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PI Perspective

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Yokohama and Beyond

The Xth International Conference on AIDS, held this year in Yokohama, Japan, has come and gone. No great breakthroughs were announced and once again much of the media coverage would lead one to believe that nothing of value happened in AIDS research during the last year. This is not the case, as there are many examples of important progress, some of which offer the hope of making major improvements in medical care for people with HIV. Overall, perhaps the most striking aspect of this year's meeting concerns the inexorable spread of the disease worldwide, further emphasizing the critical need for research solutions:

- Three million new people were infected with HIV last year, bringing the world total, by conservative estimates, to 17 million.
- The rate of HIV infection has risen tenfold in Thailand since 1990 and increased threefold in India in the same time period.
- In the northern provinces of Thailand, 20% of young men are infected.
- In Thailand overall, 4% of all the young men reporting for military service are HIV infected, as are at least 1.5% of pregnant women who come to natal clinics.
- More than ten million people are infected in sub-Saharan Africa, with the infection striking women more often than men.
- Approximately two million people are infected in Latin America and the Caribbean.
- At least one million cases of HIV infection have occurred in North America and another half million in the other major industrialized nations.
- An estimated four million men, women, and children have progressed to an AIDS diagnosis since the start of the epidemic.

Despite a modest decline in the rate of new infections in gay and bisexual men from industrialized nations, there is growing evidence of increasing infection rates among a new generation of younger men. Additionally, prevention workers from around the world reported evidence that community commitments to safer sex were showing evidence of breaking down as the epidemic continues unabated. In short, anyone who tells you that AIDS is slowing down or is not a big issue anymore is simply misinformed.

One issue which received long overdue attention at this year's conference was the impact of the epidemic on women. Women have long carried more than 50% of the burden and suffering of the epidemic, yet have been poorly acknowledged and represented. In contrast, women's issues and the presence of women living with HIV were strongly felt throughout the meeting. Many attendees noted how the social issues facing women around HIV infection were the same regardless of the country of origin. For women, even North America is in many ways a third world country. One disappointment, however, was that the new emphasis on women's issues was somewhat limited to social concerns: women as targets of infection, women as caregivers, women as mothers. Sadly, there was little new information about the medical needs of women and the failure of health care systems world-wide to address them.

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The conference sessions were weak in general on the needs of gay and bisexual people, perhaps reflecting an Asian consciousness which is not yet comfortable with the concept of sexual preference.

Also disappointing and somewhat surprising, was the lack of attention given to nutritional issues, alternative therapies and non-western systems of medicine. Considering the location of the conference and the perceived openness to these issues in Asia, many attendees expected to see special emphases in these areas. If anything, they received less attention than in recent years.

Research Advances

This issue of PI Perspective is dedicated to describing the advances made or underway which might help brighten the future for the many millions infected. Several improvements in diagnostic measures, antiviral therapy, and our knowledge of HIV pathogenesis and the immune system are poised to improve the odds for many people fighting for their lives.

Key issues from Yokohama discussed elsewhere in this issue include...

- Quantitative virology - the impending availability of new tests to measure the level of viral activity
- Update on antiviral therapy research: non-nucleosides, combination therapies, protease inhibitors, novel therapies and more
- Viral resistance and the implications for therapy
- Human growth hormone - a solution to wasting syndrome?
- Immune-based therapy update
- Advances in the treatment and prevention of opportunistic infections

Late-breaking news, post-Yokohama, includes...

- A report on the first study demonstrating an effective oral drug for preventing CMV disease.
- An update of data from the first phase II study of the protease inhibitor.
- An update on a potential new treatment for Kaposi's Sarcoma, HCG.

Finally, addressing a current hot potato in AIDS activist circles, Project Inform presents a position paper reinforcing our continued support for accelerated drug approval, as well proposing an innovative new approach to clinical research.

Antiviral Update

by Ben Cheng

Protease Inhibitors

Merck Protease, L-735-524: Additional data from early studies of the Merck protease inhibitor show clear antiviral activity. A total of 22 volunteers, all p24 antigen positive (a marker indicating active viral replication), participated in this phase I study. The first phase of the study used a dose of 400 mg four times a day for 12 days. Despite the short duration of treatment, there was a median 77 CD4+ cell increase and a 70% decline in p24 antigen levels. Four participants with between 16-90 CD4+ cells participated in a second phase of the study, which is still ongoing. They took a dose of 600 mg four times a day, which was then decreased to 400 mg four times a day because of a reversible increase in bilirubin in one patient (which can cause drug-induced hepatitis). There was a substantial decrease in both p24 antigen and HIV RNA as measured by Q-PCR, which have remained at or near undetectable levels. CD4+ cells increased substantially, with a median increase of 56 cells after 2 weeks and 136 cells after 16 weeks. As reported in the February *PI Briefing Paper*, some of these people had even more striking CD4+ cell increases. A third phase studying a dose of 600 mg three times a day is continuing. Other studies of this protease inhibitor include combinations with AZT and AZT plus ddI. Studies involving more than 1000 patients are planned.

Saquinavir: Results from a study of the Roche protease inhibitor, saquinavir (formerly Ro 31-8959), used in combination with nucleoside analogues have been released. The AIDS Clinical Trials Group study (ACTG 229) compared AZT+ddC+saquinavir to AZT+ saquinavir to AZT+ddC in people with 50-300 CD4+ cells, who had at least 4 months prior AZT therapy. The doses used were 600 mg of saquinavir three times daily, 0.75 mg of ddC three times a day, and 200 mg of AZT three times a day. The study enrolled 302 people. People receiving the triple-drug regimen had the greatest CD4+ cell benefit, showing an average increase of about 50 cells. Volunteers on both two-drug combination regimens had CD4+ cell count benefit, but the responses were not as robust as the triple-drug regimen, averaging about 25 cells over the 24 week study. Similarly, people on the triple-drug combination had a greater decrease in viral load compared to those on either of the 2-drug combinations, as measured by Q-PCR. Surprisingly, people who received AZT+saquinavir did not show as great a viral load decrease as those who received AZT+ddC. There were no differences in the number of reported toxicities between people who received the triple-drug combination and those who received the two-drug combinations. Large phase III studies are now ongoing. As we go to press, Roche has added a triple-drug combination therapy arm to its large phase III study.

Hope for A New "Nuke"

Preliminary data show that high doses of BW935U83 modestly increase CD4+ cell counts and decrease p24 antigen levels, as measured by the acid-dissociated p24 test. BW935U83 is a new *nucleoside analog* similar to AZT, ddI, ddC and d4T in that it inhibits the viral enzyme *reverse transcriptase*, an enzyme essential for viral replication. A twelve-week course of treatment was given to 40 volunteers with CD4+ cell counts between 200-500. Volunteers received either 100 mg, 200 mg, 300 mg, or 500 mg orally three times a day. This study is still ongoing and the drug seems to be well tolerated at the 200 mg three times a day dose. The major side effect noted so far has been headaches.

Antisense... A Novel Antiviral Approach

Preliminary results from a dose escalating study of single intravenous (IV) and subcutaneous (SC) doses of the antisense compound GEM 91 have been released (GEM = Gene Expression Modulator). Twenty-four asymptomatic volunteers participated in this French study. Four doses of GEM 91 were studied: 0.1, 0.3, 0.5, and 1.0 mg/kg (the 1.0 mg/kg dose was only administered intravenously). At the three lower doses, six volunteers received either the single IV or SC dose and 14 days later received the drug administered by the other method. The study found

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that levels of the drug in blood after SC administration were highly variable and thus SC may not be a viable way to administer this drug. Mass at the SC injection site and headaches were the major side effects. Multiple intravenous dose studies are now ongoing at the University of Alabama at Birmingham and at Cornell in New York. *In late-breaking news, information was presented at a conference in Paris reporting that an oral compound equivalent to GEM 91 is about to begin pre-clinical testing. The oral drug could begin human testing by the end of 1995.*

Hydroxyurea

Hydroxyurea is an FDA approved therapy for the treatment of leukemia and inoperable ovarian cancer, which has also shown activity against HIV in test tube experiments and powerful synergy with some existing therapies. The compound inhibits cellular factors necessary for viral replication. In contrast, all currently approved antivirals, including AZT, ddI, ddC and d4T slow viral replication by acting directly against HIV, though this quickly leads to development of resistant strains of virus. Attacking the cellular target instead offers hope of avoiding viral resistance. Anecdotal experience with the drug in the community suggests that toxicities are minimal and controllable, with the most common side effect being reversible bone marrow suppression. More serious side effects may occur, and people interested in trying hydroxyurea should consult with a physician and consider potential drug interactions. The dose being used in the community is 1000 mg daily. Though no US clinical studies of hydroxyurea have yet begun, a preliminary study of a related compound, used in combination with ddI, is underway in France. Thus far no data are available from human studies.

ALERT - Acyclovir Prolongs Survival

Several studies have shown that acyclovir use prolongs survival. Most of these studies compared high dose acyclovir (800 mg four times a day) to placebo for the prevention of cytomegalovirus (CMV), additionally everybody received AZT. As these were CMV prophylaxis studies, most of the participants had a previous opportunistic infection, ARC, or fewer than 150 CD4+ cells. It appears that while acyclovir was not able to prevent CMV, people taking the drug lived longer than people taking the placebo. There were no significant differences in CD4+ cell response or rate of AIDS-defining complications between the two groups. As expected, there were significantly fewer cases of herpes infections in the group who received acyclovir.

A retrospective analysis of a MACS (Multicenter AIDS Cohort Study) which involved 786 people with HIV who were taking AZT, also showed a survival benefit for people concurrently taking acyclovir. In the MACS, 488 people took acyclovir for medical reasons other than HIV (such as herpes or zoster) and 242 people took acyclovir specifically for HIV infection (the median dose of acyclovir was between 600-800 mg per day). This study found that use of acyclovir had no effect on preventing CMV or disease progression but there was a 26% decrease in the risk of death. For people who took acyclovir specifically for HIV infection, there was a 36% decrease in the risk of death, but again there was no effect on disease progression. This translates into an increased survival of about one year. There was no difference in survival between higher doses and lower doses of acyclovir. It is still unclear why acyclovir is able to promote a survival benefit, although many researchers believe that the herpes family of viruses may be "co-factors" in HIV disease. An important study being conducted through the ACTG may be able to shed light on the mechanism by which acyclovir is able to prolong survival.

Advances in Technology: Monitoring Health and HIV

by Ben Cheng

A surrogate marker is a lab value or other measurement which serves as a substitute for clinical disease progression. When such markers are available, it is easier to quickly know whether a therapy is working, because researchers need only look for changes in the marker, rather than wait for people to suffer disease progression or death. The need for better surrogate markers has become a high priority since the predictive value of small changes in averaged CD4+ counts in studies has become questionable. New technology, recently approved by the FDA, may improve the quality of CD4+ measurements. But in n the meantime, new methods of measuring the output of HIV RNA (genetic material) from cells into blood plasma (viremia) are increasingly being touted as the next important surrogate marker.

