PROJECT inform

PERSPECTIVE

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

Past_Present_and_Future@20Years

June of 2001 marked the 20th anniversary of the first official report that a deadly new illness was showing up in young young men. All those initially reported were gay men suffering from a previously unseen form of severe immune deficiency. Dr. Michael Gottlieb, an immunologist at the University of California noted five such cases in his practice and reported them to the Centers for Disease Control. In subsequent weeks and months, the illness that was initially known as Gay-Related Immune Deficiency (GRID) and eventually called AIDS began to reveal itself in additional reports, particularly through the discovery of groups of men exhibiting an otherwise rare form of cancer known as Kaposi's Sarcoma. Remembering this unhappy occasion is a difficult task at best, one fraught with the risk of hurt feelings, sad memories, or charges of inadequate attention to one or another of the communities affected by the disease. Past, present and future seems like a reasonable perspective for viewing the epidemic, as each has its share of calamities and triumphs and taken together, covers all people with HIV.

The Past

No honest story of AIDS can be told without first recognizing and honoring the generation of people who fought so hard to build the organizations, tools, and the scientific and political support we all but take for granted today as the framework for confronting the epidemic. The gay, lesbian and transgender communities and their heterosexual supporters should forever be acknowledged for their immediate, aggressive and humanitarian response to AIDS. Years before government was ready to accept its rightful role, these communities were caring for the sick, fighting for treatment and research and making remarkable changes in personal and organizational behavior to curb the risk of AIDS. Their efforts and accomplishments are without precedent in modern medical history.

On page 5, Project Inform reprints, as a memorial, the names of the many deceased who have worked with us, either directly or in spirit, since 1985 to better the lives of people with HIV and hasten the end of the epidemic. Most were honored in earlier issues of *PI Perspective*, but for many, that was a long time ago. We fully recognize that any such list of names will be incomplete and that it may bring renewed sorrow to some. We also believe it will bring joy and honor to others, especially the friends, lovers and families of those we have lost. We wish to say to them: your loved ones are not forgotten, nor will the world ever forget the contributions they made.

Many of those listed worked with Project Inform, either as staff, board or volunteers. Others are activists with whom we had the honor of collaborating. Many left their marks permanently on Project Inform and other organizations. Some are people whose work we respected, even though we didn't have the chance for direct collaboration.

Given the space, we would love to tell each of their stories and what they did. Suffice it to say that they were people who answered the hotline calls, sent out packets of treatment information, performed office duties, demonstrated in the streets, worked without pay at Project Inform, raised money, served on the board, worked with us on activist issues, organized and provoked scientists to think in different ways, fought for sane public policies and learned the science of AIDS and how to deal with drug companies. Above all else, they were people who cared for each other and the communities of people living with HIV who they served.

August 2001

In This Issue

♀ - *May be of special interest to women*

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Today's more recently infected people may not recognize the names, but they should know that without the efforts of these and others who came before them, the nationwide infrastructure of AIDS care, prevention and treatment education would not exist. Whatever weakness and failings exist in the current structures, they do provide structures to build and improve upon. Those who have passed on have left a legacy that can guide us all in the future as the epidemic cuts it way through new groups here and around the world.

If there is a single message from the past 20 years experience, it is the need for personal and community empowerment. Where once empowerment was primarily the domain of gay men with HIV, today it is becoming the domain of women, people of color and all those more recently afflicted by HIV. There are no solutions except the ones we make for ourselves. AIDS treatment, support and care will not be delivered on a platter to anyone. We must demand it as a fundamental human right. We must educate ourselves because only by knowing as much or more than the bureaucracies can we influence government and institutional policies. We must learn enough of the science of AIDS to make wise treatment decisions, rather than putting those choices in the hands of others. We must know the benefits and the limitations of treatment and the systems through which treatment and care are delivered in order to be mobilized to fight for better solutions. And we must better understand the world if we are to help combat the devastation of AIDS in developing countries.

The Present

Nothing better describes the current state of the epidemic than "a job half done." While so much has been accomplished, we still lack the ability to truly save lives. At best, today's treatment and care programs offer a respite in the fight against AIDS, a time in which the virus is not gone but at least beaten into temporary submission. But the price for this, in both dollars and quality of life, is high, too high. It is still too early to know how long people will be able to live with the current drugs. For some, it is but a matter of a few years before drug side effects and viral resistance begin to outweigh the benefits. For others it has been nearly seven years since potent triple-drug therapy became available and shifted the balance in the battle between virus and immune system. The lucky ones are still doing well and experiencing only minor side effects.

In the spirit of so many who gave their energy in the battles and activism of the 1980s and 1990s, let us all commit to a renewed war on AIDS around the globe in this first decade of the new millennium. Let's hope that day will someday come when someone gets the privilege of writing about the last five cases of AIDS seen on this planet.

It is increasingly clear that most people will not be able to stay on treatment for the rest of their lives. Between cumulative drug resistance, long-term side effects and simple weariness with the demands of the various regimens, it is almost naïve to expect people to be able to succeed for periods of 20 to 50 years or more. But that's what it will take to allow people to live a normal life span despite HIV.

Yet even this limited success is not met with equal political success. In several states, people still must wait on long lists before getting access to protease inhibitors and other new potent drugs. Making matters worse, the current Administration is proposing flat funding for the Ryan White Care Act and the AIDS Drug Assistance Program. Since the number of people being served by these programs is increasing, flat funding is in fact reduced funding. Not surprisingly, issues of international access to treatment and care remain almost completely unresolved (see more about this issue in "The Future" in this article).

In theory, better drugs are coming, but their reality seldom equals their pre-FDA approval promises. Even more worrisome is that a variety of economic and social factors are rapidly making HIV/AIDS a less than attractive target for the pharmaceutical industry. AIDS activists may debate the extent of this problem, or its possible causes, but not its reality. Two companies, Pharmacia & Upjohn and Dupont Pharmaceuticals have already sold off their HIV product lines. Several others quietly ended their HIV research projects after protease inhibitors were first approved. Another major firm has narrowed its HIV research program and will only continue with one or two drug candidates already in development, forgoing any investment in new approaches or viral targets. Still others have shifted their interest to vaccine work. More worrisome, from the companies' point of view, is that few of the recently approved drugs have been successful in the market place. Some argue that, despite their improvements over current therapy, new drugs will have a rough time facing off against the 15 better-known drugs already available unless they offer clear-cut advantages

A number of small companies have AIDS drugs in development, but history has shown us that such companies rarely are able to bring a product to market without entering into a partnership with one of the major companies. The major pharmaceutical firms are now much less inclined to take the financial risks associated with truly new product development, leaving that task instead to smaller start-up companies. At the same time, venture capital has dried up for funding high-risk AIDS drug development at such companies. Even if a small company discovers an important new concept, it must then enter into a licensing agreement with a company large enough to complete the task of development. With fewer such major companies interested in AIDS, new products will increasingly end up in the hands of the same few companies that now have large portfolios of HIV drugs, such as Glaxo SmithKline and Bristol-Myers Squibb.

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Thus, the present (and future) situation is that the pipeline of new drugs is relatively empty beyond the next few years, while more and more drugs are becoming concentrated in the hands of fewer companies, a dangerous trend for many reasons. This places even more power over pricing in the hands of the remaining companies and greater dependence upon them for future advances—a poor negotiating position to be in.

Activism surely has its work cut out for itself.

