is not the solution.

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An interesting study conducted in Vancouver, Canada shows that the use of up to 9-drug regimens may be of benefit to people with extensive previous anti-HIV therapy experience. Eighty-three people have now been treated with a combination of up to 9 anti-HIV drugs including two NNRTIs, two protease inhibitors, 3–4 nucleoside analogue drugs plus hydroxyurea (Hydrea[®]). All of the drugs were dosed twice daily. The participants had an average viral load of about 50,000 copies HIV RNA, a CD4+ cell count of about 200 and had previously received, on average, 7 different anti-HIV drugs (although about half of the participants had not previously received a NNRTI). This study is still ongoing but preliminary results show that about 40% of the participants achieved viral loads below 400 copies HIV RNA after the first month of the study but by the fifth month the number was down to about 25%. As would be expected with such an intensive regimen, about 17% of participants discontinued from the study and about 16% had severe side effects, the most common being elevated liver enzyme levels. Additionally, about 34% of the participants had to have their regimens modified because of side effects. People who were most likely to benefit from this regimen were those who had been on fewer numbers of previous anti-HIV therapies and those with lower viral load levels at the start of the study.

These study results are interesting because although the participants had been on many previous anti-HIV therapies about 40% still had a very good initial anti-HIV response. One possible explanation for this is that it is unlikely for a single virus in the body to be resistant to all of the drugs, but it might be resistant to a few of them. Therefore, by using an aggressive multi-drug approach, the chances increase that a given individual virus

People should not give up without trying new therapies simply based on a theoretical assumption of resistance and cross-resistance.

will be suppressed by at least one or more of the drugs used in the multi-drug regimen. The trade off for the kind of approach, however, is the short- and long-term side effects of using so many drugs as well as the possible difficulty of taking so many drugs on a daily basis.

In another study primarily focused on “salvage,” T-20 (pentafuside), a drug in the new class called fusion inhibitors, has demonstrated strong antiviral activity in people who had

failed on prior protease inhibitor regimens. To date, the primary side effect of the drug is pain and swelling at the injection site (T-20 must be infused either intravenously or subcutaneously). Nonetheless, this drug appears to offer genuine promise in the salvage setting. Widescale use of the drug, however, remains at least a year or more away.

Commentary

Other than the few listed here, there is a dearth of new drugs in the pipeline. In fact, some companies have scaled back or stopped their HIV drug discovery programs and with the consolidation in the pharmaceutical industry there are fewer and fewer players. The most substantial and longest-lasting benefit for people who have few or no remaining anti-HIV treatment options will probably only come from drugs which block HIV replication in different ways than those currently available. There needs to be a concerted effort on the part of researchers in academia, the pharmaceutical companies and the government to discover and rapidly develop new drugs for people in this scenario. Recognizing the weakness of the current drug pipeline, the National Institutes of Allergy and Infectious Diseases has created new funding programs to encourage the development of new types of drugs. While this is helpful, it will at best produce results several years from now.

Taken together, these facts underline the importance of patients making the wisest possible use of the therapies which are already available. This begins with careful decisions about when to begin therapy in the first place. It calls for careful thought about the initial choice of therapy and the opportunity to make such decisions as independently as possible from the promotional interests of pharmaceutical sponsors. While the concept of such possible advances as protease-sparing regimens and simple dosing sound attractive, the hard fact is that there isn't a single shred of evidence that such strategies will result in longer life, nor any evidence that they won't result in shorter life. A great deal remains to be learned about the optimal way to use the available list of therapy. Each therapy decision, no matter which drugs are chosen, affects future options for each individual. For now, the best proven and most durable therapy option remains the use of 3 drug regimens that include a protease inhibitor. The best way to use those drugs remains the way they were approved for use by the FDA.

Hope remains that at least some new drugs may remain active despite prior drug resistance in at least some patients. People should not give up without trying new therapies simply based on a theoretical assumption of resistance and cross-resistance. Individual responses can always be dif-

ferent from the “average” experience, which is all that clinical trials report on. The more wisely each new drug is used, the more likely it will add to a patient's overall length of life. With so many drugs now available, the number of choice is very wide. It may or may not yet prove possible to “retire” some drugs long enough to restore their activity after developing resistance. Perhaps the greatest hope of all remains in the increasing amount of data that shows that maintaining an undetectable

Treatment strategy, nutrition, belief in a future and a productive lifestyle all remain potent weapons in the fight against AIDS. Life does not depend solely on what the government or the pharmaceutical industry may or may not do.

viral load, while helpful, may not be necessary for long-term clinical success. A great number of people who have “failed” therapy in the current definition of “failure” do not experience rapid rates of decline and illness following treatment failure. On the contrary, there is little evidence that they do any worse, clinically, than those for whom therapy continues to work. The treatment of HIV disease remains a complex and far from fully understood subject that cannot be reduced to simple formulas based on lab tests. Life and quality of life do not depend solely upon the success of drugs or even a constant stream of new drugs. Treatment strategy, nutrition, belief in a future and a productive lifestyle all remain potent weapons in the fight against AIDS. Life does not depend solely on what the government or the pharmaceutical industry may or may not do. ■

Efavirenz (Sustiva®) Receives FDA Approval

Efavirenz (Sustiva®, formerly known as DMP 266) is the newest non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV infection in children and adults to be approved by the Food and Drug Administration. Efavirenz is the third NNRTI to be approved, with the other two being nevirapine (Viramune®) and delavirdine (Rescriptor®).

Approval was based on results showing that when the drug is used in combination with standard approved therapies (like AZT, ddI, d4T, 3TC) there was potent suppression of HIV replication (sustained reduction in HIV RNA levels) for at least 24 weeks (see *PI Perspective 25* for trial results). It is not known if efavirenz will delay progression of disease or death, but ongoing studies will answer this question.

In laboratory studies there is broad cross-resistance (resistance to one drug results in resistance to another) among the three NNRTIs. This means that if someone has developed resistance to one of the drugs, they are unlikely to get any anti-HIV benefit from the other two. There are many drug interactions with efavirenz because it is broken down by an enzyme used by many commonly used drugs (call Project Inform's National HIV/AIDS Treatment Hotline for the *Drug Interaction Chart* for complete drug interaction information).

The most studied drug interaction with efavirenz is indinavir (Crixivan®). Efavirenz decreases indinavir levels in the blood. Another potentially serious drug interaction is between efavirenz and saquinavir (Fortovase®) where saquinavir levels are decreased 62%. For more information on Efavirenz, call the Project Inform Hotline at 800-822-7422.

The most common side effect of efavirenz is central nervous system (CNS) symptoms, which can range from severe symptoms such as delusions, acute depression and mania (e.g. severe anxiety) to less severe symptoms such as dizziness, lack of concentration, sleeplessness and strange dreams. Most of the reported CNS side effects have been mild to moderate in severity and usually go away after a few weeks. However, if people experience any severe CNS symptoms, they should contact their healthcare provider immediately. It appears that people with a history of mental illness or substance abuse are more likely to develop the more severe CNS side effects. Other reported side effects include rash, nausea, vomiting, headache, fatigue and diarrhea. Some researchers recommend taking an anti-anxiety drug like lorazepam (Ativan®) to reduce CNS symptoms.

The recommended dose of efavirenz for

adults is 600mg once daily (it is recommended that efavirenz be taken at night to reduce the likelihood of CNS side effects). Recommended dosing for children is found in the table below.

It is important that efavirenz not be used alone or merely added to a failing regimen as HIV will develop resistance to the drug rapidly. Efavirenz should always be used as part of a combination where at least two of the drugs are new to an individual.

Buying and Access

Recommended dosing for children over the age of 3 years is based on weight.

Child's Weight	Dosing
10-15kg	200mg
15-20kg	250mg
20-25kg	300mg
25-32.5kg	350mg
32.5-40kg	400mg
over 40kg	600mg

Many people who are dependent upon the AIDS Drug Assistance Program (ADAP) may find that their state ADAP has been unable to add efavirenz to their list of covered drugs, primarily because the drug came to market at an unexpectedly high price.

