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PERSPECTIVE

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

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Denial Defeated, Hope Reigns

The 13th International Conference on AIDS, held in Durban, South Africa, proved to be both the most important and the most unusual meeting since the earliest days of AIDS. This is the first time that the huge international meeting has been held in the heart of the global epidemic. More than any previous conference, this one was forced, by pure proximity, to confront the most rapidly escalating human suffering associated with the disease. It riveted attention on the prohibitively high cost of drugs and the need to build the medical and social infrastructure required to support the complex treatment of HIV. Similarly, it provided an important watershed for many African countries, a time to fully acknowledge the threat they face, to ponder the cost of government inaction and the need for clear thinking about solutions.

Unfortunately, it was also a conference afflicted by great distraction, mostly from the US and European HIV/AIDS denialist movement. The denialists believe that AIDS doesn't exist, even in Africa, or that even if it does, it has nothing to do with HIV. For the first time, such views became a major part of the media coverage of the conference. There could not be a worse moment for such intellectual dishonesty, pseudo-science and arrogance to rear its head. Yet there is still hope that the sheer presence of the conference itself and the attending media attention, whatever its focus, was enough to put the issue of AIDS in developing nations in the spotlight where it belongs. By the end of the conference, attention was shifting back to the issues that really matter, such as prevention, unfair pharmaceutical pricing and the lack of medical infrastructure needed to deliver basic healthcare and treatment for HIV.

What Happened?

Several years ago, the idea of holding the 13th International Conference on AIDS in South Africa seemed like a great idea. It made perfect sense to move the conference to one of the great epicenters of the epidemic. Once that decision was made, the focus on South Africa, and Durban in particular, became fairly obvious. It was not only the right country but also the right city, one of few in the developing world that had the capacity for managing such an event. Moreover, as the wealthiest country facing AIDS in sub-Saharan Africa, there was reason to hope that bringing the conference to South Africa would be preceded by serious prevention and treatment programs that might then serve as examples to the rest of Africa and Asia.

But the outlook for the conference was confounded when South African President Thabo Mbeki stumbled into the camp of the AIDS denialists while out cruising the Internet. President Mbeki's intrigue with denialist theories caused many scientists in Africa and throughout the world to wring their hands in despair and even cancel plans to attend the meeting. Though it is clear that Mbeki made a big mistake in giving a platform to the denialists on a pre-conference panel he created, it is equally clear that he raised some critically important questions that must be addressed if Africa is ever going to be able to cope with AIDS. Unfortunately, too much attention has been focused on his involvement with discredited fringe theories. Lost in the debate are the true challenges he has raised about how to bring solutions to his country.

A Little Background

Well-confirmed estimates say that 5,000 HIV-infected babies are born each month in South Africa. Among adults, sampling surveys suggest that upwards of 1,700 people per day are infected and that some-

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In This Issue

E - *May be of special interest to women*

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where between one in five and one in ten are already HIV-positive. AIDS denialists complain that the numbers of HIV-positive people are merely estimates and not proven. But short of forced, mandatory testing of the entire population, such numbers are always estimates, based on well established sampling methods. There is simply no other way to do it.

Efforts to stop the spread of mother-to-child transmission have been hampered by a mix of high drug prices and confusion about the value of the drugs, stirred up by the AIDS denialists. They raised suspicions about the value of using drugs like AZT by inappropriately applying concerns about toxicity in long-term use to the short-term application of treatment around the time of birth. There is still no government plan in South Africa to intervene in mother-to-child transmission. Instead, the government claims it is awaiting the outcome of additional studies and building the necessary infrastructure. Independent efforts by the Nobel prize-winning group Doctors Without Borders, however, have shown that it is possible to do the job even with the existing infrastructure.

Still, no country in Africa is better poised than South Africa to make a dent against AIDS, even if some other African nations have already initiated more and better programs. Preventive treatment against mother-to-child transmission is financially feasible and the country has already invested in a wide network of clinics that could help administer the therapy in the context of prenatal care. It is frustrating that obstacles to preventing mother-to-child HIV transmission include politics and misinformation.

More challenging, perhaps, are the problems of prevention and delivery of treatment to people who are already infected. Social conditions and deeply engrained cultural practices regarding sex and the role of women render typical Western-style prevention programs all but impotent. Certainly, condoms can be useful, but only if cultural norms support their use. Rape and other abuses of women by men play a clear role in HIV transmission and must be confronted head on. But it will take time to achieve meaningful change and it will come only as a result of an enduring national debate and strong leadership. It is the lack of movement on these fronts that frustrates many AIDS workers and activists in South Africa and much of the African continent.

It is far too easy to focus on drug treatment as the solution to the problem. And President Mbeki is correct in pointing out that Western treatment programs cannot be simply transplanted to the South African environment. Even with greatly discounted drug costs, treatment for the infected population could easily bankrupt even this, the wealthiest of the sub-Saharan African nations. The raw cost of drugs, moreover, is but a single part of the picture, as today's AIDS therapies cannot be used efficiently without large investments in diagnostic tests and services as well as accompanying medical care. (See the article *Drug Pricing, AIDS and the Developing Nations* on page 12 of this issue of *PI Perspective* for more information on this topic.)

Confounding these issues is the fact that AIDS is not the only medical problem demanding attention in South Africa. Many other serious illnesses compete for government attention, along with poverty and malnutrition. All are affected by the high costs of potential solutions.

With this background, no one envies the difficult choices that must be made by the government of South Africa. There are no simple or readily available solutions. The last thing President Mbeki needed was confounding input from discredited Western scientists who themselves have little or no experience in dealing with the AIDS crisis. Yet that is exactly what he asked for and what he got.

Certainly, the early years of the epidemic in the US offer no model for governmental behavior. Whatever mistakes have occurred in South Africa have been at least partially caused by western influences and their arrogance or disinterest in dealing with a developing nation. Had we done more earlier to help support the cost of coping with AIDS and other illnesses and fought to reduce the price of treatment, the denialist diversion might never have happened. Misinformation and false solutions have a way of filling the vacuum when too little is done to solve a problem. The real work of stopping AIDS in Africa and other developing regions is just beginning. We must all do our part.

AIDS Denialists to the Rescue

The US and European-based denialist movement is mostly made up of scientists who are either long known as eccentrics in their fields, retired or who have a known affinity for contrary opinions. Few if any of them have actually played even the smallest role in AIDS research or care programs, and almost none have treated people with the disease. Most are not physicians nor are they trained in the disciplines needed to determine the cause of a disease. Their arguments have been presented and rejected over and over again in the scientific community for the last decade and a half. As a group, the denialists simply refuse to accept any data that

In Memory Of . . .

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

Stephen Gendin

Kiyoshi Kuromiya

Jere Liner

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

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contradicts their own opinions and beliefs, yet they provide no original evidence or data of their own. These factors, while well known in the scientific community, are not immediately apparent to an innocent surfer of the Internet, nor are audiences who lack formal scientific training likely to see the giant holes in their arguments.

Prior to the Durban conference, President Mbeki learned of the denialist views in a sleepless night while searching the Internet for solutions. He thought he had come upon a group of self-described noble "dissidents" who claimed to be unfairly isolated and rejected by the scientific mainstream. Their own writings fail to mention how many times the scientific peer review process has already evaluated, assessed and rejected their arguments that HIV doesn't cause AIDS, that HIV is harmless or doesn't exist, and that there really is no crisis in Africa. To Mbeki, though, "dissident" is an honored political term that he understandably relates to. He had no way of knowing the history of the denialist movement or the characters who populate its web pages, no way of knowing if they were genuine scientific experts, people pursuing a lost cause or just the latest conspiracy theorists.

Unfortunately, Mbeki's personal experience as a political dissident made him an easy target for the denialist yarn. Soon, he was inviting California denialists David Rasnick and Charles Geschectner to South Africa for consultation. Peter Duesberg was asked to send his book and data. Once the word got out, otherwise unknown writers and fringe activists working the denialist circuit were both singing Mbeki's praises and burying him in their papers, documents and opinions. No similar effort was made to seek input from genuine HIV experts, at least at first.

The scientific community in Africa and internationally were aghast, realizing that Mbeki had inadvertently opened the hen house to the foxes. Instead of getting advice from people with genuine expertise in dealing with AIDS, he was soon being told that AIDS didn't exist, that the disease wasn't infectious, that it was just a manifestation of poverty and there was nothing he need do about it. People who didn't want to see their western governments channeling funds and services to Africa at taxpayer expense were now broadcasting their message through the head of an African state. Mbeki wrote a strange and strongly worded letter to US President Clinton suggesting that those who didn't want him to listen to the denialists were somehow similar to the oppressors of South African blacks in the days of Apartheid. It must have come as a great surprise to Mbeki, however, when the main voice supporting his odd turn of direction was in fact the South African Böerstadt party, itself the right wing political remnant of the Apartheid ruling parties.

World renowned African scientists joined with AIDS researchers internationally urging him to reconsider.

The last thing President Mbeki needed was confounding input from discredited Western scientists who themselves have little or no experience in dealing with the AIDS crisis.

The Panel of Experts

Mbeki hoped to resolve the matter by calling for a meeting of international AIDS experts to address the question of HIV's role in AIDS, along with a list of truly important questions about how to deal with AIDS in South Africa. The panel was initially made up of roughly a 50-50 mix of mainstream and denialist-associated voices. The panel make-up was changed at the last minute to include a larger number of practicing AIDS experts and slightly fewer denialists.

Reports from people who attended that meeting suggest that within the first hour it became clear that little or no common ground would be found. Shortly after Mbeki himself decried the tragedy of AIDS unfolding in his country, one of the denialist leaders asserted that there was no proof that there was any problem or anything unusual happening in Africa at all. Two days of dis-

cussion went downhill from there, with the mainstream scientists and dissidents breaking off into two completely separate groups. After the weekend meeting, the discussions were to continue over a "closed" Internet discussion group, right up until the week before the International AIDS Conference in Durban. At the final meeting, a vague "compromise" was worked out that would arrange for further testing of the accuracy of HIV blood tests. After all the sound and fury, it was a curiously empty conclusion.

Durban—The Lost Opportunity

When Mbeki rose to the podium to welcome delegates to the "real" AIDS conference in Durban, there was great hope that he would now put his flirtation with the denialists behind him and call for drastic action against AIDS. He instead offered a classic politician's response, a long vague speech that left everyone wondering what he really believed. Hundreds of conference delegates walked out during the talk, which neither recognized nor denied the role of HIV. For most, it was enormously frustrating to see Mbeki squander a great opportunity to advance the fight against AIDS in Africa. All he seemed to promise was more confusion and delay. Sadly, those who walked out in protest missed the stunning presentation that followed, in which an 11-year-old boy succinctly and passionately made the case that had eluded Mbeki.