The Future

For many, the future of AIDS is seen primarily as an issue facing the developing world, particularly such places as Africa, the Caribbean, India, Asia and Central and South America, and in some cases, Eastern Europe. Countries on these continents have varying levels of medical infrastructure to make treatment feasible, and few if any have the economic ability to deliver care and treatment to all who need it. In some African countries, there is great governmental uncertainty and ambivalence about how best to deal with AIDS. After winning great reductions in the price of drugs, as well as the rights to independent production, South Africa still announces on an almost weekly basis that it has no intention of providing anti-HIV drugs to its citizens. It can no longer honestly blame the problem solely on the drug companies. Fortunately, at least some employers have clearer vision than the government and can see the economic ruin that will ensue without treatment. They are thus establishing contractual relations that will allow them to provide treatment to their employees as needed.

There is no single solution to the problem of AIDS in the developing world because "the developing world" is not a single place with uniform needs. Each country presents its own mix of challenges and opportunities. Nonetheless, the work of activists to achieve dramatically discounted drug prices and to permit generic production is a critical place to start. Without this victory, the rest of the debate would be moot, since many of the countries involved spend only a few dollars per person each year on health care. But even at greatly reduced prices, even at the cheapest generic prices, treatment still is not feasible without financial assistance from the developed nations.

Historically, we have also learned that drugs alone do not solve the problem of infectious disease in impoverished nations. Effective treatments for malaria and tuberculosis, for example, have been available at reasonable prices for decades in many countries, yet millions still die annually from these diseases. If we have learned anything from the past, it is that making public health advances in the developing world requires a long-term, worldwide commitment to comprehensive healthcare solutions. Yes, drugs will be needed, but so will supportive care, diagnostics, side effect management, clean water, sanitation and basic nutrition. We can either wring our hands in despair at the overwhelming level of need or we can acknowledge the complexity of the problem and begin collaborating worldwide to take on the challenge.

Unfortunately, the very success of people working on individual parts of the problem sometimes has the effect of setting off conflicts with those working on other parts. Great debates have raged in the last year over whether funding should be spent on treatment, vaccines, prevention or care. Each issue is supported by its own network of non-governmental and academic organizations, many of which are all too quick to feel threatened by attention being given to other parts of the problem.

To date, international AIDS activism has achieved some great successes, particularly in the area of drug pricing and production. But what is still lacking is a place or setting where the various needs can be discussed and addressed in the context of the whole problem. Neither pills, nor words of prevention, nor addressing poverty and malnutrition alone will ever solve the developing world's problems with HIV and AIDS. Somewhere, somehow, all these concerns and interests must all go on the same table and priorities and sequencing must be set.

The "table" of players needed to effectively address AIDS in developing nations must include the United Nations, the heads of the world's richer nations, the governments and NGOs of affected nations, interested and involved activist organizations, international relief agencies and major sources of private funding. Several of these groups have met separately to discuss the problem, but they have yet to all come together at the same time. The heads of African nations, for example, have met to discuss AIDS, as have the leaders of the eight largest economic powers. But they have yet to meet together or on an on-going basis. Until a forum is found to bring all the players together on a routine basis, efforts to solve this problem, perhaps the worst problem in human history, will continue to be spotty and incomplete. No single meeting or conference is sufficient for solving the worlds greatest problem. If world economics warrant the routine gathering of the heads of nations, so too must AIDS. If the world cannot find the resources and compassion needed to come together over this problem, then the future looks dark indeed. It is a test of our maturity as a civilization. So far, we are failing that test.

There is no single solution to the problem of AIDS in the developing world because "the developing world" is not a single place with uniform needs. Each country presents its own mix of challenges and opportunities.

Yet, however critical such matters may be, it would be wrong to suggest that the future is only about AIDS in developing nations. HIV and AIDS are again on the rise in urban setting in the US, and there is little reason to expect anything to the contrary in Europe, Canada and Australia. Our own prevention and education efforts are no longer sufficient, much like our drugs. If we fail to meet the standard of continual improvement in education, care and research, AIDS will once again gain the upper hand even in the richest of nations.

One major shift in thinking in AIDS research which warrants the support of activists and scientists everywhere is the increasing trend to address HIV as a disease of the immune system, rather than just as a target for anti-HIV drugs. Recent experience may already tell us the limits of anti-HIV therapy are clear: we can almost completely suppress viral replication and it helps a great deal but it cannot eliminate the virus, and it only works with continuous use. Whether people can tolerate continuous lifetime use of powerful antiviral therapy is another story. Some scientists believe that the longer people remain on anti-HIV therapy, the more dependent they become on it for controlling the virus. A more fruitful strategy may be to seek to redirect and strengthen the immune system's response against HIV, while reducing dependence on drugs. This means a shift in thinking that places more emphasis on the immune response. We already see the first stages of this today in research on the use of interleukin-2 (IL-2, Proleukin) and interest in new, more powerful generation of therapeutic vaccines. Yet such interests have the attention of only a small number of researchers, while most remain devoted solely to the pursuit of anti-HIV drugs. Surely, this must change.

Similarly, increasing attention must be given to the pursuit of a truly effective vaccine. Great progress in vaccine funding and research has occurred in recent years and the trend is clearly in the right direction. But many pitfalls may still lie ahead. Most dangerous is the possibility that strong public, political and financial interest in a vaccine may rush a product into use that is neither safe nor very effective. A real vaccine is critically needed, but we must have medical discipline to support one only when the data truly warrant it.

Moreover, we must not forget that treatment and care in developing nations will at best be only as good as what we can offer in the developed world. Currently and for the near future, that is a relatively weak standard, made up of complex treatment regimens that almost certainly fail over time and which demand an excessive cost in terms of side effects. Thus, while taking on the needs of poorer nations, at least some of the energy of activists and political workers must continue to focus on improving treatment, care and prevention in the western nations. We must continue to improve the efficiency of our scientific discovery, our regulatory (FDA) process, and the drug discovery and development efforts of academia and industry. If we fail to first meet these challenges at home, we have little of value to offer developing nations. What good are treatments for Africa and Asia if they ultimately fail those who use them, yet add complexity and toxic side effects to their lives?

Commentary

Whether our individual focus is on improving AIDS treatment and care at home, improving the equity of access throughout the US, or bringing relief of suffering to developing nations, we are all working on the same thing, fighting for the same goals. In many ways, the hardest work of AIDS activism lies yet ahead of us.

In the spirit of so many who gave their energy in the battles and activism of the 1980s and 1990s, let us all commit to a renewed war on AIDS around the globe in this first decade of the new millennium. Let's hope that day will someday come when someone gets the privilege of writing about the last five cases of AIDS seen on this planet. Such a day will only come if we continue the fight today, each in our own way. For some, this means pushing the frontiers of science to find the cure that will someday surely be found. For others, it means waging war with the tools of public health, honed in previous battles. And for still others, it means confronting the HIV-associated demons of racism, poverty, hunger and social injustice wherever they appear. If we can do all this together, each with respect for the other, surely no disease—social or biological—can stand for long. ■

20 years In Memory of . . .

We dedicate this issue of the *PI Perspective* to

Steve Abeyta
James Abrams
Larry Abreu
Chris Adams
Paul Adams
Jake Albright
Paul Anderson
David Archer
John Ashby
Chris Ayres
Bill Bailey
John Baldor
Bob Barnett
Tom Bassett
Michael Becker
Thomas Beckman
Terry Beirn
Tandy Belew
Rick Bell
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Kevin Berg
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Their memory lives on in the work that still lies ahead of us.

