

Controversies in Antiretroviral Therapy

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About this Issue

This issue of *ACRIA Update* is devoted to current controversies in HIV treatment. Dr. Carl Fichtenbaum of Washington University has contributed a timely, state-of-the-art review of the issues of stopping prophylaxis and treatment of opportunistic infections in persons on highly active antiretroviral therapy. Tim Horn, a regular contributing writer, has summarized some of the controversies surrounding drug failure and salvage therapy. In a separate article, Tim addresses the current thinking on immune reconstitution and immune-based therapies. Jill Cadman updates us on the new issues surrounding perinatal transmission of HIV, and the controversial topic of post-exposure prophylaxis is detailed in a balanced article by Mike Barr. To start, ACRIA's Medical Director highlights some of the key issues surrounding strategies of antiretroviral therapy.

Controversies in Antiretroviral Therapy

By Marshall J. Glesby, MD, PhD

Managing HIV infection is like a chess game in some ways: Strategy is a key component of a successful attack on the virus. Unfortunately, the rules of the game keep changing. As much as we'd like to sometimes, we can't undo most of the moves that we've already made. In 1998, what should our first moves be? Should we start our attack now or watch and wait? Should we go for an all-out attack or should we hold back a little and keep something in reserve? If we go for an all-out attack, can we back off after a little while? Or, if we choose to keep some of our forces in reserve, can we add them on successfully if the initial attack isn't strong enough? How should we plan to move ahead if our first attack fails? Without purporting to answer these controversial questions, this article will expand on these important clinical issues.

When to Start Antiretroviral Treatment

The lack of consensus about when to start antiretroviral therapy for someone with established HIV infection is evidenced by the differing guidelines established by various committees of experts. The need to start treatment is never an emergency, though in some circumstances it can be relatively urgent. Note that the ensuing discussion does not include persons with acute HIV infection—that is, persons who have documented HIV in their bloodstream due to very recent infection and who have not yet seroconverted (developed antibodies to the virus). Most experts believe that persons with acute HIV infection, and perhaps those within six months of documented seroconversion should be treated. In most situations, however, the decision need not be rushed and observing the trend in a person's viral load and T-cell count over time can be of great help. The bottom line is that a number of factors have to be weighed and the decision individualized ([see Table 1](#)). Guidelines are only guidelines.

The main reason to consider early treatment of established HIV infection is to delay the onset of AIDS and prolong life. We know that antiretroviral therapy has these clinical benefits in persons with advanced HIV disease (T-cells less than 200) but they have not been demonstrated in persons with less advanced disease to date. This doesn't mean that treatment won't have these beneficial effects—we just don't know yet. There are a number of theoretical reasons to believe that early treatment will be beneficial. These arguments, as well as the opposing viewpoint, are summarized below.

A major theoretical argument in favor of early treatment is that controlling viral replication early on may prevent the emergence of HIV which is resistant to drugs. Each time HIV replicates (divides) in the body, there is a chance that mistakes will be made in copying its genetic material (RNA). Some of these mistakes, called mutations, may give HIV the ability to divide in the presence of certain antiretroviral drugs. These resistance mutations can develop even before a person starts on antiretroviral drugs. The argument goes that the sooner a person starts on therapy, the less likely they are to develop a significant number of these resistance mutations and therefore the greater the likelihood that the drug regimen will be able to successfully suppress HIV replication.

Another important argument in favor of early treatment relates to the fact that HIV gradually damages the immune system. The earlier the infection can be controlled, the more likely that immune function can be preserved. Similarly, there may be a better chance of restoring immune function (immune reconstitution) if someone starts treatment early on. Specifically, the body's immune response to HIV may be preserved or restored by early treatment. The presence of a strong immune response to HIV is felt by many researchers to be a key distinguishing factor between so-called long-term nonprogressors—persons who have been infected with HIV for at least 7 to 10 years and have had little decline in T-cell counts—and persons whose HIV infection has progressed. So restoring this immune response is felt to be desirable.

On a more practical note, persons with less advanced HIV infection tend to tolerate antiretroviral therapy more easily. Fewer side effects means that persons will be more likely to adhere to and continue on their drug regimens, which should increase the likelihood of long-term success.

There are also a number of arguments against early initiation of antiretroviral therapy. A key reason to question hitting the virus early is the unproven clinical benefit mentioned previously. The average time from initial infection with HIV to the development of AIDS is nearly 10 years. The longest anyone has been on combination antiretroviral therapy is closer to three years. Although the potential to keep viral replication suppressed for a few years using combination therapy has been realized, we don't know how long this suppression will last. If viral replication is completely suppressed, resistance may not develop since replication is required for new mutations to develop. However, it is not known whether complete suppression of replication happens even when viral load is less than 40 or 50 copies per milliliter, since there may be reservoirs of replicating virus which cannot be detected with the available technology.

Another concern about early initiation of antiretroviral therapy pertains to the risk of running out of treatment options in the event of failure of the initial regimen. The risk of progression to AIDS within five years for someone with a high T-cell count and low viral load is actually quite low. Such a person is likely to do well on antiretrovirals from the viral load standpoint, at least in the short term, since they are starting out with a low viral load. However, long-term adherence to a complex drug regimen may be more challenging for someone who has no symptoms to begin with and who may develop side-effects and a reduced quality of life from the medications. If such persons develop resistance to their initial regimen early in the course of their HIV disease due to poor adherence, there is a risk that they may end up switching to multiple alternate drugs and eventually running out of drugs at a time when they are clinically well, leaving no options for the future until new classes of drugs are developed.

