PROJECT inform

PERSPECTIVE

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

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"Bridge the Gap?" or "Cut the Crap!"

The 12th International Conference on AIDS, while a useful and important meeting, not only failed to live up to its theme of "Bridging the Gap," but perhaps inadvertently served to demonstrate how wide the chasm truly is between the *have's* and the *have not's* when it comes to AIDS. Despite an endless string of speakers who seemed to know that mere expressions of dismay about the plight of the Third World would provoke thunderous applause, there was very little evidence that the world had any intention of doing anything about it.

The Conference didn't hide the fact that HIV infection is still no picnic for anyone. Most of the progress in treatment covered in this issue of *PI Perspective* is aimed at modestly improved treatment strategies with simpler regimens and reduced side effects, yet fail to deliver any true breakthroughs or hopes of an outright cure. Drug companies touted once- and twice-daily dosing regimens, effective "protease sparing" cocktails and new ways to use old drugs. These are welcome changes, symbolic of a period of refinement that should produce modest improvements in quality of life, but they primarily apply to people just beginning treatment. True salvage therapy for people failing existing regimens remains elusive, though some hope was raised that near-perfect viral suppression may not be quite as necessary for clinical well-being as once thought. Perhaps the greatest disappointments of the conference were the lack of any real progress in understanding the potential long-term side effects of protease inhibitors and the paucity of truly promising new therapies in the mid-term pipeline. What little we know of the side effect issues remains troubling and incompletely understood, just about where things were in February at the Human Retrovirus Meeting in Chicago. The pipeline issue is especially troubling for those taking a long-term view and who realize that even the best of today's drugs do not offer anything like a lifetime solution. The danger here is that industry and academia alike may coast too long and comfortably in the wake of the protease inhibitor cocktail breakthroughs of 1995–96. (see *Antivirals Update, pp 4–7*).

Surely, the one message of the Geneva Conference that will linger longest is the stark contrast between a meeting which dared to choose as its theme, "Bridging the Gap," and the harsh vision it presented of a world seemingly incapable of delivering on that promise. Even worse, perhaps, was the contrast between the theme and the garish extravagance of the industrial displays people were forced to walk through between events. And then there were the bizarre evening "perk" events at which companies tried to outdo each other with lavish dinners and entertainment for their favored guests. To the 3,000 delegates from 3rd world and developing nations, it was as if the world was saying, "Your villages are dying? Let them eat cake."

There is nothing new about flashy, expensive displays by pharmaceutical companies at medical conferences. It is, in fact, a tradition, even at previous AIDS conferences. But it's time to re-examine this tradition in light of humane concerns about the epidemic. To understand the problem, use your imagination and your best visualization skills to momentarily put yourself in the shoes of any one of the delegates who work in the plains of sub-Saharan Africa, the slums of Asia or the urban underworlds of South America. Mentally wearing these shoes, you find yourself coming from a place where there are no such things as protease inhibitors, combination therapies or simplified dosing. Where there is no prevention for opportunistic infections or any other form of prevention. Viral load testing and diagnostics? Get real. In many such countries, where the annual expenditure on health care is but a few dollars per person per year, a glass of clean water would be an almost unthinkable luxury for people living with HIV.

As a guest of some pharmaceutical company's conscience, you came to Geneva and couldn't quite figure out the Americans, who were constantly complaining that the air-conditioning wasn't cold enough. But your eyes really widened each day as you were forced to walk through the exhibit halls to get to the presentations. Most booths were larger than the homes of your middle class. They were staffed with dozens of well-paid and well-dressed representatives who spent their days in Geneva handing out color copies of presentations, showing expensive video productions on four-foot-wide exotic new high-tech screens called

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plasma displays. You learned that the video display units alone cost about $16,000 apiece, and you marveled that many booths sported five or six of them. Plus computers, printers, Internet links and dozens of other gadgets you never see at home.

Then you got your first invitation to one of the evening events, usually reserved for "important" people like 1st world physicians and American and European AIDS workers and activists. You attended one event, held on a huge party boat out on the lake: dinner, high priced entertainment, free drinks, etc. You found it hard to believe that this was only one of dozens of such events, so many that they caused frustrating conflicts among the invitees about which ones to attend. The strange thing is that you seemed to be the only person who thought there's something odd about all this.

Now, still wearing those shoes, begin to ponder just how this would make you feel. Here's how it affected a few voices heard on the floor of the meeting.

"This conference isn't about 'bridging the gap'," fumed one African doctor to Village Voice reporter Mark Schoofs. *"They're here to show us how wide the gap is."* Zambian journalist Larry Hore expressed himself clearly, *"I feel mocked."* Also speaking to reporter Schoofs, Consolata Odiemo Auma, a 32-year-old HIV-positive Kenyan woman who had never heard of such things as AZT, let alone protease inhibitors, said "*Maybe if I ask them, they'll give me the drugs.*"

Fat chance. But she was not alone in trying. Similar thoughts occurred to many 3rd world delegates. Like the Thai physician who described how she comes to these conferences primarily to meet people—US doctors, rich patients, drug company representatives, sympathetic journalists and scientists—from whom she could beg. Beg for a bottle of antibiotics, or a few months supply of AZT or 3TC from a patient who had died or stopped using the drugs. She compared this aspect of her work to that of Thai sex workers in Bangkok, saying "they don't like what they do, but they send the money home to support their brothers and sisters. I don't sell my body, but I sell my dignity, to get drugs for the children in my clinic."

Such displays of wealth offered a stark contrast to the claimed purpose of the meeting—*Bridging the Gap*. Everyone talked about bridging that gap, but hardly a single speaker even attempted to propose a solution. Perhaps more than in any previous year, even activists and AIDS workers had become accustomed to the scene, debating all too casually which of the night's parties and events would be the best to attend, which would have the most lavish meals. Admittedly, there were a few productive meetings with pharmaceutical companies where ideas and strategies got debated with activists over simple fare, but far too many of the events this year had simply become parties. The old days of activism, when activists constantly questioned their relationships with industry, have given way to a new era of activism, with less clear and rigid thinking about this issue. Some activists today are routinely playing the role of pharmaceutical consultant while accepting personal support from industry. It may be true that it's hard or even foolish to run a major organization without taking advantage of the grants easily available from industry. It's an effective way to fund service needs that might otherwise go unmet. But when individuals take money personally for their own activities, hardware or goods, or when organizations exist almost solely on the basis of pharmaceutical funding, something has changed. Something has changed when scientists have come to expect to be carted off several times per year, at industry expense, to "pre-conferences" and special closed meetings in exotic locations around the world. Something has changed when more community people are now working directly as employees of the industry than there are in AIDS activism, even if some such people are effectively fighting for change from the inside. Something indeed has changed when activists and scientists alike don't seem to notice there's anything wrong with the extravagant spending of industry at conferences like this.

"The Poor You Will Always Have with You"

A famous philosopher and religious icon once used these words to fend off a critical question about money being spent on his personal comfort. He had a point. It would be naïve to think that ratcheting down the extravagance of pharmaceutical displays and evening soirées at the international conferences would somehow save enough money to solve the problem of AIDS in the 3rd world. When will the 3rd

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"How Much Money is a Lot?"

Conversations with several pharmaceutical companies give a hint of the kind of money burned at events like the 12th International Conference on AIDS in Geneva.

The number of companies exhibiting through booths was somewhere around 50 or more. The costs of booths varied depending on size, placement, and whether or not the company is also a paying "sponsor" of the meeting and at what level of "sponsorship." A few examples serve to illustrate the real costs.

One well-known major firm, which did not offer extravagant dinners or evening entertainment, estimated its costs—exclusive of personnel and travel—to be somewhere in excess of $300,000, including a company-funded research "seminar." Much of the booth material is reused at other conferences, but extravagances such as the rental of multiple plasma displays were unique to Geneva. The company sent approximately 80 people to Geneva, a major portion of whom came from the United States.

A second, similar company, which sent only about 15 people from its US headquarters, estimated its per-person costs, including travel, meals and hotel, to be about $7,500. Like the first, this company avoided showy evening dinners and entertainment, but still shouldered the costs of dinner meetings with doctors and community representatives, as well as a major PR operation while on site.

A third major firm covered all the bases. Just shy of 100 people worldwide were brought to the meeting. There was funding for multiple evening dinner events, a lake cruise with a big name entertainer brought over from the US at a cost of around $100,000 plus a bevy of seminars and satellite sessions. Though no numbers were offered, it's easy to see that the toll ran in excess of a million dollars.

Dozens of other companies matched various parts of the packages, easily spending between $100,000 and $500,000.

Companies also hosted dozens of community activists and AIDS service workers to come to the conference, picking up airfare, hotels and sometimes meals and all expenses. Who got such offers? Pretty much anyone who had the nerve to ask. For some, it was the only way to attend. For others, it was a perk that added little or nothing to the community presence or coverage of the conference, however much it may have added to their own.

None of these figures includes the cost of the many industry-funded "conference updates" that are held throughout the US and Europe for community and physician groups after the conference is over.

Without much imagination, it's easy to see that the grand total of industrial cash flashed at the conference would be in the tens of millions or more. And this is but one of such conferences, albeit the biggest.

It would be interesting to speculate what could be done in a single country, city or village with a single year's promotional expenditures.

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world get protease inhibitors and combination therapy? Why, never, of course. The developed world has had the cures for malaria, tuberculosis, parasitic diseases and dozens of epidemic bacterial infections for decades, but these solutions have yet to be widely disseminated among the world's poor.

So what good would it do to spend less on flashy promotions? If nothing else, it would reduce the level of cultural insult hurled collectively at the poor nations and their delegates, an insult that comes not only from industry but from all of us who have come to tolerate these displays and promotions year after year. It might say to people, "we may not be able to solve your problem entirely, but at least we're not going to burn dollar bills in your face."

Second, it might lead to some creative alternatives. Imagine, for example, the news and attention that could be brought to bear on the problem if a single major pharmaceutical company decided to change its behavior. Let's say they bought only the smallest possible booth, staffed it with a single person and handed out only a single flyer. The flyer might say *"In lieu of corporate displays, marketing staff and entertainment this year, we have chosen to redirect the money to staff and fund the XYZ Mother and Children AIDS Clinic in central Uganda for the next five years. For more information about our products and services, see our Internet site or call 1-800-555-1212."* To activists, they would say, *"sorry, no dinners this year, no cruises on the river or lake, no entertainers flown in from the states. I'm sure you'll understand. If you're aware of other needy situations in 3rd world settings, please bring them to our attention."*

No one would lose critical information due to the lack of the company's booth or special meetings. No one would be less inclined to recommend their products or write less favorably about their latest research studies. On the contrary, it might affect them positively. If several companies followed suit, it would make the others still engaged in their displays look positively ugly. Plus, they'd be the only targets left for demonstrations and activist disruption. If most of them got on board and continued their financial support of the conference plus redirecting this "soft" money to worthy causes, at least a symbolic dent could be made in the 3rd world problem. Maybe it could or should be coordinated by the United Nations or by a private non-profit agency. There are endless possibilities and opportunities.

We can't pretend that this is a solution to the problems facing the world because of AIDS. But we must stop pretending that what goes on at these conferences is somehow acceptable. It may be perfectly normal and traditional for major US and European medical conferences and annual medical specialty meetings to engage in such displays and perks to influence their audience. But it's not OK to roll out the same type of show, burning the same amount of money in a meeting dedicated to a plague that is primarily wiping out the most impoverished people on the planet. There's a time and place for everything. The International AIDS Conference is neither the time nor the place for extravagant displays, parties, perks and costly entertainment.

As activists, we should be among the first to refuse to participate, and the first to demand an end to the circus these meetings have become. As the meeting moves into the year 2000 to the African continent for the first time, there couldn't be a better time to change the nature and tone of what takes place there. Indeed, there will be powerful forces that will resist change, particularly the local chambers of commerce and interests which see the huge expenditures associated with the meeting as "good for business." They will no doubt argue that "good business" will somehow trickle down to benefit the sick and the poor, but by now, we should all know such baloney when we hear it. Let the 13th International Conference on AIDS in Durban, South Africa be the first one to make humility and respect for the poor part of the price of admission. ■

In Memory Of . . .

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

James Abrams

Luis Puyol

Chuck Smith

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

Antivirals Update

Over the past few years, research has focused on optimizing the use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in combination with the nucleoside analogue reverse transcriptase inhibitors (NARTIs). This has resulted in studies of dual protease inhibitor combinations and combinations of protease inhibitors and NNRTIs, usually together with nucleoside analogue drugs. The protease inhibitors and the NNRTIs are broken down by the same liver enzymes which can result in increased drug levels of one or both drugs as well as slower elimination of the drug. This sometimes (but not always) allows for simplified dosing schedules as well as use of lower doses of drugs.

More recently, however, there has been a focus on the use of highly active antiretroviral therapy (HAART) which does not include the use of a protease inhibitor. These 'protease sparing' regimens are designed to achieve two goals. First, if successful, they will allow people to save protease inhibitors, generally considered the most potent class of drugs, for later use if they should experience an increase in HIV levels. This permits the patient and doctor to develop long-term strategies intended to spread out the effectiveness of therapy over the longest possible period of time. Secondly, this approach might make it possible to initiate HAART without risking the incidence of certain side effects that may be attributed to the use of protease inhibitors (see *Therapy Side Effects Update, p. 11*). These side effects have led some physicians to become cautious about using protease inhibitors in people in early stage disease. However, not all researchers agree that these side effects are caused directly by protease inhibitors. Some have shown data which suggests that they are a result of sustained suppression of HIV replication, while others have argued that they may be an effect of HIV itself. If the side effects are not caused by protease inhibitors, people may also get them while using other highly potent combinations, regardless of whether or not the combination includes a protease inhibitor.

Protease Sparing Regimens

One important study compared AZT (Retrovir®) + 3TC (Epivir®) + indinavir (Crixivan®), AZT + 3TC + efavirenz (Sustiva®) and indinavir + efavirenz. Four hundred and fifty people who had not previously taken anti-HIV therapy and who had a mean CD4+ cell count of 345 and a mean viral load of about 60,000 copies HIV RNA participated in this study. The data were analyzed by three different methods and AZT + 3TC + efavirenz was superior to AZT + 3TC + indinavir regardless of the methods of analysis applied. There was also a trend suggesting that efavirenz + indinavir may be superior to AZT + 3TC + indinavir, which is considered one of the most potent combinations. The results after 24 weeks, using the most conservative analysis, are shown in **TABLE I** below.

One important observation from this study was that even people with high viral loads (>100,000 copies HIV RNA) had the same level of antiviral response as people with lower viral loads. Previous studies had shown that other NNRTIs were not as effective in suppressing HIV replication in people with high viral loads. Previous studies, however, used a different and perhaps less potent package of drugs in the combination (AZT and ddI, rather than AZT and 3TC).