Quantitative polymerase chain reaction (**Q-PCR** - being developed by Roche Molecular Systems) and **branched-chain DNA** (**bDNA** - being developed by Chiron Corporation) are two tests being used in clinical trials to measure viremia and to determine whether there is a correlation between viremia and disease progression.

HIV RNA tests may quickly tell researchers, physicians and patients whether or not a drug is effective in suppressing viral activity and when its effectiveness begins to wane. Having this information may make the use and choice of antiretroviral therapies a far more rational process than it has been in the past. These tests may also help us better understand the relationship between HIV and the immune system. By using these tests, we will be able to measure the effect of cytotoxic T lymphocytes (CTLs) and neutralizing antibodies on the virus. Sensitive assays will further allow us to examine if mutations in HIV cause the virus to have different levels of virulence. Additionally, these tests may help us understand why some people progress to AIDS rapidly while others remain long term non-progressors.

The Q-PCR technique is the more sensitive of the two tests because it is able to detect very low levels of viremia. The bDNA test has a lower sensitivity, yet it's believed to be more accurate in quantifying high levels of viremia. It is expected that Q-PCR will be able to detect viremia in more than 90% of people with CD4+ cell counts above 500. In contrast, bDNA is sensitive in detecting viremia in people with fewer than 400 CD4+ cells and very sensitive in people with fewer than 300 CD4+ cells. In short, Q-PCR may be more useful in early disease, bDNA more useful in late stage disease and either may be sufficient in middle stage disease. Both tests can have a degree of error as great as 20%; therefore, small changes in test results may not be meaningful.

An analysis of samples from a study comparing AZT and ddI (ACTG 116B/117) shows that viral RNA is indeed a good marker for predicting disease progression. Viral RNA was measured in a subset of study participants taking AZT for at least 4 months (median 13 months), who then either continued on AZT or switched to ddI. Viremia decreased significantly for people who switched to ddI (about a 50% drop after 1 month on ddI) but increased for people who remained on AZT. The changes in viremia correlated with clinical outcome even when other factors such as CD4+ cell counts, disease stage (AIDS or asymptomatic) and virus type were taken into account. This decrease in viral RNA levels resulted in a 32% reduction in disease progression. This analysis also showed that people who entered the study with the highest viremia had the highest risk of disease progression. Several retrospective analyses of smaller studies have also shown similar correlation between viremia and disease progression.

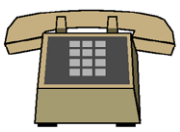
A more precise measurement of viremia under study is called quantitative competitive PCR (QC-PCR). This approach is similar to Q-PCR but may be an even more sensitive and less error-prone test than Q-PCR or bDNA, one which can detect and quantify HIV RNA in virtually all HIV-infected people. QC-PCR has also shown good correlation between increase in viral burden and clinical stage of disease. So far, however, this is a very difficult and expensive test to perform and only a few laboratories in the country have the test available. Some scientists question if the improved accuracy and sensitivity are worth the extra cost and difficulty, though few question that it is the most accurate way to measure HIV RNA.

One of the most exciting potential uses of these tests is to monitor for response to antiretroviral therapy. Viral RNA has been shown to drop in response to various types of antiretroviral strategies, whether it is starting, switching, or adding an antiretroviral therapy. Increasing viremia may also be a predictor of the development of resistance to antiretroviral therapy (although some researchers believe that viral RNA increases *after* resistance to an antiretroviral has developed). Researchers hope that changes in viral RNA may give an earlier warning of impending drug failure, a signal that can be read before a patient suffers serious CD4+ decline, clinical disease progression or death. Although the point is unproven, many researchers suspect that some levels of viremia are sufficiently low as to make disease progression all but impossible. If so, knowing such a threshold may provide a better way of knowing when to start therapy, as compared to current practice, which assigns treatment based simply on crude baseline CD4+ levels.

These tests have not yet been approved by the Food and Drug Administration. They are available to both physicians and patients officially only as an "experimental" procedure. However, the old

p24 antigen test existed for many years with similar status yet still was widely used and available. Both Q-PCR and bDNA cost around $200 per test and are not necessarily reimbursable through insurance. Over time, these costs are likely to decrease as the tests come into common use, and as they are packaged for easier local use. To order the Q-PCR test, physicians can call Roche Biomedical Laboratories at (800) 533-0557. To order the bDNA test, physicians can call the Nichols Institute at (800) 553-5445.

As these tests will most likely be used on blood plasma samples, it will be important to determine whether they accurately reflect the viral activity in other parts of the body that harbor HIV, especially the lymph nodes. Additionally, it is important to determine how great an increase in viremia warrants changes in treatment strategy. If this proves correct, it may be possible to make rational, individualized treatment decisions based on routine tests for viral RNA. For now, the absolute correlation between reduced viremia and improved clinical and survival outcome has yet to be conclusively determined. It is possible that the best predictor of disease progression may not be any single test, but a combination of tests, including both CD4+ and viral RNA. Prospective studies need to be conducted to fully validate changes in viremia as a predictive surrogate marker for HIV disease. PCR and bDNA technology are also being explored for other diseases such as hepatitis B and C, herpes, *cytomegalovirus* (CMV), tuberculosis, and *mycobacterium avium complex* (MAC) among others.



Nutrition and Wasting

by Brenda Lein

Weight loss and malnutrition are common problems associated with HIV. Weight loss can begin and become severe anywhere across the spectrum of CD4+ counts. Wasting is defined as an unexplained loss of 10% or more of normal lean body mass. There are people who report wasting despite a very high level of CD4+ cells, but the risk of wasting and serious malnutrition increases dramatically when CD4+ cell counts fall below 100. The body's ability to absorb nutrients and maintain lean body mass is associated with general good health and the ability to fight disease.

There are many approaches to managing nutrition and wasting. A comprehensive treatment strategy for managing HIV/AIDS should include a component on nutrition, and weight should be monitored with the same watchful eye as CD4+ counts and other laboratory parameters. Early intervention in weight loss is critical. Specialists note that the difference between successful treatment of an opportunistic infection and treatment failure can often depend on a few pounds of weight.

There are many options for prevention and treatment of weight loss and different approaches may be needed across the spectrum of disease. Someone who is healthy with no overt signs of weight loss will probably develop a very different kind of nutritional strategy than someone experiencing significant weight loss. Similarly, weight loss due to gastrointestinal distress, diarrhea, or other HIV-related conditions may require different interventions than weight loss that is due to chemotherapy or drug interactions. Finding a nutrition and weight stabilization program that adapts to both lifestyle and nutritional needs is critical for success. The following are a few points to consider:

+ *Evaluate nutrition and exercise as part of a comprehensive, early intervention treatment strategy for HIV.*
+ *Follow reasonable guidelines for "safer" food preparation.*
+ *Employ rigorous diagnosis and appropriate treatment for causes of weight loss.*
+ *When necessary, consider using nutritional and vitamin supplements to replenish deficiencies.*
+ *Learn the pros and cons of various intervention options.*

Evaluate Nutrition and Exercise as Part of a Comprehensive, Early Intervention Strategy for HIV.

The importance of nutrition and maintaining lean body mass cannot be overstated. Good nutrition, combined with exercise, not only relieves stress, which is proven to be immune suppressive, but also provides a solid foundation to optimize the potential benefits of HIV therapeutic regimens.

Most physicians and people living with HIV do not recognize early signs of weight loss. Careful monitoring of weight, periodic laboratory evaluations looking for vitamin and hormone deficiencies and an aggressive nutritional and exercise program can help prevent wasting and malnutrition. While complex solutions like total parenteral nutrition (TPN) can sometimes correct severe wasting, the cost is often unacceptably high, both in dollars and risks of side effects or risks associated with treatment. Whenever possible, it is far better to take action to correct nutritional problems before they become severe. This may mean intervening with improved diet, appetite stimulants or weight gain supplements before weight loss becomes unmanageable. A nutritional handout is available through the Project Inform Hotline. This handout includes dietary and alternative interventions for dealing with symptoms associated with HIV and HIV-related conditions such as diarrhea, candidiasis, hair loss, peripheral neuropathy, skin problems and appetite loss.

Like any basic program, your strategy for coping with nutritional and exercise needs should be reevaluated periodically, adapting strategies to your body's

changing needs. Two people at the same stage of wasting may use completely different approaches depending on their willingness to exercise and work at a nutritional program. Someone willing to follow a workout regimen and careful diet may rebound from wasting by simply adopting better eating habits. Someone who is less inclined to invest in an exercise regimen and finds it more difficult to follow a careful dietary plan may require more invasive intervention, ranging from the use of appetite stimulants and supplements to total parenteral nutrition (TPN). Both individuals might successfully rebound from wasting, but each intervention regimen reflects individual lifestyle factors and choices. There are pros and cons to each option. Weigh the risks and benefits and develop a realistic plan to prevent or reverse wasting.

Many people who are experiencing weight loss feel frail and shy away from strenuous activity. People who are experiencing weight loss and malnutrition have a tendency to feel depressed, a condition linked to malnutrition. The feelings often get in the way of maintaining a regimen of good nutrition and exercise. This perpetuates a cycle. It's important to remember that even if you feel frail, you are not. Your body is much more resilient than you may feel!

Employ Rigorous Diagnosis and Treatment for Causes of Weight Loss.

HIV itself and many HIV-related conditions can cause weight loss, fatigue, loss of muscle mass and chronic diarrhea. The gastrointestinal tract is a major site of early HIV infection. It is also a prime site for many bacterial, viral, fungal, and parasitic infections which can independently contribute to weight loss once a damaged immune system permits such organisms to grow unchecked.

Some health professionals conduct repeated tests to identify the cause of diarrhea and weight loss. Others only treat symptoms and never attempt to identify the cause. It is important to do both. Aggressive diagnosis should be accompanied by aggressive treatment. Diagnosing and treating unexplained weight loss and diarrhea can be difficult as there are often multiple causes operating at the same time. An infectious agent, like a parasite, might be identified but treatment may only reduce and not resolve the problem. This might be because the parasite was "masking" another infection and additional diagnostic and treatment procedures may be required to deal with the underlying problem. Similarly, some instances of wasting are due to *malabsorption*, a condition in which damage to the tissue and cells lining the intestinal tract have lost the ability to properly transfer nutrients. Knowing when this is the case has a major impact on selecting the proper treatment. Finding the cause or causes of weight loss or diarrhea is always critical to finding the right solution. Treating the symptom, without understanding the underlying cause, can sometimes do more harm than good.

An article from *AIDS Treatment News* outlining the diagnosis and treatment of gastrointestinal manifestations of HIV is available through the hotline.