Another possible reason for considering deferring antiretroviral therapy is the unknown potential long-term toxicities of the antiretroviral drugs. Alterations in blood sugar and lipid levels, abnormal fat redistribution and the occurrence of heart disease and stroke in young persons were not recognized as possible adverse effects of protease inhibitors until the drugs were widely used for close to two years. Perhaps other long-term toxicities will be recognized in the future.

In summary, there are a number of compelling theoretical reasons to support early initiation of antiretroviral therapy. On the other hand, there are important reasons to consider deferring therapy in healthy persons with low risks of progression to AIDS (i.e. high T-cell counts and low viral loads). Few would argue with the need to start therapy in someone with symptoms or who is at high risk of progression in the short term.

What to Start Treatment With

Although there are a large number of drug combinations to choose from, the current debate centers around whether to initiate therapy with a protease inhibitor-containing regimen or a protease-sparing regimen. The increasing recognition of metabolic complications attributed to (but not definitively proven to be caused by) protease inhibitors coupled with the promising results of studies of efavirenz (Sustiva®, formerly called DMP 266) have fueled this debate.

These metabolic complications, including diabetes, high cholesterol and triglyceride levels, and fat redistribution were discussed in detail in the Summer 1998 issue of ACRIA Update and will not be elaborated on here. The efavirenz data are worth mentioning, however, since they are from the first large study comparing protease-sparing regimens to one of the "gold standard" triple combinations with a protease inhibitor.

Efavirenz is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI). In the ongoing Dupont Pharmaceuticals 006 study, in which ACRIA is participating, eligible patients were either antiretroviral naive or nucleoside analog experienced, with the exception of 3TC. Their viral loads at entry were at least 10,000 copies/ml and their T-cell counts greater than 50 cells/mm³. Patients were randomly assigned to receive one of three combinations: AZT + 3TC + efavirenz; efavirenz + indinavir; or AZT + 3TC + indinavir. Data from the first 450 patients who completed 24 weeks of follow-up were presented at the 12th World AIDS Conference in July 1998. The results of this interim analysis, summarized in [Table 2](#), suggest that the protease inhibitor-sparing combination of AZT + 3TC + efavirenz is superior to the standard triple combination of AZT + 3TC + indinavir.

The relative ease of taking efavirenz compared with indinavir may partly account for the apparent superiority of the triple combination with efavirenz in this study. No clinical trial is flawless, and this study has been criticized for several reasons. First, it is an open-label study rather than the traditional double-blinded type. In other words, both the investigators and participants knew which drugs the participants were taking, which can be a source of bias in a study. An additional concern is that the drop-out rate in the triple combination arm with indinavir was quite high at 37.8% compared to 20.8% in the triple arm with efavirenz. Nonetheless, it appears as if AZT + 3TC + efavirenz is at least as effective at reducing viral load and increasing CD4 counts as AZT + 3TC + indinavir at 24 weeks. The durability of these responses is not yet known, but this protease-sparing combination may be a viable option for initial therapy.

Risks and Benefits of Early Initiation of HAART in Asymptomatic Patients*

Risks	Benefits
<ul style="list-style-type: none">• reduced quality of life from side-effects and inconvenience of drug regimens• earlier development of resistance• limitation of future treatment	<ul style="list-style-type: none">• delayed progression to AIDS and prolonged life• controlled viral replication and prevention of the emergence of resistant mutations• prevention of progressive damage to the

- | | |
|--|---|
| <ul style="list-style-type: none"> options due to the development of resistance • unknown long-term toxicity of antiretroviral drugs • unknown duration of effectiveness of current therapies | <ul style="list-style-type: none"> immune system and reconstitution of a normal immune system • decrease in the risk of drug toxicity |
|--|---|

* Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents*, Department of Health & Human Services, June 17, 1998

It is also not yet known whether the metabolic complications seen with protease inhibitors will also be seen with potent protease-sparing regimens. But the possibility of reserving protease inhibitor therapy for patients whose initial regimens may fail is an attractive one to many physicians. Along the lines of reserving classes of antiretrovirals, the availability of [abacavir](#) (Ziagen®, formerly called 1592U89), a potent nucleoside analog, will provide an option allowing for the preservation of both the protease inhibitors and NNRTIs as future treatment options.

Also, the triple nucleoside analog combination of abacavir + AZT + 3TC has been shown to be potent in early clinical trials and has the advantage of being a simple regimen of two pills twice a day if the Combivir® formulation, which combines AZT and 3TC into one pill, is used. One unresolved controversy relates to whether it is an advantage or disadvantage to start with such a regimen of three nucleoside analogs. Although this strategy may preserve other classes of drugs, there is concern that attacking the same part of the virus (the reverse transcriptase enzyme) in the same way may be less desirable than attacking different parts of the virus by using different classes of drugs. In the analogous model of cancer treatment, combinations of drugs which attack different targets of the malignant cells are superior to those attacking similar targets. An ongoing study comparing AZT + 3TC + abacavir to AZT + 3TC + indinavir should shed light on this important issue.

Aside from the decision about which drugs to start treatment with, another unresolved issue is how many drugs to use. Some authorities recommend using more than the standard three drugs for patients with high viral loads. A number of studies are addressing this question with comparisons of different combinations, like four versus three drugs.