The results from this study are encouraging because they suggest that a protease sparing and easier to use regimen may be at least as effective as one of the more highly regarded combinations using a protease inhibitor. However, scientists raise a number of concerns about these findings and generally believe it may be too early to draw a final conclusion. Since the data was reported after only 24 weeks, it is not clear how long the anti-HIV activity of the AZT + 3TC + efavirenz regimen will last. Many researchers are concerned that no matter how potent they are in the short-term, the use of NNRTI drugs like efavirenz in a combination presents an easier target for developing resistance since such drugs can be rendered useless by as little as a single mutation. In contrast, the better protease inhibitors often require the virus to develop two or more mutations before they are seriously weakened. This can only be answered by longer-term comparison studies, and therefore this study has now been enlarged to include over 1,500 people and will begin to examine long-term antiviral responses from the three treatment groups. A second concern raised about the existing data is that people in the group receiving AZT + 3TC + indinavir seemed to fare somewhat less well than others on the same regimen in other studies. Thus, it is not entirely clear if the results are truly representative.

TABLE I : Efavirenz Combination Study Results

Drug Combination	% <400 copies HIV RNA	% <50 copies HIV RNA
AZT + 3TC + indinavir	56.2%	44.1%
efavirenz + indinavir	65.0%	46.5%
AZT + 3TC + efavirenz	74.7%	59.2%

Abacavir

Another study which some people have characterized as a protease sparing regimen showed that AZT + 3TC + abacavir (Ziagen®, formerly 1592), a new NARTI (in the same class as AZT and 3TC), was superior to AZT + 3TC. One hundred and seventy-three people who had not previously taken anti-HIV therapy received AZT + 3TC + abacavir or AZT + 3TC. People were allowed to switch to abacavir and/or other approved antiretroviral therapies if their viral loads were above 400 copies HIV RNA after 16 weeks of the study. The results after 16 weeks are shown in **TABLE II** below.

Side effects reported were generally mild to moderate in severity, although people receiving abacavir appeared to experience more malaise, fatigue and headaches. As with the previous 'protease sparing' regimen reported, it is unknown how long the anti-HIV response will last with this regimen, an even more serious question in this study because of the brief 16 weeks of data. Unlike the previous study, there was no compari-

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TABLE II : Abacavir Combination Study Results

Drug Combination	% <400 copies HIV RNA	% <50 copies HIV RNA	CD4+ Cell Increase
AZT + 3TC + abacavir	75%	54%	85
AZT + 3TC	35%	15%	90

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son to a group which included a protease inhibitor. Thus it is somewhat unfair to compare the results from either treatment group to the experience of people receiving a traditional HAART regimen. The reason this is viewed as a potential "protease sparing" regimen—even though the needed study hasn't been conducted—is that the percentage of people reaching the limits of detection in the three-drug group looked at least superficially similar to what is seen in a typical three-drug combination which includes a protease inhibitor. The sponsor of abacavir, Glaxo Wellcome, is anxious to see this described as a protease sparing regimen for two reasons. First, it will allow them to market a HAART regiment composed entirely of Glaxo Wellcome drugs, and second it will allow very simple dosing of just two pills, twice a day (two abacavir and two Combivir®, which is a single pill formulation which includes both AZT and 3TC).

If the long-term data holds up as well as the short-term findings, both the AZT + 3TC + abacavir and AZT + 3TC + efavirenz regimens may turn out to be attractive first-line regimens for people initiating anti-HIV therapy for the first time. Both regimens are dosed only twice a day (efavirenz is taken only once a day, however AZT and 3TC require twice a day dosing), have no food restrictions and involve fewer pills per dose which should result in easier adherence. Taking these regimens will clearly be easier than some of the protease inhibitor containing regimens which have food restrictions, have to be taken three times a day and involve large numbers of pills. Better adherence, rather than any superiority of the drugs, certainly may be one reason why the AZT + 3TC + efavirenz regimen proved superior to the AZT + 3TC + indinavir combination in the study mentioned above. Both abacavir and efavirenz are awaiting approval from the Food and Drug Administration (FDA) and should be available in pharmacies by October/November. Currently, both are widely available in expanded access programs as well.

While awaiting FDA approval and longer-term data, many HIV infected people may face some difficult questions based on this new information. Those just starting therapy need to weigh the convenience and protease-sparing advantages of these combinations against the lack of long-term data about their effectiveness. In contrast to the short term nature of the data presented on the new combinations, other less publicized study results at Geneva showed data on protease inhibitor based combinations which demonstrated successful viral suppression for as long as three years. Thus, for a while, people may be asked to choose between a proven long-term durable therapy that may be somewhat cumbersome to use, versus new combinations which are clearly easier to use but lack any evidence of long-term effectiveness. People already on protease inhibitor-based combinations may also struggle with the question of whether to switch to one of the easier regimens. This is an attractive proposition for those who are having trouble adhering to complex current regimens. Once again, the trade-off is between convenience and the uncertainty about long term effectiveness. Neither Project Inform nor anyone else can recommend one approach over the other since we all lack the long-term data. Thus, for now, this remains a judgment call which must be made by the patient and his or her physician.

Hydroxyurea

Hydroxyurea (HU, Hydrea®) has garnered increasing attention and recent study results show that it might be particularly useful as part of a regimen for people who have not previously taken anti-HIV therapy and for people who have extensive prior use of anti-HIV therapy who are trying to creatively put together effective regimens. One of the largest studies with hydroxyurea included 183 people with an average CD4+ cell count of 350, a viral load of about 30,000 copies HIV RNA. Volunteers had not previously received anti-HIV therapy and were assigned to AZT + ddI, ddI + d4T, ddI + hydroxyurea or ddI + d4T + hydroxyurea. The dose of hydroxyurea used in this study was 500mg twice a day (total daily dose of 1,000mg). The results after 24 weeks of the study are shown in **TABLE III**.

There were no differences in the incidence of side effects between the four groups. Lymphopenia (a reduction in certain white blood cells) was the most common reported side effect affecting 5 – 13% of people in the four groups.

TABLE III : Hydroxyurea Study

Drug Combination	% <400 copies HIV RNA	CD4+ Cell Increase
AZT + ddI	35%	100
ddI + d4T	50%	90
ddI + hydroxyurea	40%	17
ddI + d4T + hydroxyurea	75%	30

A second study of hydroxyurea involved chart reviews of 18 people with advanced HIV disease and who had been on extensive prior antiretroviral therapy. All of the charts reviewed were for people who fit this description who received d4T + 3TC + hydroxyurea (500mg twice a day, total daily dose of 1,000mg). The median reduction in HIV RNA levels was almost 1.8 logs after 8 weeks of therapy. However, people experienced significantly more side effects including severe anemia (decrease in red blood cells), neutropenia (decrease in neutrophils) and hair loss. Although people with advanced HIV disease in this study experienced a good antiviral response, these results also suggest that hydroxyurea may cause serious abnormalities in blood chemistry.

Comparing Protease Inhibitors

Two different studies comparing protease inhibitors showed slightly different results. A study conducted in Denmark enrolled 257 people, 161 of whom had previously taken NARTIs. In addition to two NARTIs, study participants received either indinavir, ritonavir (Norvir®) or ritonavir + saquinavir (Invirase®). Only results for people who had not previously been on anti-HIV therapy were presented, although it was noted that the results were similar for those who had been on previous NARTI treatments. People receiving combinations with indinavir or ritonavir + saquinavir were significantly more likely to achieve HIV RNA levels below 400 copies compared to people receiving regimens which included ritonavir as the only protease inhibitor. This is probably due to the fact that ritonavir was not well tolerated and about 35% of people receiving it discontinued because of side effects. The study also showed that people receiving ritonavir + saquinavir containing regimens were more likely to achieve HIV RNA levels below 20 copies than people receiving indinavir-containing regimens.

A second study comparing protease inhibitors followed 1,251 people who received either indinavir or ritonavir. All of the participants were in advanced stage disease (average CD4+ cell count was below 20) and had been previously treated with NARTIs. Most participants took one or two nucleoside analogue drugs along with the protease inhibitor. The risk of disease progression and death were the same between the two groups, however significantly more people had to discontinue the use of ritonavir because of side effects. One additional and very important observation was that people receiving ritonavir were 20 times more likely to have elevated triglyceride levels compared to people receiving indinavir. A similar difference is likely between ritonavir and other protease inhibitors. Many researchers and physicians believe that this finding suggests that people with a prior history or risk of pancreatitis and

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people at risk of heart disease not use ritonavir as their primary protease inhibitor.

Novel Combinations

Preliminary data from a small study combining indinavir and ritonavir show intriguing results. Thirty-eight people with different histories of prior anti-HIV therapy use received indinavir, ritonavir, d4T and 3TC. The dose of indinavir and ritonavir used was 400mg twice daily (total daily dose of 800mg) of each drug. Because of the lower dose of indinavir used in this study, one group of 12 people started this quadruple regimen after being on a stable regimen of ritonavir, saquinavir, d4T and 3TC, and all had a HIV RNA levels below 400 copies for over 6 months. Participants were able to take their medications with food and did not have to drink large amounts of water as is currently recommended with indinavir to prevent kidney stones. All of these participants continued to have HIV RNA levels below 400 copies after 52 weeks on the new combination, with the majority of participants having HIV RNA levels below 40 copies. Most of these volunteers also had a substantial secondary increase in CD4+ counts of over 100 cells (over and above any CD4+ cell count increase provided by their initial protease inhibitor regimen).

A second group of 18 had previously not taken anti-HIV therapy but had a high mean viral load of about 140,000 copies HIV RNA and a CD4+ cell count of about 370. All saw their viral loads drop below 400 copies after 32 weeks of therapy. The majority fell below 40 copies HIV RNA on the more sensitive test.

A final group of 8 people were failing on a regimen containing a protease inhibitor (4 on saquinavir and 4 on indinavir) and had a mean viral load of about 180,000 copies HIV RNA. All had at least a 1.5 log drop in HIV RNA levels. Side effects from this combination were relatively mild, the most common being mild diarrhea not requiring dose modification. There were no cases of kidney stones. It is not known whether this combination will result in a higher incidence of elevated triglyceride and cholesterol levels as have been thought to be associated with protease inhibitor use, particularly with ritonavir. If longer-term data continues to follow this initial pattern, the combination of ritonavir and indinavir will make a particularly attractive protease inhibitor combination, one which reduces the complexity, toxicity, and requirements of typical indinavir or ritonavir based combinations. The outlook, however, is now somewhat darkened by the problems being reported with ritonavir production (see *Ritonavir Alert, p. 12*).

Results from a pioneering study using a once daily dosing regimen show good antiviral activity. Seventy intravenous drug users, of whom 56 were on methadone, polamidone or codeine, received ddI (400mg), 3TC (300mg) and nevirapine (Viramune®, 400mg) once a day simultaneously. Most volunteers were also co-infected with hepatitis C (HCV) and about a third had previously taken anti-HIV therapies. People entering the study had a median CD4+ cell count of about 250 and a viral load of about 125,000 copies HIV RNA. After 24 weeks about 75% of the participants had HIV RNA levels below 500 copies and a median CD4+ increase of 150 cells, results which seem comparable to much more complex regimens which use protease inhibitors. The combination was generally well tolerated with 5 people having to discontinue therapy because of rash (associated, undoubtedly, with nevirapine). Additionally, people co-infected with HCV were also able to tolerate this regimen.

The results from this study are particularly interesting, as this is the first study to employ a highly active antiretroviral regimen taken only once a day. This dosing schedule would be ideal for people who have difficulty adhering to anti-HIV medications. Longer-term follow up of these study participants is important to know if their anti-HIV responses will hold up over the long haul. Further studies comparing once daily regimens to more traditional regimens would be helpful in order to understand if resistance develops more or less rapidly depending on the dosing schedule employed.

In a study of people with early stage disease, the combination of abacavir and amprenavir (Agenerase®) showed potent activity. Forty-one people with an average CD4+ count of 756 cells, HIV RNA levels of about 26,000 copies and who had not been previously treated with anti-HIV therapies received abacavir (300mg twice a day for a total daily dose of 600mg) and amprenavir (1,200mg twice a day for a total daily dose of

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Effect of Combination Therapies on Pregnant Women and Their Children

A small study looking at the safety of anti-HIV therapy use in pregnant women and their newborn children revealed an unexpectedly high number of premature births as well as side effects in pregnant women using anti-HIV therapy with or without a protease inhibitor. Because of these concerns, the Pediatric AIDS Clinical Trials Groups (PACTG) temporarily stopped enrollment into studies which include protease inhibitor regimens for the prevention of mother-to-child HIV. However, review of all the data show that the incidence of premature births was higher in women on no anti-HIV therapy than women on 2- or 3-drug combinations, which include a protease inhibitor. As a result, all protease inhibitor studies for preventing mother-to-child transmission have been re-opened.

The 37 women in this study tended to have low CD4+ cell counts and generally more advanced HIV disease. Their treatments included either two nucleoside analogue reverse transcriptase inhibitors (NARTIs) (21 women) or two NARTIs plus one or two protease inhibitors (16 women, 9 of whom used indinavir) and all were receiving anti-HIV treatment at the time of delivery.

The most common side effect was anemia, or low red blood cell counts (low grade in 9 women, higher grade in 6). Other side effects, seen in only one or two women, included low white blood cell counts, low platelets (cells involved in blood clotting), high amylase levels (related to possible pancreas problems), diabetes, kidney stones, high blood pressure and blood sugar problems. High liver function tests and persisting nausea were each reported in 3 women.

The most common side effects in newborn children were anemia (4), possibly related to AZT which is known to suppress the bone marrow, and high bilirubin levels which can indicate liver problems (4). High bilirubin levels in children are much more serious than high bilirubin levels in adults. Children do not have a fully developed "blood brain barrier" and therefore bilirubin can have potential toxic effects on the brain in children. Eleven children were born prematurely at 37 weeks, considered mildly premature. One child had a severe malformation (exposed to AZT + 3TC + indinavir) and two had non-life-threatening bleeding in the brain (exposed to either AZT + 3TC + indinavir or d4T + 3TC + indinavir). It is not clear if these severe side effects are specifically associated with indinavir use or just a result of the high proportion of women in the group taking the drug.

In all, 21 of 37 women and 17 of 30 babies experienced at least one side effect possibly related to anti-HIV therapy, primarily prematurity in children. It is possible that the increased events in the mothers and children may have been related to weaker health status of the mothers in this group. While it is not clear how many events are related to the drug side effects, HIV or to pregnancy itself, women with HIV who are pregnant and taking or considering anti-HIV therapies should be aware of the potential risks to their newborn children and seek prenatal care to monitor their health status as well as their child's health.

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2,400mg). All of the participants had less than 400 copies HIV RNA after 48 weeks of therapy and most volunteers had fewer than 50 copies HIV RNA. Like the study reported earlier which combined efavirenz and indinavir, these results suggest that it may be possible to construct effective HAART regimens using only two drugs, as long as both drugs provide high levels of antiviral action.