The other issues that Mbeki raised in his talk, such as poverty, hunger, and sanitation, are indeed critically important. But, as many researchers were quick to point out, these conditions long pre-existed AIDS and were no worse—and often better today than 50 years ago—yet the death rate is soaring today while life expectancy plummets. What's new, obviously, is HIV and AIDS. And this is what he failed to address. Instead, he wasted time defending his exploration of denialist views, sending a signal of confusion to patients and AIDS workers throughout Africa.

The harm done may extend beyond South Africa. When a respected head of state publicly muses about whether HIV might be harmless, it makes the job of prevention far more difficult. Unless he now makes clear and unequivocal statements to the contrary, many people—themselves goaded on by the denialist literature—may choose to take the easy way out and disregard the difficult messages and behaviors of prevention. His inaction has also at least delayed the initiation of government sponsored preventive treatment against mother-to-child transmission and may ultimately make women fearful of the drugs used for this purpose.

The true blame here lies not with Mbeki but primarily with the AIDS denialists themselves who have brazenly taken advantage of a lapse in presidential wisdom.

President Mbeki had the right idea in seeking expert input, but the process was diverted by trying to address the AIDS denialist position rather than the real issues at hand. The true blame here lies not with Mbeki but primarily with the AIDS denialists themselves who have brazenly taken advantage of a lapse in presidential wisdom. Having failed to make their case in the courts of science, they changed the venue to one of politics. They placed their own narrow and repeatedly rejected views above the lives of tens of millions of African men, women and children.

The proper venue for the debate about the cause of AIDS is the scientific community, where differing views are subject to the scientific process and peer review. When a point of view fails repeatedly in this venue, its proponents have no business trying to sell their beliefs instead in the political or public arena where people lack the background and knowledge to evaluate it. If they still wish to pursue their opinions, they are ethically obliged to conduct further experiments, collect more data, and try once again to convince their colleagues. Some denialists like to compare themselves to Galileo or other famous scientists who's views were once considered heretical. But the comparison is false. Galileo and others eventually succeeded through the strength of the data they presented to their scientific peers, not by politics or rhetorical appeals to the public.

Mandela Comes Through

Whatever the weaknesses of Thabo Mbeki as a leader, South Africa still possesses one of the world's greatest treasures in the person of Nelson Mandela. It fell to the man who defeated Apartheid to write the next act in South Africa's fight against AIDS. In a stirring speech at the conclusion of the conference, Mandela subtly and skillfully asked Mbeki to put his pursuits aside and urged all of Africa to aggressively confront the problem of HIV and AIDS. He spoke forcefully on HIV prevention, condom use, treatments to block mother-to-child transmission and education for the masses. With his carefully chosen words, Mandela made it abundantly clear that there was no time to quibble over old issues and political differences. The fire was already at the door. Echoing themes stated in an earlier uplifting speech by PWA and High Court Judge Edwin Cameron, Mandela brought the house to its feet, united in a clear vision of where to go, and what to do next. For the moment at least, all of Mbeki's hesitant and confused responses seemed unimportant, just another side show.

Commentary

While it may be fair to say that the South African government has stumbled in its first efforts toward coping with AIDS, the same can be said of all Western nations. Certainly, the early years of the epidemic in the US offer no model for governmental behavior. Whatever mistakes have occurred in South Africa have been at least partially caused by western influences and their arrogance or disinterest in dealing with a developing nation. Had we done more earlier to help support the cost of coping with AIDS and other illnesses and fought to reduce the price of treatment, the denialist diversion might never have happened. Misinformation and false solutions have a way of filling the vacuum when too little is done to solve a problem. The real work of stopping AIDS in Africa and other developing regions is just beginning. We must all do our part.

While the 13th International Conference

on AIDS may not have offered as much new science of interest to western patients, it may offer the beginning of hope for tens of millions of people thus far left behind. Governments, companies, researchers and activists must now offer whatever help they can. (A special issue of *PI Perspective* will shortly follow this one summarizing research highlights from the meeting.) ■

Anti-HIV Drug Update

There continues to be progress in the development of a number of new anti-HIV drugs. Additional research has focused on optimizing the use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). This has resulted in studies of dual protease inhibitor combinations, protease inhibitor and NNRTI combinations and now dual NNRTI combinations.

Protease Inhibitors

A study at Stanford looked at the effectiveness of adding ritonavir (Norvir) to an existing three-drug regimen including indinavir (Crixivan) for people who have detectable HIV levels. The purpose of this study was to determine if higher levels of indinavir in blood would result in greater anti-HIV activity. Previous studies have shown that ritonavir substantially increases and stabilizes indinavir levels in blood.

Thirty-five volunteers with a viral load of about 1,200 copies HIV RNA and CD4+ cell counts averaging around 420 participated. The dose of ritonavir and indinavir used was 400mg twice a day for each drug. For the first three weeks of the study, volunteers did not change their anti-HIV regimens but added ritonavir. After three weeks, people were allowed to change their nucleoside analogue drugs.

These preliminary short-term results suggest that this type of intensification strategy can further decrease viral levels in people with low but detectable virus.

Drug Identification Chart

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

The addition of ritonavir increased the overall anti-HIV activity of the regimen with 48% of the volunteers reaching viral loads under 400 copies HIV RNA (up from 26%) and 28% under 50 copies HIV RNA (up from 0%) after three weeks. After sixteen weeks, 59% of the volunteers had HIV levels below 400 copies and 53% were below 50 copies. These preliminary short-term results suggest that this type of intensification strategy can further decrease viral levels in people with low but detectable virus.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Preliminary results from a study with capravirine (formerly known as AG1549, from Agouron Pharmaceuticals) show that the drug is quite potent. Laboratory studies suggest that this drug may be effective against NNRTI-resistant virus. Volunteers in this

small ten-day study received varying dose levels of 700mg twice a day, 700mg three times a day, 1,400mg twice a day, 1,400mg three times a day or 2,100mg twice a day of capravirine.

HIV levels were reduced by 1.23 logs (17 times) on the lowest dose to 1.65 logs (45 times) on the highest dose. There was no real difference in anti-HIV activity between the twice and three-times daily dosing schedules. The most common side effects were headache, nausea and vomiting, which were all considered mild to moderate in severity.

... there is a big potential for drug interactions when combining NNRTIs as well as an increased risk for side effects.

One small study looked at the effect of combining two NNRTIs in people with increasing HIV levels while on protease inhibitors. Volunteers were started on 500mg twice a day of emivirine (Coactinon, an experimental NNRTI from Triangle Pharmaceuticals) for eight days and then the dose was increased to 750mg twice daily and 600mg once a day of efavirenz (Sustiva) was added to the regimen. There was a greater than expected interaction between the two drugs which apparently reduced the effectiveness of efavirenz. The doses were changed to 500mg of emivirine twice a day and 800mg of efavirenz once a day.

Volunteers experienced moderate-to-severe side effects including rash, nausea, decreased appetite and diarrhea. Preliminary results show that people who had the highest emivirine and efavirenz levels in blood had the greatest anti-HIV responses, however they were also most likely to develop side effects.

This study shows that there is a big potential for drug interactions when combining NNRTIs as well as an increased risk for side effects. So far, though, there is no clear evidence of any gain in effectiveness. People should be carefully monitored if they are considering such combinations.

Once Daily Dosing?

Preliminary results of a once a day regimen shows promising anti-HIV activity. This study followed forty people with a viral load of about 60,000 copies HIV RNA and CD4+ cell counts averaging around 400 who were taking anti-HIV therapies for the first time. Volunteers received the experimental NRTI emtricitabine (FTC, Coviracil an experimental nucleoside analogue from Triangle Pharmaceuticals), ddI (didanosine, Videx) and efavirenz, all given once a day at bedtime.

After 24 weeks, 98% of the volunteers had HIV RNA levels below 400 copies and 93% were below 20 copies. The most common side effects were central nervous symptoms (dizziness, sleep disturbances, depression and headaches), diarrhea and rash, almost all of which were considered mild-to-moderate in severity.

Commentary

It is becoming more likely that people starting anti-HIV therapy for the first time will be able to use a potent once daily regimen. However, there is still no standard-of-care for what to do after a first or second regimen fails. As a result many approaches are being studied and sometimes combined. These include structured treatment interruptions, resistance test utilization to select anti-HIV therapies and megaHAART (using five to nine anti-HIV drugs). ■

This is Project Inform's fifteenth year of serving individuals living with HIV/AIDS.

Over these fifteen years we have seen the AIDS epidemic change. Treatment information and strategy evolve continuously, as do the many advocacy and public policy issues we confront. Project Inform's work is more vital than ever. We hope that you will consider making a special gift in recognition of our fifteenth year so that Project Inform can continue to effectively address the challenges of HIV/AIDS, both nationally and internationally.

Watch for upcoming mailings that will provide you with the opportunity to make a special fifteenth year donation—or you can respond right now by using the form on the back of the enclosed issue of *In Focus*. The dedication and support of people like you makes it possible for us to fulfill our mission of providing information, inspiration and advocacy for people living with and affected by HIV/AIDS. Thank you for your continuing support.

The Latest on Structured Treatment Interruptions

Interest in structured treatment interruptions (STIs) (sometimes mistakenly called drug holidays) continues to increase. Though research in this area is relatively new and so far inconclusive, many people are already taking unplanned or unstructured treatment interruptions due to problems with drug side effects, treatment failure and adherence problems.

During unstructured interruptions, people are not closely monitored for viral load and CD4+ cell counts. The interruption follows no particular plan. However, people taking STIs are usually tested very frequently for viral load, CD4+ cell count and sometimes resistance. This way, when they're ready to restart therapy, the decision can be made based on data and the achievement of goals while minimizing the risks.

Early results have recently been reported from several STI studies, but it's still too early to know how safe or effective an STI treatment strategy may be. STIs are now being studied in three different scenarios:

1 **Primary or chronic/established HIV infection in people with well controlled viral replication.**

The goal in either group is to improve the natural immune response against HIV, hopefully making it possible to control viral replication with less aggressive treatment. In primary infection (someone infected very recently, from a few days to a few months), the body usually mounts a vigorous immune response against HIV. Over time, though, this response often fades. In chronic/established HIV infection (someone living with HIV for at least a year), this natural immune response is often very weak or missing altogether. In both cases, the decline is thought to be associated with the success of anti-HIV therapies, which dramatically reduces the amount of new virus being produced. Because of this lowered viral activity, the immune system sees less and less of the virus and thus does less to mount a defense against it. By periodically permitting HIV to replicate, an STI permits the immune system to once again "see" and react against the virus, perhaps resulting in a strong natural anti-HIV response. See Fig. 1.

2 **Chronic/established HIV infection in people who have developed resistance to all or most of the available antiviral drugs.**

The potential goal of STI here is to replace drug-resistant virus with non-resistant virus, called "wild type." This might restore a person's sensitivity to drugs that had previously become ineffective due to resistance and allow the drugs to work again, at least temporarily.