Drug Level Monitoring: The Next Advance in Diagnostics

The past few years have brought major advances in the treatment and management of people with HIV. In many of the early trials for HIV-positive people, different blood markers were studied to determine whether they might be beneficial in monitoring the health of people with HIV and whether they might be able to predict the risk of disease progression. Many were deemed not useful including beta-2 microglobulin, neopterin and p24 antigen. Others have become part of routine standard of care including CD4+ cell counts, viral load (HIV RNA levels) monitoring and resistance testing. Many other blood markers are still being evaluated although the next major advance is likely to come from the field of pharmacology and specifically, therapeutic drug monitoring (TDM). Pharmacology is the study of how drugs are absorbed, broken down (metabolized) and eliminated in the body. TDM monitors the level of various drugs in the bloodstream.

The goal of TDM is to ensure that there are adequate drug levels in the body to effectively block HIV from reproducing. TDM involves drawing a blood sample to measure the amount of a particular drug in the blood [notably protease inhibitor and/or non-nucleoside reverse transcriptase inhibitor (NNRTI)]. Most experts believe that measuring the levels of the nucleoside reverse transcriptase inhibitors (NRTIs), like AZT, will be of little value as these drugs block HIV replication inside the cell and the levels found in blood may not necessarily correlate with those inside the cell.

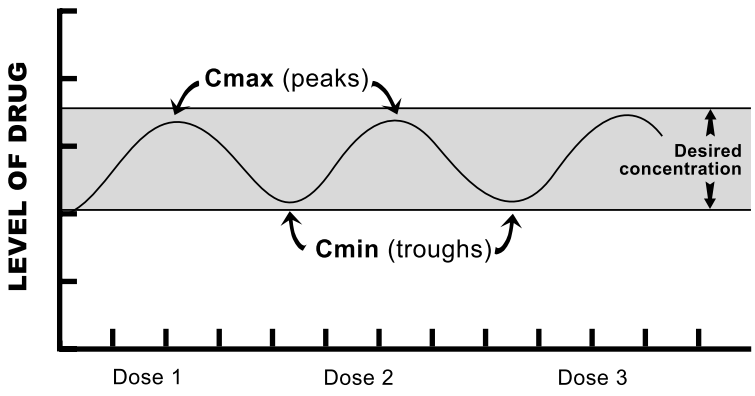
TDM may be particularly useful for the protease inhibitors as drug levels can vary greatly between individuals since there are differences in how people's body's break down and use these drugs. Ensuring that people are within a 'therapeutic range'—a range where we know the drug works and which doesn't cause excessive side effects—may significantly increase the likelihood of a durable response and may decrease risks of side effects. TDM makes it possible to adjust the dose to meet the needs of a particular person. Weight, sex, stage of HIV disease, hepatitis co-infection and presence of liver/kidney dysfunction may all affect the need for a dose adjustment of a drug for an individual. Today, we simply give a single dose calculated to work in the "average" person. For some people, this "average" dose may be excessive, while for others it may be insufficient.

The 'therapeutic range' may be different for someone starting anti-HIV therapies for the first time than for someone who has previously taken different drugs and may have developed some degree of resistance to them. It may be necessary for people with drug-resistant virus to achieve higher drug levels in order to "overcome" the resistant virus. This might be achieved by taking higher doses of a given drug or through the use of a boosting drug like ritonavir (Norvir).

There are a few hurdles that still have to be overcome before TDM can be used as part of routine care. One area of concern is the accuracy of the tests themselves.

Perhaps the bigger hurdle is determining the appropriate time to draw the blood sample to be used in detecting drug levels. Different people taking the same drug will have a different pattern in how the drug gets absorbed and eliminated from the body. Soon after a dose of the drug is taken, the maximum level of the drug, or Cmax as it is commonly known, can be found in blood. Most researchers believe that the higher the Cmax level, the more likely someone will experience side effects. Over time, the drug level gradually decreases, eventually reaching a minimal level called the Cmin. When this level is reached, the next dose of the drug must be taken to raise the blood level. If the Cmin falls below the amount needed to fully suppress HIV replication, the risk of drug resistance increases. The lower the Cmin level, the more likely resistance to the drug will develop.

For anti-HIV drugs, the Cmin level is probably the most important factor when looking at anti-HIV response, so people would need to have their blood drawn right before they take their next scheduled dose. In practice this will be very difficult to do. The more likely scenario is that



people will be coming in for blood draws whenever they can get a appointment at the laboratory or at their doctor's office and this may not be right before their next scheduled dose of their drug regimen.

Preliminary results from the ATHENA study supports the use of TDM. This study included 600 people, half of whom had not previously been on anti-HIV therapies. Half of the participants received TDM in addition to standard monitoring (CD4+ cell counts, viral load, etc.) while the other half only received standard monitoring. Results were reported only for people who had not previously received anti-HIV therapies and started on either nelfinavir (Viracept) or indinavir (Crixivan). Results on participants starting on other anti-HIV therapies and people who had previously been on anti-HIV therapies are forthcoming.

Fifty-five people started indinavir as their first-line regimen, with about equal numbers taking standard dose indinavir (800mg every eight hours) and two different doses of indinavir + ritonavir (800mg indinavir and 100mg ritonavir twice a day or 400mg indinavir and 400mg ritonavir also taken twice a day). After a year of the study, there was a trend suggesting that fewer people receiving TDM had to discontinue their therapy, primarily due to side effects. Additionally significantly more people receiving TDM achieved viral loads below 500 copies/mL after twelve months of the study.

The results for the group taking nelfinavir were slightly different. Ninety-two people took nelfinavir as first-line therapy in this study. Significantly fewer people receiving TDM discontinued therapy compared to the non-TDM group, but this was almost entirely due to fewer people experiencing virologic failure (rebound in viral load) rather than due to side effects as seen among people taking indinavir. As a result significantly more people receiving TDM achieved viral loads below 500 copies/mL after twelve months of the study than those not receiving TDM.

Additional information from this study is forthcoming including results from people who had previously been on anti-HIV therapies as well as more specific information about who were more likely to require dose adjustments based on gender, weight or other factors.

Drug Levels Inside Cells (Intracellular)

Another possible complicating factor about TDM is the recent finding of protease inhibitor levels inside cells, similar to what has been seen with NRTIs. To date, nobody has shown a connection between protease inhibitor levels inside cells and the anti-HIV effect of the drugs, but studies are now being done to examine this question. It is also not known if there's a connection between protease inhibitor levels found in blood to those found inside cells.

Human cells have certain genes called P-glycoprotein (P-gp) and Multi-drug Resistance Proteins (MRPs). They control what substances, including drugs, can get into cells and how quickly they're expelled in order to protect the cells from toxic effects.