Commentary

Most recent studies have been conducted in people who have either never taken anti-HIV drugs or have had minimal prior therapy. Pharmaceutical companies prefer to test their drugs in this patient population because it is easier to show better antiviral activity. Moreover, such studies make it easier to see just how much of the overall antiviral effect can be attributed to the new drug. This is much more difficult to determine when treating people who have used many previous therapies. There continue to be fewer studies in people who have failed multiple therapies and, as a result, there is very little guidance on what combinations may benefit people in this situation. This area of research needs to be a priority for both the pharmaceutical companies developing new therapies as well as the government sponsored clinical trial networks. In the meantime, the wider availability of the resistance tests may help eliminate some of the guesswork (see *Geno- and Phenotypic Resistance Tests, p. 9*) and some new therapies in development may be active against drug-resistant virus, but large clinical studies are needed to determine their usefulness for this population. ■

Salvage Therapy Studies

Salvage therapy refers to regimens which are used or being studied for people who have failed one or more protease inhibitor-containing regimens. In this instance, "failed" means that their treatment regimen was no longer able to suppress viral replication to levels below the limit of detection.

A small study of 20 people who were virologically failing a regimen containing indinavir showed that the addition of a NNRTI (non-nucleoside reverse transcriptase inhibitor) to a three-drug regimen results in renewed potent antiviral activity. People with an average CD4+ count of 290 cells and HIV RNA levels of about 20,000 copies received one of two regimens:

- nelfinavir (Viracept®) + soft gel saquinavir (Fortovase®) + abacavir + another nucleoside analogue drug, or
- nelfinavir + soft gel saquinavir + abacavir + nevirapine (Viramune®)

The doses used in this study were 1,250mg twice a day (2,500mg total daily dose) of nelfinavir, 1,200mg twice a day (2,400mg total daily dose) of saquinavir, 300mg twice a day (600mg total daily dose) of abacavir and 200mg twice a day (400mg total daily dose) of nevirapine. None of the participants had previously been on any of the four drugs in either regimen. The results after 20 weeks are shown in **TABLE I** below.

This study shows that simply switching to a dual protease inhibitor regimen may not be adequate to regain control of viral replication, probably due to the presence of cross-resistance between protease inhibitors. The study confirms that the best results are achieved when at least two new potent drugs are started simultaneously. In this instance, it seems clear that the addition of the NNRTI provided substantially more benefit than simply switching to two protease inhibitors. Phenotypic resistance testing was done prior to study entry and was found to be highly predictive of an antiviral response. In other words, those with demonstrated phenotypic resistance to the drugs used were least likely to see decreases in HIV levels, where as those without resistance were more likely to see decreases in HIV levels. People sensitive to two or three of the drugs at study entry experienced sustained HIV suppression whereas people who were sensitive to 0 or 1 drug experienced either no or only a transient reduction in HIV suppression. ■

TABLE I: Salvage Study Results

Drug Combination	Viral Load Reduction	% <400 copies HIV RNA	% <50 copies HIV RNA
NFV+SQV+ABA+NARTI	0.59 logs	1/7 (14%)	1/7 (14%)
NFV+SQV+ABA+NVP	2.67 logs	7/9 (78%)	6/9 (67%)

NFV=nelfinavir SQV=saquinavir ABA=abacavir NVP=nevirapine
NARTI=nucleoside analogue reverse transcriptase inhibitor

Combivir® Alert!

Discretion should be taken when considering modification of personal treatment plans with Combivir®. Some doctors may be confused about Combivir® and how it fits into anti-HIV therapy strategies. To illustrate this point, consider the following scenario:

A man was taking a two-drug combination of AZT (zidovudine, Retrovir®) and 3TC (lamivudine, Epivir®). He and his doctor began seeing a trend of increases in his viral load and decreases in his CD4+ cell count. His doctor wisely recommended that he switch to a new regimen. He then prescribed Combivir® and Indinavir (Crixivan®).

Combivir® is a combination pill form of AZT+3TC. ***It is not a new drug.*** If people have been on AZT+3TC, then switching to Combivir® is equivalent to continuing on AZT+3TC. *If someone is failing an AZT+3TC combination regimen, they will not benefit from Combivir®.* Essentially this man was put on indinavir alone, which may quickly lead to indinavir resistance which may result in decreased or no benefit from other protease inhibitors.

New Drugs in Development

Overall, the pipeline for truly new drugs is not well filled. While a modest number of new agents are working their way through the development system, only a small portion of them is likely to help people who have failed earlier therapies. Drugs aimed at new targets in the viral life cycle are few and far between. This weakness in the new drug pipeline suggests that it will be very important over the next few years for people to do their absolute best to adhere to their existing regimens to get the longest possible use out of them. Without such careful adherence and wise treatment strategies, many people may run out of effective therapies well before new and better agents make it through the pipeline.

Abbott Laboratories' second generation protease inhibitor, ABT-378, appears to be quite potent and well tolerated. A small study enrolled 32 people who had not previously received anti-HIV therapy and who had a median HIV RNA level of 100,000 copies and a CD4+ cell count of 424 cells. People received 200mg ABT-378 and 100mg ritonavir—both taken twice a day—or 400mg ABT-378 and 100 mg ritonavir again both taken twice a day. People received ABT-378 and ritonavir for three weeks and then d4T and 3TC were added. There were no differences between the two doses. After the 3 weeks of only ABT-378 and ritonavir, people had an average viral load reduction of 2 logs and the addition of d4T and 3TC resulted in a further reduction of 0.2 logs. Ninety percent of the participants had a viral load below 400 copies HIV RNA after 24 weeks and they had a median increase of 150 CD4+ cells. ABT-378 and ritonavir were well tolerated without anyone having to discontinue use because of side effects. Abbott is hoping that ritonavir increases ABT-378 levels so dramatically that this combination will be able to *overpower* protease-resistant virus. Clinical studies of ABT-378 to test whether ABT-378 will be effective are planned in people who have virologically failed protease inhibitors. (Note: the use of ritonavir in this regimen is solely intended to increase the blood levels of the ABT-378 drug. The dose used in the study is NOT a recommended dose of ritonavir and should not generally be used.)

Pharmacia & Upjohn recently started a small study with their new protease inhibitor, tipranavir (PNU-140690). Twenty-four people who were on a two nucleoside analogue regimen but who have not previously taken a protease inhibitor participated in this study. People had an average viral load of about 30,000 copies HIV RNA and a CD4+ count of 400 cells prior to starting the study. Participants added 900mg, 1,200mg or 1,500mg of tipranavir taken three times a day to their existing dual nucleoside analogue regimen. A maximum 1.3 log reduction in HIV RNA was seen among those receiving the highest dose of tipranavir, however most people had a rebound in their viral loads. This was believed to be due to lack of adherence to the regimen, for in this study, tipranavir came in 150mg pills and, therefore, people taking the highest dose regimen had to take 30 pills a day. A new formulation is being developed which will allow individuals to take fewer pills per day. In laboratory studies, tipranavir has a completely different resistance profile compared to the existing protease inhibitors and thus might be useful against protease-resistant virus. However, similar claims about previous protease inhibitors have usually not translated into clinical success in heavily pretreated patients, so it is premature to believe this drug answers the need for a true salvage therapy. Results from studies like this in general are difficult to interpret. Given that study participants added tipranavir to an existing regimen, which is not considered the standard of care, it's impossible to figure out what the actual contribution of tipranavir, used correctly, might have been. A wise anti-HIV strategy typically includes simultaneously starting at least two drugs, which have not previously been used.

Agouron Pharmaceuticals recently licensed the development of a NNRTI S-1153 from Shionogi Pharmaceuticals. In laboratory studies, this drug is not completely cross-resistant with the existing NNRTIs. Furthermore, the company asserts that it is more difficult to develop resistance to this drug, as it requires more than one mutation to cause high-level resistance and, as a result, drug failure. The current NNRTIs (delavirdine, nevirapine and efavirenz) only require one mutation to cause drug failure. In a small study of 27 people, most of whom had been on prior anti-HIV therapies, S-1153 showed good activity. People received S-1153 at a dose of 8.3 mg/kg every 8 hours, 10mg/kg every twelve hours or 12.5mg/kg every twelve hours. People had a maximum median reduction in HIV RNA levels of 1.4 logs. The drug was generally well tolerated with mild gastrointestinal problems being the most common side effect. No cases of rash were reported. ■

Adefovir Warning

People taking the anti-HIV drug adefovir (Preveon®) for more than 20 weeks may be at higher risk for developing kidney toxicity due to accumulation of the drug in their blood, according to preliminary observations. Adefovir is a new type of reverse transcriptase inhibitor—called a nucleotide reverse transcriptase inhibitor—that is in large studies. It is also available through an expanded access program. People taking adefovir are now recommended to either reduce to a lower dose (from 120mg once a day to 60mg once a day) after being on the higher dose for 20 weeks and/or increase monitoring of serum creatinine levels, which are a measure of kidney function.

Expanded Access Programs

Three new drugs are currently available in expanded access programs—abacavir (Ziagen®, formerly GW1592), adefovir (Preveon®, formerly bis-POM PMEA) and efavirenz (Sustiva®, formerly DMP266). A fourth drug, amprenavir (Agenerase®, 141W94), is likely to be available soon.

Abacavir (NARTI) **800-501-4672**
For anyone failing current therapy and requiring an additional new drug for treatment strategy.

Adefovir (NARTI) **800-445-3235**
For anyone failing current therapy and requiring an additional new drug for treatment strategy.

Amprenavir (PI)
As PI Perspective 25 goes to print, an amprenavir expanded access program is being reviewed by the FDA. For new information about this program, contact the National HIV/AIDS Treatment Hotline at 800-822-7422.

Efavirenz (NNRTI) **800-998-6854**
For anyone failing current therapy whose CD4+ cell count has ever gone below 400 and requires an additional new drug for treatment strategy.

Geno- and Phenotypic Resistance Tests

Despite the recent advances with anti-HIV therapies, some people who are taking anti-HIV therapies are experiencing returns of measurable viral load and/or increases in their viral load (HIV RNA levels) measurements. One of the most common causes of the failure of drug therapy is HIV's ability to mutate or change in such a way that anti-HIV drugs are no longer effective (known as drug resistance). Studies show that people who achieve the very lowest viral loads (less than 50 copies HIV RNA) after treatment experience the most durable antiviral response, since so little virus is reproducing and mutating, making drug resistance less likely to develop.

Recently, HIV drug resistance tests have become more widely available with several laboratories offering a variety of these tests. Some of these laboratories appear to be more reliable in their ability to provide meaningful results whereas others have a poor reputation in their ability to perform these tests. None of these tests have been approved by the Food and Drug Administration and therefore are still considered experimental. Although laboratories are offering these tests, some insurance companies, Medicare and other sources for reimbursement may not cover them.

There are two ways of measuring resistance to HIV drugs. One, called genotypic resistance testing, seeks to determine any changes to a part of HIV's genetic structure, which change the way the virus makes key proteins (like protease or reverse transcriptase enzymes). Such changes are referred to as mutations. The other approach, called phenotypic resistance testing, is a more direct measure of resistance. It examines the amount of drug needed to inhibit the growth of HIV in a laboratory setting. In its natural state (wild type virus), when HIV is not resistant to a particular drug, known levels of the drug completely suppress HIV replication. Resistant HIV requires higher levels of the same drug to get an equal level of suppression. Both are likely to be useful, but neither test can tell with certainty which therapies people will get the most benefit from.

Genotypic Tests

Genotypic resistance testing examines samples of virus taken from a patient and looks for the presence of specific viral mutations which are known to be associated with resistance to certain drugs. Many laboratories are offering genotypic resistance testing. While most laboratories use essentially the same technology with some minor modifications, a few use completely different technologies. The most common method of measuring genotypic resistance involves taking a blood sample and using a machine that can read the specific sequence of different genes that are the targets of HIV drugs (i.e. the reverse transcriptase gene is the target for the nucleoside analogue and non-nucleoside analogue reverse transcriptase inhibitors and the protease gene for the protease inhibitors). The sequence results are then compared to those from a registry that holds the 'true' genetic sequence of HIV. Certain changes from the 'true' sequence are known to correspond to resistance to certain drugs. These differences might be useful in helping to determine if someone has developed resistance to a specific drug, since almost all drugs follow a set pattern of mutations. For genotypic tests to be accurate, they generally require the use of a blood sample from a person with a viral load above 1,000 HIV RNA copies who is taking anti-HIV therapy. Otherwise, the pre-therapy strain of virus (wild type virus) will outgrow the mutant virus, and the results may show no mutations, although the mutant virus remains in the background and will quickly come back once the same therapy is re-started. Additionally, for these tests to show there are specific mutations, at least 20% of virus particles need to have that mutation to be able to reliably detect a change. In other words, these tests will not be able to pick up very low level resistant virus. The charts above show mutations associated with drug resistance (drugs being less effective).

Another technology used in genotypic resistance testing is the line probe assay (LiPA). This test utilizes different probes, or detectors of certain changes, which are designed to identify specific mutations. For instance, one probe would be designed specifically to detect any change at position 215 in the reverse transcriptase gene, which is known to be a mutation associated with resistance to AZT (zidovudine, Retrovir®). However, given the number of mutations that are associated with HIV drug resistance, as shown by the chart below, this method of fishing for specific changes may be a less practical way to measure resistance.

Another method has merged computer chip technology with biotechnology. GeneChip technology uses a chip that has thousands of probes built into it which can detect changes in the reverse transcriptase and protease gene when a blood sample is placed on it. The chip is placed into a scanner, similar to those used in desktop publishing, which reads the results from the chip. The results of the scan are compiled by a computer program which shows whether there are specific mutations in the genes.

Phenotypic Tests

Phenotypic resistance testing grows samples of virus with genetic characteristics copied from blood samples submitted by individual patients. Cultures in which the virus is growing are then treated with various available antiviral therapies to determine how much drug is needed to inhibit the virus. The results are compared to the amount of drug needed to inhibit laboratory *standard* or *wild type* virus. If high drug levels are needed to keep the virus from replicating, this suggests the virus is no longer sensitive to the drug and is likely to have developed resistance. Because they directly test the patient's virus against the actual drugs used in treatment, phenotypic tests are considered the gold standard of resistance testing. This method is routinely used to test for antibiotics resistance before someone starts taking medications to determine if the bacteria are susceptible to the drug(s).

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Company	Name of Test	Measure	Cost	Phone
GENOTYPIC TESTS				
Applied Sciences	Genotyping test	RT & Protease	$380	770-734-9872
LabCorp/Virco	VircoGen	RT & Protease	$450	800-533-0567
Abbott Diagnostics/Murex	LiPA (Line Probe Assay)	RT	To be determined	800-334-9332
Specialty Labs	GenotypR PLUS	RT & Protease	$475	800-323-9100
Stanford	ABL	RT & Protease	$300	650-723-5706
PHENOTYPIC TESTS				
LabCorp/Virco	Antivirogram	RT & Protease	$880	800-533-0567
ViroLogic	To be determined	RT & Protease	To be determined	To be determined

RT = reverse transciptase

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There are two phenotypic tests that are currently or soon to be commercially available. Both tests use a similar technology. Generally, with both, anything above a 2- to 4-fold change in resistance (2- to 4-fold higher or lower amount of drug needed to inhibit the virus by the same degree) is considered meaningful and outside the variability of the tests. With most drugs, anything above a 10-fold increase in resistance (sometimes referred to as a 10-fold decrease in sensitivity/susceptibility) is considered highly resistant and likely to mean that the drugs are no longer capable of blocking the virus from reproducing. A finding of 4- to 10-fold reduction in sensitivity to a drug is considered a moderate degree of resistance, one which might be overcome by higher drug levels. In order for phenotypic resistance test results to provide meaningful information, these tests generally require the use of a blood sample from people with a viral load of above 1,000 (but probably closer to the 5,000 range) copies HIV RNA who are currently taking anti-HIV therapies.