Consider Nutritional and Vitamin Supplements to Replenish Deficiencies.

Studies have shown that two phenomena are present at all stages in HIV disease, even when CD4+ counts are high and there are no apparent signs or symptoms of disease: (1) the virus is always actively replicating, and (2) there is some evidence of nutritional deficiency. Many people attempt to give the body an edge over the virus by complementing their diet with vitamins and other nutritional supplements. This may not only help correct minor nutritional deficiencies, but may also strengthen the body's natural immune defenses. Much research still needs to be done to fully document vitamin and nutritional deficiencies across the spectrum of HIV disease and the degree to which supplements correct these problems. Nonetheless, a reasonable level of vitamin and nutritional supplementation to replenish deficiencies just makes common sense. *GMHC's Treatment Issues* did a special edition on alternative medicine and vitamins which is available through the Project Inform hotline. This article gives an overview of research on vitamins, outlines potential side effects and lists foods which may be rich in certain vitamins.

Vitamin and nutritional supplements should not be used to replace food. Whenever possible, increasing vitamin intake through improved eating habits is preferable. For people on strict budgets, living on disability or other assistance programs, vitamins and other supplements are often too expensive. Some people spend hundreds of dollars per month on such products. This is probably unwarranted in most situations as there is little data to support the use of "mega" doses of vitamins and supplements in AIDS. Some states, such as New York, provide vitamins free through AIDS Drug Programs. Some counties have programs which help cover the cost of alternative

therapies and supplements. To find out if programs exist in your area, call your local health department.

Vitamin supplementation, like nutrition and exercise regimens, should be re-evaluated periodically. In the course of HIV-disease, there appears to be a decrease in the body's abilities to absorb nutrients and therefore incorporating amino acids and other enzymes which promote the digestion of food may be useful. In this instance, it is unclear whether taking ever-larger doses of supplements produces any added benefit. Some physicians who specialize in the use of vitamins and supplements recommend intravenous administration when absorption is a problem. This is not such a far-fetched idea, as conventional TPN formulas have always included vitamin supplements in the mix. Similarly, some hospitals include intravenous vitamin supplements when patients are restricted from oral food intake.

A "brown-bag medical checkup" is an important part of health monitoring. Each time you visit your health care provider, throw all the medications you take, intermittently and regularly, into a bag. Include vitamins, herbs, nutritional supplements and prescribed medications. Ask your doctor to have a pharmacist conduct a personalized review of your therapies for safety, appropriateness, compatibility and instructions for use. This will help avoid drug interactions and may help diagnose symptoms caused by drug side effects. Just because something is available over the counter or perceived as "alternative", does not mean it is nontoxic or safe to take with other therapies. Also, be sure to see the Project Inform *Drug Interaction Chart*, published in *PI Perspective* #14, or available from the hotline.

Learn the Pros and Cons of Various Intervention Options.

Like all other aspects of HIV/AIDS treatment, there is no free lunch when it comes to the intervention options for nutrition and wasting. There are a number of products and approaches which are helpful for many people, but no guaranteed solutions for every possible situation. Likewise, there is a fair amount of hype and misinformation about various approaches. Nutritional supplements and vitamins are often promoted aggressively, whether or not there are adequate data to support the claims made for them. There are varying degrees of effectiveness, and varying side effects. A good rule is to remember that what works for one person in one situation may not work for the next person. The best solution is to form your own opinions after collecting as much information as possible.

Weight gain supplements

Many weight gain and protein supplements are available through pharmacies and health food stores. These are not recommended as a sole source of nutrition. Protein supplements, such as those used by bodybuilders, are sometimes used by people living with HIV to prevent or help treat weight loss. It makes sense to look for products which are high in protein and low in sugars and fats. Some protein supplements claim to be better for metabolic weight gain, promoting the development of protein building. Weight gain protein drinks, including Ensure, Advera, Nutren and Resource are also commonly used by people with HIV. Advera has the lowest fat content and is highest in predigested protein. It is also the most costly. Ensure is less expensive, but higher in fat and sugars, containing both sucrose and corn syrup. Both Nutren and Resource are less expensive, but have high fat content. Again, these products should not replace solid food. Combining protein and weight gain supplements with exercise is critical for optimal success. Even if exercise is limited to stretching

exercises, anything that can help build lean body mass is important. If your diet is limited to liquid nutrition, incorporate fiber from bulking laxatives to help clear the colon and help control diarrhea.

Appetite Stimulants

In addition to adjusting eating habits and diet, some people find they need appetite stimulants in order to maintain weight and good nutrition.

Many people believe that marijuana may be useful to stimulate appetite and calm the stomach. Smoking marijuana can be hard on the lungs so some people prefer baking it into brownies or truffles. The chemical agent in marijuana, THC, has been synthesized and is the active agent in Marinol, which is FDA approved as an appetite stimulant for people with HIV. Absorption of Marinol is problematic. Sometimes it works perfectly, sometimes not at all and still other times it works a little too well, leaving folks too euphoric or "stoned" to carry on with planned activities. These appetite stimulants may not be appropriate for people in recovery from alcohol or substance abuse. Megace, a synthetic progesterone, has been shown in a number of studies to increase appetite and weight. A recent report in the September '94 *Annals of Internal Medicine* suggests that most, if not all, weight gain associated with Megace is in the form of body fat. These studies, however, show that people on Megace reported increases in weight and general well being. While side effects associated with Megace are rare, a few people in studies reported blood clotting and breast enlargement in males.

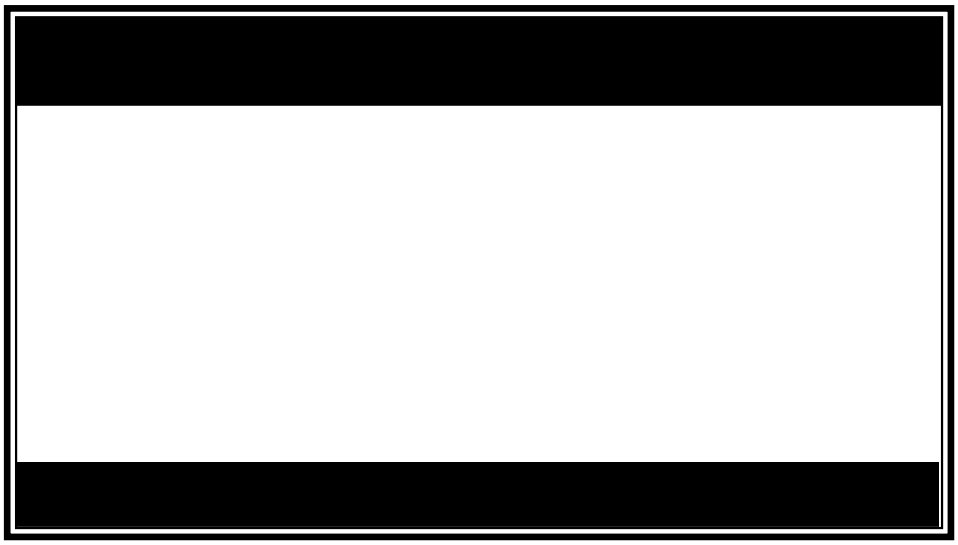
Growth Hormone Therapy and Steroids

One piece of exciting news from the International Conference on AIDS in Yokohama was new data on a trial of recombinant human growth hormone (rHGH) in AIDS wasting. In a multi-center, double-blind, placebo controlled study of rHGH, 178 volunteers were randomized to receive either rHGH or placebo for twelve weeks. People in the rHGH treated group demonstrated a decrease in body fat and an increase in lean body mass. This may indicate that rHGH helps to correct a metabolic abnormality and addresses one of the underlying causes of AIDS wasting. People receiving rHGH had an average of 1.7 kilogram lean body mass increase over the placebo group and demonstrated increases in treadmill endurance. Side effects associated with rHGH included joint stiffness, edema, elevated glucose and triglycerides and nausea. These were usually mild and resolved with dose reductions. The Canadian FDA has approved an expanded access program for rHGH. As we go to press, the FDA has banned importation of the drug to the Unitied States through the Canadian program. Project Inform has been working to get an expanded access program avalable in the United States. Finally, if data on rHGH are confirmed, rHGH will provide a non-invasive intervention for managing wasting.

Anabolic steroids, such as testosterone, may be useful to treat or prevent wasting. Anabolism refers to building protein. There have been few studies examining the use of anabolic steroids in HIV, but clinicians routinely correct testosterone deficiencies with replacement therapy. A broader and largely unanswered question is whether wider use of anabolic compounds is useful in preventing or treating wasting syndrome. There is no information currently available on the effect of anabolic steroids on viral replication, but many people are experimenting to see if using steroids can help maintain or increase lean body mass.

Cytokine Manipulation

Increases in certain cytokines (chemical messengers which are produced by immune system cells) have been associated with increases in HIV replication, KS tumor progression, HIV disease progression and wasting syndrome. These cytokines, which include tumor necrosis factor (TNF) and interleukin 1 and 6 (IL-I and IL-6), are called pro-inflammatory cytokines because they are associated with inflammatory responses. Several studies are ongoing to see if down-regulating these cytokines will impact wasting. Pentoxifylline (PTX), also known as Trental, is FDA-approved for use in blood-clotting disorders in the elderly and is therefore available "off-label" by prescription. Small studies demonstrate that PTX lowers TNF levels in people with HIV who have elevated TNF. Because TNF is an important cytokine for controlling *mycobacterium* and other HIV-associated conditions, lowering TNF to normal, but not below, may be the most beneficial approach. Studies of PTX have been small and results have been mixed. Some studies show trends toward weight stabilization while others show no impact. Studies of PTX with AZT show that the



drugs can be taken safely together. Side effects of PTX are apparently rare, but include nausea and headache. An older drug, thalidomide, inhibits TNF and reduces viral replication in test tubes. Several studies of thalidomide are ongoing in HIV, one to examine its benefits in treating HIV-related aphthous ulcers, one in HIV-related wasting syndrome and another to examine its antiviral effects. Other approaches to lowering TNF levels, including synthetic antibodies against TNF and soluble TNF receptors, are being tested at the National Cancer Institute and in Canada,

Total and Partial Parenteral Nutrition (TPN or PPN)

TPN and PPN are liquid nutrients which are delivered intravenously, through a line surgically implanted in a major vein. Some providers use PPN, in combination with solid food nutrients, to treat moderate to severe wasting. When wasting becomes severe, TPN is used. Often, due to expense (up to $13,000 per month), TPN is utilized too late to help restore body mass. As wasting increases in severity, it becomes more and more difficult to treat. Intervening early, even with TPN, is important. An IV diet is hard on the body: e.g. intestines are not "exercised," and the longer TPN is continued the more difficult it is to readjust to solid foods. TPN is very high in fatty proteins and weight gain associated with TPN is primarily fat and water weight. While this is clearly not optimal, it may help someone with severe wasting. TPN should only be used when the intestines have stopped working and other oral interventions are not being absorbed.