Induction-Maintenance Strategy

A treatment strategy termed induction-maintenance has been under study recently, though the initial trials of this approach have not been successful. With this strategy, borrowed from the cancer treatment model, an aggressive regimen is used initially to induce a lowering of viral load for a set period of time or to below the level of detection, and then a less intensive maintenance regimen is used to keep the virus suppressed. The AIDS Clinical Trials Group (ACTG) conducted a study of this approach using AZT + 3TC + indinavir as induction for 24 weeks followed by AZT + 3TC, indinavir alone, or continuation of the triple combination. The results were disappointing as 17.3% of patients on AZT + 3TC and 15.8% of patients on indinavir alone had a rebound in viral load compared with only 2.9% of those who stayed on the triple combination. The French TRILEGE study was similar in design and yielded equally discouraging results.

Preliminary results of the Dutch ADAM trial were presented at the 12th World AIDS Conference. In this study, patients were induced for 26 weeks with a quadruple drug regimen consisting of d4T + 3TC + nelfinavir + saquinavir soft gel capsules. Those patients with viral loads less than 50 copies/ml were then randomly assigned to receive either d4T + nelfinavir, nelfinavir + saquinavir, or continue on quadruple therapy. Although only data from 25 patients followed out to 36 weeks were presented, there was a striking difference between the dual and quadruple therapy arms: 9

of 14 (64%) patients on one of the two dual therapies had rebounds in viral load to greater than 50 copies/ml compared with only one of 11 (9%) on the quadruple arm.

DMP 266-006 (efavirenz) Study:

Percent of Patients with Viral Loads Less Than 400 Copies/ml at 24 Weeks

Type of Analysis*	AZT + 3TC + Efavirenz	AZT + 3TC + Indinavir
Intent to Treat		
Noncompleter = Failure	74.7%	56.2%
Last Observation Carried Forward	86.4%	64.9%
Observed Data	94.5%	88.6%

* The data were analyzed in three different ways. The intent-to-treat analyses attempt to account for patients who did not complete 24 weeks of treatment. Since patients may have dropped out of the study because they were not responding to treatment, simply ignoring these drop-outs, as is done in the "observed data" analysis, may make the regimens appear better than they really are (because those who did not respond are not counted). The "noncompleter = failure" is a conservative analysis in which patients who did not complete 24 weeks are assumed to have had viral loads greater than 400 at 24 weeks. The "last observation carried forward" analysis takes the last viral load that a non-completing patient had before s/he dropped out of the study and uses that value for the viral load at 24 weeks. For example, if a patient had a viral load of 10,000 at week 16 of the study and dropped out at that time, his/her viral load at 24 weeks is assumed to also be 10,000.

An ongoing British trial called ProCom is studying a similar approach using a four- to six-month induction with d4T + ddI + nelfinavir + saquinavir soft gel capsules. Patients with undetectable viral loads will then be randomized to d4T + ddI, nelfinavir + saquinavir, or to continue on the quadruple combination. Although the results to date have been discouraging, the induction-maintenance strategy still may be viable. Its appeal is the potential for simplifying the antiretroviral regimen after a certain period of time. Perhaps the induction phase has just not been long enough in the studies completed thus far.

Intensification Strategy

The opposite approach to induction-maintenance is called intensification. This is another cancer treatment term which refers to the addition of drugs to a regimen when the initial regimen is not yielding the desired result. The Prometheus study used this strategy in comparing the dual protease inhibitor combination of [ritonavir](#) + saquinavir to ritonavir + saquinavir + d4T. In this trial, patients in the dual therapy arm whose viral loads were not below 400 copies/ml after 12 weeks of treatment added d4T. The results presented in Geneva were interesting. The triple combination arm was superior at Week 18 but both arms were comparable at Week 48, with approximately 80 percent of patients below 400 copies/ml. In other words, intensification with d4T for patients whose viral loads did not decline sufficiently by Week 12 yielded the same net result as starting treatment with the triple combination. While these results are intriguing, further study is needed before embracing this treatment strategy.

Sequencing of Antiretrovirals

The unfortunate reality is that a significant proportion of people end up with failure of their initial antiretroviral regimens. Many factors may contribute to this, and there are different definitions of failure. It makes good sense to plan in advance for the possibility of drug failure and to choose the first attack based on the possible options for subsequent attacks if needed. This has been alluded to earlier in the discussion of initial regimens - for example, the initial choice of a protease-sparing combination enables the use of protease inhibitors in so-called salvage regimens. Salvage regimens are the subject of an [article in this issue](#) by Tim Horn. The order in which antiretrovirals are used is sometimes referred to as the sequence. A key consideration in planning a sequence is what is the likelihood that specific drugs in a subsequent regimen will work based on the choice of the initial regimen? The likelihood of cross-resistance-meaning that

once HIV becomes resistant to one drug within a class it may also be resistant to other related drugs in the same class-is one determinant of the potential success of a second or third regimen.

There are other potential reasons unrelated to resistance that could lessen the likelihood of success of a subsequent regimen. One controversial potential reason relates to how nucleoside analogs are processed inside of cells in order to become active drugs. The nucleoside analogs undergo a processing called phosphorylation, where phosphate groups are added onto the chemical structures of the drugs. Results of a very small study of patients who took d4T after having taken AZT extensively in the past suggested that phosphorylation of d4T took place less efficiently in their cells. This observation was felt to partly explain why patients in the European study called ALTIS who had taken AZT in the past did not respond as well to d4T +3TC compared to patients with no prior antiretroviral therapy. In contrast, a recent analysis from the Johns Hopkins Hospital's HIV Clinic Database suggested that prior treatment with AZT did not adversely affect the response rate to subsequent treatment with d4T. This controversy remains unresolved.

Conclusions

As more antiretroviral drugs become available, treatment options expand dramatically. A number of fundamental questions that impact how best to use the available drugs and those which may be approved in the future remain unanswered. Further research into long-term strategies for HIV management is ongoing and will hopefully shed light on these unanswered questions.