Availability

Different laboratories are currently offering tests identified in the chart at the bottom of page 9.

Commentary

Overall, many questions remain about the use of these new tests. Perhaps most important, it is unclear when and how often to use them, and just how to make decisions based on the information they provide. Phenotypic testing is very expensive ($800–1,000 per test), while genotypic testing is merely expensive, ($300–500 per test). Certainly, for those with money to spare or a generous insurance company, the tests provide information you'd rather have than not have. But because of the high costs, careful decisions must be made about the true usefulness of the tests in guiding clinical practice. Unfortunately, it is still too early to know how much additional information these tests will provide patients and physicians. There are accumulating data that the phenotypic tests can show when a drug is no longer effective. However, there is very little data showing the phenotypic tests can predict if someone will benefit from a new regimen. In other words, phenotypic results may be useful in telling someone that a drug doesn't work, but at least for the time being, it is less well-proven that it can tell someone if a drug or combination will work. One potential downside for genotypic testing is that resistance to one drug sometimes results in increased sensitivity of another drug. Probably the most discussed has been between AZT and 3TC (lamivudine, Epivir®), where resistance to 3TC reverses the resistance (increases sensitivity) of AZT against HIV. There are other examples of this phenomenon that may make it difficult for people to interpret genotypic results. Clearly, there are pros and cons to both types of resistance tests. ■

For more geno- and phenotypic information which includes resistance charts, please call Project Inform's National HIV/AIDS Treatment Hotline and request the *Geno- and Phenotypic Resistance Tests Hotline Handout*.

Genotypic Testing

PROS	CONS
Less complex test. Results usually available more rapidly.	Some mutations counteract each other, so may not be able to truly determine whether there is a drug resistance.
Less expensive.	Will not be able to give useful information on cross-resistance.
For people who may have developed drug resistance and stopped therapy, genotypic tests may be able to still detect mutant virus.	May be more accurate for the necleoside analogue and non-nucleoside reverse transcriptase inhibitors but may be less useful for the protease inhibitors which do not always have consistent mutation patterns.
Increased sensitivity (requires a lower viral load).	Should be on anti-HIV therapies to get meaningful results.

Phenotypic Testing

PROS	CONS
Results generally interpretable for all anti-HIV drugs.	Very complex test. Results take a little longer to be available.
Should be able to give useful information on cross-resistance.	Very expensive.
	Sensitivity may still be an issue (requires a higher viral load).
	Should be on anti-HIV therapies to get meaningful results.

Resource Notes

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

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

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

WORLD is a newsletter for, by and about women facing HIV disease. WORLD strives to break the isolation of HIV+ women by providing a forum for communication and information of interest to women. For more information call 1-510-658-6930.

AIDS Treatment News (San Francisco)	**1-800-873-2812**
Treatment Issues (Gay Men's Health Crisis, New York)	**1-212-337-1950**
Test Positive Aware (Chicago)	**1-312-472-6397**

Therapy Side Effects Update

Some of the enthusiasm over protease inhibitors has been dampened by reports of a redistribution of body fat (lipodystrophy) that has been observed in some people who have been on long-term protease inhibitor therapy. There is considerable debate over whether this phenomenon is directly caused by the protease inhibitors or whether it is caused by rapid and sustained decreases in viral load (HIV RNA levels) and not unique to a particular class of therapy.

Some researchers report observations of lipodystrophy in the pre-protease era, when people were treated with two-drug nucleoside analogue combinations. Further, there is controversy over the incidence of this phenomenon. Some researchers contend that they have rarely, if ever, seen lipodystrophy among their patients while others report they see it frequently. Notably, an Australian group reports an incidence rate of almost 65%, although their figures are based on self-reporting by the patients. The cause of lipodystrophy is still unknown. Information on treating lipodystrophy is sorely lacking and as yet, there isn't a standardized definition for the condition.

The most commonly accepted descriptions of lipodystrophy may include:

- wasting in face and limbs (a decrease in the fat amount in the face, arms and/or legs),
- *buffalo hump*, a protruding pad of fat accumulated at base of the neck or top of the back, or
- *protease paunch*, a pad of fat that develops behind the stomach muscles (sometimes referred to as central or truncal obesity)

From the limited information currently available it appears that people experiencing lipodystrophy are not commonly experiencing decreases or increases in their overall body weight. Individual and anecdotal reports from some patients and physicians, however, claim overall weight loss. For the most part, the distribution of weight is changing—perhaps moving away from arms and legs and into the gut area. In effect, it appears to be a change in the way and places the body stores fat. The difference between this phenomenon and normal changes in body fat distribution is that lipodystrophy results in the fat being found under the abdominal muscles and not directly under the skin where fat usually builds up. Additionally, this fatty buildup is solid and can't be pinched like a *beer belly*. Furthermore, both women and men have reported increased breast size in addition to the other changes in body composition.

Other side effects, which may be associated with lipodystrophy or independently associated with protease inhibitor therapy, are metabolic changes. These include elevated triglyceride and cholesterol levels (increases in LDL [bad cholesterol] and decreases in HDL [good cholesterol]), onset of diabetes or insulin resistance, and elevated blood pressure. One recent study indicated that the risk of elevated triglyceride levels was nearly 20 times greater in patients using ritonavir, compared to some other protease inhibitors. High triglcyeride levels might be predictive of an increased risk of pancreatitis, while excessive cholesterol levels might be associated with greater risk of heart disease. Other less common, non-metabolic side effects include increased bleeding in people with hemophilia, loss of body hair and ingrown toe nails. These changes usually occur despite effective control of HIV replication, a more robust immune system and otherwise generally improved health.

There are several theories on the cause of lipodystrophy and the metabolic changes. The Australian group has proposed that the protease inhibitors may bind to a human protein, a "lipid binding" protein, which is structurally similar to the HIV protease enzyme. The role of this protein is to gather up and destroy lipids (fatty substances). They speculate that because the protease inhibitors may be partially blocking the function of this protein, they may change the lipid concentrations in blood as well as the death of certain fatty cells resulting in an accumulation of fat under the abdominal muscle. Furthermore, this protein transports essential materials to the same liver enzyme (known as cytochrome P450 3A4) that is used by the protease inhibitors to be broken down. Since the protease inhibitors block this liver enzyme, it may further worsen the situation. This theory may partially explain why some people developed lipodystrophy before the advent of protease inhibitors as there are other drugs which potently block this liver enzyme, including the antifungal drug ketoconazole (Nizoral®).

One potential effect of these metabolic changes is heart disease. One recent report showed three cases of narrowing of the coronary arteries, which prevents an adequate supply of blood to the heart and can result in damage to the heart muscle. All three cases involved men 40 years of age or younger and who were being treated with a protease inhibitor containing regimen. Two men subsequently had heart attacks.

Several studies presented at the International AIDS conference in Geneva showed that there were differences in metabolic changes and lipodystrophy between people receiving protease inhibitors, those non-nucleoside reverse transcriptase inhibitors (NNRTIs) or no anti-HIV therapies. However, people in these studies were not matched for viral loads (HIV RNA levels) and the groups receiving protease inhibitors had much lower HIV levels. Since one of the major theory attributes lipodystrophy to high levels of HIV suppression, it may be unfair to compare the outcomes of these studies.

Another study showed that people receiving the dual protease combination ritonavir (Norvir®) and saquinavir (Invirase® or Fortovase®) were significantly more likely to have high cholesterol levels that warrants starting cholesterol-lowering therapy compared to people receiving a single protease inhibitor.

An important finding from a small study shows that men and women equally were likely to develop truncal obesity and that this type of change in body composition is not only observed among people receiving protease inhibitors and/or anti-HIV therapy.

A study looking specifically at body shape changes in women taking protease inhibitors showed that of the women (16%) who noticed body shape changes, most reported increases in breast size, increase in abdominal size and peripheral (arm and leg) wasting. For more information on these and other relevant studies on side effects and body composition changes, please call the Project Inform National HIV/AIDS Treatment Hotline and ask for the *Drug Side Effects Chart*.

There is still no strategy proven effective to combat metabolic changes and lipodystrophy. There have been mixed reports of using anti-lipidemic medications such as clofibrate (Atromid®) and gemfibrozil (Lopid®) to lower triglyceride levels. Similarly there have been mixed results with using the 'statin' inhibitors such as cerivastatin (Baycol®), fluvastatin (Lescol®), atorvastatin (Lipitor®), lovastatin (Mevacor®), pravastatin (Pravachol®) and simvastatin (Zocor®). People who are considering starting a 'statin' inhibitor who are using a protease inhibitor should discuss potential interactions between these two classes of drugs with their healthcare provider and pharmacist. These drugs are both processed through the same liver enzyme and there is a strong potential for interaction. There have been some anecdotal

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reports of success using human growth hormone to reduce the *buffalo hump* and the fatty deposit around the abdomen. However, these have involved a very small number of people and larger studies are needed to determine whether this is a useful therapeutic approach. In some severe cases of *buffalo hump*, people have had liposuction to remove the excess fatty buildup. This is usually only considered when the fatty buildup causes pain or hinders mobility. It is not yet clear whether liposuction results in a permanent solution or whether the hump will simple reoccur over time. In any case, patients should be advised that lipsosuction can sometimes have serious complications, and few if any practitioners have much experience using it for this purpose. ■

Women at the Conference[E]

While the recent 12th World AIDS Conference in Geneva provided no real surprises for women living with HIV, the conference surged forward by having numerous sessions specifically dedicated to the treatment and care of HIV+ women. There were sessions on *Clinical Care of Women with HIV* and *Mother-to-Child HIV Transmission*, as well as others devoted to prevention strategies for women, breast-feeding and body shape changes in women (see *Therapy Side Effects Update, p. 11*).

Together, these served as a clear reminder of the social, psychological and biological needs that women face in this epidemic. In addition, meetings were called by the International Community of Women living with HIV/AIDS and the International AIDS Society Women's Caucus to discuss the global needs of women in the epidemic. While there is still much work to be done, it was encouraging to see women's treatment activism beginning to flourish around the world.

Researchers have begun to look specifically at the use and effectiveness of anti-HIV therapies and therapies for gynecological conditions in women (see *Treatment of Gynecological Conditions in Women, p. 15*). But we still need to learn more about the interaction between HIV and the menstrual cycle, hormone replacement therapy, birth control, pregnancy and other issues specific to women. While some research is already underway to shed light on these issues, some areas, particularly the role of hormone replacement therapy, remain inadequately addressed by current research efforts.

Although we are seeing some slight differences in side effects and drug levels in women, more significant differences may lie in other non-biological areas, such as access to treatment and access to physicians experienced in treating people with HIV. Recent data from the National HIV/AIDS Treatment Survey indicate that women are less likely than men to receive care from physicians experienced in treating people with HIV and that women tend to be at more advanced stages of HIV disease when they first see a doctor. The result is that many women receive substandard care and therefore tend to experience disease progression sooner after an HIV diagnosis. This is certainly not true for all women, but it is especially common for women who are seeing less experienced physicians or who are more advanced in their HIV disease when they are diagnosed.

AIDS research must continue to address the concerns of women with HIV from a broader perspective, examining the women-specific treatment concerns but also the needs of women in our changing health care system. The Geneva conference's focus on women and children was encouraging and credit should be given to all the women living with HIV/AIDS, their advocates, caregivers and the researchers who continue to contribute to meaningful advances in information specific to women. ■

Ritonavir Alert

Abbott Laboratories announced they are experiencing manufacturing difficulties with ritonavir (Norvir®) capsules. The production difficulties ***apply only*** to the capsules and ***do not apply*** to the ritonavir oral solution. The concern that prompted the announcement is the development of a crystalline structure during production of the capsules. The structure influences how the drug gets absorbed in the body. Ultimately, it failed to meet quality assurance specifications for the drug. The source of the problem has not yet been identified. The crystalline structure ***has not been identified*** in any of the capsules ***currently*** on the market.

Anyone taking ritonavir capsules should be advised that a shortage of the drug will likely happen in mid-August when the existing pharmaceutical supply of capsules are depleted. Anyone who has difficulty obtaining ritonavir capsules can replace their capsule formulation with the ritonavir oral solution. The following information on ritonavir oral solution should be followed closely to optimize the use of the drug:

> The liquid should not be refrigerated and should be stored at room temperature, ideally between 68–77°F. It should be taken with food, and it can be taken with chocolate milk, Ensure, and Advera to minimize the unpleasant taste. To reduce the risk of crystal formation, shake the liquid well and use the oral solution within 30 days of obtaining the drug from the pharmacy. The oral solution can be used in the same manner as the capsule formulation, i.e., in combination with other drugs. The drug interaction profile between the oral solution and the capsule formulation should be identical. The only major difference between the two formulations is that the oral solution contains a higher alcohol content. Ritonavir oral solution comes with a measuring cap that is scored to measure doses of 400mg and 600mg.

Project Inform will continue to provide up-to-date information regarding this development with ritonavir as it becomes available. For more information on supplies of ritonavir and implications of the manufacturing difficulties, consult Abbott Laboratories toll-free at 800-637-2400.

Opportunistic Infections Update

There has been a dramatic decrease in cases of opportunistic infections (OIs) since the introduction of Highly Active Antiretroviral Therapy (HAART). However, perhaps as a consequence, there are few new therapies in development for the treatment or prevention of opportunistic infections. As a result, most of the recent studies have been conducted to optimize the use of existing therapies and to determine the effect HAART is having on particular OIs. Despite the decrease in cases of OIs, new therapies for opportunistic infections are desperately needed, especially for people who receive little or no response from HAART or who are failing their OI therapy because of drug resistant viruses or bacteria.

Hepatitis C

Confusion remains regarding the advisability of using protease inhibitors in people co-infected with HIV and hepatitis C virus (HCV). This concern arises because most of the protease inhibitors place some degree of strain on the liver, which is greatly stressed by HCV. One recent study suggests that people co-infected with HIV and HCV who start on a protease inhibitor-containing regimen may be at greater risk of developing cirrhosis, a potentially life-threatening liver disease. This study also found that people generally had higher HCV levels (as measured by a special version of PCR test) after starting a protease inhibitor and these levels remained elevated throughout the duration of therapy. There was no apparent correlation between pre-therapy HCV levels and the impact of protease inhibitor therapy on liver disease. This means that people with low HCV levels prior to initiating therapy were just as likely to develop active symptoms of liver disease as people with high pre-therapy HCV levels. Thus, people with low pre-therapy levels could not be assured that they could safely use protease inhibitor therapy. However, another study contradicts these findings. This second study found that although protease inhibitors appeared to increase HCV levels and liver enzymes, this was transient and lasted only a few weeks. In longer-term follow-up (over 2 years), people were able to use the protease inhibitors safely with no effect on HCV levels or liver enzymes.