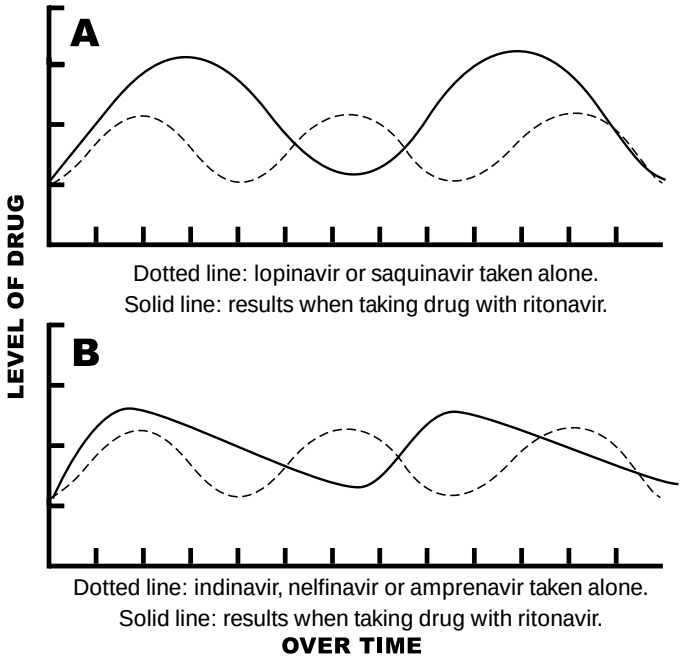
It's still not clear what role these genes play in the overall effectiveness of anti-HIV therapy, although it is thought they factor in how well drugs are absorbed and how efficiently they get into certain parts of the body, like the brain. These genes already play a major role in the effectiveness of therapies for other diseases. For instance, a high expression of these genes has been shown to make cancer cells more resistant to traditional drugs.

Drug Interactions

Many anti-HIV drugs and the therapies used to prevent or treat opportunistic infections are metabolized by the same enzymes in the body. This means that there are many possible drug interactions. As a result, it is very important to talk about this issue with your doctor or pharmacist, especially when using drugs to prevent opportunistic infections. Your doctor, as well as your pharmacist, should be aware of all the meds you're taking, including over-the-counter herbs and vitamins. More information on drug interactions is available through Project Inform's Hotline.

One of the most discussed issues on drug interactions in the past few years has been using ritonavir to boost the levels of other protease inhibitors. This approach can result in less frequent dosing and a reduced daily dose. This is achieved in one of two ways: **A**) ritonavir can greatly increase the Cmax (maximum level) of lopinavir and saquinavir in the blood without significantly changing the rate at which the other drug is eliminated from the body, or **B**) ritonavir can slow down the rate indinavir and amprenavir are eliminated from the body without greatly changing the Cmax (see charts below).

Early results suggest that ritonavir is able to boost the levels of two protease inhibitors at the same time, indicating that this may possibly be a useful strategy for third line therapy.



Dotted line: lopinavir or saquinavir taken alone.
Solid line: results when taking drug with ritonavir.

Dotted line: indinavir, nelfinavir or amprenavir taken alone.
Solid line: results when taking drug with ritonavir.

Boosting drug levels, however, may make interpreting resistance results more challenging because the higher drug levels may 'overpower' some of the drug-resistant viruses. Currently, most people consider a four-times decrease in sensitivity to a drug to mean low-level resistance while anything over a ten-times decrease means high-level resistance. This is generally considered acceptable because blood levels of a drug are usually only four to eight times higher than what is simply needed to block HIV from reproducing.

However, ritonavir boosts the drug levels of some protease inhibitors upward of fifteen times or higher and so these standard four to ten times reductions used as indicators on resistance tests may become irrelevant. In other words, you may "overpower" some of these resistant viruses by using ritonavir and another protease inhibitor even though your test results indicate you may be resistant to one or more of these drugs. As a result, it may be important for your doctor to factor in drug levels and the levels of reduced drug sensitivity when evaluating results from your tests. For more information on resistance tests, call Project Inform's Hotline and ask for the document called *HIV Drug Resistance Tests*.

Protein Binding

It is widely known that anti-HIV drugs get bound to certain proteins in the body, which results in decreased anti-HIV activity. In some cases, this has resulted in the drug being pulled from development because it lost almost all of its activity. The more a drug is bound to these proteins, the greater the loss in anti-HIV activity.

The amount of these proteins is:

1. higher in HIV-positive than HIV-negative individuals,
2. lower among people with *cirrhosis* (a liver disease caused by the loss of functioning liver cells) as the liver produces these proteins,
3. higher during periods of inflammation, and
4. different between genders and among ethnicities.

What makes this even more confusing is that tests measuring drug levels in the blood do not always reflect the effects of protein binding. Thus, a therapeutic drug monitoring test may indicate there is an adequate level of drug in the blood stream, but in fact not all of the drug is actually available to do it's job. This has been an area of intense debate among the pharmaceutical companies developing drugs because you can get very different results on anti-HIV activity depending on the amount of protein used in their lab experiments. As a result, each company claims that its drugs, at least in their labs, are more active against HIV compared to their competitors.

Commentary

There is a strong likelihood that future advances in the field of pharmacology can result in significant improvements in the care of people living with HIV by optimizing the dose of anti-HIV therapies as well as reducing the risk for certain side effects. TDM is likely to provide another useful piece of information, along with CD4+ cell counts, viral load and resistance testing, that can help in assessing the effectiveness of an anti-HIV regimen. However, there are still several issues that have to be worked out before this test can be used as part of routine care. Moreover, the level of benefits provided by TDM must be weighed against the costs and complexity of additional testing. ■

National HIV/AIDS Treatment Hotline

Project Inform's toll-free hotline provides HIV/AIDS treatment information to people living with HIV, their healthcare and service providers, and family members.

1-800-822-7422

The Basic Message

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

Women and AIDS at Twenty ♀

AIDS, first reported in women in 1981, has decidedly become a major concern for women and girls. Early misconceptions about women's perceived lack of HIV risk and the characterization of AIDS as a disease primarily affecting gay men thwarted attention afforded to women's issues early in the epidemic. Today, women account for 32% of new HIV diagnoses in the United States. Globally, women make up more than half of those infected with HIV/AIDS. As women shoulder an increasing burden of HIV, research, medical and activist responses to women's issues increase. And while more is known about and being done about women and HIV today, basic questions and gaps remain.

Access to Care

Basic disparities in women's ability to access quality healthcare persist. Poverty and lack of insurance are among the biggest barriers, but competing needs faced by women, such as work and family responsibilities, also limit access to care. Also, studies show that the healthcare system shortchanges women by not providing equitable treatment and care compared to similarly insured men with the same disease severity.

That said, model programs in several cities show the benefit of women-centered care that responds to the competing life and health demands in women's lives by coordinating HIV care, GYN care, pediatric care, psycho-social and childcare services. While women-centered care remains the exception and not the rule, these integrated programs help women seek healthcare for themselves and their families and ultimately live healthier lives.

Women and Research

Many of the barriers that women face in accessing healthcare also affect their ability to participate in studies. Enrolling enough women in studies to assess sex differences in disease progression, side effects and response to anti-HIV therapy is a continuing struggle and concern. Studies designed just for HIV-positive and at-risk women—such as the Women's Interagency HIV Study (WIHS)—concur that women-centered studies, like women-centered care, facilitates participation. Community advocates play a critical role in advising study design that facilitates women's involvement as well as asks questions pertinent to women. Largely because of the role community advocates have played, studies are increasingly developed to detect sex differences (and racial and ethnic differences), and more studies are underway that focus on women-specific diseases and responses to therapy.

Biological Differences

Early on, it was noted that women appeared to progress to AIDS and die faster than men. This difference has largely been explained by women's unequal access of care and treatment. In fact, progression and survival rates in equally treated and cared for men and women appear the same.

However, studies showing sex differences in viral load and CD4+ cell counts continue to emerge. The cause and significance of these differences remain unclear, and it's important to note that not all studies have seen sex differences in these measures. Looking at the aggregate of these studies, perhaps the best that can be concluded is that more information is needed to see if these differences really exist, and if they do what the implications might be on treatment and care of women.