Finally, good nutrition and maintaining lean body mass are core components of a comprehensive HIV treatment strategy. Weigh the pros and cons of available options and develop a nutrition and weight maintenance strategy that fits your lifestyle. Interventions are available if wasting becomes a problem, but as with almost every aspect of HIV, preventing the problem is the best solution.

Project Inform Goes OnLine!

PI is offering treatment information via a number of computer bulletin boards. For more information, call the Project Inform hotline!

Update on Cervical Dysplasia and Gynecologic Infections

by Virginia Parks

Approximately 12% of the total diagnosed cases of AIDS in the United States are among women. The presence of women and women's issues were a highlight at the International AIDS Conference this year. Most of the presentations centered on prevention, social aspects, or perinatal transmission, however. A study regarding the use of AZT in preventing transmission of HIV to unborn child carried the major headlines of the conference. This study, ACTG 076, was featured in *PI Perspective* #14. While clinical presentations were limited, two abstracts regarding cervical dysplasia merit discussion.

Preliminary data from a study comparing pap smears to colposcopic exam (a device which magnifies the cervix for better visual examination) demonstrate the two tests to be comparable. One hundred HIV+ women and 50 HIV- women underwent complete pelvic exams including pap smear and colposcopy at study entry and at 6 and 12 months. Forty percent of HIV+ women had abnormal paps at entry compared to 10% of the HIV- participants, and 37% of positive women had abnormal colpos compared to 10% of the controls - indicating that there is a good correlation between the results of pap smear as compared to colposcopy in screening for cervical dysplasia in HIV+ women. A larger study involving health care providers with less experience in GYN care is needed before these results can be generalized. With completion of the study, researchers hope to propose guidelines for frequency of paps in HIV+ women.

A second study compared the rates and severity of cervical abnormalities between HIV positive and negative pregnant women, by retrospectively examining medical records. Cervical abnormalities were found in 33% of the total uninfected group and in 63% of the HIV+ women. Women with high CD4+ counts had cervical abnormalities comparable to the uninfected group (36%), and more seriously immune-compromised women had extremely high rates (96%) of abnormalities as well as the most severe cervical dysplasia. Both studies confirm a possible correlation between *Human Papillomavirus* (HPV) infection and cervical dysplasia, although that was not the primary focus of either study. While formal guidelines have not yet been proposed, these results strongly suggest that:

- HIV+ women should have pap and pelvic examinations at least every 12 months.
- More frequent pap smears should be considered in severely immune-compromised women, with follow-up colposcopy if advised.
- Treat dysplasia aggressively, before it becomes cervical cancer!

Two other studies regarding the prevalence of gynecologic infections and sexually transmitted disease indicate that candidiasis and bacterial vaginosis (infections which are not necessarily sexually transmitted) were the most common GYN infections seen in positive women. The incidence of sexually transmitted disease in both studies was low. The low STD rates could be attributed to an increased commitment to safer sex practices among positive women. Anecdotal data suggest gynecologic infections are more aggressive and difficult to treat in immune-compromised women. It is important that women are diligent in preventing and treating infections. The following pages are Project Inform's recently completed guidelines for the *Management of GYN Infections in Women with HIV/AIDS.*

Project Inform

Infection	Symptoms of Active Infection	Diagnostic (Dx) Procedures	Treatment (Rx) for Active Infection
Chancroid ***H. durcreyi*** bacterial infection	Painful vaginal ulcers, with no evidence of HSV (herpes simplex virus) or *T.Pallidum* (syphilis) infection. Inflammation of lymph glands in the groin area (inguinal adenopathy) is also seen in approximately 1/3 of patients.	Diagnosis is made by clinical observation of symptoms and testing to eliminate the possibility of syphilis or herpes. Definitive dx requires identification of H.ducreyi in special culture media not readily available. If the dx is unclear, doctor may also recommend treatment for syphilis.	Azithromycin (1g PO 1x), Ceftriaxone (250 mg IM 1x), Erythromycin (500 mg PO 4x day x 1 wk) Alternatives: Amoxicillin (500 mg plus 125 mg clavulanic acid PO TID x 1 wk) or Ciprofloxacin (500 mg PO BID x 3 days)
Chlamydia (*C. trachomatis*) and Gonorrhea (*N. gonorrhoeae*) bacterial infections **Herpes Simplex Virus (HSV)** viral infection **Genital Warts** **Human Papillomavirus (HPV)** viral infection	Chlamydia infection is very common, especially among young adults. Most women will not experience any symptoms. IF you do, they may include: Vaginal discharge, spotting following intercourse or between periods, lower abdominal pain, salpingitis (inflammation of Fallopian tubes). Gonococcal infections (gonorrhea) among women usually produce no symptoms and HIV+ women at any risk of this STD should be tested on a regular basis. Co-infection with gonorrhea and chlamydia is common and often leads to PID. Oral infection (HSV-1): blisters on lips, tongue, or cheek, fever, swollen lymph nodes in neck. Genital infection (HSV-2): All or some of following: painful blisters in/around vagina, rectum, and/or anus, painful urination, genital irritation, fever, headaches, muscle aches, malaise. *Note: Some may experience symptoms only once. Many persons will however, experience recurrent episodes.* Multiple tiny white spots (warts) on vagina or around anus, soft whitish tumors with fine finger-like projections. Less frequent: vaginal discharge, bleeding after intercourse. Recent studies suggest that women who have vaginal HPV often also have anal HPV. Warts can lead to cervical cancer, and should be taken seriously.	Pelvic exam (Involves the application of pressure to the outside of lower abdomen to detect enlarged tubes or tender and hot abscesses) and sample of discharge for microscopic evaluation for *C. trachomatis*. *N. Gonorrhoeae* is diagnosed by culturing a sample of a vaginal discharge. See your medical provider as soon as possible. S/he will try to culture HSV from fluid of one of the blisters for an accurate diagnosis. Can sometimes be diagnosed by visual exam. Colposcopy (an instrument called a colposcope is used to magnify the cervix so that a biopsy can be taken of any warts seen), pap smear (cells brushed or scraped from cervix). External genital/perianal warts can be diagnosed visually by soaking the skin in the area with vinegar or 3% acetic acid for 5 minutes and then examining the skin directly. An anal pap smear is also advised.	Chlamydia: Doxycycline (100 mg PO BID x 1 wk), Azithromycin (1g, PO, 1x). Alternatives: Ofloxacin (300 mg PO BID x 1 wk), Erythromycin base (500 mg PO 4x/day x 1 wk), Erythromycin ethylsuccinate (800 mg PO 4X/day X 1 wk), Sulfisoxazole (500 mg PO 4X/day X 10 days). Many antibiotics are safe and effective for treating uncomplicated Gonorrhea. Recommended: Cefriaxone (125 mg IM 1X), Cefixime (400 mg PO 1X), Ciprofloxacin (500 mg PO 1X), Ofloxacin (400 mg PO 1X) PLUS Doxycycline if chlamydial co-infection is suspected. *See "Drug Interactions" for Rx during pregnancy* The optimal acyclovir dosage for HIV+ patients is being debated. Experience suggests 400 mg PO 3-5X/day until blisters are completely gone. For a very severe outbreak, IV acyclovir may be required (5 mg/kg of body weight, q 8 hrs). For acyclovir resistant dz: Foscarnet (40 mg/kg IV q 8 hr X 14 days). *Other therapies are being researched for acyclovir-resistant herpes.* *Consult your GYN provider for exact Rx regimens which may include one or more of the following:* Cryotherapy (cryo) with liquid nitrogen or cryosurgery (cryosurgery recommended for internal warts only), Podofilox 0.5%, Podophyllin 10%-25%, Trichloracetic acid (TCA) 80%-90%, or Electrodesiccation (low level electricity "burns" the wart). Cervical warts: always check for cervical dysplasia. Surgical removal may be recommended for anal or vaginal warts. Some doctors utilize laser surgery. *Note: Other Rx are being studied.*
~~**Syphilis**~~ bacterial infection **Vaginal Candidiasis** fungal infection	Primary syphilis: hard, red sores around genitals, anus, or mouth. Secondary syphilis: mucous patches in genital areas, skin rashes, fever, weight loss, headaches, hair loss. Neurosyphilis: Headaches, memory loss, confusion. Can easily be mistaken for AIDS related neurologic disorders. Has been observed in people with HIV during primary and/or secondary syphilis. *Note: Many women may not experience symptoms.* Creamy white or yellow discharge accompanied by itching or burning while urinating, raised gray and white patches on vagina. *Note: Similar symptoms could indicate other vaginal infections: vaginitis, Bacterial Vagin-*	A blood test (RPR or VDRL) drawn at least 7 days after ulcers appear is normally used. Abnormal blood results have been observed among HIV+ patients (unusually high, low or fluctuating titers), so your doctor may recommend a biopsy be taken of one of the sores for microscopic examination. Syphilis is often found in the cerebral spinal fluid (CSF) of HIV+ patients with primary or secondary syphilis infection and could affect the central nervous system (CNS). So, your doctor may also want to check the CSF by lumbar puncture (a thin needle is inserted into the spine and fluid is withdrawn). Often by observation. A sample of the discharge should be taken for microscopic	Benzathine penicillin G 2.4 million units administered IM is preferred Rx. Some experts recommend additional Rx, such as multiple doses (2.4 million units, 1 dose a week for 21 days, IM) or other antibiotics in addition to benzathine penicillin. If pt. is allergic to penicillin, she may be desensitized (by administering gradually increasing doses), then treated with regular adult penicillin regimen (a minimum 6-12 mo. f/up is recommended) If penicillin doesn't work: Doxycycline, (100 mg PO BID) or Tetracycline (500 mg PO 4x day) may provide effective Rx. Non-prescription meds (OTC, over-the-counter): Gynelotrimin, Monostat -7, etc. Stronger treatments if OTC treatments are not effective: clotrimazole, ketoconazole, itraconazole, or fluconazole, applied either

Legend: IV = intravenously IM = intramuscularly PO = by mouth TID = 3 times a day