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Update on Mother-to-Child Transmission

By Jill Cadman

In an ongoing effort to drive the rate of mother-to-child transmission of HIV (vertical transmission) to ever lower levels, numerous strategies are being explored. At the World AIDS Conference in Geneva this summer, several very encouraging reports on the effectiveness of Caesarean sections (C-sections) were presented. In addition, several small studies assessed the benefits and safety of combination therapy during pregnancy and had mixed outcomes. In the developing world, the transmission of HIV to infants through breast-feeding continues to be a major problem.

Elective C-sections

A three-part course of AZT treatment (administered before birth orally, during labor with an IV infusion, and to the newborn orally) has been proven to reduce the rate of vertical transmission by two thirds, from 25% to 8%. However, the role that the mode of delivery plays has been less clear. Since a large proportion of vertical transmission occurs at or near delivery, any intervention at this time might prove beneficial. Elective (non-emergency) C-section prior to the time the mother's water breaks can prevent the infant from being exposed to maternal blood and secretions. Up until now, studies attempting to demonstrate the effectiveness of such C-sections in reducing vertical transmission have been inconclusive. Presentations at Geneva revealed the most convincing data as yet on enhanced reduction in vertical transmission in women who were both on antiretroviral treatment and chose elective C-sections.

Several European studies provided important information. A large French group reported that among 902 women treated with AZT, elective C-section resulted in a rate of vertical transmission of only 0.8% compared to 6.6% for normal vaginal delivery. A Swiss group reported that there were no cases of vertical transmission among 45 women who completed the full three-part AZT treatment and had elective C-section. A German study of 80 women who had elective C-section

performed in addition to AZT treatment found that the rate of transmission was 2.5% as opposed to 7% for vaginal deliveries. In Italy, a five-year international trial of pregnant HIV-positive women with similar antiretroviral regimens found that of the 133 children delivered by C-section, 3% contracted HIV compared to 10.3% of 132 infants delivered vaginally.

The largest survey by far was conducted by the NIH-funded International Perinatal Group, which performed an analysis of data from five European and ten North American prospective studies on a total of 8,533 mother-child pairs. After adjusting for receipt of antiretroviral therapy, maternal disease progression and birth weight, risk of vertical transmission was reduced by over 50% with elective C-section compared to other modes of delivery. In women who received antiretroviral therapy, the rate of transmission was 2% with elective C-section and 7.3% with other modes of delivery.

The enhanced protection of an elective C-section must be weighed against the risk of postoperative complications and each woman's situation should be considered individually. Obviously, not all women will have access to or be able to afford a C-section, especially in the developing world.

Combination Therapy

Beyond AZT, there is not much information from clinical trials to help an HIV-positive pregnant woman make treatment decisions. While using combination therapy may be best for her own health, she will also be concerned about the safety of her infant. Ongoing studies are assessing the effect of combination therapy on pregnancy outcomes.

San Francisco General Hospital reported that choice of treatment among pregnant HIV-positive women has shifted from monotherapy to dual to triple combination therapy over the past three years. Among women in the clinic, combination therapy has been well tolerated. No maternal or fetal complications have been observed. Of the 60 infants born since 1995, 43 are uninfected and 17 are less than six months old but have so far tested negative.

The Los Angeles County-University of Southern California Medical Center presented the results of a case review of 14 HIV-positive pregnant women who received triple combination therapy including nevirapine, AZT and another nucleoside analog. The regimens have been well-tolerated in the women. Eight participants have delivered and seven of the newborns have tested negative for HIV. Test results for the one remaining baby are pending. All infants were born without abnormalities.

Concerns were raised by a Swiss study of 37 HIV-positive pregnant women. Forty-three percent received a protease inhibitor-containing regimen. While the mothers experienced no unexpected or life-threatening adverse events, of the 30 infants born to date, 33% were premature. There were three serious adverse events among the newborns: two infants experienced non-life-threatening cerebral hemorrhages and one had a rare birth defect that caused a malformation in the bile tract. The rate of vertical transmission was low with one HIV-positive infant identified.

The sample size of this study was small, some of the women were IV drug users (which contributes to premature births), and there was no control group. Also there was no adjustment for the CD4 count and disease stage of the mother, which may be important risk factors for problems at birth. Since women on combination therapy treatment are more likely to have lower CD4 counts and more advanced disease, the increase in premature births may be because the women are sicker, not because of therapy. Nonetheless, the results of the Swiss study underline the potential risks to the newborn of combination therapy. Four NIH-sponsored ACTG trials on protease inhibitor use in pregnant HIV-positive women recently were put on temporary hold after it was determined that out of 11 infants born thus far, four were delivered prematurely. It is not clear if the premature births in these trials are due to antiretroviral therapy, the severity of

maternal HIV disease or other risk factors. Ongoing reviews are evaluating how these factors may contribute to premature births. The trials will probably reopen with revised entry criteria to exclude women at high risk for premature delivery. In the meantime, NIH officials recommend that pregnant women on combination therapy continue their regimens as prescribed by their physicians.

The Breast-Feeding Dilemma

In industrialized countries, it is not recommended that HIV-positive women breast-feed their infants, as this is a known route of vertical transmission. However, breast feeding continues in many parts of the developing world due to lack of affordable and safe infant formulas. Breast-feeding can provide protection against diarrhea, respiratory disease and malnutrition. Mothers who do not nurse their infants may be stigmatized in their communities. Unfortunately, the number of infants infected by breast milk worldwide is estimated at a staggering 273,000 each year, according to the CDC.