3 **Chronic/established HIV infection in people who have become physically or psychologically intolerant to currently available anti-HIV drugs.**

The goal of STI in this context is give the person—mind, body and spirit—a chance to rest and recover from the stress of anti-HIV therapy. Some people develop bothersome side effects to anti-HIV drugs, either quickly or after years of use. Side effects such as liver and kidney problems can become serious, even life-threatening, and limit a person's ability to use the drugs. Other effects, such as *lipodystrophy*, may have unknown long-term consequences in addition to their visible impact. Many also develop psychological obstacles. Over time, it gets more difficult to adhere to the regimen. Whether the cause is physical or psychological, intolerance of the drugs will cripple their ability to aid in the fight against HIV. While these factors may affect only a portion of people on treatment at any moment, over time they are likely to effect everyone who hopes to live out a normal life span with HIV.

STIs in Scenario #1

Primary Infection: A Boston study followed 15 people with primary infection treated with HAART for over a year. Seven took an STI and their viral loads and CD4+ cell counts were measured weekly. Their immune response to HIV, or HIV-specific cytotoxic lymphocyte (CTL), was also measured. HIV-specific CTLs are cells that target and destroy HIV-infected cells.

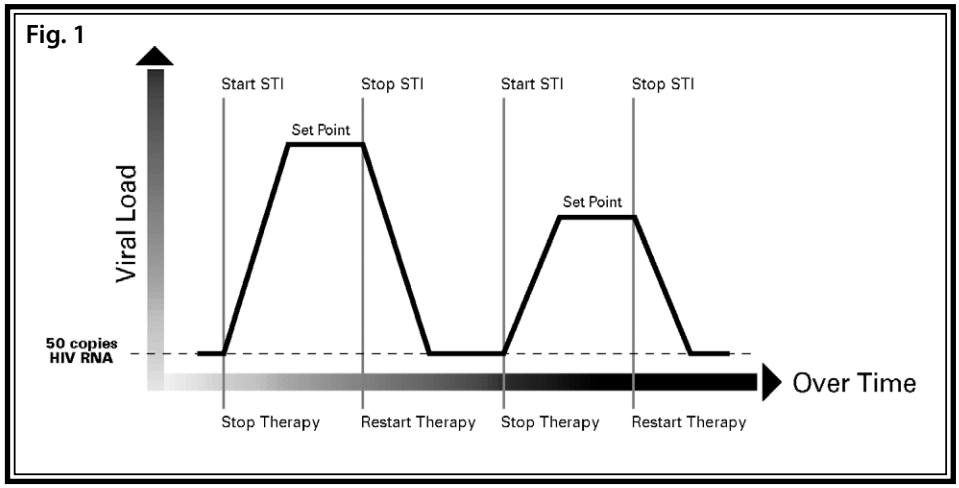
At the start of their STIs, the seven participants had low level CTL responses and undetectable viral loads. During the STIs, all saw their HIV levels increase, as expected, so they restarted HAART. Everyone also experienced increases in HIV-specific CTL responses after the STI.

Three of the seven went on to a second and third cycle of STI, and with each cycle they had higher HIV-specific CTL responses. After each STI, the returning levels of viral load were lower than in the previous STI and it often took longer for viral load to reappear. This suggests that the improved HIV-specific CTLs were at least partly effective in controlling HIV replication.

Chronic Infection: A Barcelona study followed 26 people with HIV levels below 50 copies for over two years. Fourteen continued on HAART while the other twelve took an STI. Among the twelve, five had two courses of interleukin-2 (IL-2, Proleukin) while on HAART; the other seven took their same HAART regimen as before their STIs. Those on STIs were closely checked for viral load (every two days to determine the rate of increase in HIV levels).

This study was designed for people to restart HAART either after 30 days of interruption or when their viral loads went above 3,000 copies HIV RNA. They then took their HAART regimens for three more months before taking another STI.

During the first STI, two had no detectable HIV levels during the 30-day period. However, on the second STI, only one person continued to have undetectable (below 50 copies HIV RNA) HIV levels during the 30 days off therapy. In most, HIV levels



increased after 14 or 15 days off therapy during the first and second STI. The percentage of CD4+ and CD8+ cells did not change during the STIs. There was no difference between people who used IL-2 and those who did not.

Early results found little or no improvement in the immune response to HIV and all participants experienced significant increases in HIV levels during STIs. However, it is possible that more cycles of STIs are needed before the immune system can mount a stronger response against HIV.

The largest study to date involving STI is the Swiss-Spanish Intermittent Treatment Trial, currently enrolling 120 people with CD4+ cell counts above 300 with viral loads under 50 copies HIV RNA for at least six months. The study design involves alternating between two weeks off HAART and eight weeks on, for a total of four cycles. After 40 weeks, anti-HIV therapy will be stopped indefinitely until a person's viral load increases to 5,000 copies HIV RNA, when therapy is then restarted.

Early results from this study involve 96 people who had one STI, 54 people a second and 23 a third STI. All had viral load increases during the STI. So far, there's no indication that the viral load set point is lower or that there are any significant changes in CD4+ cell counts with each STI.

All of these studies have found that when people restart HAART, viral loads decrease and, in almost all cases, go back to under 50 copies HIV RNA. This suggests that participants are not developing anti-HIV drug resistance. However, people should be cautious with efavirenz (Sustiva) and nevirapine (Viramune) when undertaking an STI since these drugs remain in the bloodstream far longer than other anti-HIV drugs. Researchers recommend that they be stopped two to three days before stopping other drugs when initiating an STI.

STIs in Scenario #2

A Frankfurt study of people who had developed resistance to most or all currently approved anti-HIV drugs reported that three-quarters of them shifted from multi-drug resistant virus to wild type virus during the STI. Groups in London and San Francisco have duplicated this observation.

The San Francisco study followed 18 people who had developed resistance to protease inhibitors and nucleoside analogue drugs. During the STI, all experienced decreases in CD4+ cell counts (an average of about 100 cells) and increases in HIV levels (about a ten-fold increase). Sixteen of the eighteen shifted from protease inhibitor-resistant virus to protease inhibitor-sensitive virus during the STI, although seven retained some degree of resistance to the nucleoside analogue drugs.

However, when using extremely sensitive techniques, researchers found that about half the participants had very low levels of drug-resistant HIV. In others words, they did not find protease inhibitor-resistant virus in blood when using standard tests but did find it when using extremely sensitive tests. Since no participant had restarted therapy when these results were presented, the significance of these findings is unknown.

STIs in Scenario #3

Little research has yet been conducted on the use of STIs for combatting physical or psychological intolerance of drug regimens. However, this scenario probably reflects the most common form of "unstructured" interruption in which people simply stop treatment to recover from side effects and give themselves a rest. There is some work underway to create observational databases of the experiences of such people.

Commentary

These early studies primarily looked at the potential risks rather than the benefits of STIs. They suggest that, at least in the short-term, there's a low risk for developing drug-resistant HIV. However, decreases in CD4+ cell counts to pre-treatment levels and increases in HIV levels in some people suggest the need for frequent and careful monitoring, particularly if the resulting CD4+ count falls into the ranges with increased risk of opportunistic infections (under 200 for some OIs, under 100 for others). When this occurs, people should resort to earlier strategies of treatment, such as Bactrim for preventing pneumocystis pneumonia.

Numerous STI studies are planned for the near future. They will explore different lengths of STIs and different lengths of time on therapy as well as possibly using therapies, like IL-2 and therapeutic vaccines, that affect the immune system.

More results will be available soon that will help determine the role of this strategy in treating people with HIV. Project Inform, the Foundation for AIDS and Immune Research (FAIR) and the Treatment Action Group (TAG) will convene a second workshop on STIs in the fall of 2000. At this meeting, new results, ideas and observations will be discussed and incorporated into future studies. ■

"Switch" Studies for People with Lipodystrophy

Many people are considering or have already switched to a regimen without protease inhibitors in hopes of reversing fat redistribution, or lipodystrophy syndrome(s), and/or to lower cholesterol and triglyceride levels that have been associated with using anti-HIV therapy. The studies below suggest that this strategy may be somewhat effective in reducing triglyceride and cholesterol levels. But there is conflicting information on whether it is effective in reversing fat redistribution.

Sydney Study Results

A group from Sydney, Australia which has conducted a great deal of lipodystrophy research reported on a study of 80 people who either continued using protease inhibitors or switched to a regimen of abacavir (Ziagen) + adefovir + nevirapine (Viramune) + hydroxyurea (Hydrea). People who switched had a decrease in triglyceride and cholesterol levels, but there was no change in HDL or "good cholesterol".

Additionally, those who switched had some reduction in abdominal fat (fat around the gut, or *central/truncal obesity*) but continued to lose peripheral fat from their arms and legs. They also lost, on average, about six pounds in body weight. It's not clear whether the weight loss is due to switching anti-HIV drugs or to other factors. (Several studies have reported that people on adefovir lose weight.) People who continued using protease inhibitors continued to gain abdominal fat.

Changing anti-HIV therapies may or may not be useful in reversing fat redistribution.

Barcelona Study Results

A study conducted in Barcelona followed 106 people who continued using combinations which included protease inhibitors or switched to ddI (didanosine, Videx) + d4T (stavudine, Zerit) + nevirapine. People who switched significantly lowered their cholesterol and triglyceride levels while those who continued using protease inhibitors saw no change in either measurement. Neither group experienced changes in glucose levels.

The loss of peripheral fat seemed to stabilize among people who switched to the nevirapine regimen while those on protease inhibitors continued to lose peripheral fat. There were no significant reductions in abdominal fat in either group. There were also no differences in viral load rebounds (from below to above 50 copies HIV RNA) between the two groups after 36 weeks of the study. Those switching therapy had a small increase in CD4+ cell counts.

Commentary

These and other results suggest that protease inhibitors are primarily responsible for the reported increases in triglyceride and cholesterol levels. Switching to a regimen without protease inhibitors does appear to lower these levels. However, it's unclear whether this is the case for all non-protease inhibitor drugs. For instance, several studies have shown that the non-nucleoside drug, efavirenz (Sustiva), also increases triglyceride and cholesterol levels.

Changing anti-HIV therapies may or may not be useful in reversing fat redistribution. It is entirely possible that some of the side effects are due to specific drugs and is not drug-class specific. In other words, one protease inhibitor may increase triglyceride and cholesterol levels while another may not. Some emerging results support this theory.

For example, based on some relatively short-term studies, the protease inhibitor amprenavir (Agenerase) does not appear to increase triglycerides and cholesterol as much as the other currently available protease inhibitors. Other studies suggest that d4T affects the loss of peripheral fat more than the other nucleoside analogue drugs. Two studies have shown that people who switched from d4T to other nucleoside analogue drugs had increases in peripheral fat but no change in abdominal fat. These observations suggest that some fat redistribution may be reversible. ■

The major points from *"Switch" Studies*

- Switching to a regimen without protease inhibitors may lower elevated cholesterol and triglyceride levels.
- Switching may or may not effect fat redistribution.
- Switching doesn't necessarily lead to a loss of viral control

PI Perspective

PI Perspective provides comprehensive information from the most recent studies plus perceptive analysis in state of the art AIDS treatment and research.