Project Inform encourages people who are dependent upon ADAP or have no other payment source for their prescription drugs to check with their state ADAP coordinator. That number can be obtained by calling the Access Project at 800-734-7104. If the state is unable to immediately place the drug on formulary, patients should sign up as quickly as possible with **Dupont Pharma's Patient Assistance Program**, which can be reached at:

1-800-334-4486

In this instance, we believe that complaints about lack of coverage of the drug by ADAP should be generally directed to the manufacturer, Dupont Pharma, and not to the ADAP directors. ■

Abacavir Update

As we go to press, the Antiviral Drugs Advisory Committee to the Food and Drug Administration (FDA) recommended that abacavir (Ziagen®) be approved to treat HIV disease for adults and children. Abacavir is expected to be available in pharmacies before the end of the year. Abacavir will be the sixth nucleoside analogue drug to be approved by the FDA, the others being AZT (zidovudine, Retrovir®), ddI (didanosine, Videx®), ddC (zalcitabine, Hivid®), d4T (stavudine, Zerit®) and 3TC (lamivudine, Epivir®). Studies suggest that abacavir has the most potent anti-HIV activity of all the drugs in its class, when used by people who have not previously been on any anti-HIV therapies. However, for people who have developed resistance to multiple previous therapies, the potency of abacavir tends to drop substantially.

The recommended dose of abacavir is 300mg (a single pill) twice a day for a total daily dose of 600mg. When it is used in combination with AZT and 3TC (Combivir®), the total regimen requires only two pills twice a day (four pills total, per day). The simplicity of the regimen is expected to be one of its most attractive features. The recommended dose for children is 8mg/kg taken twice a day. Abacavir can be taken without regards to food. The most common side effects reported in the clinical studies are nausea, fatigue, headaches and diarrhea. A more serious side effect which affects about 3% of people taking abacavir is a hypersensitivity reaction to the drug. This reaction is usually systemic (throughout the body) and includes fevers, malaise, nausea, vomiting and sometimes rash. This reaction appears relatively soon after starting abacavir (about two weeks) and resolves one or two days after stopping the drug. It is important not to try and take abacavir again (re-challenge) if there was hypersensitivity to the drug as the subsequent reaction is potentially fatal.

AZT	Retrovir [®] , zidovudine	NARTI [*]	<p>DOSE 1 CAPSULE = 100mg DOSE 2 CAPSULE = 300mg DOSE 3 CAPSULE = 600mg TDD = 600mg</p>	<ul style="list-style-type: none"> • Can be taken with or without food. • Most common side effects are headache, nausea and general sense of feeling ill. Side effects usually diminish after 6 to 8 weeks of therapy. • Most serious side effect is anemia, if caught early treatable with erythropoietin (EPO).
AZT+3TC	Combivir [®]	NARTI [*]	<p>DOSE 1 CAPSULE = 150mg 3TC / 300mg AZT DOSE 2 CAPSULE = 300mg 3TC / 600mg AZT TDD = 300mg 3TC / 600mg AZT</p>	<ul style="list-style-type: none"> • Can be taken with or without food. • See comments from AZT and 3TC sections.
ddC	Hivid [®] , zalcitabine	NARTI [*]	<p>DOSE 1 CAPSULE = 0.75mg DOSE 3 CAPSULE = 2.25mg TDD = 2.25mg</p>	<ul style="list-style-type: none"> • Can be taken with or without food. • Most common side effect include peripheral neuropathy (pain/tingling in feet and/or hands), thrombocytopenia (low platelets) and mouth sores. • Most serious side effect is pancreatitis, which has been fatal in some people. Symptoms include sharp pain in upper abdomen, nausea and vomiting. Stop drug immediately and consult a doctor if this occurs. Alcohol use increases risk of pancreatitis.
ddI	Videx [®] , didanosine	NARTI [*]	<p>DOSE 1 CAPSULE = 100mg DOSE 2 CAPSULE = 400mg TDD = 400mg</p>	<ul style="list-style-type: none"> • Must be taken on an empty stomach (without food). • Cannot be taken within two hours of drugs which require an acidic stomach environment, including many protease inhibitors and common therapies, such as dapsone. • Most common side effects include increases uric acid levels (a measure of kidney function), headaches, sleeplessness, diarrhea and peripheral neuropathy (pain/tingling in feet and/or hands). • Most serious side effect is pancreatitis, which has been fatal in some people. Symptoms include sharp pain in upper abdomen, nausea and vomiting. Stop drug immediately and consult a doctor if this occurs. Alcohol use increases risk of pancreatitis.
d4T	Zerit [®] , stavudine	NARTI [*]	<p>DOSE 1 CAPSULE = 40mg DOSE 2 CAPSULE = 80mg TDD = 80mg</p>	<ul style="list-style-type: none"> • Can be taken with or without food. • Most common side effect is peripheral neuropathy (pain/tingling in feet and/or hands). May cause anemia. • Rare incidence of pancreatitis has been observed. Symptoms include sharp pain in upper abdomen, nausea and vomiting. Stop drug immediately if this occurs. Alcohol use increases risk of pancreatitis.
3TC	Epivir [®] , lamivudine	NARTI [*]	<p>DOSE 1 CAPSULE = 150mg DOSE 2 CAPSULE = 300mg TDD = 300mg</p>	<ul style="list-style-type: none"> • Can be taken with or without food. • Side effects associated with 3TC are rare, but may include headaches, nausea, general sense of feeling ill, diarrhea, anemia and hair loss.
Adefovir	Preveon [®]	NARTI	<p>DOSE 1 CAPSULE = 60mg DOSE 2 CAPSULE = 120mg TDD = 60mg TDD = 120mg</p>	<ul style="list-style-type: none"> • Adefovir is only available through studies and early access programs, as of October 31, 1998. • Can be taken with or without food. • Most common side effect is kidney dysfunction.

* Dose modifications of one or more drugs in a combination may be necessary when taking a protease inhibitor or an NNRTI with 1) another protease together or NNRTI; or 2) common therapies, whether over-the-counter medication or prescription drugs. For more detailed information, call the National HIV/AIDS Treatment Hotline at 1-800-822-7422.

• NNRTI = Non-nucleoside reverse transcriptase inhibitor. ^{*}NARTI = Nucleoside analogue reverse transcriptase inhibitor. ^{**}NARTI = Nucleotide analogue reverse transcriptase inhibitor.

Strategy Update: Protease-Sparing Regimens

Since the Geneva International AIDS Conference, the notion of using therapy combinations which delay the use of protease inhibitors has been a hotly debated topic. The rationale for protease-sparing regimens is to use a three-drug combination that reduces viral load below the limit of detection while saving protease inhibitors for later use. The theoretical advantage of a protease-sparing regimen is not only that it saves the most potent therapy for later use, but that it also delays the risk of side effects associated with long-term use of protease inhibitors. Those who promote the protease-sparing regimens believe that this makes for a better long-term strategy and may extend the length of time that drugs are effective.

Not everyone agrees with the rationale behind protease-sparing regimens. Some researchers still believe that the best shot a person has against HIV infection is the first shot. They argue that even initial therapy should begin with our strongest anti-HIV drugs. This, they believe, will result in the longest duration of effective therapy while also introducing the most potent drugs at a time when the patient is in the best health and best able to fend off side effects. At the moment, there simply is no hard data to say which of these strategies will help a person live longer. They are simply matters of opinion.

In recent months, the promotion of protease-sparing regimens, particularly with the use of efavirenz (Sustiva[®]), has reached a fever pitch. Many doctors are routinely using the efavirenz regimen as a first choice for people just starting therapy, and some cases, taking people off of protease inhibitor combinations in favor of an efavirenz combination. The data which serves as the primary justification for using the efavirenz / protease-sparing regimen is a single trial in people who have never previously taken anti-HIV therapy which compared the efavirenz combination to a typical indinavir (Crixivan[®]) combination. That study, reported in *PI Perspective* 25, seemed to show the efavirenz combination to be equal, if not superior, to the indinavir combination. Even though the simplicity of use offered by efavirenz is a real benefit, there is good reason for caution in making wholesale judgments about the value of this approach. They can be easily summarized:

- *The principle efavirenz vs. protease inhibitor study has officially reported results from only 24 weeks of follow-up.* Unreviewed data extends this to 36 weeks. In comparison, protease inhibitor studies now show durable treatment

response over two years of follow-up, even in people who have previously used anti-HIV therapy.