Another study that looked at historical medical records observed that people who were co-infected with HIV and HCV did not respond as well to anti-HIV therapy compared to people who were not HCV infected. Compared to their pre-therapy levels, those co-infected tended to have increased HIV RNA levels and decreased CD4+ cell counts whereas people who were not HCV infected had decreases in HIV RNA and increase in CD4+ cell counts. In this sense, the presence of HCV infection could be considered a co-factor which stimulated the activity of HIV. Because this study simply looked back at medical records it is difficult to interpret whether these HIV drug failures can be directly attributable to HCV infection or if there were other factors contributing to the differences between the two groups.

On a positive note, a treatment study found that people co-infected with HCV and HIV responded equally well to interferon-alfa, a treatment for hepatitis C, compared to HCV infected individuals who are not HIV-infected. This is contrary to the experience of people co-infected with HIV and hepatitis B virus who usually do not respond well to interferon treatment. Study participants received thrice weekly injections of interferon-alfa (3 million units) for three months. Those who responded to therapy continued for another 9 months. This study found that both HIV infected and HIV negative individuals had similar decreases in HCV RNA levels and normalization in liver enzyme tests, with approximately 25% of both groups having a sustained response past one year of therapy. However, people who were co-infected and had HCV levels over 10,000,000 copies or a CD4+ cell count below 500 were less likely to have a response. It should be noted, however, that treatment with interferon-alfa alone is no longer considered state of the art treatment for hepatitis C. The FDA recently approved a treatment which combines interferon-alfa with the broad-spectrum antiviral drug ribavirin (Rebetol®) and is marketed as a combination known as Rebetron®. Ribavirin was previously studied for use in HIV disease. This combination appears to be far more effective than single drug therapy for HCV. People who are co-infected with HIV and HCV should be aware that use of this new recommended treatment for HCV infection can cause some interactions with anti-HIV therapies. In particular, the use of ribavirin tends to increase the potency of ddI several fold. Ribavirin also has an interaction with AZT which results in decreased anti-HIV activity of AZT.

Mycobacterial Infection

Results from a recent study show that the addition of rifabutin (Mycobutin®) to a standard anti-*mycobacterium avium complex* (MAC) regimen of clarithromycin (Biaxin®) and ethambutol (Myambutol®) resulted in no additional benefit in reducing symptoms of MAC disease, but may prevent the development of clarithromycin-resistant MAC. This is important as clarithromycin is considered the most active drug against MAC; but once resistance to this drug sets in, a patient's ability to combat MAC is dramatically reduced. Almost 200 people with active MAC participated in this study and received clarithromycin + ethambutol +/- rifabutin. At the end of the 16 week study, there were no differences in reduction of MAC colony forming units (a measure of the amount of MAC found in blood), rate of relapse, symptoms of MAC disease or survival between the two groups. However, of those who relapsed and again developed active MAC, only one person who had previously received the 3-drug combination developed resistance, whereas six who had received the 2-drug regimen developed clarithromycin-resistant MAC. While the addition of rifabutin might not result in a long-term benefit, it may be able to delay or prevent the emergence of clarithromycin-resistant MAC.

Stopping Therapy

There have been many anecdotal reports of people stopping prevention and maintenance (to prevent relapse of an infection) therapies for opportunistic infections after getting a good virologic and immunologic response from HAART. Results from a few studies offer some guidance on who might be able to successfully stop OI therapy.

A Swiss study enrolled 230 people whose CD4+ cell counts rose and remained above 200 and sustained a 14% total lymphocyte count for at least three months prior to stopping their PCP preventative therapy. After 12 weeks of follow up, there have been no cases of PCP. However, given the short follow-up time, it may be premature to make conclusive recommendations about stopping the use of PCP preventative therapies.

In a study designed to examine cytomegalovirus (CMV)-specific immune responses in people stopping CMV retinitis maintenance

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therapy, it was found that 9/13 people developed vitritis (an inflammation in the eye) in the same eye as that of the retinitis. The vitritis was associated with decreased vision and led to blindness in some people. In general, people developed vitritis about 3 months after stopping CMV maintenance therapy and there was no evidence of re-emergence of the retinitis. Interestingly, people who had higher CD4+ cell count increases and stronger immune responses specific to cytomegalovirus were more likely to develop vitritis. The researchers believe that ironically people with stronger immune systems are still responding to residual cytomegalovirus in the eye and thus are experiencing this inflammatory response. If the inflammation is because of residual CMV, it may be possible to minimize the risk of vitritis by continuing on CMV maintenance therapy for a longer period of time. For those people who do decide to stop CMV maintenance therapy, it is advisable to be routinely monitored by an eye specialist (ophthalmologist). One caveat to these results is that the study was conducted at the University of California, San Diego where they routinely use intraocular injections (injection directly into the eye) of cidofovir (Vistide®) to treat people with CMV retinitis. This is not the approved route of administration for this drug. Additionally, there have been anecdotal reports of vitritis in people treated with intravenous (injections into the veins) cidofovir while on HAART.

Fungal Infections

A Thai study found that a combination of amphotericin B (Fungizone®) and itraconazole (Sporanox®) was significantly better at treating cryptococcal meningitis than amphotericin B alone. One hundred and thirty-three people with cryptococcal meningitis received amphotericin B (0.7 to 1mg/kg/day) or amphotericin B and itraconazole (200mg twice a day). Twenty-seven percent of the people receiving amphotericin B alone were considered treatment successes (two consecutive cultures from the cerebral spinal fluid which were clear of cryptococcal antigens) whereas 60% receiving the combination were considered treatment successes. Two important findings came out of this study. One is that this is potentially a highly effective combination regimen for people in the developing world with cryptococcal meningitis. Second is that it has long been argued that there is a potential antagonism between amphotericin B and the azole drugs (such as itraconazole and fluconazole). This study shows that this is clearly not the case, at least for treating cryptococcal meningitis.

AIDS-Related Diarrhea

Chronic diarrhea remains a problem for people with HIV disease. Diarrhea can be caused by HIV itself, by a parasite or by any number of different drugs commonly used by people with HIV. A recent study shows that a product (SP-303) derived from a plant found in the Central and South American rain forest may provide benefit for people with chronic diarrhea. The product blocks the amount of chloride that is produced in the gut and is therefore likely to be useful against many different forms of diarrhea. Fifty-one people with an average CD4+ count of about 225 cells, a viral load of about 8,000 copies HIV RNA and chronic diarrhea participated in the study. It appears likely that most study participants had diarrhea associated with the protease inhibitors or other medications. In only three people was the diarrhea known to be caused by a parasitic infection. Overall, volunteers had CD4+ cell counts and viral load levels associated with relatively low risk for parasitic infections. Participants received SP-303 (500mg every 6 hours) or placebo for 4 days, and the study required that all participants be admitted into the hospital for a five day stay so that they could be routinely monitored. Participants receiving the active drug had over 50% reduction in stool volume and also a reduction in stool frequency. SP-303 is thus likely to be a useful therapy for people with diarrhea. However as this drug might reduce the frequency of diarrhea, people should remember to also treat the underlying cause of the diarrhea.

Commentary

Although the overall incidence of opportunistic infections has decreased in developed countries since the introduction of the protease inhibitors, they remain a major issue for people who have had little or no benefit from them. Since developing nations have limited or no access to these new therapies, the overall incidence of opportunistic infections has not decreased in those countries. Furthermore, the most common opportunistic infections found in developing nations are often different than those in developed countries, the most common being esophageal candidiasis (a fungal infection in the esophagus), wasting disease and tuberculosis. One of the most urgent needs is to make sure that pharmaceutical companies continue to develop new therapies for opportunistic infections and to make sure that all medications are affordable and accessible in every country. ■

Nerve Growth Factor for Peripheral Neuropathy

Interim results from a study of nerve growth factor (NGF) shows that the drug may be an effective treatment for people with peripheral neuropathy. Two hundred and seventy people with peripheral neuropathy received 0.1 mcg/kg NGF given twice daily by injection under the skin, 0.3 mcg/kg twice daily injection or placebo for 18 weeks. People who received NGF had significantly lower pain scores—from tests which were self-administered—with the group receiving the higher dose having the best results. Additionally, NGF did not cause HIV RNA levels to increase. However, 25% of the people receiving the lower dose and almost 50% of the people receiving the higher dose of NGF complained of pain at the injection site. In no case did this result in stopping NGF. Genentech, the developers of NGF, has been slow in developing this drug for HIV-associated neuropathy and needs to start an expanded access program immediately. Many questions remain, however about when, how, and in whom nerve growth factor should be used, since neuropathy takes many different forms and has several possible causes. It is not yet clear whether nerve growth hormone is appropriate in all situations.

National HIV/AIDS Treatment Hotline

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

1-800-822-7422

Treatment of Gynecological Conditions in Women[E]

Research has shown that higher doses of standard treatments for some gynecologic complications may be required in women with HIV compared to doses required for treating the same conditions in HIV-negative women. This difference reflects the reduced contribution of the immune system to fighting infections in people with HIV. Different treatment doses are particularly required for syphilis, genital herpes, candidiasis (yeast or fungal infection), genital warts, and CIN, VIN and AIN (cervical, vaginal and anal intraepithelial neoplasias, types of pre-cancerous lesions). Moreover, women with HIV tend to have higher rates of treatment failure for conditions such as candidiasis and cancer.

However, treatment responses appear to be no different between HIV positive and negative women with conditions like gonorrhea, chlamydia, trichomoniasis, pelvic inflammatory disease and bacterial vaginosis, suggesting that no special dose adjustments are necessary when treating these conditions. It is hoped that as women begin to access and use highly active combination therapies, decreased viral replication and improved immune responses will lead to better responses to treatment for these gynecologic conditions.

HIV, HPV and Cervical Cancer

A number of studies have confirmed that a higher percentage of women with HIV are co-infected with human papillomavirus (HPV) than HIV-negative women of the same age, level of drug use and the same number of sexual partners. HPV is the virus that causes genital warts and certain types of cancers (cervical and anal cancers). Risk factors associated with HPV infection include young age at first intercourse, high numbers of sexual partners, sex with men with higher numbers of partners, young age (<30 or 40 years) and smoking. Women with HIV are more likely to have infection with multiple HPV types, often including the "high-risk" HPV types (types 16 and 18), more commonly associated with the development of cervical cancer (42% of infected women vs. 16% of HIV-negative women). In addition, studies have found that 70% of HIV-positive women with low CD4+ counts (<200 cells) had HPV infection. This suggests that as CD4+ counts decline, women are more likely to acquire HPV infection if exposed or that existing virus is reactivated at a stage when the immune system is no longer able to control it.

Not surprisingly, HIV-positive women have higher rates of complications due to HPV infection, such as SIL (squamous intraepithelial lesions) and CIN (cervical intraepithelial neoplasia), types of pre-cancerous abnormalities usually found by pap smear or colposcopy (a small section of cervical tissue). Women co-infected with HIV and HPV who have CD4+ cell counts <200, who are infected by multiple HPV types or by high-risk HPV types, are at the greatest risk of developing these pre-cancerous abnormalities.

Researchers and people with HPV are wondering if highly active antiretroviral therapy (HAART) might help prevent the development of these HPV-related conditions in the first place, especially cancers. Unfortunately, the role of HAART on HPV infection or its complications remains unclear. While current anti-HIV treatments have been shown to reduce development of Kaposi's Sarcoma, at present anti-HIV therapy seems to have no effect on HPV infection or cervical cancer. In theory, by decreasing HIV levels and thereby reducing immune system damage, one may see an improvement in the body's ability to fight infections and thus delay cancer development.

While it is unclear whether HAART can prevent or delay the development of these conditions, preliminary results from one encouraging study do show that effective anti-HIV therapy appears to prevent relapse of one HPV-related condition—genital warts—after initial treatment (see *Effects of HAART on HPV Box*). It has been shown time and again that people with HIV and HPV infection have higher relapse rates, meaning that despite what appears to be effective treatment of the HPV-related condition, the HPV infection recurs more frequently in people with HIV. While this has been shown with genital warts, longer follow-up studies are needed to see if, over time, women with HIV tend to have higher relapse rates of cervical cancer after initial treatment than HIV-negative women. It remains to be seen if potent anti-HIV therapy can similarly prevent relapse of cervical cancer, CIN and SIL.

What is known at present is that women with HIV are more likely than HIV-negative women to harbor HPV infection and develop complications due to HPV. These conditions tend to be more difficult to treat. Future research needs to find out whether HAART can actually prevent or delay the development of such conditions altogether and if HAART can reduce recurrence rates after initial treatment as has been shown with genital warts. Because of the long time required for conditions such as cancer to present themselves, there is increasing concern that as people with HIV live longer, these conditions could become a larger problem. Thus, it is important that research efforts into treatment and prevention of HIV-related cancers become a higher priority. It is equally important that women with HIV continue to monitor for HPV infection and its consequences by having a regular (every 6 months) pap smear and, if necessary, a colposcopy. For more information, call the Project Inform hotline for the *Women and HIV Discussion Paper*. ■

[E]Effect of HAART on HPV

Results from a study of 40 people with HIV showed that highly active antiretroviral therapy (HAART) could help reduce recurrence of genital warts after surgical treatment. Genital warts, like cervical and anal cancers, are a result of infection by human papillomavirus (HPV). Current treatment for genital warts is surgical removal, and the rate of recurrence tends to be higher in HIV-infected people. In this observational study, 13 people used a 3-drug treatment regimen, 21 used two drugs of the nucleoside analogue class (e.g. AZT, ddI, d4T, ddC and/or 3TC) and 6 used no anti-HIV therapy. Relapse rates 6 months after surgical treatment in 24 people were 0% among those receiving three drugs, 10% among those using two drugs and 75% among those receiving none. Relapse rates at only 1 and 3 months after surgery were equal among all three groups, suggesting that the effects of anti-HIV therapy in contributing to improved treatment of genital warts become increasingly apparent over time. The relapse rates also correlated with viral load such that as they decreased, people were less likely to experience a relapse in genital warts.

Transmission of Resistant HIV

Researchers at the University of California have published the first evidence of the transmission of multi-drug resistant virus from an HIV-positive person to a person previously uninfected. Although the potential for such transmission has long been known, this case report presents the first hard evidence that such transmission of virus resistant to multiple drugs not only *can* occur but also *does*. Since the beginning of the protease era, Project Inform and others have argued this risk was real and that it made careful adherence to therapy regimens and continued safer sexual practices not only personal matters but ones that can have public health consequences.

Even from the first reports of the success of protease inhibitors in suppressing HIV to unprecedented levels, researchers have been concerned with the ability of HIV to develop resistance to this new class of drugs. The fear was raised for two reasons: first, it was clear that it was not overly difficult to develop resistance to protease inhibitors, thus undermining these most potent weapons. Second, it seemed likely that resistant virus would be capable of establishing infection in people exposed to it, who would begin their course of HIV disease already resistant to most or all of available drugs.