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Bone Problems

There are a growing number of reports of bone problems (*avascular necrosis* and *osteonecrosis*) among people with HIV. These problems are caused by a lack of blood supply in the bone, which leads to the deterioration and death of bone tissue. Generally, bones try to repair themselves. But bones that support a lot of weight, like the hip, can weaken when this condition occurs. This may cause the bone to fracture or collapse. This condition can also lead to severe pain and inflammation or overgrowth of bone in and around the joints (osteoarthritis). While still relatively uncommon, people should be aware of reports of avascular necrosis that have led to hip fracture or dislocation. Symptoms or pain associated with avascular necrosis also commonly affect the shoulder and/or knee. Avascular necrosis is different from *osteoporosis*, a general term for a progressive loss in bone density that results in skeletal (bones that make up the framework of the body) weakness.

What causes avascular necrosis in people with HIV is not known. Some attribute the problems to anti-HIV therapies. Others believe it may be linked to the metabolic abnormalities (e.g. lipodystrophy, changes in body composition and changes in the way that the body stores and uses fat and sugars) that have been discussed in previous issues of *PI Perspective*. In HIV-negative people, corticosteroid therapy (e.g. prednisone), alcohol abuse, Gaucher's disease (a metabolism disorder) and connective tissue disease are all associated with avascular necrosis. Other diseases that may result in avascular necrosis include diabetes, atherosclerosis (thickening and hardening of the arteries), fatty liver and pancreatitis.

Detection and Diagnosis

Early detection of avascular necrosis is related to better outcome. Magnetic Resonance Imaging (MRI) is most commonly used to diagnose avascular necrosis. It is especially useful in early disease when the hip or other bone collapse may still be preventable.

An X-ray or CT scan is sometimes used to rule out advanced stage disease. By the time avascular necrosis shows up on a common X-ray, it is usually irreversible. The amount that avascular necrosis impacts bones that support weight is the most reliable predictor of outcome. Treating this condition often involves surgery.

Symptoms of Bone Disease

Individuals experience different symptoms with avascular necrosis. When the hip is affected, people often experience groin pain. This sometimes results in limping and a limited range of leg motion. A distinct feeling of a 'click' in the joint often occurs when moving from a sitting position.

Almost all people with avascular necrosis affecting the knee report severe pain and tenderness in and around the knee. When the shoulder is affected, people rarely experience pain because the shoulder is not a *weight-bearing* bone. However, movement of the shoulder is usually restricted.

Early intervention with surgery may offer the best chance of preventing serious dysfunction of the hips and knees. Bone transplants may help support the hip as the body tries to restore the flow of blood to the damaged area. Another approach that shows some success is cutting through the bone (osteotomy) to change how the joints function and to redistribute body pressure away from the hips. Crutches must be used for several months after both transplants and osteotomies. Yet another option is to drill out parts of the hip to reduce the pressure inside the bone. About 75% of people who undergo this procedure avoid hip replacement in the future.

Hip and knee replacements are usually done only for people with severe pain who also have osteoarthritis.

As avascular necrosis appears to be an emerging problem, there needs to be more awareness of it. Research is underway to better understand what causes avascular necrosis in people with HIV. More information should be available in the near future. ■

The major points from *Bone Problems*

- Complaints of bone problems, called avascular necrosis and osteonecrosis—usually affecting the hips, knees and shoulders—are being reported among people with HIV.
- Special X-rays (called MRI and CT scans) are needed for diagnosis
- Early detection and treatment can prevent the need for hip replacement surgery.
- In severe cases, treatment requires surgery.
- Research is ongoing to better identify the cause of this condition.

Meeting Explores Gender Differences in Viral Load

On January 29, 2000, Project Inform co-sponsored a meeting with the National Institute of Health's Office of AIDS Research and the National Institute of Child Health and Human Development on the issue of gender differences in HIV levels. The meeting convened HIV researchers, physicians and women living with HIV to review the research to date, identify potential gaps and develop a research agenda.

The issue of gender differences in viral load gained momentum in December 1998 when a major study reported that women may progress to AIDS with half the viral level of men. Since then conflicting findings about possible differences in viral load between women and men have emerged.

A driving question of the meeting was, "*Is there enough evidence to conclude that there is a gender difference in viral load?*" Based on an extensive research review, meeting participants concluded that observed differences in viral load are real and present in the first several years of HIV infection and disease. These differences may lessen or disappear within five years after initial HIV infection. Data were conflicting as to whether or not gender differences persist after the first five years of HIV infection. Some studies suggested they do, while others seemed to show that they do not.

The significance of these differences remains unknown. Because of this and because there is increasing debate about the best time to start anti-HIV therapy, the meeting concluded that, at this time, recommendations for treating HIV-positive women should not be changed. In essence, recommendations should remain the same for both men and women. However, participants agreed that discussion of these differences should be significantly expanded in the Federal Guidelines for using anti-HIV therapy and should be taken into consideration when starting treatment.

Attempts to identify and describe causes for gender differences in viral load were discussed. Many gaps exist in our understanding of gender differences in HIV disease—not only in viral load, but also in CD4+ cell count and dynamics, and the effect of sex hormones on these various measures.

Not surprisingly, hormonal cycles were suggested as a possible cause for differences in viral load. Despite new information describing viral load variation during the ovulatory cycle, meeting participants agreed that there simply were not enough data to support a conclusion that hormones caused these observed differences. However, further research is needed in this important area.

Underscoring this need were compelling data presented from the Women and Infants Transmission Study. It showed that viral load is consistently lower (though not to a statistically significant degree) in infant girls than boys. Infancy is a time when the hormonal environment is similar in both females and males, suggesting that something other than hormones influence these viral load differences. However, in the last three months of pregnancy, baby boys are exposed to a surge of testosterone. It is unknown whether this may affect a boy's viral load.

Finally, researchers highlighted the fact that there appeared to be race and ethnicity differences in viral load which may confuse and further complicate the picture. In short, African Americans and Latinos appear to have lower viral levels than Caucasians. These findings stress the need to consider race and ethnicity as well as gender when studying viral load differences and HIV disease progression in general.

Some of the scientific goals identified for future exploration include:

- identifying the cause for lower viral levels in women during the first years of infection;
- determining if men and women harbor and clear HIV differently**;**
- determining if gender differences exist in CD4+ cell count and the dynamics of cell production and destruction;
- understanding the effect of hormones and other factors on viral load and CD4+ cell count; and,
- determining if race and ethnicity affect markers of HIV.

The major points from *Gender Differences*

- Project Inform co-sponsored a meeting on gender and viral load.
- Women may have lower viral levels than men in early HIV disease (first five years of infection).
- Differences may not persist over time; the cause and significance of these differences remains unclear.
- No changes were recommended for the use of anti-HIV therapy among women.
- Racial and ethnicity differences in viral load may be equally important and should be explored.

Commentary

In order to answer the many important questions borne out of the meeting, more women need to be enrolled in studies. Moreover, to determine clear differences between gender, more men of color need to participate in studies as well. Current studies and networks should be used to address these issues and maximize findings. New initiatives and collaborations—particularly between basic science and clinical researchers—focusing on gender, racial and ethnic differences in HIV disease markers and progression need to be forged.

It is important to consider that there are no reports of increased survival based on gender alone. Still, varied access to healthcare and HIV treatment places many women at a disadvantage. Finally, race, ethnicity, socioeconomic background, age and co-infections must also be considered as factors that may influence differences in viral load, CD4+ cell counts and rates of disease progression. ■

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

The upcoming issue will have highlights from the 13th International Conference on AIDS.

Recent issues include:

- Sex and Transmission, a Continued Concern for Positive Women
- Gender Difference in Viral Load?

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Drug Pricing, AIDS and the Developing Nations

As world attention shifts to the problem of AIDS in Africa and other developing nations, it is clear that we need something other than "business as usual" if HIV-infected people are ever going to have access to treatment. The North American and European model, which relies on annual expenditures of ten to twenty thousand dollars a year per person for drugs and support services, will never meet the needs of countries that spend only a few dollars per person annually on health care. It is against this backdrop that world attention has begun to search for ways to stop or at least slow the growing death rate from AIDS.

There are no simple solutions. Any effort that focuses solely on providing the needed drugs themselves is an over simplification. Simply dumping drugs in the poorest countries would not only fail to solve the problem but would most likely make things worse. Effective solutions must address not only the provision of drugs but more importantly the creation of a healthcare infrastructure to deliver them. They must also include patient education networks to help enable informed and safe use of the therapies. Without the needed clinics, clean water, basic nutrition, diagnostic testing, medical supplies and public education about the proper use of the medicines, a supply of drugs alone would quickly lead to multi-drug resistant strains of virus. Supplies of drugs without a medical infrastructure for their delivery would lead to drugs rotting in shipping docks or uncontrolled black marketing, inviting both political and public corruption. Additionally, without a proper medical infrastructure, people may develop irreversible side effects. And perhaps above all else, drugs delivered without clean water and nutritional support simply couldn't work.

Yet, assuming goodwill and a major international effort, these problems can be addressed over time, eventually making it reasonable to focus efforts on drugs and the unrealistic prices currently charged for them. Some laudable private efforts, such as the work of the group *Doctors Without Borders* and other less well known programs, are already distributing medical treatment for AIDS in areas once thought impossible to reach. The question next becomes how to widen such efforts and address the entire population in need, not just selected portions of it.

Some discussion has focused on ways for impoverished countries to either make the drugs themselves, negotiate lower prices from the pharmaceutical companies, or to import them from other countries where they are sold at the lowest available prices. "Compulsory licensing" is a provision of international law that allows countries with a desperate health care crisis to forcibly obtain a license to manufacture and distribute a needed drug on its own while paying only a minimal royalty to the patent holder. "Parallel importing" allows countries to shop for drugs in other countries at the lowest available prices. Normally, industry sets drug prices separately in each country and one country cannot buy drugs from another to get around high local prices. Both these approaches have been encouraged by a wide spectrum of activist

and public policy groups. A key question, however, is whether they can make enough of a difference to solve the problem.

Recently, in response to these concerns, a small consortium of the major pharmaceutical companies announced their intentions to work with the United Nations to improve access to treatment. Few details have yet been announced. What's known so far is only that the program will place a high emphasis on working with countries where there is adequate attention paid to issues of healthcare infrastructure, not just drug discounting. It will not participate in dumping drugs but focus, quite correctly, on comprehensive solutions. While some of the motivation for this is humanitarian, it is also hard not to suspect that it is at least partly driven by increased public pressure and industry's great dislike for other proposed solutions, such as compulsory licensing and parallel imports, which they see as a major threat to their patent rights.