- *Because efavirenz was easier to use than indinavir (once daily dosing vs. 3 times daily without food), it is not clear whether the study outcome is a result of efavirenz being a more potent drug or a result of better adherence.* If better adherence explains the outcome, then these study results are not applicable to patients who are able to adhere effectively to an indinavir regimen.
- *The principle efavirenz vs. protease inhibitor study was "open label" rather than "blinded."* This means that patients and physicians alike knew which drug the patients were getting (re-

ferred to as "open label"). Many people joined this trial primarily to gain access to efavirenz. When they got indinavir instead of efavirenz, some dropped out yet were counted ultimately as "failures" on indinavir. This may have produced bias in the results of the study. In any case, open label studies are never considered to be as reliable as double-blinded studies (studies where neither the participants nor the personnel of the research site know what therapy is being received in an attempt to eliminate bias).

- *Efavirenz (like nevirapine and delavirdine) presents a "low genetic barrier" to drug resistance.* This means that the appearance of a single genetic mutation can completely cripple the drug's effectiveness. In contrast, protease inhibitors like indinavir typically require 2 or 3 or more mutations before complete failure. Consequently, many researchers wonder whether efavirenz combinations will remain effective as long as a typical protease inhibitor combination. It may work very well initially, but the real question is how well will it hold up over time?
- *The group that received indinavir in this study performed more poorly than people in almost any other indinavir study.* In other studies of similar patient populations given the same indinavir combination, a significantly greater percentage of people reached and sustained viral suppression below the limit of detection. Why the indinavir group performed weakly in this study is unclear, but it is evident that the experience with indinavir was not typical.

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Drug	Common Side Effects	Drug Interactions	Special Concerns or Benefits
Delavirdine (Rescriptor [®])	Rash (lowest incidence of the 3 drugs)	Generally boosts blood levels of protease inhibitors and some other drugs.	Commonly used with protease inhibitors to modulate their dosing needs or increase potency; probably the least side effects of the three; dosed three times a day; lowest price of the three.
Efavirenz (Sustiva [®])	Nervous system disturbances; elevated triglycerides and cholesterol levels; rash	Generally reduces the blood levels of protease inhibitors and some other drugs.	Stresses liver, probably not a good choice for people with concurrent hepatitis; troubling neurologic side effects; triglyceride and cholesterol effects, like protease inhibitors; highest price, by far; dosed once a day.
Nevirapine (Viramune [®])	Rash	Generally causes only a small decrease of blood levels of other drugs.	Easiest on the liver; higher incidence of rash than delavirdine; currently dosed twice daily, some initial good experience with once-daily dosing; moderate price.

... continued from page 14

Promoters of the efavirenz combination also strongly imply that efavirenz is a better choice for such protease-sparing regimens than other drugs in this class, notably nevirapine and delavirdine. Salesmanship aside, there is simply no evidence to support this view. No studies have directly compared efavirenz to other drugs in its class. Both nevirapine and delavirdine came to market with the reputation of being somewhat weaker than protease inhibitors, but this perception was derived primarily from studies which used them in inadequate, two-drug combinations. Subsequent 3-drug combinations using either drug as the anchor for a regimen have shown results similar to the efavirenz study in regards to the percentage of people who achieve viral load below the level of detection. Since efavirenz has been priced nearly 60% to 70% above nevirapine and delavirdine respectively, the comparative value of these three drugs is important. Until directly comparative studies are run, there is no valid basis for suggesting that any one of them is superior to any other. In other words, people contemplating the use of a protease-sparing regimen should not automatically assume that such a regimen must be based on the use of efavirenz. Whether efavirenz, delavirdine or nevirapine is used as an anchor for a protease-sparing regimen, it is important to use any of these drugs in combination with at least two nucleoside analogue drugs (e.g. AZT [zidovudine, Retrovir], ddI [Videx], d4T [Zerit], etc.) which are new to the individual. A brief comparison between the three non-nucleoside reverse transcriptase inhibitors is provided on page 14.

While the three drugs are probably roughly equivalent, no head-to-head comparative studies have yet been conducted. Some issues to consider when making a decision about the three drugs might include their dosing schedules, side effect profiles and drug interactions. Efavirenz is probably the easiest drug to use, requiring only once daily dosing. Of the three drugs, it probably has the most side effects, however. Like the protease inhibitors, efavirenz has been shown to elevate triglycerides and cholesterol levels, in some people. People considering a protease-inhibitor-sparing regimen because of fears the long-term effects of elevated cholesterol and triglyceride levels should be aware that this is also a potential side effect of this drug. Moreover, efavirenz use is associated with neurologic side effects, including bizarre dreams, feelings of disorientation and feelings of being "hungover." Delavirdine is commonly being used as an adjunctive therapy to a protease inhibitor containing regimen, to modulate the blood levels of other drugs to allow for decreasing dosing. In general practice

today, delavirdine is rarely the cornerstone of a triple-drug regimen. This was because early studies were not conducted using delavirdine in a 3-drug regimen (only in 2-drug regimens) and its effective was under question. More recent study results, where delavirdine was used in a 3-drug combination, showed that it was potent when used in an optimal strategy regimen with two other drugs. While it requires three times daily dosing, it is probably causes the least side effects of the three drugs. While both delavirdine and

The bottom line is that no one has adequate information to make proven recommendations about the use of these protease-sparing regimens, or about the comparative value of efavirenz, nevirapine and delavirdine.

nevirapine has rash as the most common side effect, the incidence of rash is much lower among people using delavirdine. Nevirapine requires only twice daily dosing, making it easier to take than delavirdine and because it doesn't have the additional neurologic and metabolic (e.g. increasing cholesterol/triglycerides) side effects of efavirenz it is increasingly being used as the "middle ground" option for people choosing a protease-inhibitor-sparing regimen, particularly for people who are co-infected with HIV and hepatitis or who have other signs or symptoms of impaired liver function.

While not a concern in protease sparing regimens, an additional point to consider arises when efavirenz is used in combination with a protease inhibitor. When used in combination, the drug substantially diminishes the level of some protease inhibitors. Indinavir levels are reduced by 31% and saquinavir (Fortovase) levels are reduced by 62%. As a result, when efavirenz is combined with either of these protease inhibitors, the dose of the protease inhibitor needs to be adjusted. Nevirapine (Viramune) will also, to a lesser degree, reduce indinavir and saquinavir levels, while delavirdine (Rescriptor) has the opposite effect, increasing the blood levels of some protease inhibitors. This property of delavirdine may allow for either reduced doses of protease inhibitors or increased potency.

Commentary

None of these concerns rule out the use of efavirenz or protease-sparing regimens in general. The unresolved question of long-term durability

applies equally to all drugs in the non-nucleoside class and lead some researchers to believe that the best use of this class of drugs will be in combination with protease inhibitors, rather than as an alternative. It is critical to remember that if a patient develops resistance to any of the three current non-nucleoside drugs in a protease-sparing regimen, this class of drugs will not be useful later in the course of HIV disease.

The bottom line is that no one has adequate information to make proven recommendations about the use of these protease-sparing regimens, or about the comparative value of efavirenz, nevirapine and delavirdine. For some people, the simpler dosing regimens offered by all the non-nucleosides may be a compelling, overriding factor in choosing a combination. For others, concerns about the long-term outcome may outweigh factors of convenience. Given a few more years and a few directly comparative trials, people may not have to choose in this manner, but for now, it is all that the data will allow. ■

Expanded Access

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

Amprenavir (PI) 800-248-9757

For anyone tolerate or failing current protease inhibitor therapy and requiring an additional new drug for treatment strategy.

Abacavir (NARTI) 800-501-4672

For anyone failing current therapy and requiring an additional new drug for treatment strategy.