Recent data from Africa, presented in Geneva, indicate that the risk of vertical transmission from breast milk increases with the duration of time. It is the norm for women in developing countries to nurse for an average of two years. One possible way to balance the risks and benefits of breast feeding is to wean the infants at four or six months, thereby reducing the risk. Another option is to provide breast milk alternatives. The Joint United Nations Programme on AIDS (UNAIDS) is launching projects in developing countries to provide a short course treatment of AZT to pregnant HIV-positive women to reduce the risk of prenatal transmission. The projects will also provide counseling and formula, if possible, to women who opt to bottle-feed to reduce the risk of transmission after birth.

Jill Cadman is the associate editor of GMHC's Treatment Issues, and also serves on the ACRIA board of directors.

Drug Failure and Salvage Therapy

By Tim Horn

Let's begin with a quiz. Which of the following statements best describes someone who is experiencing drug failure?

- A) Patient A had not taken any antivirals in the past and had a viral load of 100,000 copies/mL prior to beginning highly active antiretroviral therapy (HAART). His viral load was undetectable for more than a year after starting HAART therapy, but has since rebounded. For six months, his viral load has been stable at 2,000 copies/mL.
- B) Patient B has been on HAART for six months and her viral load is undetectable, according to a lab that uses the first generation PCR test (not capable of detecting less than 400 copies/mL of HIV-RNA). Her lab then acquires the second generation test (capable of detecting down to 50 copies/mL of HIV-RNA), which shows that she has a detectable viral load of 200 copies/mL.
- C) Patient C has taken many antiretrovirals in the past and is not able to achieve an undetectable viral load result while on his most recent combination. His viral load after six months of therapy is 20,000 copies/mL-down from 700,000 copies-but his T-cells (CD4 count) keep on going up.

So who is experiencing drug failure? That depends on who you ask. Some researchers and primary care physicians would argue none of the above while others might argue all of the above. One reason for this discrepancy might be that "drug failure" embodies two distinct terms: "virologic failure" and "clinical failure." Yet, people who experience virologic failure aren't

necessarily experiencing clinical failure, or vice versa. The United States Public Health Service (USPHS) has published an official definition of virologic failure in its Guidelines on the Use of Antiretroviral Agents, published and updated almost every month. According to the USPHS, virologic failure is characterized by any of the following:

Based on these criteria, it was recently estimated that the number of people experiencing virologic failure while on HAART is as high as 70%.

The rate of virologic resistance among patients who have their viral load checked using the newest PCR test is expected to be even higher. Research results from studies using the newest test were recently submitted to the FDA for review and are expected to be approved soon. In clinical trials, a sizeable number of patients who were undetectable using the standard PCR assay (less than 400 copies/mL) were found to be detectable using the second PCR assay. The USPHS has not yet examined the potential use of the newest "ultra-sensitive" PCR test but is likely to do so once it is approved. In turn, the guidelines regarding when to switch therapy may become even more strict than they currently are.

The term clinical failure refers to continuing disease progression (i.e., experiencing an opportunistic infection) while on HAART, and the term immunological failure refers to the decrease of CD4 count while on HAART. While many patients who experience virologic failure also experience clinical and/or immunological failure, there have been several documented exceptions to this rule. For example, some patients who experience virologic failure as defined by the USPHS may also continue to see a rise in their T-cells. For such patients, continued monitoring may be acceptable, at least until their HIV rebounds to levels greater than three times the lowest stable viral load measurement (e.g., if viral load increases from 4,000 copies to greater than 12,000 copies). Some doctors, may want their patients to wait even longer before switching therapies, especially in the presence of an increasing or stable CD4 cell count.

The primary problem with virologic failure is that HIV is no longer being maximally suppressed. In turn, this means that HIV is replicating, albeit much more slowly, and is likely to produce a large multidrug-resistant population of the virus. The relevance of increasing T-cells in the presence of virologic failure has also been called into question. According to Dr. Doug Richman of the University of California at San Diego, very high levels of T-cell recovery may actually signify impending failure; with more T-cells in the blood, HIV has more targets to attack as it escapes drug suppression.

Even as the eradication hypothesis dwindles, many researchers argue that the goal of HAART remains the same: Patients on HAART who manage to keep their viral load down stand the best chance of leading the longest, healthiest lives. In turn, the need for salvage therapies will likely increase dramatically over the next several years.

When to Switch

As with drug failure, many doctors and researchers view salvage therapies differently. For starters, there are opposing views regarding when one combination should be dropped and another should be initiated.

According to proceedings from the International Workshop on Salvage Therapy for HIV Infection held this past April in New Orleans, many researchers and physicians agreed that patients experiencing any degree of virologic failure should be switched from their "failing" regimen to another, more potent one. As discussed above, it is generally believed that the longer a patient stays on a treatment that allows some viral replication, the more likely drug-resistant strains of HIV will accumulate. On the other hand, some researchers and physicians made it clear that switching at such an early stage does not always pay off, especially with so few "unique" drugs to

choose from. In turn, some recommend waiting to see if there is a trend in viral load increases and T4 cell decreases before switching to a salvage regimen.

It has been suggested that drug resistance assays will make it much easier for patients and their doctors to choose HAART regimens more carefully. Not only will these tests help determine whether or not resistant strains of HIV are present before initiating therapy, but they may also be of incredible value in deciding which therapies to switch to after failure has occurred. At the present time, it is highly recommended that a patient experiencing failure drop the entire regimen and switch to an entirely new regimen of drugs (though this is not always possible). With resistance testing, it may be possible to determine which drug(s) is causing the regimen to fail, ultimately allowing a selective switch over a universal one.