If industry insists upon the tightest possible control of patents, the price it must pay is to be the supplier of lowest cost for developing nations.

While this industry effort has been received with cautious support, a few key requirements must be met if it is to provide meaningful solutions and not just improved public relations. There are at least three basic principles that this program must adhere to if it is serious about helping developing nations. We urge international agreement on these principles:

Industry's offer of drug discounts must come without strings. It must not require participating countries to abandon their rights to other possible solutions, such as compulsory licensing and parallel imports. Since industry is so deeply concerned about the patent issues and protecting its intellectual property, there is fear that discounts might be offered only to countries that agree to swear off these alternatives. Such a provision would be unethical and immoral.

If industry really feels threatened by compulsory licensing and parallel imports, the way to discourage their use is by offering lower prices than could be achieved by such methods. Despite the apparent appeal of local manufacturing, no one can produce the needed drugs cheaper or with greater quality assurance than the manufacturers themselves. Industry already has the factories, production lines, quality control facilities and packaging structures in place and paid for by earlier sale of the drugs elsewhere. It is able to buy raw materials cheaper than any other possible source. No fledgling startup effort, either by country or a generic manufacturer could even come close to the economies of production already available to the drugs' manufacturers. The only real question is whether industry will cut profits to the bone, as needed, and sell the drugs at the cheapest possible price. If it does, this will simultaneously meet the needs of impoverished countries and industry's own perceived need to protect patent rights.

If industry insists upon the tightest possible control of patents, the price it must pay is to be the supplier of lowest cost for developing nations. The real power of compulsory licensing and parallel imports is the negotiating leverage they provide to force price cuts. For that reason, no country should ever give up the right to these mechanisms and activists should aggressively support them.

Deep discounting will not threaten the economics of the pharmaceutical companies. The basic costs of drug development and licensing for AIDS drugs are routinely paid for by sales and profits in the western nations. Industry can afford to think in terms only of raw materials and manufacturing costs, which are quite small. If even a relatively tiny amount of profit is built into the selling price of a drug, industry still stands to make money—perhaps a great deal of it—despite hugely discounted prices. The number of people in need in developing nations is so much higher than in western nations that even a very small profit per unit sale, applied across therapy for tens of millions of people, can add up to substantial profitability. Industry will not go bankrupt from becoming a good world citizen.

Offers of deep discounts on drugs must include all the newest and most recently developed therapies, not just older drugs. As a group, the new therapies are both more effective and easier to use, two factors that are even more critical in developing nations than in North America and Europe. To date, offers of discounts have only specifically mentioned older drugs such as AZT and 3TC. While these drugs may still be useful, and are used in combination with the newer drugs, they are not "state of the art" when used alone. Discount programs must not be used to unload older and less desirable drugs on poorer nations. The temptation to do so is very high within the pharmaceutical industry, which would like to find new markets for drugs whose sales have waned in the wealthier nations. The UN and other supporters of the discount initiative must prevent this from happening. Additionally, the countries that need the deep discounts must

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act quickly to license the newer therapies. If not, their own laws will limit the programs to older, less effective therapies.

3 Any discount program must provide sliding prices appropriate to the needs of individual nations, not a fixed discount rate for all. Developing nations differ widely in their economic ability to assist with the cost of treatment. Some, like South Africa, can afford to pay higher prices than other less economically fit nations. Western nations tend to view all of Africa as one large impoverished jungle, but in fact many African nations are quite sophisticated and have substantial economies and industrial growth. Others, however, are afflicted by wide scale, extreme poverty. They cannot all pay the same rates.

A fundamental principle of fair pricing must recognize that for the poorest nations, the only effective discount level is 100%—in other words, drug must be provided free of cost.

A fundamental principle of fair pricing must recognize that for the poorest nations, the only effective discount level is 100%—in other words, drug must be provided free of cost. Such provisions already exist in most western nations, where the pharmaceutical industry routinely offers free drug to impoverished people with no other means to access therapy. Admittedly, the numbers in need are far greater in developing nations, but the principle of "free drug for those in the greatest need" is well established. Nations with the worst economic conditions have all they can do to make even small contributions to their health care infrastructure and cannot be burdened, at any price, with the cost of pharmaceutical drugs needed to fight an epidemic. No discount level other than 100% will make treatment feasible.

Moving up from the poorest nations, some reasonable formulas must be established for setting prices. One possibility might be to link drug prices with the amount of money a country is able to spend per person annually on healthcare, or the percentage of its population living at levels of extreme poverty. These are only suggestions—no one yet knows the best or the right way to do this. But the sliding scale of pricing, however it is scaled or linked to economic conditions, must begin at zero—free drug for poorest nations. No other framework is morally acceptable.

Even with such principles, providing treatment for AIDS in developing nations will be no easy task. The cost of drug is only a small part of the problem. Building the necessary medical infrastructure will also be costly, as will be meeting the most fundamental needs for food and clean water. Concerned nations must also—or perhaps first—mount effective prevention campaigns to stop the spread of HIV, almost certainly beginning with efforts to block mother-to-child transmission. Treatment without prevention will simply create an endless cycle of pain, suffering and expense.

Newly proposed programs for addressing the problem of AIDS in the developing nations are only the beginning. It will take decades to bring 21st century healthcare across the globe. AIDS is hardly the only medical problem developing nations face and it must compete with other national priorities. A truly effective, global approach to AIDS must begin with a meeting of heads of State. President Clinton has declared the spread of AIDS in developing nations an urgent matter of US national security. If we believe this, then he and other western heads of state must begin to treat it as such. Just as they met to discuss intervention in Bosnia or to launch warfare against Iraq, they must now meet to plot out national and international strategy against this threat. They must begin negotiations and planning efforts with the heads of the affected nations, as well as grass roots representatives of the people in those nations. And they must begin to adjust their thinking in terms of dollars. Current efforts amount to a few hundred million extra dollars here and there, this from a country that spends roughly one and a half billion each time the space shuttle makes a supply run to orbit.

Commentary

The pharmaceutical industry can and must be made to do its part in confronting AIDS, but it would be extremely naïve of us to believe that lower drug prices alone will solve the problem. Blaming industry for the entire problem is a convenient but false solution. There is a huge need for additional funding from the developed nations and the major international private foundations, as well as a sustained and corruption-free effort on the part of nations in need. There is plenty of blame to pass around for having let things get as bad as they are. AIDS is the world's problem, and until we learn to address it as such, no real progress will be made. ■

Managing Diarrhea

Two recent studies show that using supplements is helpful in treating diarrhea associated with the use of nelfinavir (Viracept), the most common side effect of this protease inhibitor. In one study, people took two psyllium husk fiber bars one hour before bedtime with a large glass of water. Almost all participants showed improvements and the severity of diarrhea was reduced. In the second study, people took 500mg of calcium supplements twice a day (total daily dose of 1,000mg). All participants reported dramatic improvements while two thirds of them reported a resolution of their diarrhea. The improvement noted with the husk fiber bars is consistent with earlier recommendations that called for the use of soluble fibers as a tool for combating the diarrhea. ■

Herbs, Supplements and HIV

Vitamins, supplements and herbs have long been used by people with HIV in hopes of helping manage side effects of other therapies and/or improve overall general health. In fact, studies suggest that upwards of 70% of people living with HIV and about 50% of the general population use some form of complementary therapy, with the most common being approaches such as massage and acupuncture. Unfortunately, not many approaches have been studied in people with HIV or been looked at to see how they might interact with commonly used medications, or whether they add to the overall benefits of therapy. Recently, a number of reports have questioned the safety of some complementary approaches in the setting of HIV and beyond.

The intention of this article is not to discourage the use of complementary therapy, but rather to supply some food for thought when contemplating decisions about these remedies. The companies that promote herbs, supplements and vitamins advertise the potential benefits of the products but the consumer has very little information about the products themselves—their true value for treating specific conditions or even information about the actual content of the products they are buying. Promoters of supplements and herbs are often the first to criticize prescription drugs as the products of "big business," but supplements and herbs are themselves part of a huge industry with annual sales of around $20 billion. This article will highlight emerging concerns about the use of various complementary approaches and also address ways to minimize potential risks associated with the use of these therapies, where possible.

A Little Background …

Under current law, vitamins, supplements and herbs do not have to be evaluated by any regulatory agency (e.g. the Food and Drug Administration) prior to their sale. All they need do is assert that the product is "generally regarded as safe." What this means is that there is no requirement for studies to demonstrate the effectiveness and safety of these products—leaving the consumer with little or no meaningful information about benefits or side effects of therapy. Some manufacturers vaguely reference "studies" in their promotional literature, but these are seldom more than very small, uncontrolled studies. Also, these products do not have to be manufactured in accordance with the rigid guidelines established for the manufacturing of pharmaceutical products, called Good Manufacturing Practices. As a consequence, there is extremely wide variability between products in terms of their active ingredients, and even between batches of the same product from a single manufacturer. In fact, studies have shown that some of the products being sold on the market today contain no amount of the claimed active ingredients, whatsoever. Other products being sold as herbal supplements have been shown to contain dangerous chemicals (e.g. arsenic and lead, both potentially deadly). Still other products have been shown to actually contain pharmaceutical medications. The best manufacturers, however, make a serious effort to deliver the real product in the amounts claimed, but due to the lack of regulatory requirements, there is no simple way to determine who is telling the truth.

People should be aware of these things and take measures to reduce their risk of buying contaminated products or products without active ingredients by seeking out reputable sellers of herbs, vitamins and supplements. Seek guidance from a trained alternative medicine practioner (e.g. an herbalist or nutritionist who specializes in HIV) and gather information about the products you are considering using. Taking the word of people selling the product in stores is no guarantee of accuracy. On the actual package, or on their websites, some manufacturers of herbs and supplements will claim that their products have been tested for active ingredients. Do a little research and see what you can learn. For example, some consumer publications, such as *Consumer Reports* and other similar groups like consumerlab.com, periodically test supplements and list what is actually in various brands. Even this, however, doesn't tell you whether the product will benefit you. As a general rule of thumb, if a company has shown integrity in some of its products that have been tested by consumer groups, it is a reasonable sign that they maintain similar standards for other products in their line. According to researchers who are evaluating these therapies, the quality products that undergo evaluation by the manufacturer are *in general* not the ones that you'll find at your average grocery store or pharmacy.

Don't assume that simply because something is available over-the-counter or is natural that it doesn't have side effects or won't interact negatively with other medications that you are taking.

Drug Interactions

St. John's Wort, a popular over-the-counter herbal supplement (also known as hypericin) used for mild depression, has been shown to have potentially serious interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors

(NNRTIs). See *PI Perspective* 29 for more details of this study. This doesn't mean that St. John's Wort doesn't "work" for helping people deal with depression, but rather it poses a serious drug interaction problem that could jeopardize the effectiveness of anti-HIV therapy.