One proposed explanation for these differences is the role of female hormones. Studies so far have suggested possible connections between estrogen and viral load differences seen between men and women. Also under consideration is the effect of female hormones on either increasing or decreasing CD4+ cell count; and an effect of HIV disease progression on hormone levels and menstrual irregularities. Several anti-HIV therapies interfere with the metabolism of oral contraceptives, suggesting a possible interplay between anti-HIV therapies and naturally produced hormones. For now, these are just theories and it will take more research to determine whether, and to what degree, these factors are responsible for observed differences on lab tests.

Women-specific manifestations of HIV infection, specifically GYN complications, were noted fairly early on in the epidemic. In 1993, the definition of AIDS was modified to include cervical cancer as an AIDS-defining condition. Studies continue to show that positive women have a higher incidence of cervical cancer than negative women, but improved screening methods and anti-HIV therapy have reduced progression of cervical abnormalities somewhat. Rates of other HIV-related illnesses are similar in men and women.

Treatment

Most studies show that anti-HIV therapy is equally effective in men and women. A few suggest that women have greater increases in CD4+ cell counts, though less dramatic decreases in viral load, when treated with potent therapy. While women appear to equally benefit from therapy, women have greater and more frequent drug side effects. This may be due to an interaction between the anti-HIV drugs and female hormones and/or due to the fact that women generally weigh less than men but are given the same dose. In some studies, this has led to women changing their regimens more frequently than men.

Women may also experience different forms of body shape changes than men and, in some studies, more frequent laboratory abnormalities (like hyperglycemia) while

taking anti-HIV therapy. It is difficult to say for certain whether these effects are directly related to specific medications or other factors, like age or stage of disease.

There are many potential reasons for differences in drug side effects, including body size, hormones, metabolism and other factors. Unfortunately, the number of women enrolled in studies is small, hindering the ability to detect sex differences in response to therapy and side effects. It also hinders the ability to determine the potential causes of differences when they are shown to exist. Effort to expand women's participation in studies must be prioritized in order to better understand this.

Prevention

In the US and parts of Europe, great strides have been made to all but eliminate the transmission of HIV from mother to child. Some studies have shown risk of transmission as low as three percent with anti-HIV therapy and elective C-section. Short course and single dose anti-HIV therapy holds promise for reduced transmission risk in resource poor countries as well.

Given these incredible successes, it is shocking that we still lack an effective, widely available, truly female-controlled HIV/STD prevention method. Initial hopes of the female condom providing this have been tempered by the reality that it still requires partner participation. Another method giving women the power to protect themselves and their partners from HIV and other STDs is long overdue.

Conclusion

Over the past 20 years, the numbers of women becoming infected with HIV has continually increased. In the past decade, our knowledge regarding women and HIV has greatly improved. There are still countless questions to be answered, particularly about sex differences that may affect disease progression and the toxicity of anti-HIV drugs. Research and healthcare settings must be enhanced to respond to the needs of women. As always, women living with HIV and other community advocates play a critical role in this process and must be supported in this effort. ■

New Peg-interferon Results

Encouraging results were recently presented of the pegylated interferon products used in the treatment of hepatitis C (HCV). Pegylated interferon is a form of interferon to which polyethylene glycol (PEG) has been added. Adding PEG stabilizes interferon in the body and helps sustain a more even and long lasting level of the drug. The studies show that this new formulation, when used in combination with ribavirin (Rebetol) is more effective in treating HCV than the standard regimen of regular interferon-alfa combined with ribavirin (Rebetron).

One study showed that about 35% of people who did not benefit from standard Rebetron as first line therapy achieved a virologic response (a reduction in HCV RNA levels) with the combination of peg-interferon alfa-2b (peg-Intron, developed by Schering Plough) and ribavirin after 24 weeks of therapy. Although the preliminary results are encouraging, the usefulness of this combination as second line therapy will not be known until the study is completed.

Another study showed that 61% of the participants, who had not previously received anti-HCV therapy, had a sustained virologic response after 72 weeks of the peg Intron/ribavirin study. More specifically, 48% of people with genotype 1 (the most difficult type of HCV to treat) and 88% of people with genotypes 2 or 3 had a sustained response. The dose of peg-Intron used was 1.5mcg/kg once a week in combination with at least 10.6 mg/kg of ribavirin daily. This represents a very significant improvement in therapy for almost all HCV-infected people.

Peg-Intron is approved by the FDA (Food and Drug Administration) to treat HCV when used alone, but not in combination with ribavirin. It is only modestly effective when used alone. However, the result from the second study supports the use of the combination, for which it is likely to be approved soon.

Results from a study of a different pegylated interferon (Pegasys, developed by Hoffman-La Roche) are also encouraging. This study included 1,121 people who had not previously taken anti-HCV therapies and received the standard interferon/ribavirin combination (Rebetron), Pegasys alone or Pegasys in combination with ribavirin. The dose of Pegasys in this study was 180mcg once a week and the dose of ribavirin was 1,000-1,200mg daily. At the end of the 72-week study the percentage of people with HCV levels below 50 copies/mL were:

	Pegasys alone	Rebetron	Pegasys + ribavirin
Overall Response	30%	45%	56%
Response for genotype 1	21%	37%	46%
Response for genotype 2 or 3	45%	61%	76%

Further analysis of this study found that people who did not have a response by week 12 were highly unlikely to achieve undetectable HCV levels by the end of the study. Additionally, people who were over 80% adherent to their medications were significantly more likely to achieve undetectable HCV levels at study end. Side effects overall were similar between the three groups, although there appeared to be less severe flu-like symptoms and depression among people receiving Pegasys and ribavirin than those on Rebetron. ■

Organ Transplantation

As people live longer due to using potent anti-HIV therapy, there appears to be an increase in the percentage dying from non-AIDS defining conditions, including organ failure. Long-term infection with hepatitis B or C can lead to liver failure. Some research suggests that liver disease is accelerated when a person is also fighting HIV. Transplantation is virtually the only option for people with severe liver disease. HIV-related kidney diseases, specifically HIV-associated nephropathy, is of major concern to African Americans and represents the third leading cause of end-stage kidney failure in African American adults. Other causes of organ failure may include side effects of therapies to treat HIV and associated conditions. In cases of organ failure, transplantation is the only viable option. For people with kidney dysfunction, dialysis may provide a short- or even long-term solution. For people with HIV experiencing organ failure, transplantation needs to be an option.

Current guidelines make it difficult for people with HIV to get organ transplants. While groups that distribute organs will include people with HIV on waiting lists, most surgeons will not transplant an organ into a positive person and third-party payers will often not pay for them. These policies, which assume that positive people will all die in a relatively short time, were put in place during an era when little was known about HIV disease and today's potent therapies were not available.

In recent years community activists and researchers have been working together to move the organ transplant field to reassess this issue and reconsider organ transplantation for people with HIV. Previous information suggests that people with HIV undergoing organ transplants may have a poorer outcome (11% lower survival rates) than people who are not infected with HIV. Whether this holds true today, when people with HIV are living longer and experiencing fewer opportunistic infections, needs to be examined. As a result a group in Pittsburgh has agreed to perform a number of these transplants and a group at the University of California, San Francisco (UCSF), in strong collaboration with the Pittsburgh group, is spearheading efforts to develop a nationwide study to make available and evaluate organ transplantation in people with HIV. Some individuals, on a case-by-case basis, have had success in convincing institutions to perform organ transplants for them, despite their HIV status.