Management of GYN Infections in Women With HIV/AIDS

Prophylaxis (Px) and Maintenance (Mx) Options	Possible Side Effects From Treatment	Drug Interactions
Px: Avoid infection or reinfection by using condoms. It is best to avoid sex while infected to help the sores heal. Mx: Follow-up in 3-7 days with additional follow-up if not beginning to heal by 7 days. If unable to follow-up, the single dose azithromycin or ceftriaxone is NOT recommended.	Erythromycin: upper abdominal pain, nausea, vomiting, diarrhea, hepatitis. Amoxicillin: nausea, vomiting, diarrhea. Antibiotics often cause yeast infections. See candidiasis prophylaxis. ~~Azithromycin: gastrointestinal disorders.~~	Erythromycin: inhibits metabolism of therapeutic agents, particularly theophylline, carbamazepine, digoxin, warfarin, and oral contraceptives. Concurrent use of erythromycin and theophylline may increase theophylline serum levels. *Ciprofloxacin should not be used during pregnancy.*
Px for newborns: Erythromycin (0.5%) ophthalmic ointment applied topically, one time. Or tetracycline (1%) ophthalmic ointment applied topically, one time. Px for adults: Avoid new infections or reinfection by using condoms.	Erythromycin: see chancroid. Tetracycline: nausea, vomiting, anorexia, skin rashes. Doxycycline: same effects as tetracycline. Antibiotics often cause yeast infections. See candidiasis prophylaxis.	Azithromycin with antacids: decreased azithromycin absorption, so administer these drugs at least 2 hrs. apart. *Recommended Tx for Chlamydia during PREGNANCY: Erythromycin base (500 mg PO 4x/day x 1 wk). Alternatives: Erythromycin base (250 mg PO 4 x day X 2 wks), Erythromycin ethylsuccinate (800 mg PO 4X/day X 1 wk), or if Erythromycin cannot be tolerated, Amoxicillin (500 mg PO TID X 1 wk) Gonorrhea Tx recommended during PREGNANCY: Cefuroxime axetil 1 gm PO 1X), Cefpodoxime proxetil (200 mg PO 1X) PLUS Erythromycin or Amoxicillin if co-infection exists. Women who cannot tolerate Cefuroxime should receive Spectinomycin (2g IM 1X)*
Mx: Acyclovir (200 mg PO 3-5X day) Px: Use condoms to avoid exposure of partner or re-exposure to yourself. "Shedding of virus" and transmission of HSV has been documented to occur without ANY physical evidence of an outbreak.	~~Acyclovir: Most people tolerate acyclovir ex~~tremely well. If side effects are noticed, they may include: dizziness, headaches, nausea, diarrhea.	Acyclovir with AZT: increased in vitro antiretroviral activity. Acyclovir with alpha interferon: increased in vitro antiretroviral activity. Acyclovir with probenecid: 30% decreased acyclovir clearance. *Note: At this printing, the safety of acyclovir during pregnancy has not been firmly established. If you require acyclovir during pregnancy, report it to the mfg's registry (800/722-9292 ext.58465)*
Mx: Repeat pap smear every 3 months after treatment. Px: Condoms	~~Cryosurgery: Involves freezing of the cervix,~~ causing a watery discharge for approx. 2 wks post therapy. Podophyllin: scarring, nausea, vomiting, fever, confusion, rarely coma, renal failure. Laser therapy: local pain, vaginal discharge, periurethral swelling, vulvar itching, swelling. Other Tx may be recommended, consult your doctor on side effects.	*Podofilox and podophyllin should not be used during pregnancy.* *Self-treatment is not recommended, consult medical provider before initiating any HPV therapy.*
Px: Condoms. Topical antibiotics, chemicals, and creams are NOT effective for prevention. Mx: Monitor for increases in syphilis titers which may indicate a treatment failure OR relapse. Watch for neurologic manifestations.	~~Benzathine and procaine penicillin: skin~~ rashes, edema, fever, chills. Amoxicillin: see chancroid. Ceftriaxone: see chancroid. Antibiotics often cause yeast infections. See candidiasis prophylaxis.	Penicillin with tetracycline: may antagonize bactericidal effect of penicillin. Amoxicillin with penicillin: hypersensitivity. *Doxycycline and tetracycline are contraindicated for use during pregnancy. Only penicillin is recommended.*
Px: Acidophilus bacteria (e.g. lactobacillus) in capsule form or 8oz of yogurt daily. Garlic capsules also found useful. A study is underway considering fluconazole as Px in women with low CD4 counts. Note: Many antibiotics used to treat HIV-related infections are "broad-spectrum" meaning they kill all bacteria in your body including the useful flora naturally found in the vagina which helps to prevent overgrowth of candidiasis. If taking antibiotics, take acidophilus as well.	~~Oral azoles: liver toxicity.~~ Creams and suppositories are often oil-based and may weaken latex condoms and diaphragms. Refer to product labeling for further information.	Avoid alcohol with azoles. Fluconazole: avoid warfarin, rifampin, oral contraceptives. Clotrimazole: raises liver function tests. Ketoconazole: antacids and ddI may interfere with absorption, so take them 2 hrs. apart, avoid tuna fish. *ONLY topical azole therapies are recommended for use during pregnancy, most effective: clotrimazole, miconazole, butoconazole, and terconazole. A 7-day regimen is advised.*

BID = 2 times a day X = times mg = milligrams kg = kilograms (1kg = 2.2 lbs.)

A Revolution in Clinical Trial Design

After hundreds of clinical trials testing therapies for AIDS, our knowledge of how to treat the disease remains meager. The most important questions - how to best extend the lives of patients - are often unanswered by clinical trials. To some degree, this is simply a reflection of the difficult medical challenge posed by HIV, compounded by the mediocre quality of the drugs currently available. Most researchers would agree that clinical trials have not done a very good job of providing the kind of information physicians need in order to best treat their patients. In a recent meeting sponsored by the Food and Drug Administration (FDA), some argued that this is partly due to the accelerated pace of AIDS drug development and that we should return to larger, placebo-controlled trials. Any suggestion of slowing AIDS drug approval was resoundingly beaten back by the outcry from patients and physicians.

It should be possible to improve clinical trials without slowing the approval process, although several groups, including Project Inform, do not believe this will be accomplished with traditional clinical trial models. Meeting the dual goals of improved information and rapid drug development in a disease as complex as AIDS will require a major rethinking of how clinical trials are conducted. A new trial design, called a "medical strategy trial," has been proposed by several community and research groups which promises a revolution in making trials far more relevant to the needs of people living with HIV.

The Problem(s)

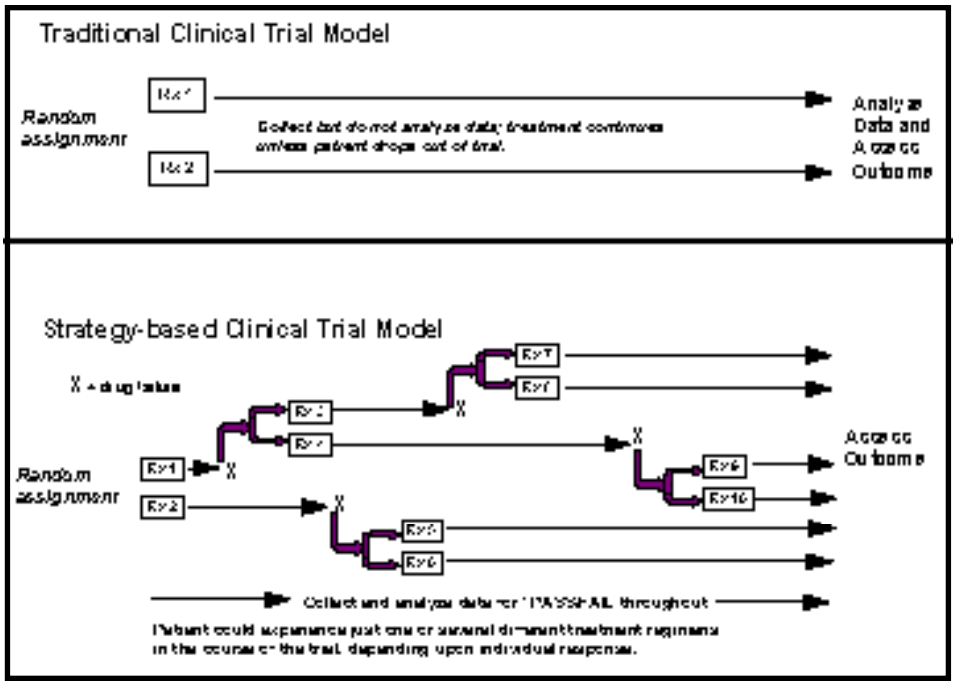
Ideally, researchers would like to know how a drug affects clinical and survival outcomes. Clinical trials which seek this kind of information are necessarily quite long and require treating large numbers of volunteers in a similar and controlled fashion. A new drug is compared either to standard therapy or a placebo, while measuring the average group outcome. An increasing number of researchers question the utility of the standard trial model and its relevance in a complex disease like AIDS. Patients have questioned such trials from the beginning, often voting with their feet either to not participate or to quit the trials before completion. In the end, the best guidance these trials have been able to give patients and physicians about a new drug is "try it and see what happens." Three key problems have rendered such trials problematic:

- The study model derives its statistical power from averaging the results achieved across a large number of people. Such averaging only makes sense if the people are relatively alike in their disease process. HIV disease is highly individualistic, even among patients with similar CD4+ counts. "Averaging" the response to a drug masks the fact that a study group often has responses which range from striking improvement to complete failure. The "averaged" response of the group, which typically comes out modestly positive or neutral, tells us little about how the drug affects individuals. Good drugs can be lost in the process, and bad ones hidden from clear view.
- The study model assigns people to receive a single drug or combination and then attempts to follow volunteers using it for the duration of the study, even if they fail on the drug somewhere along the way. Most studies purposely do not permit people to switch to newer or different therapies. The study relies on people failing therapy, since the number of failures - in the form of death or progression to more serious disease states - is the study's basis for comparison. Few physicians would ever treat patients in this manner. Instead, an effective physician relies on a broader strategy, monitoring a patient's response to drugs and carefully altering medication at the first sign of drug failure. In the traditional trial mode, people who begin to fail on a drug often drop out before the study is completed and little or nothing is learned from their experience.
- Overall, the traditional study design asks the wrong question - *"what is the average effect of this individual drug?"* A more relevant question, at least to people whose lives are on the line, might be *"what is the individual effect of an overall medical strategy, which might include several different drugs at different times?"*

Compounding these problems is the sheer number of new drugs coming into study: over 20 different protease inhibitors, seven new nucleoside analogues, three non-nucleoside drugs, antisense products, therapeutic vaccines and cellular therapies. It will soon be logistically impossible to conduct individual large, long-term trials of all these agents. There simply aren't enough patients to go around, and those who are eligible for trials are increasingly unwilling to stay in long-term studies. In the near future, we will be forced either to abandon long-term studies measuring clinical outcomes altogether, or to employ new and different study methodologies.

A Solution?

Several groups have proposed the concept of "strategy-based" trials. Medical strategy trials will seek to measure the overall effect of therapy strategy on survival and clinical disease progression. Unlike traditional trials, this approach recognizes and responds to individual diversity, allowing physicians to adjust the trial process in hopes of doing what's best for the patient. In turn, this should improve the willingness of people to participate in trials to their conclusion. Because the trial process mimics the way physicians treat their patients, the outcome of studies will be highly relevant to the practice of medicine. The medical strategy trial model will:



1. *Compare two or more competing medical strategies, not just individual drugs.* A medical strategy might be a series of drugs or combinations and a plan for deciding when and how to use them. The overall goal will be to keep the patient as healthy as possible for as long as possible. The model is driven by people's needs, rather than the needs of drug companies to study their products.