Adefovir (NtARTI) 800-445-3235

For anyone failing current therapy and requiring an additional new drug for treatment strategy.

Gynecological Complications in Women with HIV^E

While gynecological (GYN) complications are but one area of concern for women with HIV, they are critically important because they are the most commonly reported condition of women living with HIV and AIDS. When evaluating HIV-associated GYN conditions and the provision of appropriate gynecological care, it is important to consider what GYN health reveals about the status of a woman's immune system.

What does it say about the health of a woman's immune system, for instance, when a common GYN condition like vaginal candidiasis becomes progressively more difficult to treat? What does the absence of an HIV infected woman's period (amenorrhea), a common menstrual abnormality in women with HIV, tell us about immune function? How does the marked increase in the rate and severity of cervical abnormalities experienced by women with HIV correspond to a weakening immune system? These are some of the questions that must help guide women and health care providers in the evaluation and treatment of GYN complications in women with HIV. These complications should also be considered in light of CD4+ cell count, an important marker of immune function. A chart of common GYN conditions is found on pages 17-18. A flow chart of screening guidelines are presented on page 19.

Common GYN Complications

Vaginal candidiasis (vaginal yeast infections) is a fungal infection common in many women. It is the most common initial manifestation of HIV in women, and its prevalence increases as CD4+ cell counts decline. As immune suppression worsens, the primary location of the candida infection may shift from the vagina to the mouth (for more information on candidiasis, call our hotline and request the *Candidiasis Fact Sheet*). Recurring vaginal candidiasis is often associated with more

rapid HIV disease progression.

Fortunately, there are several effective forms of treatment for vaginal candidiasis, including topical creams and suppositories such as clotrimazole (GyneLotrimin[™]) which are available over-the-counter and by prescription. If the candidiasis is unresponsive to such treatment, the antifungal drug fluconazole (Diflucan[™]) may be necessary. For women not responding to fluconazole, the antifungal ketoconazole (Nizoral[™]) may be an effective alternative. Dietary modifications such as decreasing sugar intake or adding lactobacillus containing yogurt or acidophilus capsules may help prevent recurrences of candidiasis.

Refraining from using bleach and fabric softeners when doing laundry might also be useful.

Several studies show that the sexually transmitted disease, herpes simplex virus (HSV) type II, may take an altered course in HIV-infected people. For instance, the painful sores in and around the genitals and/or anus caused by herpes tend to be more frequent, persistent and requiring of higher doses of treatment in people with HIV. HSV ulcers persisting for over 1 month are associated with severe immunosuppression and

are considered an AIDS-defining illness. Acyclovir (Zovirax[™]), an oral pill, is most commonly used to treat genital herpes. For women with frequent HSV outbreaks, acyclovir may be helpful in preventing future outbreaks.

Pelvic inflammatory disease (PID) represents a range of inflammatory disorders of the upper genital tract, including fallopian tubes, uterus, ovaries and, in advanced stages, abdominal lining. Common symptoms of such inflammation involve chronic, moderate-to-severe pain, tenderness in the abdomen, irregular menstrual cycles, non-menstrual bleeding and painful and frequent urination. Like other gynecological conditions, PID appears to be more prevalent, severe and resistant to treatment among women with HIV, and especially women with AIDS. Indeed, the Centers for Disease Control and Prevention recommends hospitalization and intravenous antibiotics for treating PID in women with HIV. Studies indicate that relapse of PID occurs more often in women with impaired immunity.

Human papillomavirus (HPV), a sexually transmitted disease which primarily affects the cervix, plays a primary role in the development of cervical *dysplasia* (abnormal cells) and cancer of the cervix in women. Recent studies have demonstrated that women with HIV,

Gynecological complications further compromise the immune system.

Consequently, it is very important GYN complications be diagnosed, monitored and treated under the guidance of a health care provider.

particularly those with low CD4+ cell counts, have an increased frequency and severity of HPV-related cervical dysplasia. The outcome for HIV-positive women with cervical cancer, the most severe form of cervical dysplasia and an AIDS-defining illness, is much worse than for women without HIV. However, if detected early, less severe grades of dysplasia (CIN I or II) are fairly easily treated, stressing the need for regular and timely screening.

If symptoms occur, they often include multiple small warts on the vagina or around the anus. Multiple types of therapy are available. However, recent studies caution against the use of one common treatment option called cryotherapy, which involves freezing the wart. Cryotherapy can cause normal tissue to heal over deeper areas of dysplasia, causing future genital screenings to appear normal while abnormal tissue grows undetected underneath. Anecdotal reports also indicate that the aftermath of cryotherapy can be extremely painful.

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1999 National Conference on Women & HIV

October 8 – 13, 1999
Los Angeles City Convention Center
Los Angeles, CA

For information, you may call toll-free 877-266-3966.

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Common GYN Complications in Women with HIV/AIDS

This table is a partial listing of complications. For complete information, call Project Inform's National HIV/AIDS Treatment Hotline at 800-822-7422 and request the *GYN Conditions in Women with HIV Fact Sheet*.

Complication	Symptoms	Diagnosis	Treatments
<p>Vaginal Candidiasis (Vaginitis, Yeast Infection)</p> <p>Fungal infection of the vulva and vagina. It is the most common initial manifestation of HIV infection in women and one of the most common complications experienced.</p>	<p>Vulvar itching with a thick vaginal discharge; burning upon urination; redness and white patches at the sites of infection; occurrence of pain during penetrative sexual intercourse.</p>	<p>Usually first diagnosed by appearance and symptoms. If symptoms do not resolve after initial treatment, lab tests may be performed.</p>	<p>Topical creams and suppositories such as clotrimazole (GyneLotrimin®) are available by prescription or over-the-counter. The antifungal fluconazole (Diflucan®) orally, 200mg 3 times a day/every 4 days; ketoconazole (Nizoral®), 400mg a day for 14 days.</p>
<p>Chlamydia</p> <p>A bacterial infection which often affects the cervix and pelvic organs. Most commonly sexually transmitted.</p>	<p>Unusual vaginal discharge and burning when urinating. Later symptoms include lower abdominal pain; pain during penetrative intercourse; bleeding between periods and low-grade fever.</p>	<p>Laboratory inspection of fluid from an infected site.</p>	<p>Antibiotics such as azithromycin (Zithromax®), ceftriaxone (Rocephin®), or doxycycline taken orally.</p> <p><i>Note: treat sexual partners even if they have no symptoms. Avoid sex until treatment is completed.</i></p>
<p>Gonorrhea</p> <p>A bacterial infection that is sexually transmitted.</p>	<p>Pus-like discharge from cervix; lower abdominal pain; fever.</p>	<p>Culturing fluid from the cervix, vagina or urethra.</p>	<p>Penicillin, tetracycline and/or cephalosporin taken orally.</p>
<p>Pelvic Inflammatory Disease</p> <p>Serious, potentially life-threatening spectrum of inflammatory disorders in genital tract of women. Often caused by untreated sexually transmitted infections, particularly chlamydia and gonorrhea.</p>	<p>Chronic, moderate-to-severe pain in the abdomen; irregular menstrual cycles; non-menstrual bleeding; increased vaginal discharge; painful and frequent urination; nausea and fever.</p>	<p>Usually diagnosed by symptoms and pain on the pelvic exam. Sonogram may be performed and occasionally a surgical diagnosis is required.</p>	<p>Combination of antibiotics including clindamycin (Cleocin®), gentamicin, cefoxitin (Mefoxin®) or a combination of cefoxitin and doxycycline.</p>
<p>Human Papillomavirus</p> <p>Viral infection of multiple types that lead to the disruption of the genital cell structures, particularly the cervix. Some HPV types are associated with high risk of cervical cancer or precursor lesions (CIN, SIL).</p>	<p>Symptoms frequently not experienced. Sometimes there are multiple small warts (white spots) on the vagina or around the anus; vaginal discharge or, rarely, pain during penetrative sexual intercourse.</p>	<p>Can often be diagnosed visually, but diagnosis should be made by biopsy since warts may be associated with cancer or pre-cancer lesions anywhere in the genital tract. Diagnosis can be made by Pap smear, but should follow up with colposcopy.</p>	<p>Multiple options to remove viral symptoms include:</p> <ul style="list-style-type: none"> * trichloro-acetic acid (strong acid solution); * electro-cautery (tissue destruction by electric current); and * imiquimod (Aldara®)
<p>Cervical Intraepithelial Neoplasia (CIN)</p> <p>Dysplasia of the surface layers of the cervical cells. CIN is classified according to degrees of severity (grades I, II or III).</p>	<p>Symptoms frequently not experienced.</p>	<p>Diagnosis is often made by Pap. Colposcopy plus biopsy is advised if Pap shows any atypical cellular activity (including persistent inflammation).</p>	<p>CIN-I: no therapy needed. CIN-II-III:</p> <ul style="list-style-type: none"> * laser vaporization; * loop electric excision procedure (LEEP); * biopsy; and * cryotherapy (This option may be least desirable, it may mask future problems).
<p>Herpes Simplex Virus</p> <p>Infection caused by herpes virus types II or I. Type II herpes (genital herpes) is transmitted sexually.</p>	<p>Herpes Simplex I commonly produces oral herpes, and is characterized by cold sores or fever blisters on the mouth or eyes. Herpes Simplex II causes painful sores in the genitals and anus; itching and soreness may present before outbreak; painful urination; swollen lymph nodes in groin; muscle aches; fever.</p>	<p>Can sometimes be diagnosed by visual exam. Some fluid from the sores should be taken to culture (try to grow in a laboratory) to confirm infection. Blood tests can also confirm infection, but not if infection is currently active.</p>	<p>Type I and II:</p> <ul style="list-style-type: none"> * Acyclovir (Zovirax®) in topical, oral and, in severe cases, intravenous form. Oral acyclovir, 200mg five times a day for 10 days, is the general recommendation. * For frequent and severe cases, oral acyclovir may be used at 200 to 400mg two to five times a day.
<p>Bacterial Vaginosis</p> <p>A bacterial infection of the vagina. Can be sexually transmitted.</p>	<p>Odorous, frothy discharge; Inflammation of the vagina.</p>	<p>Microscopic inspection of vaginal discharge.</p>	<p>Metronidazole (MetroGel®) taken orally Note: treat female sex partners.</p>
<p>Trichomonas (Trich)</p> <p>A protozoal infection of the urethra and vagina. Most commonly sexually transmitted.</p>	<p>Excessive and odorous yellow or green vaginal discharge; extreme itching and pain and soreness around the vagina.</p>	<p>Microscopic inspection of vaginal discharge.</p>	<p>Metronidazole (MetroGel®) taken orally. Note: treat all sex partners.</p>