A group in the United Kingdom (UK) examined eight people with HIV who underwent liver transplantation at King's College Hospital in London. Five of the transplant recipients were experiencing end-stage liver disease (ESLD), four associated with hepatitis C and one with hepatitis B. Three were experiencing liver failure, two associated with hepatitis B, one associated with hepatitis non-A or non-B.

Of the four transplant recipients who had ESLD associated with hepatitis C, all died following transplantation (at 3, 6, 15 and 25 months). CD4+ cell counts in this group ranged from 160 to greater than 500. Of the two individuals with viral load measures available, both had well suppressed HIV levels, one below 400 copies/ml and the other at 965.

Of the four transplant recipients who are alive, CD4+ cell counts at time of transplantation ranged from 124 to 293; none had well-controlled HIV levels at time of transplantation with measures ranging from 25,000 to 197,000 copies/ml. Currently these individuals have been alive 1, 5, 15 and 35 months following transplantation. Of the four people alive today, three have reported CD4+ and viral load measurements (the fourth, alive one month post transplant, did not have measures available at time of data presentation). In all cases, CD4+ cell counts rose and in all cases HIV levels are well controlled, two to below 50 copies/ml and one to 64 copies/ml.

The observations from the UK group suggest that the cause of liver disease, and the subsequent ability to control that disease with medications following transplantation, may be more important than HIV-related immune and virologic characteristics in predicting who might best respond to liver transplantation. These findings support re-evaluating inclusion criteria for the proposed US study, allowing people with measurable viral load in the study. More work is needed to determine who with hepatitis C might best thrive following liver transplantation.

... activists and researchers have been working together to move the organ transplant field to reassess this issue and reconsider organ transplantation for people with HIV.

The team at the University of California has preliminary data from their pilot study for liver and kidney transplants. This study is the basis for a larger, multicenter project that is being developed. Inclusion criteria for people in need of liver and kidney transplants are slightly different. For kidney transplants, people must have a CD4+ cell count greater than 200, whereas

for liver transplants CD4+ cell counts must be above 100. In both groups, volunteers must have undetectable viral load for three months prior to transplantation. Kidney transplant recipients must show no signs of serious liver damage (cirrhosis) associated with hepatitis C infection. Volunteers may not have had previous opportunistic infections (with the exception of treatment-sensitive candidiaisis) or cancers.

To date six individuals, one Latino, three African Americans and two Caucasians, have received transplants under this study, one liver and five kidneys. At the time of data presentation all six volunteers were alive, 40 to 315 days after their transplantations. The Latino man who received the liver transplant did have hepatitis C associated liver disease leading to the need for transplantation. Following transplantation his hepatitis C virus levels have been controlled with ribavirin and interferon-alpha therapy. Not long after data presentation, however, this man died due to transplant complications not associated with HIV. Of note, two volunteers discontinued anti-HIV therapy for short periods of time following transplantation. This resulted in minimal and delayed return of measurable HIV levels. It is theorized that the immune suppressive therapies used to prevent rejection of the organs (mycophenolate and cyclosporine) may have some direct or indirect anti-HIV activity.

As the epidemic changes, new areas of activism and research are emerging as high priorities.

It is expected that the multicenter organ transplant project will receive funding early next year and will be available to more people with HIV across the country. Efforts are being made to include heart transplantation in this project as well. As the epidemic changes, new areas of activism and research are emerging as high priorities. Organ transplantation is one such area. ■

Highlights from IAS 2001

The following are highlights from the 1st International AIDS Society Conference on HIV Pathogenesis and Treatment held in Buenos Aires, Argentina during July 2001.

Structured Intermittent Therapy

More data were presented from the National Institutes of Health structured intermittent therapy study. Early data were reported in *PI Perspective #31*. Ten people were started on seven days of anti-HIV therapies [d4T+3TC+indinavir (Crixivan) + low dose ritonavir (Norvir)] followed by seven days off. The seven-day cycle was chosen because in previous studies, including people who received optimal anti-HIV therapy, it generally took at least seven days before viral loads climbed back up to detectable levels (over 500 copies/mL HIV RNA) after a therapy interruption. All ten people who participated in this study had taken and responded well to therapy before. As a result, at the start of the study, they had an average CD4+ cell count of about 800. Five volunteers have been in the study for more than six months and an additional three for more than a year. All have undetectable viral loads (below 500 copies/mL) although some have had intermittent blips. An interesting observation was that people who stopped therapy for ten days or longer were more likely to have a blip in viral load. Everyone experienced a significant decrease in triglyceride and cholesterol levels, commonly increased due to the protease inhibitors, especially ritonavir. Further, there have been no indications of resistance developing to any anti-HIV drugs nor are there signs that HIV is replenishing the sites where it likes to hide, such as the lymph nodes.

Tipranavir

Study results were presented for tipranavir, a new protease inhibitor being developed by Boehringer Ingelheim. Considerable interest in this drug is driven by data suggesting that it remains active against HIV resistant to most other protease inhibitors. One study compared 1,200mg tipranavir taken twice a day to either 300mg or 1,200mg tipranavir together with 200mg ritonavir taken twice daily. This was only a 14-day study and none of the 31 volunteers had taken anti-HIV therapy before. At study end, there was an average viral load reduction of about 1.5 log (32-fold) among the two groups on tipranavir with ritonavir and about 0.7 log (5-fold) reduction among those taking tipranavir alone. Side effects included diarrhea in all three groups and nausea among those on the high dose tipranavir/ritonavir combination.

A second study involved 41 people who had previously taken multiple regimens that included protease inhibitors but not non-nucleoside reverse transcriptase inhibitors (NNTRIs). At the beginning, participants took twice daily regimens of either 1,200mg tipranavir + 100mg ritonavir or 2,400mg tipranavir + 200mg ritonavir. They also received the NNRTI efavirenz (Sustiva) and one new nucleoside reverse transcriptase inhibitor (NARTI). During the study a new formula of tipranavir was developed and people on the 1,200mg and 2,400mg doses were changed to 500mg and 1,000mg of the new formula respectively. The dosing schedule and dose of ritonavir was not changed. After 48 weeks, 79% of those on the lower dose of tipranavir had viral loads below than 400 copies/mL and 68% were below 50 copies. Of those on the higher dose, 50% had less 400 copies/mL and 41% had less than 50 copies. In other words, those receiving the lower dose combination had more pronounced viral load reductions. Some researchers speculate this may be due to poorer adherence on the higher dose regimen. Another possible explanation is that the new formulation may not be as stable or effective as hoped. The most common side effects included diarrhea, nausea, headache, dizziness, fatigue and abnormal dreams. ■

New Discoveries in HIV Research

Over the past twenty years there has been a vast wealth of discoveries in HIV research, perhaps unparalleled in the history of biomedical investigation. Since the early days of the epidemic, scientists' understanding of HIV and the immune system has advanced by leaps and bounds. Yet, the fruits of very basic science research do not always show themselves immediately. Certainly the scientific process is far from ideal in translating information learned in the laboratory to therapy and patient care advances at the bedside. Still, advances in basic science have greatly improved the care of people living with HIV. This article will briefly overview a few major discoveries and shed light on a new emerging theory about the role and implications of cholesterol in HIV infection.