Part of what led researchers to look at St. John's Wort for potential interactions with anti-HIV therapy is that the herb is processed in the body by the same enzyme used for processing many drugs, including protease inhibitors and most NNRTIs. This enzyme is called the p450 enzyme. A number of dietary supplements and herbs have reported effects on the p450 enzyme. Depending on how they interact with p450, using anti-HIV therapies with these products could lower the blood levels of the anti-HIV therapies (possibly putting people at risk for developing resistance to their anti-HIV drugs) or they could increase the blood levels of the anti-HIV therapies (putting people at greater risk for serious side effects). Herbs with reported effects on the p450 enzyme include:

- St. John's Wort
- Garlic
- Ginseng
- Melatonin
- Milk Thistle (silymarin)
- Geniposide
- Scullcap

Dr. Piscitelli of the National Institutes of Health (NIH) is championing a series of interaction studies to provide people with HIV information to enhance the safe use of complementary therapies with anti-HIV medication. In a recent presentation, Piscitelli noted that the most common supplement used by people attending the NIH's HIV clinic is garlic. Piscitelli will evaluate this in future studies. A woman recently initiated a ritonavir (Norvir)-containing anti-HIV regimen and then began garlic supplementation. After starting the garlic, she developed severe nausea and vomiting which resolved after she stopped the garlic. It may be that garlic increased the levels of ritonavir, and thus its side effects. There has also been a second report where it appears garlic supplementation may have enhanced the side effects associated with ritonavir. Garlic may also increase the risk of side effects associated with other anti-HIV therapies. This information, coupled with knowledge that garlic has a reported effect on p450, suggests that until more is known people should use caution when combining high doses of garlic with anti-HIV therapies that use the p450 pathway (e.g. protease inhibitors and NNRTIs). Moreover, people using the supplement with anti-HIV drugs who experience serious stomach problems (diarrhea, nausea or vomiting), might consider discontinuing it to see if these symptoms lessen.

To lessen the likelihood of herb-drug interactions, Dr. Piscitelli encourages people to have more in-depth discussions about the use of complementary therapy with their doctors and pharmacists.

According to a recent article in the medical journal, *The Lancet*, there are a number of reported herb-drug interactions that include the following herbs:

- Betel Nut
- Chili Pepper
- Devil's claw
- Dong quai
- Garlic
- Ginkgo
- Ginseng
- Guar gum
- Kava
- Papaya
- Psyllium
- St. John's Wort
- Saiboku-to
- Shankhapushpi
- Sho-saiko-to
- Xiao chai hu tang
- Valerian
- Yohimbine

To lessen the likelihood of herb-drug interactions, Dr. Piscitelli encourages people to have more in-depth discussions about the use of complementary therapy with their doctors and pharmacists. This may take some getting used to for both patients and doctors. Doctors may need to learn to listen and support their patients, in a nonjudgmental way, about the use of complementary therapy. Undoubtedly it may well be patients who drive this learning curve. Patients need to be open and honest about what they are using and considering. The only way to capture information about drug interactions and side effects is if they are recorded in a *complete* drug history, including herbs, vitamins and supplements that you are using. It's also important for patients, doctors and pharmacists to keep up on the latest information about drug-herb interaction studies.

What About Side Effects?

The biggest myth about complementary therapies is that they are non-toxic. There is a widely held misconception that because something is natural, or sold over-the-counter, that it doesn't have side effects. To the contrary, there have been numerous reported cases of people with HIV experiencing side effects from complementary therapy. Chinese herb preparations that contain deer antler, for example, can cause nausea, diarrhea and other kinds of stomach upset. One man stopped all his anti-HIV medication in an attempt to determine which of his medicines was upsetting his stomach and quality of life. It turned out that when he stopped his Chinese herbal preparation (that contained deer antler), his problems cleared—it wasn't the anti-HIV therapies causing the problems at all. High doses of vitamin C can cause severe diarrhea. Taking too many B vitamins can lead to a complication that lands one in the hospital and excessive levels of vitamin A can be highly toxic to the liver. Side effects associated with herbs, vitamins and supplements might not reveal themselves immediately. It may take a number of weeks after starting a therapy for side effects to emerge as a problem. Keeping an accurate record of every therapy you are taking, including when you start and stop therapies and documenting the onset of side

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www.projectinform.org

Vitamin	Potential Side Effects of Supplementation
Vitamin A and beta-carotene	Perhaps the most toxic vitamin. At high doses (greater than 25,000 IU per day) toxicities are more likely, including loss of appetite, weight loss, bone malformations, spontaneous fractures, internal bleeding, liver toxicities and birth defects.
Vitamin B-6 (pyridoxine)	Reversible neuropathy has been reported in people taking high doses (500mg to 6 grams a day) over extended periods of time.
Vitamin B-12	In very rare instances, allergic reactions have been reported.
Folate	High doses have been associated with reduced zinc absorption.
Vitamin C	High doses can cause diarrhea and gastrointestinal distress. Buffered formulations are available and may decrease stomach problems. People with a history of kidney stones should consult a physician before taking high doses.
Vitamin D	Potentially very toxic, can cause bone lesions. Toxicities reported with single high dose supplementation.
Thiamin	Very high intravenous doses have caused intoxication, headache, convulsions, muscular weakness, paralysis and cardiac arrhythmias.
Biotin	No reported toxicities.
Vitamin E	No reported toxicities.
Riboflavin	No reported toxicities.
Pantothenic Acid	No reported toxicities in humans.
Vitamin K	No reported toxicities in humans.
Niacin	Toxicites may be related to formulation. Nicotinic acid can cause itching, nausea, vasodilation and vomiting at doses of 2 to 4 grams/day. Nicotinamide only rarely produces these toxicities.

effects may help to sort out which therapy is causing the problem.

The following is a list of herbs with known serious side effects:

Herb	Known toxicity
Borage	Liver toxicity
Calamus	Kidney toxicity
Coltsfoot	Liver toxicity, light sensitivity
Comfrey	Vaso-occlusive disease
Ephedra	Heart failure, stroke, hypertension
Germander	Inflammation of the liver (hepatitis)
Life root	Veno-occlusive disease

At the top of the page, you will find a list of vitamins with known side effects.

Unlike pharmaceutical products, large studies are not required to document side effects associated with complementary therapy and potential side effects are typically not noted on the package materials. The key to minimizing the risk of potential side effects with these therapies is to learn about them, monitor for early signs and implement measures to minimize the risk.

Buyer Beware!

Recently, a number of Chinese herb supplements to manage diabetes have been pulled from the shelves by the California Food and Drug Board (FDB), a state equivalent to the Food and Drug Administration (FDA). The action followed an incident where a person with diabetes was hospitalized after taking one of the supplements. The supplements were tested and found to contain pharmaceutical medication used to treat diabetes. The additional medication in the claimed "natural" product lead to an overdose of medication for the individual.

There are numerous herbal remedies that contain controlled and potentially dangerous substances that are banned by the FDA. The FDA readily admits that it simply doesn't have the enforcement potential to ensure that these products stay off the shelves of some stores. Media exposés on this topic in California reveal countless tales of people harmed by such products that contain lead, arsenic, anabolic steroids and other controlled and potentially dangerous substances.

To protect yourself, seek reputable sellers, investigate the product and seek guidance from trained professionals.

Conclusion

Herbal remedies and other vitamins are sold as "food supplements" and do not undergo the rigorous testing that other medications do. They are not regulated and may not reveal on the label all of the product's contents, nor do they necessarily contain the ingredient listed or the amount of it claimed. Don't assume that simply because something is available over-the-counter or is natural that it doesn't have side effects or won't interact negatively with other medications that you are taking.

In the United States alone, it's estimated that $20 billion dollars were spent on complementary therapies last year. The use of complementary therapies has risen almost 400% in the past eight years and it's estimated that 50% of people in the US use complementary therapies. The sale of complementary products is an ever growing industry and at the current time that industry has done very little to document the safe and effective use of its products. It's unlikely that it ever will. The U.S Government, through the NIH, has established two botanical centers to evaluate complementary and alternative therapies with a budget of $68 million dollars. A third center will be funded shortly. Every few years, new discussions are held about whether and how to better regulate the marketing of nutritional

supplements and herbs.

There is a great difficulty in evaluating herbs and herb-drug interactions because often times the active ingredient of the products and its dose are not known. Moreover, drug interaction studies for pharmaceutical products typically take a matter of a week to ten days. Drug-herb interaction studies are expected to take much longer, and as a consequence be more expensive, as it's likely that people will have to be taking herbs for a matter of weeks before an effect is seen. Even when the interactions are determined for one particular product, it is unclear how they will relate to other similar products because of the lack of control over dosing. Because no studies have determined the appropriate or best dose of many complementary therapies, researchers face an additional challenge in first selecting the dose of herbs to use in studies. Necessary funding for the studies will remain a problem and limitation to moving forward rapidly. Many companies selling herbal and other complementary approaches are reluctant to fund studies that may reveal that their products are not useful, have side effects or have interactions with commonly used medications. This information could hurt their "bottom line" of profit. Pharmaceutical companies are also unwilling to fund these studies for many of the same reasons, and the FDA does not require them.

Whatever the possible benefits of herbs, vitamins and supplements, there simply is no information to guide decision-making with regard to using these remedies. Be aware that using them entails some element of risk. ■

New Advances in Hepatitis C Therapy

There is encouraging news for people with hepatitis C virus (HCV). A new form of interferon-alfa, known as peg-interferon (PEG-Intron from Schering Plough), shows better activity than the current version of the drug. This new version is bound to a chemical (called *polyethylene glycol*), which makes the drug active in the blood for longer periods than standard interferon-alfa. *PI Perspective 29* reported on early results of a different peg-interferon (Pegasys) that also showed improved activity over existing therapy.

PEG-Intron was compared to standard interferon-alfa in 1,219 people with HCV and abnormal liver enzymes (an indicator of liver injury). This study did not involve people co-infected with HIV and HCV. People took the drug for 48 weeks followed by a 24-week follow-up period in which they took no therapy. They either used 0.5mcg/kg, 1mcg/kg or 1.5mcg/kg of peg-interferon or three million international units of interferon-alfa. Both formulas require injections under the skin.

Almost 70% of the participants had genotype 1 HCV (the most difficult type to treat), and about 75% had HCV levels of over 2 million copies. Results after 48 and 72 weeks are in the table below:

People taking the 1.0 and 1.5mcg/kg doses of peg-interferon experienced slightly more side effects than those on the other two doses. The most common side effects included headaches, fatigue, flu-like symptoms, depression, and decreases in white blood cell counts, platelets (cells needed for blood-clotting) and neutrophils (a type of

Treatment	% <100 HCV RNA @ 48 weeks	%<100 HCV RNA @ 72 weeks
0.5mcg/kg peg*	33	18
1.0mcg/kg peg	41	25
1.5mcg/kg peg	49	23
3MIU interferon-alfa**	24	12

* "mcg/kg" means "micrograms per kilogram," a varying dose level based on a person's weight.