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Complication	Symptoms	Diagnosis	Treatments
<p>Syphilis</p> <p>A bacterial infection that is usually sexually transmitted.</p>	<p>May remain with no symptoms for years with initial presentation as a chancre (ulcer). If untreated, syphilis progresses through three stages: primary (painless ulcers or lesions); secondary (widespread lesions and swollen lymph glands); tertiary (advanced lesions in organs and tissues).</p>	<p>Primary syphilis is usually diagnosed by microscopic evaluation of an ulcer scraping; secondary syphilis by the appearance of symptoms and blood tests; tertiary syphilis by positive blood tests.</p>	<p>Penicillin or ceftriaxone taken orally.</p>
<p>Menstrual Disorders</p> <p>Often accompany chronic illness. Specific disorders experienced by women with HIV may be exacerbated by weight loss, anemia, HIV medications, street drugs and depression.</p>	<p>Absence or suppression of menstruation (amenorrhea); irregular periods; abnormally heavy or light periods; intermenstrual bleeding; worsening of symptoms associated with PMS.</p>	<p>It is important to investigate menstrual disorders with a health care provider as such problems can adversely affect the health of a woman with HIV.</p>	<p>Current standards of care for HIV-positive women neither approve nor forbid the use of hormonal therapies or birth control for menstrual regulation. Stress management and nutrition may relieve symptoms.</p>
<p>Cervicitis</p> <p>Inflammation of the cervix, usually due to sexually transmitted diseases such as chlamydia, gonorrhea or trichomonas.</p>	<p>May have no symptoms. When present, symptoms may include intermenstrual bleeding; vaginal discharge that increases after menstruation; bleeding after penetrative intercourse; painful urination; low back pain.</p>	<p>Diagnosis can be made upon visual examination of the cervix.</p>	<p>Depending on the cause of cervicitis, treatment options include: tetracycline, metronidazole or Ceftriaxone taken orally.</p>
<p>Molluscum</p> <p>Viral infection that is transmitted via skin-to-skin contact.</p>	<p>Small dome-shaped, flesh-colored bumps (papules) on face or in the groin or genital skin. May cause itching and rapid spreading.</p>	<p>Usually diagnosed by visual exam. Early biopsy is recommended for atypical lesions.</p>	<p>Multiple removal options include: * topical application of liquid nitrogen; * electro-cautery (tissue destruction by electric current); and * surgical removal</p>



WISE words

WISE Words is the three-times yearly publication of **Project WISE**, Project Inform's interdepartmental 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!

If you would like to get on the mailing list for WISE Words, you may do so by calling Constituent Services at 415-558-8669 or emailing at WISE@projinf.org.

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Screening

Given that women with HIV have higher rates and generally more severe cases of GYN complications, it is important to screen frequently and regularly. Screening is normally done with one of two diagnostic tools, the Pap smear and/ or colposcopy.

The ability of Pap smears to adequately screen for cervical cancer in women with HIV is currently under debate. Studies have shown that 15-30% of Pap smears that are considered normal are, upon subsequent colposcopy and biopsy, found to be "false-negative." In other words, abnormal precancerous cell growth passed undetected during the Pap test. The problem of false-negative Pap smears has led some health care providers to suggest colposcopy plus biopsy as a more accurate screening procedure, particularly among HIV-positive women where early detection is most critical.

Still, colposcopy has drawbacks of its own. Not only does it require management by a specialist, colposcopy is often accompanied by a biopsy and can be a painful experience with some risk of infection and bleeding. At this point, it is difficult to say whether or not colposcopy screening is a necessary routine screening procedure for HIV-positive women without signs of an abnormal Pap smear.

A promising new screening tool called *Pap Plus Speculscopy* (PPS) has recently gained FDA approval. It is almost as sensitive as a colposcopy plus biopsy, is less invasive and painful and does not require a specialist.

Conclusion

Many of the GYN complications HIV-positive women experience also affect women who are not living with HIV. The same conditions tend to occur more frequently, are more serious and more difficult to treat in women with a compromised immune system. At the same time, GYN complications further compromise the immune system. Consequently, it is very important that GYN complications be diagnosed, monitored and treated under the guidance of a health care provider.

For more complete information, call Project Inform's National HIV/AIDS Treatment Hotline and request the *Gynecological Conditions in Women with HIV Fact Sheet*. ■

GYN Screening Guidelines^E

As follow-up after any treatment for dysplasia, have a Pap smear at three months.

<ul style="list-style-type: none"> n If result is negative, repeat a pap smear every three months for one year. n If result shows inflammatory changes, treat dysplasia again and repeat a pap smear at three months. n If result is abnormal, one of three conditions exist: atypical cells of undetermined significance (ASCUS); mild dysplasia; or moderate/severe dysplasia. Refer below for these conditions. 		
Atypical Cells of Undetermined Significance (ASCUS)	Mild Dysplasia	Moderate to Severe Dysplasia
<p>If abnormal pap smear result shows ASCUS, a COLPOSCOPY is recommended.</p> <ul style="list-style-type: none"> n IF THE RESULT IS NEGATIVE, repeat another colposcopy in 3 to 6 months. n IF THE RESULT IS POSITIVE FOR MILD ASCUS, repeat another colposcopy in 3 to 6 months. n IF THE RESULT IS POSITIVE FOR MODERATE TO SEVERE ASCUS, your physician should diagnose and treat the condition. 	<p>If abnormal pap smear result shows mild dysplasia, a COLPOSCOPY is recommended.</p> <ul style="list-style-type: none"> n IF THE RESULT IS NEGATIVE, repeat another colposcopy in 3 to 6 months. n IF THE RESULT IS POSITIVE FOR MILD DYSPLASIA, repeat another colposcopy in 3 to 6 months. n IF THE RESULT IS POSITIVE FOR MODERATE TO SEVERE DYSPLASIA, your physician should diagnose and treat the condition. 	<p>If abnormal pap smear result shows moderate to severe dysplasia, then a COLPOSCOPY is recommended.</p> <ul style="list-style-type: none"> n Your physician should diagnose and treat the condition.