The discovery of HIV as the cause of AIDS in the early/mid-1980s and the subsequent ability to grow the virus in large quantities in the laboratory quickly led to the development of the HIV antibody test. The wide scale availability of HIV testing allowed people to learn if they were living with the virus and take health-promoting action. The ability to grow the virus in the laboratory also allowed for the development of drug-screening tests, where compounds could be evaluated rapidly in a test tube to see if they had activity against the virus.

Researchers began efforts to characterize the structure of key enzymes critical for HIV to reproduce. One such effort focused on the protease enzyme, which makes it possible for newly formed particles of virus, made by infected cells, to assemble into a viable and infectious virus. Once the structure of the protease enzyme was identified, scientists began their quest for compounds that could block the activity of protease. By the mid-1990s, several compounds had been selected and brought through the drug testing and approval process. The use of protease inhibitors revolutionized HIV treatment in the developed world.

A similar effort has been underway, with less success, in characterizing the structure of the integrase enzyme and therapies that might inhibit its activity. Integrase is important for helping the virus integrate into the machinery of immune cells, taking over the cell's function and using the cell as an HIV particle production plant of sorts. This field is moving slowly and has been fraught with many disappointments. Only a single integrase inhibitor is undergoing testing in people at this time, and most companies have abandoned their efforts in this area. Still, perhaps one day integrase inhibitors will be added to the arsenal of anti-HIV therapies.

Laboratory work on better understanding HIV and its components have led to the development of a new class of therapies called *fusion inhibitors*. Penafuside (also called T-20) is furthest along in development. This approach interferes with a protein on HIV, called gp41, that is critical for HIV to attach to a cell.

In the mid-1990s, an important discovery was made about the role of proteins on a variety of immune cells, called *G7 transmembrane proteins*. HIV latches onto these proteins and uses them to get inside of a cell. There are a variety of these proteins, notable are ones called CCR5 and CXCR4 (also called *fusin*). Efforts are underway to find drugs that can bind to CCR5 and CXCR4, effectively putting a bandaid on them that will block the ability of HIV to infect a cell. (Visit Project Inform's website or call the hotline for more information on CCR5 and Co-receptors.)

CCR5 and CXCR4 are called *adhesion molecules*, because they bind or adhere to particles in the blood and help to transport material across the cell membrane and into the inner workings of a cell. CCR5 and CXCR4 are just a few of many adhesion molecules that are on the cell surface, however, and it's been shown that all major adhesion molecules have interaction with HIV. When adhesion molecules are present on the cell surface, HIV binding to a cell increases from a few hundred to thousands of virus binding to the cell. These molecules not only increase the ability of HIV to bind to the cell, but they also increase the ability of HIV to infect the cell and actually help to transport the virus into the cell. Moreover, when HIV is bound to one of these molecules, it's much more difficult for the immune system to effectively target and neutralize or eliminate it.

In addition to the role that adhesion molecules play in facilitating HIV binding and infection of cells, they also have a key role in allowing infected cells to release new HIV. The virus has to get into the cell in order to take over the machinery of the cell and reproduce, but it also has to get out of cells. Work by Dr. James Hildreth of Johns Hopkins University, and others, have shown that over 90% of HIV budding out of cells occurs at a region of the cell rich in adhesion molecules called *lipid rafts*. These *lipid rafts* are important for cholesterol trafficking and also in transporting materials into, out of and through-

When adhesion molecules are present on the cell surface, HIV binding to a cell increases from a few hundred to thousands of virus binding to the cell.

out cells. Lipid rafts have not only been shown to be important for HIV, but other viruses, such as influenza and measles as well, which also selectively bind and bud from them. Understanding the role of lipid rafts in HIV may have important implication for future directions in AIDS therapies.

Understanding the role of lipid rafts in HIV may have important implication for future directions in AIDS therapies.

Cholesterol is found in all tissues, oils, fats, blood etc. It is a key component of lipid rafts. Hildreth and his team at John Hopkins Medical School conducted a series of experiments to identify the role of cholesterol and lipid rafts in HIV infection.

Using a compound call beta-cyclodexin (BCD), Hildreth was able to change the cholesterol level in cells, eliminating about 90% of the cholesterol in a cell within one hour. Through a collection of laboratory experiments Hildreth's team discovered the following:

- Removing cholesterol from cells with BCD made the cell resistant to HIV infection.
- Cholesterol-depleted cells release non-infectious HIV particles (the cells that were cholesterol-depleted by BCD produced less than 5% of infectious HIV compared to cells that were not cholesterol-depleted). When these cells are given back cholesterol, the infectivity of the virus they produce is restored.
- Interestingly and importantly, Hildreth's team used BCD to deplete cholesterol from HIV itself. When HIV was depleted of cholesterol, it became inactivated and rendered non-infectious. When the virus was given back cholesterol, its infectivity was restored.

Hildreth's work underscores the importance of lipid rafts and cholesterol in HIV infection and budding of cells. Cholesterol depletion of HIV infected cells resulted in the production of non-infectious virus and cholesterol depletion of HIV inactivated the virus. Restoration of cholesterol in the cells or in the virus completely reversed these activities. Hildreth concludes that intact lipid rafts and cholesterol are required for HIV infectivity.

Hildreth's team is particularly interested in applying these discoveries to the invention of a topical microbicide that might be useful in HIV prevention efforts. Topical microbicides are usually creams or gels that could be used as vaginal suppository, perhaps even added to lubricant. The goal is to identify a compound with anti-HIV activity that could disable HIV and prevent sexual/vaginal transmission of the virus. The group at Johns Hopkins University has been exploring the potential of using beta-cyclodexin as an HIV microbicide.

Unlike nonoxynol-9, a much studied topical microbicide, BCD is not toxic to cells, particularly cells in the vaginal tract (called epithelial cells). Animal studies suggest that nonoxynol-9 completely destroys epithelial cells, which are important to protect women from virus infections and other critters that can cause gynecologic complications in women. In this same model, however, BCD showed minimal toxicity to epithelial cells and it significantly inhibited HIV transmission/infection, whether the BCD was simply used to treat vaginal cells or if it was delivered intravaginally.

While cholesterol-depleting approaches may have important implications for HIV prevention and microbicides, there are also potential implications for treatment that have yet to be fully explored and warrant immediate investigation. Dr. Eric Freed of the National Institutes of Health has also conducted laboratory studies of BCD and shows that the anti-HIV activity of BCD is dose dependent (e.g. the higher the dose, the greater HIV is inhibited) and also confirms that BCD is not causing overall toxicity to cells. Dr. Freed has examined a readily available cholesterol-lowering agent, a statin inhibitor called simvastatin (Zocor). Dr. Freed's work suggests that simvastatin can decrease HIV replication/production and posits that the widespread use of statin inhibitor drugs for the treatment of high cholesterol raises the opportunity to explore whether these compounds are useful as anti-HIV agents.

Basic science discoveries about the immune system and HIV often seem esoteric and removed from the real world of people living with HIV. Discoveries that happen in the laboratory and in the test tube have major potential implications for future treatment and directions of research, however. One of the major obstacles in facilitating discovery from the bench to the bedside rests in the very structures of how research is conducted and funded. The very infrastructures that support science in America are too often the biggest barriers to progress. This is not only a problem for AIDS research, but also a problem for all areas of research on human disease. As we move into the third decade of AIDS, it's critical that the community and the scientific establishment take a hard look at where there is success and where there are failures and find both the will and courage to struggle for meaningful reforms to expedite the process of discovery toward a cure.