What to Switch to

By far, the most frustrating issue in terms of salvage therapies is cross-resistance - when HIV that is resistant to one drug is resistant to other drugs in the same class. While many of the nucleoside analogues boast fairly unique resistance patterns, often allowing for successful switches, their antiviral potency is somewhat limited. Protease inhibitors and non-nucleosides are much more potent, but tend to cause a significant amount of cross-resistance to each other. As a result, the long-term benefits of salvage therapies tend to be short-lived.

Of course, the success of salvage therapy is highly dependent on a patient's prior antiviral experience. For example, someone who has never tried a non-nucleoside analogue may benefit significantly by switching from a protease inhibitor-based combination to a non-nucleoside-based combination. Some patients who are failing their first HAART combination have also been shown to benefit greatly from switching to a second combination. Options as easy as these, however, are more difficult to come by for patients with extensive prior protease inhibitor and non-nucleoside analogue experience.

In the absence of protease inhibitors and non-nucleoside analogues with truly unique resistance profiles (although several are currently in the drug development pipeline), researchers have been experimenting with drug combinations consisting of four or more compounds-mega-HAART, if you will-in an attempt to find acceptable salvage regimens.

Salvage therapies that combine ritonavir with the first saquinavir formulation (Invirase®) have been the most extensively studied to date. According to an analysis presented at the 5th Conference on Retroviruses and Opportunistic Infections in January 1998, Dr. Joel Gallant of the Johns Hopkins Hospital in Baltimore found that 12 out of 17 (70.5%) patients failing indinavir who switched to ritonavir, saquinavir and two new nucleoside analogues achieved undetectable viral load for at least 33 weeks. At the salvage therapy conference in New Orleans, Dr. Keith Henry of St. Paul's Regions Hospital reported similar findings in patients who were failing nelfinavir: 24 weeks after switching to ritonavir/saquinavir, 17 out of 24 (71%) patients were undetectable (less than 500 copies/mL; Chiron's Quantiplex bDNA assay). Other studies have shown however, that patients with extensive protease inhibitor experience - loosely defined as two or more protease inhibitors in the past-are much less likely to experience viral load reductions similar to these; only 5% of heavily pretreated patients typically see their viral load fall below the level of detection upon switching to ritonavir and saquinavir.

For patients who have failed multiple protease inhibitors (including ritonavir, saquinavir, and indinavir), preliminary data suggest that a combination of six drugs-saquinavir, nelfinavir, nevirapine, d4T, ddI, and 3TC - reduces viral load significantly. At the retrovirus conference, Dr. Cassy Workman of Australia found that this combination, which used a nelfinavir dose of 1000 mg three times daily (750 mg doses are standard), helped 9 out of 12 patients with an extensive history of failing protease inhibitors achieve undetectable viral loads for at least 12 weeks. Similar results from a study conducted by Dr. Schlomo Staszewski of Germany-using between six and eight different drugs-were reported at the salvage therapy conference: 90% of patients with

extensive antiviral experience achieved a 2 log (99%) reduction in viral load upon starting therapy with six or more drugs.

As for hydroxyurea's role in salvage combinations, some data presented at the 12th World AIDS Conference suggests that it is an effective base from which to build salvage therapies. However, hydroxyurea's side effects reared their ugly head in at least one salvage therapy study; 25% of patients with extensive antiviral experience and low CD4 counts (<100 CELLS) ENROLLED IN ONE STUDY WERE FORCED TO GO OFF THE DRUG DUE TO SEVERE NEUTROPENIA (LOSS OF PARTICULAR WHITE BLOOD CELLS CALLED NEUTROPHILS) OR BONE MARROW FAILURE.

Several salvage therapy studies involving new antivirals-including abacavir, adefovir dipivoxil, amprenavir, and efavirenz - are either underway or expected to open soon. Unfortunately, these compounds do not appear to be much different from those already approved and may not radically improve salvage therapy options. Looking further down the pipeline, however, many "second generation" antivirals-drugs specifically designed with resistance in mind-are now entering phase II clinical trials and are expected to expand both first-line and salvage treatment options considerably. But even in the absence of new drugs to choose from, salvage therapy research consisting of recycled and/or multidrug combinations continues to yield impressive results.

OI Prophylaxis and Treatment in the Era of HAART

By Carl J. Fichtenbaum, MD

There are a number of infections, cancers and neurologic problems that affect people with HIV infection. Collectively, these opportunistic illnesses (often called OIs) are the hallmark of the progressive immunodeficiency associated with HIV infection. These illnesses often result in hospitalization, disability, and time off from work, and are responsible for most of the deaths in persons with AIDS. The most common OIs are recurrent bacterial pneumonia, oral and esophageal candidiasis (thrush), *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus infection (CMV), *Mycobacterium-avium* complex infection (MAC); HIV-associated dementia, lymphoma, Kaposi's sarcoma and HIV wasting syndrome. Fortunately, many of these infections can be prevented.

The introduction of highly active antiretroviral therapy (HAART) and protease inhibitors has resulted in improved survival and decreased hospitalizations in persons with advanced HIV infection. This has been accompanied by an overall decline in the number of most OI events, and has led to the coining of a new phrase, "immune reconstitution", which leads to a number of important questions:

- What is immune reconstitution?
- How does a person know when s/he is "reconstituted"?
- Can individuals still get OIs if they have immune reconstitution?
- Can OI prophylaxis be stopped if immune reconstitution has occurred?
- What should patients and physicians do right now?
- What is being done to determine if it is safe to stop OI prophylaxis? For example, should a person with a CD4 count of 50 cells/mm³ that rises to 350 cells/mm³ after using HAART stop taking prophylaxis for PCP, MAC, toxoplasmosis, candidiasis or other infections?