** "MIU" means "Millions of International Units," a fixed dose level.

The major points from *Hepatitis C Therapy*

- Peg-interferon is more effective than the current interferon-alfa.
- Still needs to be combined with other anti-HCV therapy.
- Not yet studied in people with both HIV and HCV.
- Expanded access program for Pegasys is expected in fall 2000.

white blood cell that helps control bacterial and other infections).

Although its success rate is superior to the current interferon-alfa, PEG-Intron is still not overly impressive compared to standard HCV therapy, which is a combination of interferon plus ribavirin (Rebetol). It's likely peg-interferon will still have to be combined with ribavirin or other new anti-HCV therapies in development to get optimum results. Ongoing studies are now using peg-interferon with ribavirin to determine whether this will be more effective than peg-interferon alone.

PEG-Intron is likely to be approved by the Food and Drug Administration in spring 2001 and should be available by prescription shortly thereafter. However, an expanded access program for Pegasys is expected during the fall 2000. ■

Join Project Inform's Treatment Action Network

Since the beginning of the AIDS epidemic, grassroots advocacy has been the heart of many political victories. In the current political environment, your involvement is needed more than ever. Join over 1,500 Treatment Action Network members and become an influential advocate for AIDS care, treatment and research funding and policies!

If you would like to sign up to be a part of the Treatment Action Network, call Project Inform at 415-558-8669, FAX to TAN Coordinator at 415-558-0684, or email **TAN@projectinform.org.**

Advances in Treating CMV

Long-awaited results from a study of treating CMV (cytomegalovirus) retinitis show that a new formulation of oral (by mouth) ganciclovir, known as valganciclovir, is as effective as the intravenous (IV, injection into the vein) version of the drug. This is the first time that an oral drug for treating CMV has been shown to be as effective as the IV version.

The use of valganciclovir results in similar drug levels in blood as those produced by the IV form. This is a major improvement over the currently approved oral form of ganciclovir (Cytovene), which is hampered by poor absorption into the bloodstream and consequently weak control of CMV. The standard version of oral ganciclovir is only approved for maintenance therapy (to prevent CMV from recurring in people who have already been treated for the disease) and for preventing initial CMV disease (though the data for prevention use are weak and conflicting). It is not approved for treating the active disease.

Study Results

The study included 160 people with active CMV disease and CD4+ cell counts averaging around 25. About 25% of the volunteers were not on highly active anti-HIV therapy when they started. Participants received either 900mg of valganciclovir twice a day for three weeks followed by one week of 900mg daily or 5mg/kg of IV ganciclovir twice a day for three weeks followed by one week of 5mg/kg daily.

There was no difference in rates of CMV disease progression between the two groups at the end of four weeks. About 10% in each group continued to have progressive CMV disease, and about 65% in each group responded well in controlling the virus. There are no data yet to show whether valganciclovir is equivalent to the IV formulation in the time to relapse (when CMV recurs).

Future Study

A large study is planned to look at the effectiveness of preventive CMV treatment with valganciclovir. It will study the drug's use in people without CMV disease who have measurable CMV levels in their blood (called CMV PCR positive). Several studies have shown that CMV PCR positive people are more likely to develop CMV disease than CMV PCR negative people.

If this strategy works, it will mean that only people at risk for developing CMV disease would need to use preventive therapy. This is unlike the current standard in which people consider CMV prevention therapy based solely on their CD4+ cell counts. This will reduce the cost of HIV care as well as spare people from risking the side effects of potentially unnecessary therapy. ■

The major points from *Treating CMV*

- A new oral drug, valganciclovir shows effectiveness in treating CMV.
- This is the first oral drug shown to be as effective as standard IV therapy for treating this condition.
- Future studies will examine how useful this drug is in preventing CMV.

Immune Therapy: In Brief

A number of very small studies of immune-based therapies have reported data. The most that can be concluded on the basis of small studies is whether or not a therapy is safe and if it warrants further study. It may be years before large studies of these types of approaches are launched. The following are brief summaries of results from studies of these novel approaches to treating HIV.

HIV Vaccines for People Living with HIV

The goal of giving an HIV vaccine to someone living with HIV is to enhance the immune system's ability to control the virus. Many such approaches have been tried with limited success in the past. A new approach attempts to enhance the ability of immune cells to seek out and destroy HIV-infected cells (called cellular immunity). The new vaccine combines a previously studied vaccine (called rgp160) with a live virus vaccine carrying four HIV genes. The live virus used in this study (called canarypox) is a virus that birds get that does not cause disease in humans. The product is called vCP1452. The study included eight volunteers who had started taking anti-HIV medication within 90 days of initial HIV infection. At the time of the study, participants had sustained control of HIV levels for at least two years. Researchers presented results of the first six people who completed four injections with the vCP1452/rgp160 vaccine over a six-month period.

All volunteers demonstrated increases in anti-HIV immune responses over time, though not all had the same magnitude or breadth of response. There were no reported side effects and the vaccine approach was deemed safe. Future studies will assess whether or not these improved immune responses lead to decreased risk of HIV disease progression or improved outcomes, over time.

G-CSF (Neupogen) Enhances Function of Neutrophils

Neutrophils are important cells in fighting bacterial infections. The function of these cells is impaired in people with AIDS. Also, many commonly used therapies for HIV can cause a decrease in neutrophil counts. Granulocyte colony stimulating factor (G-CSF, Neupogen) is commonly used to treat people with HIV who have low neutrophil counts (neutropenia).

A small study including 30 people with CD4+ cell counts below 200 who did not have low neutrophil counts evaluated three different doses of G-CSF. Volunteers received G-CSF, given by daily injection in doses of 75, 150 or 300mg for seven days. Neutrophils were examined and shown to have increased ability to destroy bacteria in a dose dependent manner (i.e. the larger the dose, the more effective the neutrophils are in killing bacteria). Also, cells were less likely to self-destruct (undergo programmed cell death) as higher doses were used. The benefits of G-CSF therapy lessened within three days of stopping G-CSF therapy, however, suggesting that turning this into a practical therapy would require daily injections.

Immune Suppression for Treating HIV

As a person's HIV disease progresses, their levels of immune cell activation increase, most likely in response to increases in HIV viral load. Markers of immune activation have been associated with HIV disease progression and increased HIV replication. It is well established that inactive infected cells produce very little new HIV. Some researchers believe that much of the harm attributed to HIV infection may be linked to excessive immune activation. The concepts have lead to the study of cyclosporine (CsA, Neoral), an immune suppressive drug that is commonly used in organ transplant patients to prevent their immune systems from rejecting the newly transplanted organ.

A recent study included 28 people with CD4+ cell counts above 400 and low but measurable HIV levels. They received CsA (4mg/kg daily) or placebo for three months. Volunteers were either on no anti-HIV therapy or on two-drug therapy with NARTI anti-HIV drugs. (This study was started before the time three-drug therapy was standard-of-care).

Levels of immune activation decreased in people receiving CsA and either remained stable or increased in those receiving placebo. Measures of immune function, however, also slightly decreased in those receiving CsA. The impact of CsA on both immune activation and immune function was only modest. In general, the therapy was deemed safe and worthy of further evaluation, especially among people with HIV undergoing organ transplantation.

New Form of Interferon-alpha May Be Useful in Treating HIV

Some researchers believe that much of the harm attributed to HIV infection may be linked to excessive immune activation.

Interferon-alpha (INF-a) is a naturally occurring immune chemical with antiviral activity. A man-made form of the chemical is currently approved for treating Kaposi's Sarcoma, an AIDS-related cancer. It is also one of the therapies used for treating hepatitis C virus. In the past, injectable INF-a was studied as an anti-HIV therapy, but side effects were deemed too severe to warrant continued research. The most common side effects include flu-like symptoms and depression.

Interest re-emerged in INF-a when studies of third-line therapy indicated that it may be a useful addition to anti-HIV therapy in people who need mega-HAART type regimens to control viral load. A new form of INF-a, called PEG Intron, binds INF-a with

a chemical that makes the INF-a stay in the blood for longer periods of time requiring less frequent dosing.

A study of 31 people on stable anti-HIV therapy with CD4+ cell counts greater than 200 and viral levels greater than 500 copies per/ml assessed varying doses of PEG intron. Doses evaluated included 1, 1.5, 2.25 or 3.5mg/kg, delivered by injection under the skin (subcutaneously) once per week for eight weeks.

PEG Intron seemed to cause nearly a 1 log (10-fold) drop in HIV RNA levels at the end of the study. There appeared to be no affect on CD4+ cell count (or percentages) over time. Volunteers who started with high levels of immune activation were least likely to experience HIV RNA decreases resulting from PEG Intron therapy. Higher doses were correlated to greater decreases in viral load. Since this was a pilot study and it did not compare treated patients to a control group, it is not yet possible to conclude that the drug was responsible for the changes in outcome. Larger studies using PEG intron will begin in the near future.

CD4+ Cell Expansion

CD4+ cell counts decrease over the course of HIV infection, as do their function. Researchers have identified a method to grow CD4+ cells, outside the body, in a way that may make them somewhat resistant to HIV infection. To evaluate the safety of CD4+ cell expansion in people with HIV, a small eight-person study was conducted through the U.S. military.

Dr. Carl June expanded cells and delivered increasing numbers of cells, every six weeks for three courses of therapy. After the first three courses, volunteers received cell infusions every eight weeks for one year. Side effects included fevers, chills and fatigue. Side effects were more severe when higher numbers of cells were infused. Overall, people experienced no changes in viral load associated with cell therapy. Seven of the eight volunteers experienced increases in CD4+ cell numbers, and all experienced increases in CD4+ percentages.

The use of aggressive anti-HIV therapy became more widely available during the course of this study. As it did, people made adjustments in their anti-HIV therapies. It is therefore impossible to note what (if any) changes in CD4+ cell counts are due to CD4+ cell therapy and which are due to anti-HIV therapy.

The new CD4+ cell expansion approach used in this study has since been adopted as a part of other cell therapy studies that include gene therapy (e.g. modifying cells with genes that may help protect them from HIV infection). The researchers conclude that this approach is safe. Whether it is financially feasible is another matter.

HIV-specific CD8+ Cell Therapy

HIV-specific CD8+ cells (also called HIV-specific cytotoxic lymphocytes, or CTL) are cells that seek out and destroy HIV-infected cells. Researchers in Seattle have been studying HIV-specific CTL therapy in people with HIV.

Most recently this group has reported on a study of five people with CD4+ cell counts between 200 and 500, on stable anti-HIV therapy, without prior history of opportunistic infection, who received two infusions of HIV-specific CTLs at one-week intervals.