Cholesterol depletion of HIV infected cells resulted in the production of non-infectious virus and cholesterol depletion of HIV inactivated the virus.

Project Inform has written information on a variety of emerging basic science discoveries. To learn more, consider the following reading materials, available through Project Inform's website and the hotline:

- Human Retrovirus Conference – Selected Highlights on Immunology
- Project Immune Restoration
- CKR5 and Fusin Co-receptors
- Highlights of the 1998 Meeting of the Institute of Human Virology, Baltimore
- Highlights from the Clinical Immunology HIV Symposium ■

Time to Get Involved, Again

The federal government's response to the HIV/AIDS epidemic in the United States has improved greatly over the past 20 years although there are still many challenges. In the earliest years, it was often hard enough simply to have key policymakers utter the word "AIDS" and acknowledge that there was a problem. Driven by the devastation of a deadly epidemic and confronted with a lack of treatment options, people living with HIV/AIDS and their advocates took up the fight for a reasonable government response. At the same time, we were forced to develop an unprecedented community care structure. Federal advocacy focused with urgency on researcher and regulatory reforms and securing funding for research, care, treatment, prevention, and housing programs. At the same time, we had to fight many attempts at passing harmful or discriminatory legislation and to guarantee protection from institutional and private bias.

In many ways, HIV/AIDS advocates combined tactics and strategies from other movements to create a comprehensive model for successful healthcare advocacy. These tactics included educating ourselves about the policy, research and drug development processes, lobbying, analyzing and working to develop reasonable policy, grassroots organizing, media advocacy, and direct action. These efforts combined to produce many important advances in patient's rights, research, drug approval, and access to treatment and healthcare.

Some of the hard won results include the formal declaration of the right of patients to import drugs otherwise not available to them (1985). Congressional approval of $30 million for delivery of AZT, the first drug approved to fight HIV, in 1987. In 1989, many government research meetings and advisory boards were opened to the patient community. The Food and Drug Administration (FDA) shortened the drug approval process in 1987, 1989 and 1991 in response to pressure and proposals created by HIV/AIDS activists. In 1990, the Ryan White Comprehensive AIDS Relief Emergency (CARE) Act was passed, providing direct funding to areas of the country heavily affected by the epidemic and supporting the community based structure that was filling the gaps in traditional healthcare. In 1994, community prevention planning was put in place through the Centers for Disease Control and Prevention (CDC). In 1997, President Bill Clinton challenged the scientific community to move more quickly in the search for a vaccine. In 1998, members of the Congressional Black Caucus, led by Representatives Maxine Waters and Louis Stokes, put the Minority AIDS Initiative in place, directing funding toward heavily impacted communities of color. In the late 1990s, people living with HIV/AIDS, U.S. activists and activists in other countries began to push the U.S. to respond to the international epidemic. In 2000, the FDA put in place the Clinical Hold Rule which allows the agency to delay or suspend any clinical trial found to be excluding women (or men) because of their "reproductive potential".

However, for all the hard won victories spurred by people living with HIV and their advocates, we have had limited success in addressing the social realities underlying and driving the epidemic. Government still refuses to deal effectively with the politics of racial and gender inequity, sexuality, drug use, poverty and general inequity in access to healthcare. For example, though scientific studies have shown for the past ten years that needle exchange helps prevent HIV disease, the federal government won't fund it. Publicly funded prevention efforts continue to lack the courage to address the needs of gay men and others. The Bush administration appears to be advocating a move back toward failed policies promoting abstinence from sex as the gold standard in prevention tactics. Although it has long been reported that African Americans have borne a heavy burden in the HIV epidemic—disproportionate to their numbers in the general population—we have yet to effectively address disparities in access to quality healthcare for African Americans and other communities of color. Violence against women continues to increase. As people with HIV in the US live longer, these social inequities and the effects of poverty often pose a greater, or at least a more immediate, challenge than HIV disease. In addition to addressing HIV disease, we must continue to partner with those working on broader issues of healthcare access and inequities.

This year we face perhaps one of our biggest challenges in U.S. HIV/AIDS advocacy. At the same time that so much work remains to be done, we have to ensure we don't lose ground in the care and support programs so many have struggled to put in place. We can't allow the Bush administration to turn back gains already made in funding for U.S. HIV/AIDS programs. While President Bush has made a verbal commitment to fighting HIV/AIDS, his recently released budget proposal for Fiscal Year 2002 does not live up to his words. In particular, his proposed budget calls for no increase to the Ryan White CARE Act, which funds treatment and healthcare services including the AIDS Drug Assistance Program (ADAP). This marks the first time since

the CARE Act became law that a President hasn't proposed an increase. With the growing number of people needing services and the rising cost of healthcare and treatments, a flat-funding request actually translates into a cut in CARE funding.

This is especially problematic as ADAPs nationwide are currently reporting difficulties providing adequate services. In some states, these programs never were able to reach and serve all those in need, and with flat funding, unmet need will grow as many states cut back on their coverage. Last year, ADAP federal funding fell $60 million short of the projected amount needed to maintain adequate services. According to a recent report by the National Alliance of State and Territorial Directors (NASTAD), ten states (AL, AR, GA, IN, KY, ME, MT, OK, SC and SD) have closed enrollment to new clients. Seven more (ID, FL, MD, MO, OR, RI and WV) are expected to implement waiting lists or other restrictions by the end of September. Even states with the most comprehensive, well-financed ADAPs such as California, New York, and Pennsylvania have indicated they may need to place restrictions on their programs. Without a sufficient increase in ADAP funding, people with HIV/AIDS across the country will find it much more difficult to access treatments.

Equally troubling is that the President is also asking for no increase to the Congressional Black Caucus Minority HIV/AIDS Initiative, which funds care and prevention services in communities of color.

Fortunately, the President's budget does include increases for some programs. While increases in one area do not make up for the lack of funding in others, it's important to note the positive part of the President's request. He is asking for an 11.5% increase for HIV/AIDS research at the National Institutes of Health (NIH). However, that figure doesn't match the overall 13.5% increase that the NIH is proposed to receive. We must protect the increase in research funding and ask that it be proportional to the overall increase. The proposed budget also provides modest (but insufficient) increases for the Housing Opportunities for People With AIDS (HOPWA) program and CDC HIV prevention programs.

This is not a time to rest on our laurels. It is clear that past advances can be reversed and future gains made more difficult when the administration or Congress changes. Today, we must remember our past and what it took to achieve our earlier victories. This means a renewed commitment to organizing across communities of people living with HIV, letter writing, lobbying, policy work, and, when necessary, direct action. We can't take for granted that the administration will share our values and goals. We need to continue work within the U.S. with renewed commitment, even as many activists begin to work on international issues.

What can you do as an individual to affect policy and funding change at the federal level? Ask the national and state HIV/AIDS groups with which you're connected what they do to support appropriate federal funding and HIV/AIDS policy. Find out if you can join their efforts. Many get involved by joining TAN, Project Inform's Treatment Action Network. TAN members receive regular policy updates and alerts detailing and supporting individual actions such as letter writing, emails and phone calls to their elected officials and other decision makers. For more information, call Project Inform's Hotline. You can also volunteer for and support the advocacy work of their local organizations. Together, we moved mountains in putting AIDS in the forefront of American politics. Let's work together to move them again. ■

Yes, I want to help Project Inform remain at the forefront of HIV treatment information!

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