What is Immune Reconstitution?

Immune reconstitution is the process of regeneration of the normal body defenses against

specific infections and illnesses. Immune reconstitution, or bringing the body's immune defenses back to a level where they can defend themselves against these OIs, is one of the critical benefits of HAART. This process probably involves several parts:

1. First, reduction in the amount and effects of HIV within the body
2. Second, repopulation of both memory and naive T-cells back to levels sufficient to prevent disease
3. Third, functional return of many of the components of the immune system that have been lost with HIV infection.

How Does One Tell When Immune Reconstitution Has Occurred?

A number of research groups are investigating how the human immune system regenerates in response to HAART. It would be rather simplistic to believe that immune reconstitution is a numbers game of lowering viral load and raising CD4 counts. There are a number of crude measures of immune function: reaction to skin tests (a test where some material is injected under the skin to see if the body reacts normally); return of the normal numbers of lymphocytes in the appropriate proportions; and the return of functional reactivity of lymphocytes to specific challenges with different stimuli. All of these tests are research tools that are not available (or interpretable) in clinical practice. None of the tests available are completely reliable or are able to fully explain what is actually happening with the use of HAART. Thus, the best measure of immune reconstitution is the lack of any OI occurring in a person who is taking HAART who was previously susceptible to OIs.

Do Individuals with Immune Reconstitution Still Get OIs?

Several recent studies have demonstrated conflicting data on the recovery of specific T-cell lymphocyte phenotypes (naive and memory cells) in response to HAART. This has led researchers to speculate that full recovery may not occur in everyone, particularly those with very advanced HIV infection (CD4 count of less than 50 cells/mm³). Thus, some patients may have very high levels of T-cells but still develop an OI because somehow they've permanently lost the ability to fight off that disease. In addition, several recent studies of HAART demonstrate that even though the virus level may drop below detection, OIs still occur (usually within the first three months after starting HAART). It may be that these infections were brewing even before the new antiretroviral therapy was started. Finally, there are reports of OIs occurring in individuals with higher T-cell levels and very low HIV viral load levels. At Washington University, we have observed this to occur in several of our patients with progressive multifocal leukoencephalopathy, a uniformly fatal infection of the brain.

Can OI Prophylaxis Be Stopped?

The quick answer is probably "Yes, but DON'T DO IT YET." This is the subject of intense study. Until there is sufficient safety data available, physicians and patients should be very cautious about stopping medications that have been proven to save lives. A number of small studies which have yet to be published demonstrate that OI prophylaxis can be stopped in some patients. Dr. Francesca Torriani and her colleagues at the University of San Diego have stopped anti-CMV therapy in patients who had CMV retinitis, and only one of 11 has recurred to date. Dr. Judy Aberg at the University of California at San Francisco stopped MAC therapy in four patients treated for at least one year without recurrence of their disease. Recently, researchers in the Swiss Cohort trial presented interim data at the 12th World AIDS Conference on the safety of stopping PCP prophylaxis. The results were quite encouraging. Collectively, these and other studies suggest that it may be safe to stop prophylaxis but more evidence is needed.

What is Being Done to Determine the Safety of Stopping OI Prophylaxis?

The AIDS Clinical Trials Group (ACTG) and a number of other research groups have designed several studies to test whether it is safe to stop these medications in persons who respond to HAART. One trial will determine whether it is safe to stop MAC prophylaxis. In ACTG 362, individuals whose T-cells have risen from less than 50 to above 100 cells/mm³ will be

randomized to continue MAC prophylaxis with weekly azithromycin or receive a placebo. If their CD4 count declines again below 50, then MAC prophylaxis will be resumed. This study is almost fully enrolled, and results should be available within the next 18 months.

To study the removal of PCP prophylaxis, Dr. Susan Koletar and her colleagues in the ACTG have designed a trial for individuals whose CD4 count rises from below 100 to above 200. Prophylaxis for PCP will be discontinued in all patients. About half the patients will have had PCP previously. Prophylaxis will be resumed if the CD4 count drops back below 200. In a third trial, individuals who have been treated for MAC disease for at least 12 months without symptoms and who are on HAART will be allowed to discontinue their MAC treatment (ACTG 393). If their CD4 count falls below 50, then they will start standard MAC prophylaxis. Frequent monitoring and MAC blood cultures will be done to detect any failures early.

Another study will discontinue CMV retinitis treatment in persons whose disease has responded to therapy and are now on HAART (ACTG 379). In this trial, the primary objective is to estimate the time-to-reactivation of CMV retinitis in HIV-infected subjects with treated and healed non-immediate sight-threatening CMV retinitis who have discontinued CMV maintenance therapy. Subjects will be divided into different groups: those who have CD4 counts greater than 100 in response to HAART and those who have CD4 counts of 50 to 100 and a 2 log (99 percent) decrease in viral load or a viral load below the limit of detection (less than 400 copies/ml) in response to HAART. One additional ACTG study involves the discontinuation of maintenance therapy for histoplasmosis, a fungal infection, in persons on HAART. Each of these trials has an immunologic component that is meant to evaluate whether there are specific responses that can predict who will still need and who may discontinue OI prophylaxis. There are several other groups throughout the United States, Europe and Australia that are also studying these questions.