In the case reported, a person began suffering classic symptoms of acute HIV infection (fever, night sweats and fatigue) a few days after an unsafe sexual exposure (receptive anal intercourse without a condom, including withdrawal prior to ejaculation). Although the new patient was initially negative for HIV antibodies (as expected so early on), evidence of infection was established by the more sensitive quantitative p24 antigen test, and subsequently on a quantitative PCR (polymerase chain reaction) test. Treatment was begun a few weeks after the patient joined the Options Project, a study of primary HIV infection at the University of California. Unlike 36 other primary infection patients treated there, this patient did not respond to triple drug therapy nor to subsequent change to a second protease inhibitor. Since there was little or no doubt about the initial source of infection, researchers sought out the source patient. Upon contact, he volunteered to be studied. Researchers quickly learned he had been failing on the same treatment regimens as the other patient. Furthermore, he acknowledged poor adherence in his use of the treatments. Extensive resistance analysis of the virus present in each patient showed them to have nearly identical strains of virus and nearly all the same mutations and patterns of drug resistance.

Some researchers had hoped that mutated virus might be so crippled by the presence of the many mutations needed to achieve multi-drug resistance that it might not be capable of easily establishing infection in a new person. These data end that theory conclusively. It may still be that multi-drug resistant virus is less fit or less harmful in some undiscovered way, but it is clear that it remains capable of causing new infections. European researchers at the conference in Geneva reported similar cases, and a magazine article described the case of a man in the US who believed he had recently infected his lover with drug resistant virus. Thus, the theoretical concerns voiced about transmission of resistant virus when protease inhibitors first came to market are now proven facts. The need for careful adherence to therapy regimens and the need to pick the most appropriate regimen in the first place is now dramatically emphasized.

Despite these disturbing data, it's important not to stir public panic over the issue. We do not know whether such transmission is or will ever be common. All researchers can say for sure is that it has happened a few times. Undoubtedly, there are more cases that have not been studied or reported, but it would be a mistake to believe that such transmission has become a routine occurrence. It is far too early to define the scope of the public health issues concerned.

What about "Positive to Positive" Transmission?

These cases emphasize the importance of a second related question: whether or not it is possible to transmit drug resistant virus from one HIV-positive person to another. This has become a critical question because many have convinced themselves that sexual precautions are not necessary between two positive partners. Somewhere, many people acquired the belief that infection with one strain prevented later infection by a different or mutated strain. There is plenty of evidence to the contrary—the fact that there are many cases of people infected with both HIV1 and HIV2. Other examples include people who harbor both syncitium inducing HIV (*SI virus*, usually seen in people with advanced stage disease and considered more infectious) and non-syncitium inducing virus (*non-SI virus*) at the same time. However, the belief that sexual play need not be safeguarded between infected partners is strongly held by some, for whom this view is perhaps seen as the only "good" thing about being HIV positive. Sadly, this "good thing" very likely is untrue. In light of the new findings from the Options Project proving the transmissibility of multiple mutated HIV, it is critical research be done to determine whether such drug-resistant virus is also being passed back and forth between infected partners. If so, as most scientists suspect, it will be an emotional blow to those engaged in such practices. But the answer must be known. Researchers at the Options Project and elsewhere are currently discussing potential protocols for ethically testing this concept. The sooner we get an answer, like it or not, the better. ■

Sildenafil (Viagra®) Drug Interactions

The recently approved drug, sildenafil citrate (Viagra®), for erectile dysfunction (impotence) should not be used by people who are using organic nitrates in any form, including 'poppers' and certain drugs taken to decrease high blood pressure. Sildenafil can increase the hypotensive (lowering of blood pressure) effects of nitrates which could be fatal. The protease inhibitors and delavirdine (Rescriptor®) will likely increase sildenafil levels while nevirapine (Viramune®) and efavirenz (Sustiva®) will likely decrease sildenafil levels. People taking either a protease inhibitor or delavirdine and are thinking of starting sildenafil should consider using a 25mg dose, since using a higher dose may increase sildenafil's effectiveness and the incidence of side effects. Other drugs commonly used by people with HIV can also affect sildenafil levels. Ketoconazole and itraconazole will likely significantly increase sildenafil levels while rifampin and rifabutin are expected to decrease sildenafil levels in blood.

Immune Based Therapy Update

The major focus of immune-based therapy presentations at this year's World AIDS Conference was new information on the use of interleukin-2 (IL-2). Just a day before the conference an international steering committee met to put the finishing touches on plans for a large international study of IL-2 which will enroll 4,000 volunteers at over 200 sites worldwide. Some new preliminary data on the use of the immune-based therapy HIV-1 Immunogen (Remune®), were also reported. A small study of the thymus provided encouragement that this important organ for new T cell development may regenerate if HIV replication is significantly reduced.

Interleukin-2 (IL-2, Proleukin®)

Researchers presented four IL-2 studies at the conference. Three included people with generally higher starting CD4+ cell counts (~above 350) and one included people with low CD4+ cell counts and advanced disease. All confirmed the ability of IL-2 to induce dramatic CD4+ cell increases without triggering increases in viral load levels. Moreover, these increases were observed in people who administered IL-2 through injections under the skin (subcutaneous injections), a simplification of the methods used in previous studies. Most previous IL-2 studies administered the drug by continuous infusion into a vein (intravenous infusion). Side effects associated with IL-2, when administered by injection under the skin, proved less severe than those observed with intravenous IL-2.

Perhaps the most important of the four studies, a European trial called ANRS 048, compared the impact of IL-2, delivered through different routes of administration, on CD4+ cell count, HIV RNA levels and a number of measures of immune function. ANRS 048 included 94 people with CD4+ cell counts ranging from 250 to 550. The mean, or average, CD4+ cell count at baseline was about 380 in all four study groups. Protease inhibitor therapy was not available at the outset of the study. Volunteers received one of four regimens for one year (a total of 7 cycles of IL-2 therapy):

- Anti-HIV therapy alone (AZT + ddI)
- Anti-HIV therapy + IL-2 administered subcutaneously, twice daily, for five consecutive days, every 8 weeks. (The mean dose used after dose adjustments to decrease side effects was 4.5 million international units (MIU) of IL-2, twice daily, total daily dose of 9 MIU.)
- Anti-HIV therapy + PEG IL-2 administered by infusion directly into a vein, over a short time course, about an hour or two, once every 8 weeks. (The mean dose used after dose adjustments was 3.6 MIU). (PEG IL-2 was a special version of the drug which is no longer being studied).
- Anti-HIV therapy + IL-2 administered by continuous infusion into the vein, for 5 days, every 8 weeks. (The mean dose used after dose adjustments was about 10 MIU, daily.)

Of the groups receiving IL-2, those who received PEG IL-2 had the least favorable responses in CD4+ cell count increases. After one year, the group receiving anti-HIV therapy alone demonstrated a CD4+ cell count increase of 55. Those receiving PEG IL-2 showed a mean CD4+ cell increase of 105. The group receiving IL-2 by subcutaneous injection experienced a CD4+ cell increase of 564 and those receiving IL-2 by continuous infusion experienced an increase of 707.

Those receiving either the injections or continuous infusion of IL-2 had the most significant and pronounced CD4+ cell increases. Those receiving IL-2 by continuous infusion, however, were also most likely to experience side effects with nearly 60% experiencing fever and a sizeable number (~14%) experiencing nausea and/or diarrhea. These side effects were also seen among those who received IL-2 by injection, but less frequently. Fever was noted in about 40% of those receiving IL-2 by injection and only about 4% of this group experienced nausea and/or diarrhea. These side effects were primarily limited to the 5 day IL-2 therapy period and did not persist through the 8-week intervals between treatment. The most common laboratory abnormality among IL-2 users was a change in liver function tests, with about 25% of injection IL-2 and 9% of continuous infusion IL-2 recipients experiencing changes in liver function tests. Viral load changes were similar among all groups, but slightly more favorable among those receiving only anti-HIV therapy. Those receiving only anti-HIV therapy demonstrated a mean drop in viral levels of about 1.5 logs, those receiving PEG or injection IL-2 demonstrated a viral load decrease of 1.2 logs and those receiving continuous infusion of IL-2 experienced only a 0.9 log reduction in viral load. These differences were not considered significant.

Virtually all measures of immune function were more favorable among both the injection and continuous infusion IL-2 recipients, compared to those who received either anti-HIV therapy alone or anti-HIV therapy in combination with PEG IL-2. This study is important as it represents the most comprehensive comparative study of the immune effects of IL-2 and suggests that the profound CD4+ cell increases observed with IL-2 therapy are accompanied by improvements in immune function. Only a large study, however, will be able to confirm this definitively.

Long-term follow up on a National Institutes of Health study of IL-2 administered by injection under the skin was also reported. In this study, volunteers receiving anti-HIV therapy with an average CD4+ cell count of 600 received either 1.5 (total daily dose of 3) or 7.5 (total daily dose of 15) MIU of IL-2, twice daily for 5 days, every 4 or 8 weeks. The frequency of the cycles did not impact the magnitude of CD4+ increases observed in either dose group. Study results at 6 months of IL-2 therapy, those receiving the lower dose had experienced an average CD4+ cell increase from 600 to 780. Those receiving the higher dose had experienced a doubling of their CD4+ cell counts, from 600 to 1200. After 6 months of therapy, all volunteers were allowed to modify their IL-2 dose. Many receiving the lower dose increased their IL-2 dose in order to achieve more pronounced CD4+ cell count increases and many receiving the higher dose reduced their dose to lessen the severity of side effects. After 18 months of therapy, the average dose used was 5.8 MIU, twice daily (total daily dose of 11.6 MIU). The average interval between IL-2 therapy cycles, necessary to maintain CD4+ cell increases, was 1 year. At 18 months, the average CD4+ cell count was 1,200, regardless of which dose was originally used.

This study is important for many reasons. First, initiating IL-2 therapy at the higher dose of 7.5 MIU, twice daily, for five days, every 8 weeks is preferable to 1.5 MIU for inducing pronounced increases in CD4+ cell counts. Unfortunately, a middle dose of 4.5 MIU, twice daily, was not examined in this study. Given the median dose used at 18 months was about 5.8 MIU, twice daily, it's possible that starting at a lower dose might be more tolerable and still induce dramatic CD4+ cell count rises. Second, once a CD4+ cell count increase has been realized, the length of time between IL-2 cycles can be extended to maintain CD4+ cell count increases. Once CD4+ cell counts have risen to the upper limit of normal ranges, it is probably unwise to

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induce CD4+ increases to above normal limits. Side effects associated with IL-2, predominantly flu-like symptoms, are associated with the time that IL-2 is being administered (the 5 day cycle of therapy). It's encouraging to note that the median interval between cycles, at 18 months, had extended dramatically, obviously lessening the number of times volunteers experienced IL-2 associated side effects.

The third study, from Argentina, examined three different IL-2 doses. Volunteers with CD4+ cell counts greater than 350 received either potent anti-HIV therapy (HAART), or potent anti-HIV therapy in combination with injections of 1.5, 4.5 or 7.5 MIU, twice daily for 5 days, every 8 weeks (total daily doses of 3, 9 or 15 MIU of IL-2). After 6 months, 55% of those receiving only anti-HIV therapy and 75% of those receiving anti-HIV therapy in combination with IL-2 had viral load measures below the limit of detection of the tests. CD4+ cell count changes at 6 months are reported in **TABLE I** below. This study demonstrates that both of the higher IL-2 doses, 4.5 and 7.5 MIU, twice daily for five days, every 8 weeks, in combination with anti-HIV therapy is superior to both the low IL-2 dose and anti-HIV therapy alone in inducing pronounced CD4+ cell increases.

Finally, preliminary data were presented by community physicians in Chicago on an observational study of 15 people with low CD4+ cell counts and more advanced stage disease. Early observations of IL-2 therapy in people with CD4+ cell counts <200 were not encouraging. These studies were conducted prior to widespread availability of protease inhibitors and sophisticated measures of viral load (HIV RNA). This study included people with CD4+ cell counts <200 who had previously had an opportunistic infection, or people with CD4+ cell counts below 50. The mean CD4+ cell count of volunteers, prior to starting IL-2 therapy, was 100 and viral load levels were relatively high, about 50,000 copies HIV RNA. All were on stable 3-drug regimens prior to initiating IL-2 therapy. At time of the presentation, volunteers had received varying numbers of IL-2 cycles and the mean CD4+ cell count was 470. One volunteer discontinued IL-2 because of related side effects. While these data are very preliminary, they are encouraging as no one in the study has yet to experience a new opportunistic infection, been hospitalized or died. The study was largely a retrospective report on the IL-2 use in a treatment setting, so its findings cannot be directly compared to more structured studies. They do provide a bit of comfort in designing future studies of IL-2 for people with lower CD4+ cell counts and measurable viral load.

For more information on IL-2, other studies reported to date and information on side effects, call the Project Inform Hotline.

TABLE I : Argentinean Study Results

Group	Proportion with greater than 25% CD4+ cell count increase.	Proportion with greater than 200 CD4+ cell count increase
AVT* alone	20%	10%
AVT + 1.5 MIU, twice daily	40%	10%
AVT + 4.5 MIU, twice daily	65%	45%
AVT + 7.5 MIU, twice daily	80%	60%

AVT = antiviral therapy. MIU = million international units.

HIV-1 Immunogen (Remune®)

The HIV-1 Immunogen has been studied for many years. Known as a *therapeutic vaccine*, it uses the same strategy employed in traditional vaccine development, but rather than prevent or moderate infection it is hoped that it will trigger the immune defenses to better control HIV disease in people who are already infected. The HIV-1 Immunogen is an inactivated form of HIV that cannot reproduce and cause disease, but because it has features similar to the virus it is hoped that the immune system will mount a response that will prove useful in controlling HIV. A possible flaw in this logic is that there is plenty of the real HIV floating around the body and clearly the immune system, despite being chronically stimulated by real virus, is still not able to control infection. Thus, many researchers question why the addition of some modified, impotent version of HIV would stimulate a stronger immune response. Even so, this concept has experienced renewed interest in the era of HAART.

A largely promotional satellite symposium sponsored by the company developing the HIV-1 Immunogen garnered much attention. It appears that individuals who are believed to have received the HIV-1 Immunogen in studies were more likely to have HIV-specific CD4+ responses than those who are believed to have received placebo. The study is still "blinded" so researchers don't actually know who received the drug and who received the placebo. Because of the blinded nature of the study, all the researchers can say for sure is that there appears to be a group of people in the study who are having improved HIV-specific CD4+ cell responses. If the HIV-1 Immunogen is truly capable of enhancing or preserving HIV-specific CD4+ responses, this could be quite important because it may help the body control HIV with less reliance on antiviral drugs. Unfortunately the test to measure HIV-specific CD4+ responses has not yet been validated and thus far it remains unclear what exactly the test is measuring and whether its results have any bearing on disease progression.