The researchers expanded the cells and "marked" them with a gene that would show them where the cells went in the body after they were re-infused. The cells were detected in the blood as well as other organs (e.g. lymph nodes) for 18 days after infusions. Sporadic detection of cells was noted 4 - 6 weeks after the second infusion of cells. The cells appear to travel to the lymph nodes appropriately and maintain their anti-HIV capacity.

In Conclusion …

Most immune-based therapies are still in very early stages of research. The most that can be concluded about small studies like those described above are that the approaches appear safe and warrant further investigation. These types of studies pave the way for future directions in HIV research. ■

The Basic Message

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

Striking a Balance: HIV Testing for Pregnant Women and Newborns

We have learned a lot about how to prevent HIV transmission from a mother to child during pregnancy, birth and infancy (sometimes called *vertical transmission*). Improved preventive care and voluntary HIV testing have drastically reduced vertical transmission rates in developed countries. However, while good testing policies work hand in hand with improved care options to produce better outcomes for women and children, testing policies can't in and of themselves reduce vertical transmission. Therefore, the goal of testing policies must be to encourage women to know their status and whenever possible, link women with the healthcare necessary to take advantage of their options.

Most people agree on the goals of testing in the context of pregnancy—reducing vertical HIV transmission and optimizing care for mother and child. However, when it comes to setting testing policies, there is disagreement about the best way to achieve these goals. Because HIV testing policies can work for or against women, it is critical that testing policies for pregnant women reflect good public health policy by encouraging—not discouraging—women from seeking the healthcare they need; thereby reducing risk of vertical transmission. This is an important balance to strike.

Testing Pregnant Women

Every pregnant woman should be *offered* an HIV test as early as possible in her pregnancy. The offer to test should be accompanied by individual, culturally competent counseling and should discuss the benefits of determining her HIV status, as well as its implications for her life, pregnancy and, potentially, her unborn child.

If a woman chooses to test and the result is positive, optimally, she will have increased information and options for her own personal healthcare. If she chooses to continue her pregnancy, she will also likely have more information and options to reduce the risk of vertical transmission.

For a woman who tests negative, counseling regarding HIV prevention should be available and if she chooses to continue her pregnancy, counseling discussing a safe pregnancy, including prevention of HIV, should be a standard part of all care.

Testing Newborns

HIV testing of newborns is different than testing pregnant women. Depending on the type of test used, babies born to HIV infected women may test positive at birth simply because they are carrying some of the HIV antibodies from their mother. As the baby gets older, the mother's antibodies will die off and allow for an accurate HIV test. Thus, the presence of HIV antibodies at birth only reveals the mother's status.

Testing babies at birth, particularly if the mother has not yet tested for HIV and has not given an informed consent to test her baby, raises a number of issues. Before attempting to formulate policies for testing newborns, women and policy makers must be clear on what different types of HIV tests can and can't determine, how much time is necessary to obtain accurate results, and what options exist for preventing vertical transmission after delivery.

Types of Testing

There are three primary policies of HIV testing for pregnant women and newborns.

Voluntary testing: In this setting, pregnant women are advised and counseled about HIV testing and the implications of being tested and are *offered* a test. Many policies call for a written informed consent

The major points from *Striking a Balance*

- There are three general approaches to HIV testing: (a) voluntary, (b) routine/universal and (c) mandatory.
- The Institute of Medicine recommended universal HIV testing, with patient notification, as a routine component of prenatal care.
- Activists are concerned that to eliminate or de-emphasize pre-test counseling and informed consent could result in the loss of a woman's right to participate in her own healthcare and could drive some women from healthcare altogether.
- Project Inform believes all pregnant women have the right to an informed consent for an HIV test and should be *offered*—and have the right to decline—an HIV test as early as possible in their pregnancy.
- Testing does not equal care—all women should receive quality healthcare, including prenatal and anti-HIV care.
- Testing policies alone do not reduce vertical transmission.

signed by the woman. Written informed consent has the advantage of documenting that the woman was advised about HIV testing. Women have the right to accept or refuse the test. Voluntary testing coupled with counseling and informed consent facilitates a woman's ability to make informed decisions about her healthcare and that of her newborn. Since 1995, voluntary testing has been the policy recommended by the US Public Health Service Guidelines.

There are many reasons to support this policy. First and foremost, it works. Quality prenatal care and effective HIV prevention strategies coupled with voluntary testing and counseling have dramatically decreased vertical transmission rates. When appropriately offered a voluntary HIV test, women overwhelming accept. Indeed, acceptance rates have been shown to be 90% and higher. Moreover, counseling and voluntary testing are also the best mechanisms to actively engage women as equal partners in their care.

Quality prenatal care and effective HIV prevention strategies coupled with voluntary testing and counseling have dramati-cally decreased vertical transmission rates.

Universal or routine testing: This policy includes an HIV test in the standard battery of tests that all women receive when they are pregnant. With routine testing there is often no guarantee of counseling. Routine testing should carry a right of refusal. However, this, too, can take several forms—some must be signed by the woman and documented in medical records. Recently, this policy has gained the support of some policy makers and medical groups.

Although there are several ways that a universal testing procedure could be implemented, it is likely that there would be a decreased emphasis on pre-test counseling and informed consent. Additionally, the use of documented refusals with no protection from legal action can be more coercive or intimidating than voluntary testing, particularly for immigrant women.

Some policymakers and healthcare providers argue that universal or routine testing could further decrease vertical transmission. Many argue that HIV is no different than other diseases women are tested for during pregnancy and that counseling is difficult or embarrassing. However, there are strong reasons why individual counseling in the context of HIV testing during pregnancy and infancy needs to be maintained.

In spite of much better understanding of HIV disease and growing acceptance of people living with HIV, stigma against women living with HIV is still strong, especially in some cultures and communities. There is documented evidence that women who disclose their positive status have experienced discrimination, abandonment, severe psychological reactions, and even domestic violence. Appropriate counseling is key to helping women assess the risks and benefits of knowing their status and develop the necessary support systems in their lives. Support is essential for most pregnant women to take full advantage of quality prenatal HIV care and the advances in the prevention of vertical transmission.

Mandatory testing: In this setting, all pregnant women and/or newborns get tested for HIV. Mandatory testing generally means that there are sanctions or penalties for those who refuse to test, including criminal penalties. Currently, New York and Connecticut are the only two states with mandatory testing policies.

A testing policy that doesn't allow a woman to make informed decisions violates her right to be an active participant in her own healthcare. Coercive HIV testing also runs the risk of alienating women from HIV testing and appropriate follow-up care. This may be especially true for certain groups of women, including immigrants.

In the worst cases, coercive, involuntary, or poorly handled testing could cause a woman to leave care altogether. If the goal of public health efforts is to ensure that every pregnant woman is able to access and use the information and care that will benefit her and her unborn child, efforts to mandate testing or treatment should be defeated.

Access to Care

No form of testing can guarantee the care necessary to prevent transmission or benefit a woman's health. Women who can't get prenatal care should be offered an HIV test in any care setting they may have access to, but the offer of a test in such settings may be much less likely to happen. Women of color, low-income women and women living with HIV have less access to quality prenatal care and HIV care compared to other women. People without health insurance are disproportionately people of color. In addition, even with insurance, people of color and women still often receive substandard healthcare.

Reducing vertical transmission of HIV requires a focus on access to quality healthcare for all pregnant women. In a recent forum hosted by Project Inform, women and clinicians alike agreed that the best means of preventing vertical transmission was to ensure access to high quality, woman and family-centered healthcare.

Policy Issues

Although the testing of pregnant women and newborns has long been debated in public policy, several factors caused a heightened focus on the issue in the early 1990s. A major push to mandate testing was driven by a study showing decreased vertical transmission when women and their newborns were treated with AZT (zidovudine, Retrovir). In spite of misguided efforts to use the results of the trial to mandate testing, the Public Health Service (PHS) issued rational guidelines calling for universal HIV counseling and voluntary testing of pregnant women in 1995.

Since the implementation of these guidelines, and further advances in the knowledge of how to prevent vertical transmission, there have been dramatic decreases in the rate of mother-to-child HIV transmission in the US. Regardless, the push for mandatory testing and/or elimination of informed consent persists. There was an amendment attached to the Ryan White CARE Act in 1996 that

attempted to tie federal funding to a mandate that states test all newborns for HIV. The amendment also called for the Institutes of Medicine (IOM) to report on the state of HIV vertical transmission in the U.S.

The IOM Report: Setting a New Standard?

In October of 1998, the IOM released its report, *Reducing the Odds: Preventing Perinatal Transmission of HIV in the United States.* The IOM acknowledged that substantial progress had been made in reducing vertical HIV transmission. However, it identified several barriers to reaching full implementation of universal counseling and voluntary testing of pregnant women including:

- Financial and other access barriers for women seeking prenatal care
- Time and other constraints that may discourage providers from counseling women appropriately about HIV disease and the importance of testing
- Language and cultural barriers at prenatal care sites that may cause women to refuse testing
- Financial and logistical problems that may make testing and treatment difficult

In its conclusion, the IOM recommended universal HIV testing, with patient notification, as a routine component of prenatal care. It also de-emphasized the need for counseling, going so far as to state that it is too difficult and even "embarrassing" for providers. The American Academy of Pediatrics and the American Medical Association support these recommendations. In addition, the American College of Obstetricians and Gynecologists has recently advocated routine HIV testing of all women during gynecological exams, in addition to universal testing of pregnant women.

However, many advocates continue to argue that voluntary testing with appropriate counseling is working. They argue that most of the barriers outlined in the IOM report are not addressed by universal testing. To eliminate or de-emphasize pre-test counseling and informed consent may work for providers who find it too difficult, but for pregnant women it could result in the loss of a woman's right to be an active participant in her healthcare. Again, in the worst case scenario, it could drive women to, or deter women from seeking quality healthcare, including prenatal care.

Where We Are Now

This issue continues to be debated at the federal and state levels. Some members of Congress may try to implement policies on HIV testing of pregnant women and/or newborns as part of this year's reauthorization of the Ryan White CARE Act. Meanwhile, the Centers for Disease Control and Prevention (CDC) is expected to release revised guidelines of HIV testing for pregnant women shortly. In addition, legislation has been introduced in some states regarding mandatory testing of pregnant women and/or newborns, and a routine testing bill is being debated by the California State Legislature.

Project Inform will continue to monitor these debates at the federal and state levels. You can play a role in this effort by joining the Treatment Action Network (TAN), and letting your elected officials know how these policies affect you and those you care about. To join TAN, call Ryan Clary at (415) 558-8669 x224 or e-mail tan@projectinform.org. ■

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

☐ Enclosed is my **Pledge Partner** ***pledge***: $_____ per month for _____ months.
($40 or more per month for a year entitles you to Partners In Hope membership)

☐ Enclosed is my ***donation***: ☐ $35 ☐ $50 ☐ $100 ☐ $250 ☐ Other $_____

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Credit Card # Exp. Date

Print Name Shown on Card Phone Number

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