If no history of abnormal Pap or treatment in 12 months, have a Pap smear at three months.

<ul style="list-style-type: none"> n If result is negative, repeat a pap smear every six months for one year. n If result shows inflammatory changes, treat dysplasia and repeat a pap smear at three months. n If result is abnormal, one of three conditions exist: atypical cells of undetermined significance (ASCUS); mild dysplasia; or moderate/severe dysplasia. Refer below for these conditions. 		
Atypical Cells of Undetermined Significance (ASCUS)	Mild Dysplasia	Moderate to Severe Dysplasia
<p>If abnormal pap smear result shows ASCUS, a COLPOSCOPY is recommended.</p> <ul style="list-style-type: none"> n IF THE RESULT IS NEGATIVE, repeat another colposcopy in 6 months. n IF THE RESULT IS POSITIVE FOR MILD ASCUS, repeat another colposcopy in 6 months. n IF THE RESULT IS POSITIVE FOR MODERATE TO SEVERE ASCUS, your physician should diagnose and treat the condition. 	<p>If abnormal pap smear result shows mild dysplasia, a COLPOSCOPY is recommended.</p> <ul style="list-style-type: none"> n IF THE RESULT IS NEGATIVE, repeat another colposcopy in 6 months. n IF THE RESULT IS POSITIVE FOR MILD DYSPLASIA, repeat another colposcopy in 6 months. n IF THE RESULT IS POSITIVE FOR MODERATE TO SEVERE DYSPLASIA, your physician should diagnose and treat the condition. 	<p>If abnormal pap smear result shows moderate to severe dysplasia, then a COLPOSCOPY is recommended.</p> <ul style="list-style-type: none"> n Your physician should diagnose and treat the condition.

If there's a history of abnormal Pap or colposcopy in past 12 months, have a Pap smear at three months.

<ul style="list-style-type: none"> n If result is negative, repeat a pap smear every six months for one year. n If result shows inflammatory changes, treat dysplasia again and repeat a pap smear at three months. n If result is abnormal, one of three conditions exist: atypical cells of undetermined significance (ASCUS); mild dysplasia; or moderate/severe dysplasia. Refer below for these conditions. 		
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Interleukin-2 (IL-2): A Path Toward Functional Eradication?

Recent research has demonstrated that antiviral drugs can be extremely effective in reducing or practically eliminating all evidence of HIV in the bloodstream and in actively replicating cells. However, careful study shows that HIV infection persists despite this.

In one study, which included people treated with Highly Active Anti-HIV Therapy (called HAART) very early after initial infection with HIV, virus capable of reproducing was found in every individual treated despite the fact their HIV levels were below the limit of detection with currently available tests. The apparent cause of this is the presence of a population of resting T-cells which are infected by HIV. While in their resting state, the cells provide a near perfect harbor for HIV. The immune system doesn't recognize them as infected cells because they aren't expressing virus or the surface markers that would indicate they are infected. The immune system

Despite this intensive unprecedented search for the virus, researchers were still unable to find replication competent virus in three of the five individuals.

can only detect the presence of HIV when a cell is actively producing new virus, which identifies the cell as infected. Similarly, anti-HIV drugs can play no role with resting cells for the same reason. Drugs can only interfere with the production of new virus or the infection of new cells by active virus. Therefore, they can't do anything when the virus is resting inactive inside a cell. These resting, or quiet cells, are believed to be the major reservoir of HIV infection.

These cells can persist indefinitely, and virus lurking within them can rekindle active HIV infection. When and if these cells become active, they can begin producing virus. This reservoir of resting cells is believed to be one of the major barriers to completely eliminating HIV from a person's body.

Researchers who are attempting to achieve eradication (e.g. the complete elimination) of HIV are now planning to test different methods of converting these resting T-cells into active cells. Once activated, these cells should be vulnerable to the immune system and to antiviral drugs, just like other

cells. Interleukin-2 (IL-2 or Proleukin[®]) stimulates resting cells, thus exposing both virus and cells to the effects of anti-HIV drugs as well as the immune response against HIV. Using IL-2 therapy may help to decrease or eliminate this hidden pool of virus.

In August, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID, the institute which funds the majority of AIDS research efforts worldwide), presented new findings from an exploratory study of IL-2 used in combination with potent anti-HIV therapies.

At the International AIDS Conference in Geneva, Dr. Fauci and his colleagues raised the question of whether people treated with HAART plus IL-2 are any different from those treated with HAART alone. Specifically, they wondered whether IL-2-treated patients would have similar or different levels of the resting, infected T-cells compared to people on HAART alone.

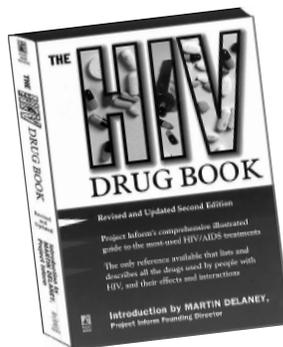
After Geneva, they conducted a study to answer this question. The study compared two groups. The first consisted of 13 people with viral load levels below the limit of detection for 6 months or more using a very sensitive test (limit of detection 50 HIV RNA copies per ml).

All were participating in NIH studies of HAART and IL-2. The second group recruited volunteers taking a HAART regimen for 6 months or longer and who had viral levels below the test's limit of detection. The two groups were very similar with regard to baseline CD4+ cell counts and viral load, length of prior therapy with HAART and other characteristics.

The research team then used sensitive tests to look for the presence of HIV DNA inside resting T-cells capable of reproducing (replication competent virus). Initially, they looked at about 10 million cells per individual. This has been sufficient in other studies to find infected cells and replication competent virus in virtually all HIV-infected people. Replication competent virus was readily found in resting cells in all 13 people who received HAART alone. In six people who had received HAART in combination with IL-2, however, the researchers could not detect replication competent HIV or latently infected cells.

Five of the six individuals who had been receiving the IL-2-containing regimen and had no detectable replication competent virus were studied further. Even more sensitive tests were run by searching through greater numbers of cells, more than 300 million cells from each person. Despite this intensive unprecedented search for the virus, researchers were still unable to find replication competent virus in three of the five individuals. To make sure this wasn't a temporary phenomenon and recheck their accuracy, the tests were repeated several weeks later in all six patients. The results were nearly identical, except this time the researchers searched even further, through more than 400 million cells, without finding HIV in the

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same three people.

Although virus was not found when looking at more than 300 million cells, it does not necessarily mean that virus has been completely eliminated from these people. To make such a claim, Fauci said one would technically have to examine every cell in the body, and no one is likely to ever do that. An even more intensive search is underway now looking for virus in

Thus far, lab studies suggest that CD4+ cells increased as a result of IL-2 therapy appear just as normal and useful as cells generated after successful HAART therapy.

deeper immune compartments, such as the lymph tissue. The next step, underway now, is to sample lymph tissue from the rectal mucosa and to examine spinal fluid.

The relevance of these observations might only be understood when or if these few people choose to stop their anti-HIV therapy. If there are still extremely small amounts of virus somewhere in the body, stopping HAART might allow the virus to re-establish itself and rekindle the fires of HIV disease. The real question is not whether HIV is completely eradicated, but whether there is enough of it still present to rekindle an active state of infection.