While some people have gotten quite excited about the HIV-1 Immunogen information, Project Inform finds it impossible to draw any conclusions with regard to the HIV-1 Immunogen or the value of the HIV-specific CD4+ test. Early studies in people with HIV showed that the HIV-1 Immunogen was safe, but volunteers receiving the drug had no appreciable increases in CD4+ cell counts or decreases in viral levels (HIV RNA). One would hope that if a drug was able to "boost" immune responses against HIV there would be some kind of noticeable impact on these validated measures of disease progression. If changes in HIV-specific CD4+ response fail to correspond to decreased viral load, increased CD4+ cell counts, decreased disease progression or improved survival then, it would be hard to say the product has value. The current study of the HIV-1 Immunogen is following a large enough number of people to determine whether there is a difference in disease progression or survival between those receiving the HIV-1 Immunogen and those receiving a placebo so a clear answer can be expected. Until then, the current enthusiasm over the company sponsored presentation is probably a little more hype than hope, and at best merely an interesting observation.

Perhaps the best news out of the study is that HIV-1 Immunogen continues to appear safe and is associated with very few side effects, primarily pain at the site of injection as would be expected with any type of vaccination.

New Information on the Thymus

The thymus is an important organ for new T cell development (both CD4+ and CD8+ cells). Previously, Project Inform has reported on data from Dr. McCune and his colleagues at the Gladstone Institute in San Francisco which suggest that adults with HIV infection are more likely to have detectable thymus mass compared to their HIV-negative counterparts. Moreover, thymus mass was more likely to be present in people with higher CD4+ cell counts (above 300) compared to people with lower CD4+ cell counts. The presence of thymus mass was associated with higher CD4+ cell counts and higher percentages of naïve cells, suggesting evidence of thymic function. Questions remain regarding

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the ability of the thymus to regenerate in people with low CD4+ cell counts in the context of suppression of HIV replication.

A small study of thymus scans in children before and after therapy with potent anti-HIV regimens provides encouraging preliminary results suggesting that the thymus can regenerate if viral replication is brought under control. The study was very small, including children at different stages of HIV disease. The researcher highlighted the case of a 7-year-old child with advanced (CDC stage III) stage AIDS. Prior to therapy the child had virtually no detectable thymus (0.07 cm3). After one year of successful anti-HIV therapy, the child had an over 100 fold increase in detectable thymus mass (19.4 cm3). Observed increases in thymus mass were associated with decreases in viral load and increases in both CD4+ cell counts and percent naïve cells. It is not as clear, however, whether these results can be expected to be the same in adults as in children. The thymus is generally larger and believed to contribute more to new T cell development in children compared to adults. This study is certainly encouraging with regard to the impact of anti-HIV therapy on the thymus in children. In the highlighted report referenced above, however, the child was 8-years-old at the time of the second thymus scan and in many regards the immune system of an 8 year old is more similar to the immune system of an adult than it is to a newborn. Thus, there is at least this one hint that the results might also apply to adults with advanced-stage AIDS. However, the study certainly needs to be duplicated in the adult population. ■

Antivirals and Children[E]

New studies have begun opening the doors for broadening therapeutic options for children with HIV. Only six drugs [AZT (zidovdine, Retrovir®), ddI (didanosine, Videx®), d4T (stavudine, Zerit®), 3TC (lamivudine, Epivir®), nelfinavir (Viracept®) and ritonavir (Norvir®)] are approved for use in children. However, ongoing studies in children are testing the safety and effectiveness of a broader range of therapies. It is critical this work proceed as quickly as possible to better inform parents and pediatricians who end up experimenting with adult therapies out of desperation when their short list for children is exhausted.

The recently updated pediatric treatment guidelines (*Federal Guidelines Box, p. 21*) seem to agree with the more aggressive pediatricians. It suggests all approved therapies, including those approved for adults, can be used to treat children with HIV. Three-drug combinations including a protease inhibitor have been shown to be the most effective in reducing viral load (HIV RNA levels) and increasing CD4+ cell counts in children. However, more studies are needed to assess the appropriate dosing regimens, risk of side effects and long-term potency. Pediatricians, parents and their children should not be expected to figure out such matters for themselves.

Ritonavir

Preliminary results are available from studies looking at combinations of ritonavir with one or two nucleoside analogue reverse transcriptase inhibitors (NARTIs) in children with advanced disease who have previously taken anti-HIV therapy. These studies show that anti-HIV regimens including ritonavir can provide decreases in viral load and increases in CD4+ cell counts in the short-term, but it remains to be seen if long-term benefits can be maintained. There is little reason to believe, however, that the long-term outcome would be any different than in adult studies.

One retrospective study looked at ritonavir (350mg/m^2 twice daily; total daily dose 700mg/m^2) with 1 or 2 NARTIs in 21 children with advanced HIV disease. The children had previously taken many of the available anti-HIV therapies. After 12 months of a ritonavir-containing regimen, children aged 1–5 had an increase of over 500 CD4+ cells and about a 1.3 log reduction in viral load. Children aged 6–12 had an increase of about 450 CD4+ cells and a viral load reduction of about 0.5 logs. Since most of the children had previously been on many NARTIs, it is not surprising they had only a modest reduction in HIV levels as ritonavir was probably the only active drug. It is now known that the optimal way to treat HIV disease, for both adults and children, is to combine at least two potent drugs which the person has not previously taken. (When comparing these results to adult studies, particularly in terms of CD4+ cell increase, remember that young children generally have much higher natural CD4+ counts than adults and tend to have larger numeric increases in response to therapy.)

A second retrospective study looked at ritonavir plus 2 NARTIs in 63 children with advanced disease who had not previously taken a protease inhibitor (median age 55 months). The doses of ritonavir ranged from 150mg/m^2 twice daily (total daily dose 300mg/m^2) to 430mg/m^2 twice daily (total daily dose 860mg/m^2). After 6 months of the study, the mean CD4+ count increased by 486 cells and viral load levels dropped by almost 1 log. Fifteen children had to discontinue ritonavir because of side effects, including vomiting and diarrhea.

A large US study (the Pediatric AIDS Clinical Trials Group study 338) compared two- and three-drug combination regimens in children who had previously been on anti-HIV therapies. The study showed that children who received d4T + ritonavir or AZT + 3TC + ritonavir did significantly better than those receiving AZT + 3TC alone. The study included 298 children at a median of 7.1 years of age with a median viral load of about 25,000 copies HIV RNA. Data at 12 weeks are presented in **TABLE I** on page 20.

It remains to be seen how long the antiviral response will last and if the combinations are safe and tolerable for the long-term. The results from this study are not unexpected. Previous studies in adults have all shown only limited antiviral activity of AZT + 3TC, especially in people who have been on previous NARTI therapies, and AZT + 3TC is not considered an optimal therapeutic regimen.

A final ritonavir study looked at the effects of simply adding ritonavir (350mg/m^2 twice daily (total daily dose 700mg/m^2) to existing 2-drug regimens in 35 children (mean age 7.4 years). Prior to adding ritonavir, the mean viral

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load was 247,000 copies HIV RNA and the mean CD4+ cell count was 239. After 12 weeks, the mean viral load reduction was 1.1 logs, and 31% (11/35) of children reached levels below 400 copies HIV RNA. CD4+ cell counts increased by about 225. However, 42% of the children experienced side effects, including gastrointestinal problems (primarily diarrhea) and increased triglyceride levels. Again, the results here are not unexpected. Since the children had high viral loads (HIV RNA) prior to adding ritonavir, it can be safely assumed they were failing their 2-drug regimens and were likely to have developed resistance to those drugs. As a result, ritonavir was probably the only active drug in most of these regimens, resulting in only a modest antiviral response. It has been well established that when changing therapies, at least two new drugs should be added or changed in the regimen. The addition of a single drug is an ineffective way to suppress HIV and can lead to the rapid development of drug resistance. It is difficult to understand why an ethical review board would approve a study of this type, given the well-established recommendation to avoid simply adding a protease inhibitor onto a failing (or even stable) 2-drug regimen. This is another sad example of how pediatric research sometimes fails to learn from basic principles established in adult research.

TABLE I : Ritonavir Combinations in Children

RTV=ritonavir

Drug Combination	% <400 copies HIV RNA	Median Viral Load Drop
AZT + 3TC	12%	0.35 logs
d4T + RTV *or* AZT + 3TC + RTV	60–63%	1.6 logs

TABLE II : Abacavir Combination Study Results

Drug Combination	% <10,000 copies HIV RNA	% <400 copies HIV RNA
AZT + 3TC + abacavir	49%	13%
AZT + 3TC	35%	2%

Nelfinavir

Results from a small study comparing two different nelfinavir regimens (one combined with AZT + 3TC and the other with d4T + ddI) showed sustained viral load decreases after 6 months in both study groups, but surprisingly no lasting increases in CD4+ cell counts. Fourteen children who had received no prior anti-HIV therapy (median age 68 months) received one of the two three-drug combinations. The dose of nelfinavir was 20–30mg/kg three times daily (total daily dose of 60–90mg/kg). The median viral load decrease after 24 weeks was more than 2 logs, with 9 children below 500 copies HIV RNA. CD4+ cell counts increased from an average pre-study level of 650 cells (the range was 40–2,250 cells) to 925 after 12 weeks, but returned to pre-study levels after 24 weeks. The unusual lack of a sustained CD4+ cell response may be due to problems with adherence, study design, or perhaps just a function of the small number of children in the study. Overall, the regimens were well-tolerated, but there were difficulties in administering the doses to small children.

Saquinavir

Two studies provided new information on the use of the enhanced saquinavir soft gel capsules (saquinavir sgc, Fortovase®) in children. While saquinavir is not yet approved for use in children, these studies show that combination therapy with saquinavir sgc may provide yet another option for HIV-infected kids. However, saquinivir is still only available as tablets and a liquid formulation needs to be developed to make the drug accessible to children who cannot swallow tablets.

The first study looked at saquinavir sgc (33mg/kg three times daily; total daily dose of about 100mg/kg) in combination with two NARTIs (at least one of which had never been used before) in 14 children aged 3–13 years, most of whom had been on previous anti-HIV therapies. The most common nucleoside combination used in this study was d4T + 3TC. At study entry, the average CD4+ cell count was 446 and viral load was about 40,000 copies HIV RNA. After 16 weeks of therapy, CD4+ counts increased by an average of 229 cells, and the average viral load decreased 2.1 logs, with 8 of 13 children below 400 copies HIV RNA. While the regimens were safe and well-tolerated, five had to add nelfinavir because they did not achieve adequate saquinavir levels to effectively stop HIV replication. In addition, as is true for most drugs, children clear saquinavir from their bodies more quickly than adults and thus may require even higher doses per kilogram body weight.

A second study showed that adding nelfinavir (30mg/kg three times daily) to a combination of saquinavir sgc (33mg/kg three times daily) plus 2 NARTIs can help maintain higher saquinavir drug levels. In adults, adding nelfinavir increased saquinavir levels by 392% without any increase in side effects. This study included 14 children aged 3–16 with average pre-study CD4+ counts of 587 cells and HIV RNA levels of 31,000 copies. After 16 weeks on therapy, there was an average viral load decrease of 1.8 logs and a CD4+ count increase of 109 cells. While this combination does appear to substantially increase the levels of saquinavir sgc, there seems to be little evidence that addition of nelfinavir results in any increased benefit in terms of viral load reductions and CD4+ cell increases. This parallels the adult experience and raises questions about whether the addition of a second protease inhibitor is worth the cost and inconvenience involved. It also raises the question of whether clinical outcomes can be predicted based on pharmacokinetic observations of drug blood levels. Overall, it would seem more important to trust well established outcome markers like viral load and CD4+ counts to assess the efficacy of a drug regimen.

Abacavir

Latest results from a study of the NARTI abacavir (formerly 1592, now also known as Ziagen®) in combination with AZT and 3TC show that the drug is safe and more effective than AZT + 3TC alone. The study included 205 children (ages 90 days – 12 years) who had previously received anti-HIV therapies and had CD4% less than 15, which is considered moderate to severe immunosuppression in children. Mean pre-study CD4+ cell counts were about 675 cells and the mean viral load level was about 40,000 copies HIV RNA. The children received either AZT + 3TC or a combination of AZT + 3TC + abacavir (8mg/kg twice daily) and had the option to switch to abacavir plus any two NARTIs if they had more than a 0.5 log increase in viral load after 8 weeks or had greater than 10,000 copies HIV RNA anytime after 16 weeks of the study. Preliminary results are shown in **TABLE II** above.

Side effects were similar in both treatment groups, except for two suspected allergic reactions to abacavir. The most common adverse events were nausea and vomiting, respiratory infections, fever and diarrhea. These rather lukewarm results may be due to the fact that the majority of children were shown to have developed resistance to the approved NARTIs which may also have resulted in resistance to abacavir.

Commentary

While these sometimes encouraging data suggest that children now have greater and more effective treatment options than ever before, it appears that children, like adults, will have to continue taking therapy for a lifetime. The side effects, drug interactions and taste problems

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of many drugs make it imperative that more effective, less toxic, and easier to use treatment options be developed for children. These issues also increase the difficulties and highlight the importance of adherence to these strict regimens. Helping families overcome barriers to adherence is an important goal for the treatment of children with HIV to allow these therapies to provide the most potent and longest-lasting response. While further studies of safety and effectiveness of anti-HIV therapies in children are critical, equally important are efforts to make drugs more palatable, establish appropriate dosing regimens and seek ways to help families and their children adhere to these regimens.

In addition, it seems that pediatric drug trials continue to repeat the mistakes of trials in adults. Too many children who bravely participate in trials are receiving sub-optimal combinations or are receiving single drugs in succession, both of which allow only moderate viral suppression and therefore increase the likelihood of developing drug resistance. Future trials need to be designed to treat children with the highest standard of care, a three-drug regimen with at least two potent drugs never used before. ■

Federal Guidelines for the Treatment of Children with HIV

The recently updated Federal Guidelines for the treatment of children with HIV recommend that infants and children receive combinations that include two nucleoside analogues and a protease inhibitor, and that adolescents be treated based on adult guidelines. The guidelines suggest that all 11 anti-HIV drugs approved for use in adults can also be used in children despite that fact that not all are approved for pediatric use. The following is a summary of the guidelines on how to monitor HIV disease, when to initiate therapy and when to change therapy.

How do you monitor HIV disease in children?

- *CD4+ cell counts:* Tests should be done to establish a 'baseline' and then every three months thereafter. "Normal" levels in children depend upon age, and younger children tend to have higher "normal" levels. CD4 percentage (CD4%) is a useful marker of immune status because there is no variability by age.
- *Viral load levels:* Disease progression differs in children—HIV RNA levels are generally low at birth, reach high levels (over 100,000 copies) at two months, and then decline very slowly without any therapy. A viral load change is considered significant if it is greater than 0.7 logs in children less than 2 years or 0.5 logs in children older than 2 years.

When should children change therapy?