2. *Assign a planned series of therapies directed by the use of "controlling endpoints" (decision-points within the study* - benchmarks which would trigger a change in therapy).
   - Example: (in an antiviral therapy strategy) People will be monitored to see whether a new drug or combination is reducing the amount of virus in each individual. If it succeeds, the individual patient remains on the therapy. If it fails to reduce viremia, the individual patient is switched to an alternate drug or combination.
   - Each volunteer will be continually monitored for signs of impending drug failure, such as rise in virus levels. When lab data suggest drug failure, the patient is immediately assigned to a new regimen. The process is repeated as long as possible or until the planned study duration is achieved, while collecting clinical and survival data.

3. *Assess clinical/survival outcomes of the strategy at the study end.*

Such a trial design would:

- Provide more relevant information to guide the practice of medicine.
- Give every volunteer the best possible opportunity to benefit individually from the trial.
- Eliminate many of the most common factors which cause people to drop out of trials before their completion.
- Measure the effect of our medical strategies on extending the lives of people with HIV/AIDS.

The model could readily compare medical strategies such as:

- Beginning and changing treatment based on markers of virus activity (Q-PCR or bDNA) vs. making decisions based on CD4+ counts.
- Beginning treatment with a single drug vs. a combination therapy.
- Comparing a series of 2-drug strategies to 3-drug strategies.
- Comparing combinations using drugs of similar modes of action to combinations with differing modes of action.
- Early vs. late treatment, using optimum combinations and switch points.

Critics who object that this model won't necessarily tell us the precise value of any single drug are missing the point. There is no great need in an overall medical strategy, with many options, to know the absolute contribution of any single drug. That value is highly variably in individuals anyway. What matters is the impact of the medical strategy, and whether or not a drug plays a role in a useful strategy. Medical strategy trials would not eliminate the other phases of study for new drugs, so considerable information would be gathered about each drug from Phase I and II testing before it is tested in the medical strategy. The principal reason that current studies focus so intensely on individual drugs, rather than strategies, is because the research process is driven not by the medical interests of people, but by the need for drug companies to meet FDA licensing requirements. The FDA has already shown sufficient flexibility with its requirements in the study of AIDS drugs to make medical strategy trials feasible.

The future of HIV treatment is clearly a model which will rely upon individualized use of multiple therapies, employed in combinations and sequences, driven by the effect of such drugs on the underlying infection, HIV. Now is the time to begin conducting clinical trials which provide reliable information about such treatment strategies.

Update on Opportunistic Infections

by Ben Cheng

Preventing Mycobacterium Avium Complex

Preliminary results from a study comparing clarithromycin (500 mg twice a day) to placebo show that clarithromycin is effective in preventing disseminated *mycobacterium avium complex* (MAC). There was a 68% reduction in risk of developing MAC on clarithromycin compared to placebo. Nearly 700 people, with fewer than 100 CD4+ cells, were randomized to receive either clarithromycin or placebo. People who received clarithromycin had significantly fewer cases of MAC. Fifteen cases of MAC occurred among people receiving clarithromycin (4.5%) compared to 42 cases among those on placebo (12.5%). There were significantly fewer deaths on the clarithromycin arm, only 74 (22%) compared to 98 (29%) on placebo. People taking clarithromycin had more cases of nausea while people taking placebo had more fevers.

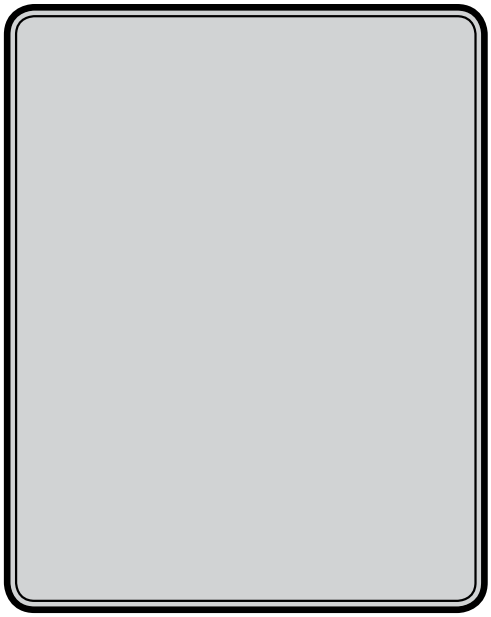
Nine of the 15 people (60%) who developed MAC while receiving clarithromycin as prophylaxis became resistant to the drug. This means that those 9 participants will receive lesser or no benefit if they use clarithromycin alone to treat their MAC infection, and there is a very strong likelihood that they will also receive no benefit from azithromycin. All of the participants on placebo who developed MAC remained sensitive to clarithromycin. Although the number of participants who developed MAC while receiving clarithromycin was small, the development of resistance is a reason for concern. Clarithromycin and azithromycin are almost universally considered the most active part of a combination of drugs used as first-line therapy for the treatment of MAC disease. If the majority of participants who develop MAC while receiving clarithromycin as prophylaxis are then unable to use that drug as a treatment for the disease, this will limit their treatment options.

People who are considering MAC prophylaxis need to discuss these concerns with their healthcare providers. A study comparing clarithromycin versus rifabutin (currently the only approved MAC prophylaxis) to the combination of clarithromycin and rifabutin is still ongoing. There may be some results from that study next year.

Treating Toxoplasmosis

A very small French study showed that clarithromycin (0.75-2 grams/day) used in combination with minocycline (200 mg/day) was a good salvage therapy for the treatment of toxoplasmosis. The combination of clarithromycin and minocycline was well tolerated. A larger study needs to be conducted to confirm these data.

Treating Herpes Zoster



A study comparing Sorivudine (BV-ara-U) to acyclovir for the treatment of herpes zoster shows Sorivudine to be superior in stopping new lesion formation. One hundred and thirty-seven participants were randomized to receive either Sorivudine (40 mg once daily for seven days) or acyclovir (800 mg five times a day for seven days). While Sorivudine stopped new lesions from developing, there was no difference between the two study groups in time to resolution of acute neuritis pain.

New Treatment for Fungal Infections

Fluconazole-resistant candida and cryptococcus has been a growing concern in recent years, as the only effective treatment for those conditions would be the very toxic intravenously administered drug amphotericin B. A small European study shows that some people with fluconazole-resistant candidiasis may benefit from a new oral drug, D0870. Twenty-seven HIV-positive people with fluconazole-resistant candidiasis were enrolled in this study. Two participants had complete clearance of signs and symptoms of candidiasis after 7 days of therapy with D0870. In test tube studies, the candida found was in fact sensitive to fluconazole and not resistant as originally thought. Fifteen of the participants that had fluconazole-resistant candidiasis did show some improvement after 7 days of treatment, while 8 others had no benefit after 7 days of treatment. One additional participant withdrew from the study early because of lack of response.

Another small trial studied D0870 for the treatment of candida. Thirty-seven HIV-positive people with oral candidiasis were enrolled in this study, most of whom had experienced previous episodes of candidiasis. The study compared different doses of D0870, given orally as a single daily dose for five days. All of the volunteers responded to D0870, showing improvement by the third dose. The drug was generally well tolerated except for a few cases of headaches and dizziness. Further studies with D0870 need to be conducted to determine the effectiveness of this drug as a treatment and prophylaxis against different fungal infections.

A Potential Herpes Vaccine?

A study of a herpes vaccine (GD2T) show that the vaccine is safe and provokes a strong immune response. Eighty volunteers, half of whom were seronegative for herpes and the other half were seropositive received either the GD2T with an immunostimulant or the immunostimulant alone. All participants developed antibody responses similar to those seen after natural infection with herpes; however, the people receiving GD2T and immunostimulant showed a faster antibody response as well as a longer lasting cellular immune response. This cellular immune response may be very important in preventing initial herpes infection and in reducing the severity and frequency of herpes outbreaks. A large Phase III study is planned for the end of this year to determine whether this vaccine will be able to prevent herpes infection. Another study is underway to determine the efficacy of this vaccine as a treatment of recurrent genital herpes.

CMV - Prophylaxis, at Last?

by Ben Cheng

CMV (cytomegalovirus) is one of the last common major opportunistic infections for which effective prevention has so far been unavailable. New data presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) conference in Orlando, Florida showed that an oral version of the drug ganciclovir may prevent CMV disease.

CMV is the most common viral opportunistic pathogen found in people with HIV. CMV belongs to the herpes family of viruses. Approximately 60-90% of the general population, and about 90% of gay men, have been exposed to CMV. Although most people have been exposed to it, CMV infection seldom leads to disease except in people with compromised immune systems, such as people with HIV infection or people who must use immune-suppressive drugs after a transplant operation. In immune-compromised people, CMV can become active and lead to various diseases, depending on the organ infected, such as retinitis (loss of vision, infection of the eye), colitis (in the colon), esophagitis (in the esophagus), and pneumonitis (in the lungs). Retinitis is the most common form of CMV disease in HIV-infected people, affecting approximately 25% of people with AIDS. People with fewer than 50 CD4+ cells are at the greatest risk, but people with somewhat higher CD4+ cells have occasionally been known to develop CMV disease. The disease is rare in people with CD4+ counts above 100.

Preliminary results from ICM 1654, a study sponsored by Syntex, the manufacturer of oral ganciclovir (GCV), showed that people receiving oral GCV had a significantly lower incidence of CMV as compared to those receiving placebo. The study followed 725 volunteers of whom 486 were randomized to receive 1000 mg of oral GCV three times a day while 239 received placebo. All of the volunteers had either fewer than 100 CD4+ cells and a prior AIDS diagnosis (due to an opportunistic infection) or fewer than 50 CD4+ cells. The results of the study are shown in Table 1.

In short, the preliminary analysis of the study showed that the use of oral GCV resulted in a substantial reduction in the number of active CMV infections, whether measured overall or in specific body locations. The reduction appears to be about 50%.

Although complete data are not yet available, the study also showed that there was a trend towards longer survival for people receiving oral GCV. Whether impact on survival is due to reduced complications of CMV infections, or to the impact of the drug on other infections, such as herpes, is uncertain. Additional data will be available at the beginning of next year. Another CMV prophylaxis study comparing oral ganciclovir to placebo is still ongoing. Based on the data from these studies, it is likely that the sponsor will seek quick approval for use of ganciclovir to reduce the incidence of CMV infections in AIDS.