There is already some indication that full eradication is not necessary to prevent recurrence of active infection. For example, more than 10 patients in the US and Europe are currently being studied who have already gone off therapy on their own choosing. Whenever researchers have looked, these patients have measurable levels of replication competent virus—unlike those in Fauci's new study. Yet these 10 people have been off of all anti-HIV therapy from 3 to 18 months without experiencing a return of measurable viral load. Fauci's patients would seem to have at least as good a chance as these people of successfully stopping therapy.

Preliminary results from this study are extremely encouraging and go beyond any data reported elsewhere. Still, another larger study needs to be designed quickly to confirm the findings. While in laboratory studies IL-2 appears to stimulate HIV replication, it may be that when used with anti-HIV therapy, IL-2 may help flush the reservoir. That in turn may expose virus to the effects of anti-HIV therapy as well as the immune response against the virus and then ultimately assist in more greatly decreasing the amount of HIV in the body.

IL-2 studies in people with HIV show that the therapy has the most profound and dramatic impact on CD4+ cell count than any therapy in the history of AIDS research. Numerous studies have confirmed the ability of IL-2 to effect pronounced CD4+ cell increases over and above what is realized with anti-HIV therapy alone. Thus far, lab studies suggest that CD4+ cells increased as a result of IL-2 therapy appear just as normal and useful as cells generated after successful HAART therapy.

It remains unclear if these increases will contribute to decreases in the risk of developing HIV-related infections or prolonged survival, though there seems to be no reason to expect otherwise. A study to answer this question is being planned and will hopefully begin to enroll early next year. A component of the trial, being conducted through a community based clinical trial network (CPCRA), is currently opening in sites throughout the US. For more information about trial sites, call 1-800-TRIALS-A and ask for CPCRA IL-2 study sites in your area.

Personal Decisions About IL-2 Therapy

While the growing bulk of results from IL-2 studies are increasingly encouraging, those contemplating becoming involved in an IL-2 study should be aware the therapy can be hard on patients. The most common side effect associated with

IL-2 is mild to severe flu-like symptoms. Nearly everyone using IL-2 can expect to experience this side effect during the time therapy is taken (e.g. the 5-day course of IL-2).

IL-2 therapy is not taken every day. It is cycled and taken for 5 days in a row, every 8 weeks. Therapy is delivered through injection directly under the skin (subcutaneous). Time between cycles may be extended in IL-2 recipients who realize pronounced and prolonged CD4+ cell increases.

In a recent report on the long-term follow up of people in a NIAID study of IL-2, the average duration between cycles to maintain CD4+ cell counts at about 1,200 was 1 year. However, the individuals in this study had very high CD4+ cell counts (about 600) to start. This kind of immediate response is not expected among people who initiate IL-2 with lower CD4+ cell counts, where increases may take longer to realize. Sustaining those increases may require continued and frequent dosing.

For more information on IL-2, call Project Inform's National HIV/AIDS Treatment Hotline and request the *IL-2 Fact Sheet*. ■

HIV/AIDS Resource Notes

National Trials Hotline. The AIDS Clinical Trials Information Service provides information on federally sponsored studies (and many others) open to enrollment nationally. Call 1-800-TRIALS-A (1-800-874-2572). 800-AIDS-012 TTY/TTD serves the deaf and hearing impaired. The service also provides free copies of the AmFAR Treatment Directory, which also lists studies conducted by private industry.

National AIDS Hotline. This Hotline operates 24 hours a day and provides referrals to local services throughout the U.S. and information about a wide variety of non-treatment related topics. Call 1-800-342-AIDS (2437). Spanish-speaking operators are available 8AM – 2AM EST at 1-800-344-SIDA (7432). For the deaf and hearing impaired, call 10AM – 10PM EST at 1-800-AIDS-TTY (243-7889).

STEP Perspective is a newsletter produced by the Seattle Treatment Education Project. Call 1-800-869-STEP for information on their publications.

WORLD is a newsletter for, by and about women facing HIV disease. WORLD strives to break the isolation of HIV+ women by providing a forum for communication and information of interest to women. For more information call 1-510-986-0340.

AIDS Treatment News (San Francisco)
1-800-873-2812

Treatment Issues (Gay Men's Health Crisis, New York)
1-212-337-1950

Medicaid Expansion Update

Health care reform has re-emerged as a serious issue in Washington, DC. The spread of managed care has brought with it a multitude of horror stories about denial of medically necessary services, difficulty seeing the doctor you choose and getting the medicine and diagnostic tests you need. Even among those who have not experienced denial of care, the fear of one day being faced with it is high.

Before the current impeachment debate, Washington was rushing to embrace the consumer concern over regulation of managed care that, according to a recent TIME/CNN poll, ranks third on the public's priority list for Congressional action. Patient protection bills, which would ensure a broad array of rights to individuals covered under managed care, were introduced in both houses of Congress. President Clinton vowed to pass legislation that would protect the more than 150 million Americans in managed care. Although it is unlikely anything will move before the next session of Congress, managed care reform will hopefully be taken up again in January 1999. There is no question the outcome of these health care reform measures will be important for people living with HIV/AIDS. They should be monitored and fought for at the federal level.

While discussion of health care reform in DC is an important first step in addressing *insured* patient rights, it does absolutely nothing to help people without insurance. The number of uninsured Americans is over 43 million and lack of health care among this growing group is not being addressed in the current debate. Perhaps the most vulnerable are the uninsured living with chronic or life-threatening illness. One nationwide study showed that approximately 30% of HIV-positive people are uninsured and this is likely to increase in coming years. Another significant group of individuals is the underinsured, – people who only get a portion of the care they need (e.g. health care visits, but not prescription drugs) covered by third-party payers. Many, if not most, uninsured and underinsured Americans who are working but do not receive benefits from their employer and can't afford to purchase them.

In an attempt to begin to address this gap for people living with HIV, there are various proposals to expand Medicaid to include low-income people living with HIV. Medicaid is a joint federal and state safety net health care delivery program designed for low income individuals. However, to get Medicaid, people living with HIV have to qualify both by income and through the Social

Security definition of disability. Social Security uses the Centers for Disease Control and Prevention's definition of AIDS along with evidence of functional impairment as proof of disability. In other words, under the current system, an HIV-positive person who can't afford health care insurance has to get sick before he or she can access the health care that might have prevented sickness in the first place.

This is obviously bad health policy and it ends up costing more money for the health care system. It is more expensive to treat someone with a serious illness than it is to try to prevent it. This public health strategy is particularly devastating given that new HIV infections are rising among groups that have been traditionally underserved. Women, youth, people of color, low income individuals and injection drug users have significantly less access to comprehensive health care. Many people newly infected with HIV will eventually be eligible for Medicaid but only after they get sick enough to meet the disability requirements. If proposed reforms moved

One nationwide study showed that approximately 30% of HIV-positive people are uninsured and this is likely to increase in coming years.

forward, broadening eligibility for Medicaid to all low-income people with HIV, regardless of health status, everyone would benefit.

As research and discussion continues on the optimal treatment for HIV, one fact of medical care remains constant: the sooner an HIV-positive person knows his or her status and seeks quality medical care, the better the expected outcome. Regardless of whether an individual chooses to start therapy, monitoring the disease and establishing a strong patient/provider relationship is essential. People without comprehensive and supportive medical care have much less chance of benefiting from the full promise

of HIV treatments. Programs have been established in an attempt to fill gaps in care for people with HIV, however, they remain a patchwork of services that are more comprehensive in some areas, less in others and often times underfunded.

The History

The original proposal to expand Medicaid to people living with HIV was put forward in 1997 by community advocates. Driven by the availability of more effective treatments, advocates believed that, in addition to being a humane thing to do, earlier treatment would reduce costs of treating opportunistic infections and hospital care. Therefore, it would be possible to serve more people.

Medicaid expansion at the federal level would ensure states provided more equal benefits to people living with HIV. Because Medicaid is a joint federal/state program, each state would have the opportunity to create its own program but it would have to be based, at a minimum, on federal criteria for eligibility and benefits.