Any of the following should signal the need for a change in therapy:

- Less than a 1 log change after 8–12 months on 3-drug combinations OR less than a 0.7 log change on two NARTI combinations.
- Repeated detection of HIV RNA in children who previously had undetectable levels.
- Persistent increases in viral load levels in children who originally responded to treatment (at least a 0.5 log increase in children older than 2 years and 0.7 log increase in children younger than 2 years).
- Persistent decline in CD4+ cell percentage of five percent or more (i.e. 15% down to 10%).
- Rapid decrease in absolute CD4+ cell counts.
- Clinical disease progression as seen by lack of growth, neurological symptoms or other signs of HIV disease.The principles of thinking about developing a long-term anti-HIV therapy strategy are similar in adults and in children. For more information on developing a long-term antiviral strategy, called the Project Inform Hotline.

When Should Children Start Treatment?

Health Status	Treatment Recommendation
All children with symptoms of HIV disease or clear immune suppression at any age	Begin therapy
All children less than 12 months regardless of general health status	Begin therapy
Children greater than 1 year with no symptoms of HIV disease	Two Options: • Start therapy (preferred) in all children, OR • Defer therapy (alternative) but regularly monitor viral load, CD4+ cell counts and general health

With Which Regimen Should Children Start?

Regimen	Explanation
Preferred	1 protease inhibitor and 2 NARTIs. NARTI combinations that have been well-studied include AZT + 3TC and AZT + ddI
Alternative	Nevirapine (Viramune®) plus 2 NARTIs
Secondary alternative	2 NARTIs (but the antiviral response may not be long-lasting)

NARTI=nucleoside analogue reverse transcriptase inhibitor

NOTE: Like all aspects of the Federal Guidelines, these recommendations will almost certainly change over time as new information and new therapies become available. The current Guidelines may not even represent the best possible use of existing therapies. However, they do represent the state of the art in our current knowledge about available drugs. Additional studies, even of older drugs, may lead to future revisions. The Guidelines should be used as a starting point for strategies based on proven information, but they are not a substitute or cookbook for the practice of medicine. Physician experience and patient individuality must always be incorporated into medical judgments. It is the duty of every physician treating people with HIV disease to remain abreast of these Guidelines and their future updates, which will always be available through the Project Inform Hotline.

Prevention of Mother-to-Child HIV Transmission[E]

The prevention of HIV transmission from mother-to-child (also called vertical or perinatal transmission) garnered much attention at the recent 12th World AIDS Conference. Promising data continued to show that anti-HIV therapy and other important prenatal (before birth) and postnatal (after the birth, early infancy) health care tools can significantly reduce HIV transmission to newborns. However, drug regimens continue to be inaccessible for the majority of women living with HIV throughout the world. It is becoming increasingly clear that while anti-HIV therapy plays a significant role in reducing mother-to-child transmission, successful prevention efforts include prenatal care and continued support and care for both the mother and child.

The Bay Area Perinatal AIDS Center (BAPAC) at San Francisco General Hospital has developed a program for prevention of mother-to-child HIV transmission. The program provides women with the latest in anti-HIV therapy along with case management, counseling and education, and has a strong focus on the basic principles of mother and child health. BAPAC has been able to reduce transmission of HIV in this setting to virtually zero. Of the 61 children that have been born in the past 3 years, 52 appear to be free of virus past 6 months of age. The remaining 9 infants are less than 6 months of age, but all have preliminary test results suggesting that they are not infected with HIV. In the BAPAC group, the majority of mothers of children born between 1994 and 1996 chose to use AZT alone during pregnancy. In 1997, 17 of 26 mothers chose two-drug therapy and 6 out of 26 chose a triple combination. In 1998, 10/17 pregnant women either started or continued triple-drug, protease inhibitor-containing combinations during their pregnancies, consistent with the Public Health Services recommendation that all women receive optimal anti-HIV therapy regardless of their pregnancy status. All mothers, regardless of the regimens they were taking, chose to have AZT administered through a vein (intravenously) during labor and chose to treat the newborn with AZT for a period of time after birth. The BAPAC program has focused on the total needs of women, addressing not only their anti-HIV therapy needs, but also their food, housing and general health concerns. The program has emphasized empowerment of women with counseling and education sessions to allow women to make their own choices about care for themselves and their newborn children. Adherence to the sometimes complex therapy regimens was difficult, especially during the first trimester and after delivery when the focus quickly shifts from a mother's own health needs to the needs of her child. Studies have shown that children are much healthier and less likely to die when an HIV-positive mother stays healthy herself. Before delivery, pregnant women and their physicians should plan ahead and discuss strategies for adherence and for preserving the mother's health. Despite difficulties with adherence, the program has clearly shown that a combination of anti-HIV therapy and a strong focus on prenatal care and maternal health can prevent almost all mother-to-child HIV transmission and leads to the best health outcomes for both women and their children.

The importance of the mother's health on the health outcomes of children was shown in a recent study of multivitamin use during pregnancy. The study included 1075 pregnant women with HIV in Africa and showed that use of multivitamins during pregnancy can significantly reduce the number of fetal deaths, low birth weight babies, and premature births. Researchers do not yet know if vitamin supplements can reduce mother-to-child HIV transmission.

Interestingly, while prenatal care, nutrition and anti-HIV therapy are independently important in improving maternal and infant outcomes, they are also related. One study showed that many women do not receive the full recommended regimen as used in the AIDS Clinical Trials Group (ACTG) 076 study—the study which led to the recommended use of AZT for preventing mother-to-child HIV transmission. In ACTG 076, mothers took 100mg AZT (zidovudine, Retrovir®) five times daily (total daily dose 500mg) until labor. During labor, they received 2mg/kg of AZT intravenously for one hour followed by 1mg/kg each hour until the child was delivered. The newborn received 2mg/kg of AZT orally (by mouth) or 1.5mg/kg intravenously every six hours for 6 weeks. Lack of prenatal care was the most common reason for not receiving the full regimen of AZT during pregnancy and throughout labor with subsequent AZT therapy to the newborn. Indeed, another study revealed the importance of receiving all regimen components. Mother and child pairs who received the full ACTG 076 AZT regimen had an HIV transmission rate of only 2.8%, much lower than the rates in women who received only partial regimens (9%) or none (31%).

Breast Feeding

There are a number of other practices that can reduce mother-to-child HIV transmission. HIV can be passed from mother to child through breast milk. Thus, whenever possible, and if nutritionally sound milk supplements are available, women with HIV should avoid breast feeding their children.

However, in many parts of the world where clean water is not available to reconstitute formula powder into a milk solution, women need to weigh the risks of HIV transmission through breast feeding with other infections that may result by using contaminated water.

In such countries, this issue is particularly confounded by lack of access to healthcare and health monitoring tools. In a third world country, an HIV-positive mother who gives birth to a child infected with HIV might best be helping that child, nutritionally, by breast feeding. If the child is not infected, however, she risks infecting the child. The tests to determine if the child is or is not infected, however, are not routinely available in the third world.

Ceasarean Section

Due to the major risk of transmission at the time of delivery, researchers have compared the effects of delivering the baby by a Ceasarean section to natural vaginal birth on the rate of mother-to-child HIV transmission. Studies show that, if used along with AZT, a Ceasarean section performed before labor can reduce rates of HIV transmission compared to a vaginal delivery. However, one study showed that there is no difference in HIV transmission rates between the two methods of delivery in women who do not use AZT therapy during pregnancy and throughout delivery. Also, while Ceasarean section may reduce the risk of HIV transmission, it is a surgical procedure and thus carries a number of additional risks to the mother. Therefore, it is important for the mother to weigh the risks and

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benefits to both herself and her child, remembering that her health after the child is born can impact on the health of her child.

Commentary

While AZT is the only drug that has been thoroughly studied in pregnant women, the Public Health Service Guidelines recommend all women receive the highest standard of care regardless of pregnancy status. Women are using a variety of therapies for their own health and to prevent HIV transmission during pregnancy. Small studies data are slowly emerging about the safety and effectiveness of combination drug regimens to prevent HIV transmission and the possible side effects these regimens may have on pregnant mothers and newborn children (see *Combination Therapies on Pregnant Women Box, p. 6*). It is important researchers explore the effects of anti-HIV treatments not only on mother-to-child transmission, but also on the health of women with HIV. More research is also needed on the way HIV and anti-HIV therapies affect common conditions seen in pregnant women such as glucose intolerance, diabetes and nausea.

It is increasingly clear that prenatal care and attention to the mother's general health concerns play an important role in the prevention of mother-to-child transmission. Women with HIV who are pregnant or are considering pregnancy should remember that a successful prenatal prevention regimen includes prenatal care, support and education in addition to a well thought out anti-HIV treatment strategy. Physicians are reminded that women with HIV need all important aspects of care to help prevent HIV transmission and maintain their own health before, during and after pregnancy. It is imperative to develop ways to help women and children adhere to therapy early in pregnancy and immediately after delivery. Obviously, the BAPAC program, addressing the spectrum of needs of HIV-positive pregnant women, has been able to do what ACTG 076 AZT therapy alone, could not do—bring mother-to-child HIV transmission rates to apparently zero. Programs which incorporate such comprehensive approaches must be established nationwide. The benefits of programs such as the BAPAC program, in both rural and urban areas, could result in the end of the pediatric AIDS epidemic in the U.S. and other developed nations. Those interested in learning more about the BAPAC program and developing such a program in their area can contact Karen Beckerman at 415-206-8276. ■

Report from the Seventh Immune Restoration Think Tank

The seventh meeting of the *Immune Restoration Think Tank: The Dobson Project* took place in San Francisco in March 1998. The theme of the meeting was 'Back to Basics' and emphasized basic research questions that must be revisited in light of new information about the immunologic consequences of highly active antiviral therapy (HAART).

The ability to potently suppress HIV replication for an extended period of time opens opportunity to study how well the immune system is able to correct defects caused by viral replication. It creates opportunity to try and rekindle the immune response using methods often considered too risky while viral replication continued at a high rate. The following topics from the meeting highlights only a few of the recommendations for future research.

The Environment

A recurrent topic of discussion was the state of the immune environment. A key question was whether the environment where cells are derived (e.g. bone marrow) and where they mature (e.g. thymus) are intact. Much work, largely inspired by previous IRTT meetings, has proceeded with regard to understanding the role and state of the thymus in HIV disease. Simultaneously, two studies have been conducted on thymus transplantation, one funded by Project Inform in association with the Foundation for AIDS and Immune Research.

Dr. McCune of the Gladstone Institute in San Francisco conducted CT scans of the thymus in people at varying stages of HIV disease and across the spectrum of age. Common belief in HIV disease has long been that the thymus is prematurely destroyed or damaged. However, when comparing CT scans of HIV-positive and -negative individuals regardless of age, Dr. McCune found that people living with HIV tend to have more detectable thymus material. Moreover, people with HIV in mid-stage disease (e.g. CD4+ cell counts of 300–500) appear more likely to have detectable thymus material compared to those in early-stage (e.g. CD4+ cell counts >500) or more advanced-stage (e.g. CD4+ cell counts <300) disease. These results have been quite encouraging. It remains to be seen whether thymus material will eventually regenerate in people with low CD4+ cell counts if the virus is adequately suppressed. If the thymus does not regenerate, thymus transplantation or other approaches to augment its function may need to be further explored.

In light of these findings, some participants suggested it may now be appropriate to reopen the study of several compounds, including thymic factors which are believed to promote maturation of thymus cells. While thymic factors have been studied for over 35 years for a variety of medical conditions, research has been overwhelmingly disappointing. Older studies typically pitted thymic factors against specific disease conditions and asked whether they led to clinical improvement. Newly proposed studies would instead ask if the use of these compounds results in the promotion of new cells maturing through the thymus. Prior, unsuccessful research on thymic factors in HIV disease was conducted before the advent of HAART. Think Tank participants recommended that these types of approaches be re-examined in light of recent advances in HIV therapeutics. In addition to re-evaluating thymic factors, including Thymic Humoral Factor, Thymosin-alpha 1 and thymopentin, the group noted a number of other compounds which might have an effect on cell maturation. These compounds include flt3 ligand, IL-2, recombinant human growth hormone (rHGH, Serostim®) and Insulin-like Growth Factor (IGF-1). Similarly, it was recommended that additional studies be conducted on therapies used in the treatment of HIV disease which are known to inhibit cell maturation in

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the thymus, including interferon-alpha, androgens, testosterone and glucocorticoids.

Surprisingly, discussion revealed that very little is known about the status of bone marrow in patients throughout the course of HIV disease. If the bone marrow environment is "hostile" or cannot support new cell development, bone marrow transplantation or approaches which augment the maturation of bone marrow cells into the spectrum of immune cells may need to be applied. To move this important research forward, a working group was formed to develop the needed research protocols. Understanding the status of the bone marrow may be critical in understanding how the immune system ultimately fails in its fight against HIV.

Emphasis on New Technologies

A persistent obstacle in immune restoration research is the lack of tools to measure immune responses and assess the status of the immune system. Developing new tools remains a high priority recommendation from Think Tank participants. An example is the need for cell labeling techniques which can safely be used in humans. It is difficult to understand whether or not cells are migrating out of the bone marrow and maturing properly, or even track where cells go in the body, without ways to mark cells and follow what they do. Dr. McCune and Dr. Hellerstein of UC Berkeley have developed a labeling technique which appears very safe and is being moved forward into studies in people with HIV. The technique involves intravenous infusion of something akin to sugar water. Cells will absorb the material and researchers will be able to track what happens to these cells over time, where they go and hopefully learn what they do.

Participants unanimously called for intensification of efforts to define, develop and validate tools to measure immune responses. A working group formed and discussed the best ways to move this important research forward. Over the upcoming year the group will interact with the National Institutes of Health to get new information gathered and analyzed. Also, a more comprehensive and descriptive list of immunologic assays will be developed to prioritize further development of promising new tools.

Advanced-stage Disease Therapies

A number of immune-based therapies exist that need to be further explored in the context of HAART in people with advanced-stage HIV disease. These include interleukin-2 (IL-2) approaches which might enhance thymus function, immune suppressive approaches, such as cyclosporine and a re-evaluation of approaches which may be useful in boosting immune responses, such as therapeutic vaccination. Some studies are already underway, having been initiated by Think Tank participants prior to the meeting. A study of low dose IL-2 use in people with advanced-stage HIV disease (e.g. CD4+ cell counts <200) is currently being developed. A study of cyclosporine in people with CD4+ cell counts >300 is enrolling in San Francisco, and a study of the drug in people with more advanced disease is enrolling at Case Western Reserve Hospital in Ohio. Researchers are currently evaluating which thymus enhancing approach to test in a study and others are considering which therapeutic vaccine approaches to re-evaluate.

Through the Think Tank process, Project Inform brings together top researchers from around the world, working inside and outside the field of AIDS, to come together in unique ways to plan new directions for immune restoration research. In the few short years since the first Immune Restoration Think Tank, the project has received international acclaim for moving this field of research forward leaps and bounds. In addition to being featured at many national and international AIDS conferences as a model for community interaction with HIV research, the project has yielded great success in pushing the frontiers of science and fostering research efforts into novel approaches targeting advanced HIV disease. ■

For more information on Project Immune Restoration and the Immune Restoration Think Tank, call the Project Inform National HIV/AIDS Treatment Hotline and request the *Immune Restoration Think Tank Discussion Paper*.