Ganciclovir Maintenance Therapy

Syntex has filed a New Drug Application (NDA) with the Food and Drug Administration (FDA) for the use of oral GCV as a maintenance treatment (after the infection has occurred and has been stabilized) for CMV retinitis. It is expected that the Antiviral Drugs Advisory Committee to the FDA will be reviewing this application in mid-November 1994. Results from two studies, both sponsored by Syntex, have been widely reported. ICM 1653 enrolled 161 participants of whom 123 were randomized to either intravenous (IV) GCV (60 participants) or oral GCV (63 participants). The dose of oral GCV used in this study was 500 mg six times a day. This study found that IV GCV was superior to the oral formulation in delaying relapse of CMV retinitis. The results are shown in Table 2.

In short, the use of IV GCV resulted in a slightly longer time before relapse from CMV infection, and a somewhat more consistent response than oral GCV. However, there were significantly more side effects for people on IV GCV.

A second study, ICM 1774, was similar but participants were randomized to receive either IV GCV or one of two different doses of oral GCV (500 mg six times a day or 1000 mg three times a day). This study also found that IV GCV was superior to the 500 mg six times a day dose of oral GCV but was comparable to the 1000 mg three times a day dose. The results are summarized in Table 3.

In this study, using oral GCV at a higher dose, but only three times per day, produced slightly better results than the smaller dose taken more often. Statistically, this result was almost equivalent to that of IV GCV.

Oral GCV at a dose of 500 mg six times a day had less effect in delaying the progression of CMV retinitis than the IV regimen; however there were some people who benefited from the oral drug and the increase in quality of life has to be factored in. There may be somewhat better antiviral activity on the 1000 mg three times a day dose.

Several other studies are in progress involving oral GCV. These include a study which looks at higher doses (up to 6 grams a day) as maintenance treatment as well as a study of IV GCV versus GCV implant versus GCV implant plus oral GCV. Data from these studies will not be available for at least a year.

An expanded access program is currently open for people with active CMV disease who have had catheters removed at least twice due to infection or thromboses. An expanded access program is also planned for primary prophylaxis of CMV disease.

Immune-Based Therapy Briefs

Immune Restoration Think Tank

Project Inform is currently planning for the fourth meeting of the Immune Restoration Think Tank (IRTT), which will take place this winter. The goal of IRTT is to focus research attention on the problem of late-stage AIDS, and push for the implementation of studies which maximize currently available treatment options in combination with immune reconstitution approaches. Nearly all of the technologies which were initially recommended by IRTT have now been tested in the clinic. The immediate task at hand is to review the successes and the failures of each approach and look toward optimizing therapies. Antiviral approaches along with prevention and treatment of opportunistic infections are important pieces of a comprehensive treatment strategy. Immune reconstitution, repairing the damage to the immune system, is a key component of HIV management that has been overlooked. Project Immune Restoration and the IRTT have been *the* primary force of advocacy to move this field forward.

Cytokine Therapy (Interleukin 2)

A highlight of the International Conference was a presentation of an NIH study of interleukin-2 (IL-2). Volunteers received 18 million IU/day IL-2 intravenously for 5 days, once every 8 weeks, with dose reductions to control for toxicities. Six of ten participants showed substantial (greater than 50%) CD4+ cell increases. One volunteer's CD4+ count rose from 458 to over 2,000 and remained above 1,000 for over 7 months without further IL-2 therapy. IL-2 is known to stimulate HIV replication and therefore all volunteers were required to be on antiretroviral therapy. Viral levels increased during and immediately after IL-2 infusion, but dropped back to or below baseline in between infusion cycles. Several community physicians have offered their patients similar regimens to those administered in the NIH study, and are reporting similar substantial increases in CD4+ counts. Side effects associated with IL-2 include fever, rash and flu-like symptoms. These can sometimes be severe, but resolve when therapy is stopped. In previous studies of people with less than 200 CD4+ cells, IL-2 stimulated HIV replication and did not result in CD4+ benefit. For this reason, studies of IL-2 are limited to people with higher CD4+ counts. People should not consider IL-2 unless they are using a proven antiretroviral and regularly monitoring viral activity.

HCG and Kaposi's Sarcoma

Human Chorionic Gonadotropin (HCG), an FDA approved therapy for treating infertility in women and hypogonadism (low testosterone) in men, has demonstrated activity against Kaposi's Sarcoma (KS) in laboratory animals as well as people. HCG is a hormone produced by the placenta during pregnancy. Initial interest in pursuing this approach came from observations by researchers in Dr. Gallo's lab at the National Cancer Institute, of HIV+ women with KS, who experienced remission of KS during pregnancy, an effect which was later duplicated in animal studies. Small programs in Europe and California have treated with HCG and preliminary observation suggests that HCG holds promise. Investigators report seeing KS legions "melt away" on the body. This, of course, is very preliminary information and cannot be considered as meaningful as data from controlled clinical trials. At this stage, we also don't know whether the patients involved were new to KS therapy or were dealing with resistant or old lesions. Many things can make KS "melt away" in people who have just begun treating.

Results reported by physicians who have tried using HCG have varied, but this parallels the early animal experience. One variable seems to be the actual product used, since the animal data suggests that only the "beta" chain of HCG is active against KS. Most of the available products contain a mix of the "alpha" and "beta" chains. The product which has appeared most active in the animal studies, and apparently in some of the human work, is the Wyeth-Ayerst product. HCG is not without side effects and reports thus far are still preliminary, based on what is little more than a compilation of the experiences seen in a small number of patients. A side note regarding HCG is that it may also be useful in managing wasting syndrome. HCG has been used by bodybuilders are part of anabolic steroid regimens, typically to "kick start" the body's natural testosterone production as boosting with testosterone has a tendency to shut down normal production. Thus far, studies on the use of HCG in HIV-associated wasting have not been conducted. Moreover, it is unclear what kind of effect HCG will have on viral replication. For more information about the administration and use of HCG in KS, call the Project Inform hotline.

Understanding Antiviral Drug Resistance

by Ben Cheng

All currently approved antiretroviral therapies (AZT, ddI, ddC and d4T) slow viral replication by interfering with the same HIV enzyme, *reverse transcriptase*. The usefulness of these therapies is often short-lived. As these drugs are not able to completely suppress viral replication, resistance develops and ever-increasing doses are needed to sustain antiviral effectiveness. Other factors may also contribute to their diminished effectiveness over time. Eventually, resistance may render a drug completely ineffective. Development of resistance appears to be more rapid in people with lower CD4+ cell counts compared to those with a more intact immune system. This is probably because people with low CD4+ counts have higher levels of viral activity. Several studies have shown that approximately 20% of people who are asymptomatic develop resistance to AZT after one year of therapy compared to about 75% of people with advanced disease. Several clinical studies have also shown that developing resistance to AZT can lead to more rapid disease progression.

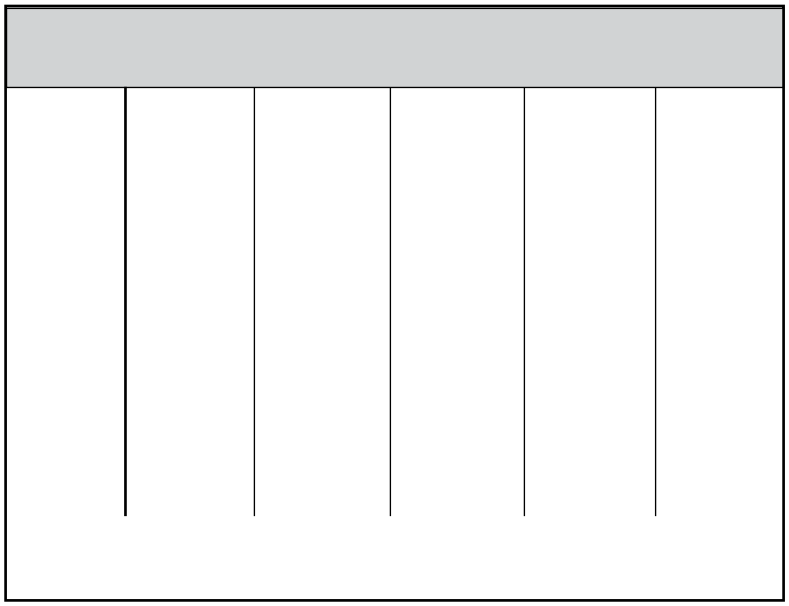
Most of the research on HIV resistance has been done in test tube studies. It is still unclear how much of the information from test tube studies is relevant to human experience. Now, however, there is increasing research on antiretroviral resistance built in to clinical studies. Studies are underway to see if switching or combining therapies can delay resistance.

Measuring drug resistance is difficult, labor intensive and expensive. Only a few university-based laboratories can perform these tests. As a result, small studies are usually 'nested' within larger studies to look for resistance. New diagnostic tools may soon be available that will make detecting resistance cheaper, less complicated and more widely available.

Most resistance research conducted in clinical studies has been with AZT. Much information regarding AZT resistance has come out of a study comparing AZT and ddI (ACTG 116B/117). This study showed that people who entered ing AZT

the trial with a high level of AZT resistance progressed significantly faster than without it. People who were resistant to AZT and then switched to ddI received no clear benefit from switching therapy, though the study may not have been large enough to measure this effect. Study participants who switched to ddI before developing AZT resistance progressed less rapidly than those who simply continued on AZT. This suggests that it may be important to know when drug resistance is beginning, so that patients might be able to switch therapies while they can best benefit from doing so.

Test tube studies show that there is some degree of cross resistance between AZT and some of the other nucleoside analogs - d4T and ddC. If this bears out in human studies, people who have developed resistance to AZT may also see diminished benefit from drugs which show cross resistance. There is no cross resistance between AZT and either ddI or 3TC, so this may make these drugs a good choice for follow-up after AZT use or in combination with AZT. In test tube studies, 3TC is able to cause viral mutations which make AZT resistant virus sensitive to AZT again. Studies are now ongoing to see if this occurs in humans.



Resistance to ddI is well documented in test tube studies. It appears that ddI resistance develops less rapidly than AZT resistance, though this does not necessarily mean that ddI works for a longer period than AZT in human use. There is considerable cross resistance between ddI and ddC. There may be some cross resistance between ddI/ddC and 3TC. Current data show that ddI is not able to re-sensitize virus to AZT as originally thought. Though there is some return to AZT sensitivity after using ddI, it is so short-lived as to be meaningless. When people switch back to AZT, AZT-resistant virus quickly recurs. Preliminary clinical data of AZT in combination with ddI indicate that while combination therapy may lead to greater suppression of viral replication, it does not delay the development of AZT resistance. Combination therapy may delay ddI resistance, however. Other studies are testing whether resistance can be delayed when ddI is used in combination with other drugs.

Resistance to d4T has not been studied extensively. Some of the test tube studies suggest that there may be cross resistance between d4T and ddI/ddC and perhaps some cross resistance between d4T and AZT. Further research needs to be conducted on d4T resistance to understand how to use this drug most effectively.