Vice President Gore endorsed the Medicaid expansion proposal early in 1997 as a humane and cost effective way to deliver more effective HIV treatments to low income people. Gore requested a study to assess the possibility of expanding Medicaid. Although it is not law, it has been the Clinton administration policy that changes to Medicaid programs must be "budget neutral," meaning they can't cost the federal government additional money.

In late November of 1997, the Health Care Financing Administration (HCFA) presented cost estimates that showed significant overall increases in the cost for Medicaid expansion. Many advocates felt that the numbers presented were too high. Others felt that trying to prove cost neutrality within the Medicaid program in the prescribed time wasn't a reasonable way to determine if expansion was feasible and cost effective. If cost was to be a primary factor, advocates felt there are potential savings outside of the Medicaid system that could be included in the analysis. These might include savings on disability benefits, reductions in other government safety net programs, and taxes on the wages of those who are able to continue working because of maintained good health. The Clinton administration, however, appeared to be backing away from the proposal even before the cost figures were released. The discussion of expansion at the federal level slowed despite advocates' best efforts.

State Expansion

Several states, however, began exploring the possibility of expansion. A state can implement a Medicaid expansion at any time as long as it meets federal requirements, including cost

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neutrality and approval by HCFA. Maine, Massachusetts, Florida, Wisconsin, Colorado and now Texas are all exploring this possibility. Maine and Massachusetts are probably the furthest along in the process, with Maine expecting to submit a plan by the end of 1998. By all accounts, HCFA appears to be receptive to state efforts.

There are a number of factors states must consider in developing expansion programs:

Eligibility: States make the decision as to who will be eligible for the program. Medicaid generally has several criteria for eligibility, including income, assets and sometimes health status. Income eligibility is important because even people making above \$20,000 annually may find themselves impoverished by medical expenses associated with HIV disease. Additionally, income level is one determinate of how many people will qualify and, therefore, an important consideration in overall program cost. Medicaid normally requires that people have less than about \$2,000 in assets to qualify, excluding a home and car. Asset requirements will be an important point to consider if one of the objectives of expanding Medicaid is an attempt to keep people working and self-sufficient. People should be able to accumulate more than \$2,000 in assets and still qualify for services. States may also want to look at medical criteria that would be in accordance with federal guidelines for HIV disease care, such as CD4+ counts of 500 or less or elevated viral load. However, medical criteria for determining eligibility for Medicaid may not be in the best interest of the patients because standards of care can change fairly quickly, causing the need for an official change in eligibility or inappropriate exclusion of certain individuals.

Benefits: The scope of benefits the plan will offer is another point of consideration. Maine is looking at a limited benefit through its plan, including primary care and medications. Massachusetts is considering a broader, more standard Medicaid plan. A standard plan is comprised of a range of services, including mental health benefits, home health care, etc.

Service Delivery: Medicaid services are delivered through a mix of managed care and traditional fee for service models. The role of managed care in any Medicaid expansion proposal needs to be thought through carefully. Managed care may have benefits and drawbacks as well as different cost structures. For further information on managed care and people with HIV, call the PI hotline for the managed care discussion paper.

Community Input: Every state currently planning an expansion program stressed the

importance of constructive community involvement. Community advocates and potential consumers are able to bring real life experience to the planning process. Planning for a Medicaid expansion is a collaborative process and is probably best approached by working with rather than against Medicaid and other state departments that will have the responsibility of implementing the program.

Legislative Requirements: In addition to the development of the plan and the waiver (documentation outlining the plan that must be submitted to HCFA for any Medicaid expansion), states may need to request legislative authority to submit and/or implement the waiver. For example, in Colorado, a waiver proposal must go through the legislature, an action made more complex as Colorado has instituted term limits. Newly elected legislators may have less familiarity with HIV/AIDS issues.

Costs: Perhaps the biggest hurdle for Med-

A state can implement a Medicaid expansion at any time as long as it meets federal requirements, including cost neutrality and approval by HCFA.

icaid expansion is proving cost neutrality. The obvious benefits of providing health care and treatment to low-income HIV-positive individuals should be enough to move the proposal. However, it seems unlikely, given the Clinton administration's commitment to balancing the budget, that proposals which can't prove neutrality within five years will be seriously considered. Encouraging law makers to consider the cost savings impact on other state and federal programs may be key to leveling the debate around cost impact of Medicaid expansion.

This doesn't appear to be an impossible task. There are significant cost effectiveness data, much of which appeared at the International Conference on AIDS in Geneva this year. Reductions in care costs associated with highly active antiretroviral therapy (HAART) were reported in the areas of hospital stays, diagnostic costs for opportunistic infections, treatment for opportunistic infections and skilled home nursing care. Even when increased drug costs were added, there were overall reductions in the cost of HIV care.

The question that needs to be addressed for Medicaid expansion is how the reduction in the cost of care relates to the cost of serving increased numbers of people. A study authored by James

G. Kahn and B. Haile at University of California San Francisco and S.W. Chang at Kaiser Family Foundation found that the expansion of the US Medicaid system could not only significantly delay thousands of deaths and AIDS diagnoses but is also affordable. It relied on reduced costs

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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 anti-viral treatment.**
-  If viral measures do not decline below the limit of detection, **consider a more aggressive antiviral 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 antiviral regimen** if not already on one and **learn about preventive treatments** against other opportunistic infections. **Learn about drug interactions.**
-  If you have begun preventative therapies and your CD4+ count rises as a result of antiviral therapy, **remain on any preventative treatments you have started for at least six months.**
-  If CD4+ count stays below 75, **intensify monitoring**, consider prevention against MAC/MAI and CMV infections. **Learn about preventive therapies.**

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not only in Medicaid but in other programs as well, including ADAP (AIDS Drug Assistance Program), Supplemental Security Income (SSI) and Social Security Disability Insurance (SSDI). It also relies on a small reduction in HIV drug prices to the Medicaid system. The study concluded that over a five year period there would be 11,400 fewer AIDS diagnoses and 4,200 fewer deaths if Medicaid was expanded nationwide. Moreover, another project—the Treatment Access Expansion Project—is looking at creating an interactive software program that would allow a cost/ benefit analysis of Medicaid expansion across several social service programs and is working on attaching a cost to productive years lost if expansion were not to happen. These efforts bode well for helping to justify Medicaid expansion at the federal and state level.

Next Steps

Although the action on Medicaid expansion from the Clinton administration has been disappointing, there is some continued federal effort. Rep. Nancy Pelosi gathered 68 signatures from members of the House of Representatives on a *Dear Colleague Letter* (a Congressional member's sign-on letter) asking Donna Shalala, Secretary of Health and Human Services, to reconsider Medicaid expansion, given the new cost efficacy data. Representative Pelosi and others worked

to include directions in the federal 1999 budget that encourage HCFA to provide technical assistance and evaluation to states developing expansion plans. Additionally 7 signers of the *Dear Colleague Letter* also wrote to President Clinton asking him to expand Medicaid for low income people living with HIV and at a minimum to include it in his budget request for Fiscal Year (FY) 2000. Moreover, the Supreme Court recently ruled that a woman living with HIV disease was covered under the Americans with Disabilities Act (ADA)—legislation prohibiting discrimination against people with disabilities. Many hope the ruling will lend even more weight to proposals ensuring medical coverage to low income people with HIV.

Meanwhile, some states continue to move forward. Many of those states are working with the Kaiser Family Foundation to develop appropriate cost modeling, share information and receive assistance on their waiver process. Other states, including California, have begun feasibility discussions.

Although there are hurdles ahead for Medicaid expansion, now is the time to move forward. Developing mechanisms for people to access comprehensive care should improve the general health of people living with HIV, create opportunities for education regarding prevention of HIV disease and decrease overall rates of progression to an AIDS diagnosis. It

may also decrease the number of lives lost to HIV disease. Moreover, it should decrease costs to other government programs. It may allow people with HIV disease to continue working for longer periods of time, contribute to overall productivity of the nation and ultimately the tax base. Medicaid expansion for people with HIV could also be an important model for filling a gap in US health care coverage for, at a bare minimum, all those who are most vulnerable to health care problems. ■

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