Resistance to the non-nucleoside reverse transcriptase inhibitors like nevirapine and delavirdine has been extensively studied in test tubes. Resistance to both of these drugs develops rapidly. In some clinical studies, resistance developed after a few days of starting therapy, though it is less clear whether this is the case when higher doses of the drugs are used. Several studies are now ongoing to determine if combination therapy can delay the development of resistance to this class of compounds.

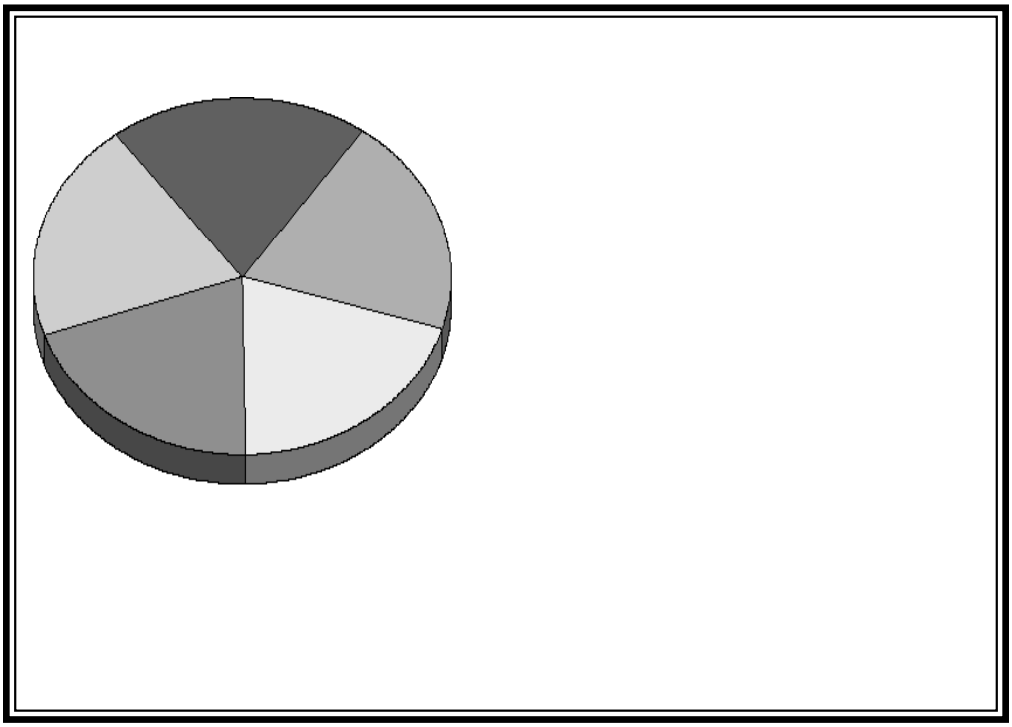
Resistance and Other Antivirals

Test tube studies show that resistance can also develop to all of the known protease inhibitors. Clinical studies indicate that some degree of resistance can develop after 12 weeks of therapy. This information is based on an incomplete understanding of the optimum doses of these drugs. Anytime a drug is used at an other than optimal dose, the likelihood of developing resistance increases substantially. The dose of a drug, either too high or too low, can effect the development of resistance. As with the nucleoside drugs, resistance is likely to develop at different rates at different stages of disease progression. There is some cross-resistance between the protease inhibitors. Several clinical studies are ongoing or planned to determine whether combination therapy with a nucleoside analogie can delay resistance to one or both classes of drugs. Another planned study will combine two protease inhibitors in an attempt to delay the development of resistance.

Some researchers believe that the problem of drug resistance in HIV is comparable to a similar problem faced years ago in the development of therapies for tuberculosis. A single drug capable of curing the disease was never developed. However, studies of resistance and cross-resistance of the available drugs led to the careful use of combinations which eventually solved the problem. Only time will tell whether this can be achieved in HIV disease.

For now, findings about resistance in clinical trials are still preliminary, as they come from relatively small studies and like all clinical trial data, do not necessarily predict what happens in each individual. Perhaps the most important step toward coping with resistance will be the development of new diagnostic tests that can predict and measure early signs of resistance on an individual basis. This, combined with better knowledge of the cross-resistance patterns of different drugs, will eventually lead to better clinical strategies.

How to Use Project Inform



In the last ten years, Project Inform has evolved into one of the largest and most respected sources of HIV treatment information and advocacy in the country. Each year, more than 70,000 people call Project Inform's toll-free hotline or receive its free publications. Project Inform's message of hope and empowerment through information is sought by HIV+ women, men and children of all ethnic and social backgrounds, their families and friends, health care and service providers, and those working in scientific research.

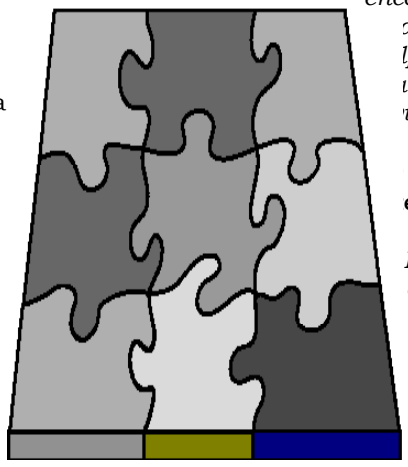
Making Choices:

The information that Project Inform provides gives people the tools to make knowledgeable decisions about treating HIV. In fact, the first step to building an effective strategy for living well and staying healthy is learning to make informed decisions. Personal empowerment is the heart of Project Inform's mission, and is also the key to using its many services. Becoming empowered about your health and life means developing a decision making process which encompasses how you feel about therapies. This includes:

- monitoring your general health and laboratory results;
- considering potential side effects and drug interactions;
- information from clinical trials, and;
- when to start, add, switch or stop a particular therapy.

Project Inform helps in this process by providing a critical piece of the puzzle, namely: the results of scientific studies and observations, and what they mean.

How do you currently make decisions about your health? What sources do you rely on to help you make those decisions?



9 **Do you rely primarily on your health care provider for information or to make decisions for you?**

No matter how good your doctors may be, very few were trained in medical school to deal with HIV. Most health care providers have had to make a personal effort to learn about HIV and how to treat it. Some are much better informed than others. Some would prefer that you leave the decision-making completely up to them, while others are willing to help you make your own decisions. Many physicians appreciate well-informed patients who bring new information and ideas to their attention.

9 **Do you rely primarily on your friends or your community for information?**

What works for one person may not work for you. This is true for any disease and especially HIV. Similarly, a therapy that someone else may have had a bad experience with may not cause similar problems for you d may actually prove helpful. Though studies can lp determine how beneficial or harmful treatments ve been on average, they cannot predict how they ill affect you personally.

Do you rely on popular media such as newspapers and elevision to give you information about HIV?

HIV disease is one of the most complex medical problems our society has ever faced. There is much about the disease that is still not fully known and even the experts have differing opinions about many aspects of it. Because

of this, most newspaper and popular magazine articles tend to oversimplify what they are reporting about and often give misleading impressions about new treatments.

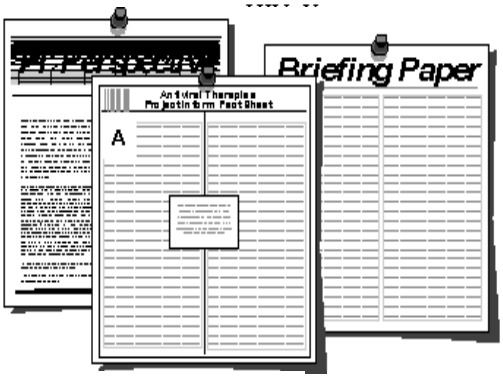
By advocating for the rights of people living with HIV to have access to promising treatments, Project Inform has built relationships with the top HIV researchers and policy-makers in government, academia, and private industry and has been invited to sit on the most influential advisory panels in the nation. Project Inform attends all of the most important conferences and gatherings where progress and news on treatment research are discussed. This allows for the immediate distribution of the latest information on treatments, without waiting as much as one to two years for these findings to be published in medical journals and the media. The following is a description of the many ways you can use Project Inform's services to benefit from this valuable information.

Hotline:

More than 70,000 people across the United States called Project Inform's toll-free Hotline last year. The Hotline is open six days per week, Monday through Saturday, 10 AM - 4 PM Pacific time. When you call the hotline you reach skilled operators, many of whom are HIV positive themselves and are trained to answer questions about the latest treatments for HIV and its related opportunistic infections. They are supported by one of the most extensive files of HIV information in the nation, with over 500 subject headings which can help you negotiate the many issues related to choosing an ideal treatment strategy. If you ask a question they can't answer right away, they'll know where to look to find the answer for you.

Publications:

Project Inform produces many types of written information each year. This is sent free of charge to all who request it, and ranges from easy-to-understand overviews on early intervention to in-depth discussions of individual treatments. Our publications include the *PI Perspective,* a quarterly HIV treatment journal, fact sheets on therapies and diseases and position papers on complex and timely issues around HIV treatments and research. In addition, Project Inform maintains an extensive library on all topics related to treatment of HIV. You can receive any of this information simply by calling the hotline. Our mailing list is confidential and private.

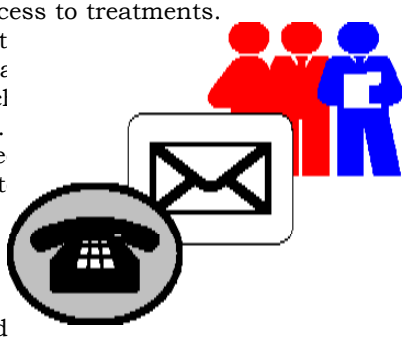


Outreach:

Project Inform has been conducting HIV treatment "Town Hall Meetings" twice monthly in San Francisco since 1985. These meetings provide information on recent research advances and occasionally provide an in-depth focus on specific areas of interest such as nutrition, opportunistic infection management, and long-term survivors. Project Inform also takes these meetings on the road, and this year visited more than 30 cities around the country.

Advocacy:

Many people living with HIV find that one of the most powerful "treatments" for HIV is getting involved. For some this may mean volunteering. For others this includes becoming politically active in HIV/AIDS issues. Project Inform's Treatment Action Network (TAN) is a grassroots network of more than 900 people around the country who respond to public issues on HIV research and access to treatments. TAN plays an important in protecting and increa funding for AIDS researcl tion, care and housing. would like to get involve TAN we'll help you writ letters, make phone calls, and ensure that your elected officials are hearing the voices of people affected by and living with HIV.



If you would like a little help negotiating the often confusing world of choices that exist for treating HIV, please don't hesitate to give us a call. We believe you always have a right to a second opinion - your own. Get the information you need from Project Inform.

It's Never Too EARLY...

... To Take Charge of Your Health!