Summary

The introduction of HAART has resulted in the longer survival of persons with AIDS. The lowering of HIV levels and increases in T-cells have led to the speculation that OI prophylaxis may not be necessary in patients responding to HAART. This is the subject of intense investigation. If true, this could result in the simplification of treatment for persons with HIV infection. The table on the left lists specific pathogens/diseases for which there is or is not evidence that the use of HAART decreases the chance of reoccurrence. Patients should discuss stopping prophylaxis with their medical provider before taking any action. Withdrawal of OI prophylaxis is not advisable until there is more evidence that it is safe.

What OIs can HAART Alone Prevent?

If HAART alone is effective, you may not need specific prevention or treatment for:

- Mucosal candidiasis (thrush)
- Cryptosporidiosis
- Cytomegalovirus (retinitis) (CMV)
- Mycobacterium-avium complex (MAC)
- Pneumocystis carinii (PCP)
- Progressive multifocal leukoencephalopathy (PML)

These OIs may occur even if HAART is effective:

- Cryptococcus
- Histoplasma
- Mycobacterium tuberculosis
- Bacterial pneumonia (Streptococcus pneumoniae)
- Herpes simplex virus

- Varicella-zoster virus

It is not yet known whether HAART is effective for:

- Kaposi's sarcoma (KSHV)
- Non-Hodgkins Lymphoma (EBV)
- Toxoplasmosis

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Immune-Based Therapies

By Tim Horn

Slowly but surely, immune-based therapies (IBTs) are beginning to steal some of the spotlight away from HAART. Given what is now known about the limitations of HAART, many researchers are now focusing on some of the impressive research involving IBTs. In recent months, numerous researchers have been suggesting-with a hearty amount of bravura and confidence-that IBTs will prove to be the answer to HAART's shortcomings.

Unfortunately, this new wave of research comes along with much of the same controversy and confusion that has plagued IBT research for years. Unlike antivirals, which have been clinically proven to keep HIV-infected people healthier and alive longer, no IBT has yet been proven to have the same effect. In essence, the burden of proof falls twice on IBTs: Not only must they live up to their suggested biological activities, they must also prove to have a safe and significant impact on the length and quality of patients' lives.

HAART and the Immune System: A Primer

We've come a long way from CD4 counts, baby. Not long ago, all researchers could hope for was that antivirals would boost the amount of an HIV-infected patient's T-cells. Then came combination therapy, viral load, and the quest towards maximal viral suppression. Today, the stakes are even higher: HAART must not only increase T-cells and suppress viral load, but must also aid in the restoration of some of the immune system's more complicated functions.

Many positive immunological effects of HAART have, in fact, been documented, including:

- The ability to reduce the number of hyper- active immune system cells, called CD38+ cells. A high CD38+ cell count can mean that the immune system is concentrating too heavily on HIV and not enough on other disease-causing pathogens; and
- The ability to correct the balance of memory CD4 cells (called CD45RO+ cells) and naive CD4 cells (called CD45RA+ cells), both of which are needed to help the immune system ward off new infections and keep old infections in check.

Some preliminary research has suggested that HAART can help at least temporarily rebuild a key part of the immune system's defense-called the lymphoproliferative response (LPR)-from infections like Candida, M. tuberculosis, and Pneumocystis. LPR is virtually nonexistent in almost all HIV-positive people except long-term nonprogressors.

Yet, HAART falls short of overcoming a few key immunological obstacles:

- The improved LPR associated with HAART is often short-lived. Moreover, the resulting LPR is very weak against HIV, meaning that the immune system remains incapable of initiating its own response to the virus.
- Eradication of HIV from the human host may prove to be impossible with HAART alone. Antiviral drugs are not active against latently infected, dormant immune cells harboring HIV, most of which can live for more than 10 years.

IBTs: The Final Frontier?

While HAART plays a large role in reconstituting the immune system, its activity is limited, at best. In striving towards more complete immune reconstitution, many research teams are now focusing on some of the following IBTs:

IL-2: Beyond the Basics

For many years, it has been known that recombinant interleukin-2 (IL-2)-a synthetic version of the human cytokine responsible for stimulating CD4 cells-can significantly increase CD4 counts in asymptomatic HIV-infected people (See Craig Sterritt's article in Volume 6, Number 4 of ACRIA Update). Keeping up with the times, a great deal of data presented at the 12th World AIDS Conference confirmed that IL-2 combined with HAART increases CD4 counts more effectively than HAART alone. Yet, it is still not known whether or not these CD4 count increases are, in fact, clinically relevant. In other words, it's still not known whether or not IL-2 will keep patients alive healthier and longer.

While researchers continue to grapple with this fundamental question, some recent studies have zeroed in on some of the other immunological benefits of IL-2. According to Dr. Clifford Lane of the National Institutes of Health (NIH), IL-2 may play a role in eradicating HIV. According to Dr. Lane, IL-2 stimulates the cytokines IL-6, tumor necrosis factor, and GM-CSF, all of which can "turn on" latently infected cells harboring HIV. Once these cells are activated by IL-2, HIV is expelled and ultimately destroyed by antiviral drugs. Dr. Lane also suggests that IL-2 blocks T-cell death (apoptosis) caused by HIV. This, in turn, allows both naive and memory T-cells to proliferate and continue their important functions.

As promising as these theories are, they are currently based on test tube study results, imperfect mathematical models, and a healthy amount of optimism. Short of HIV eradication in a large number of patients, the utility of IL-2 therapy will remain unknown.

IL-10 and IL-12

Like IL-2, both IL-10 and IL-12 are synthetic versions of cytokines produced by the immune system. Both cytokines are currently being studied in clinical trials and both show great promise as IBTs.

Unlike IL-2 and IL-12 (discussed below), both of which are responsible for stimulating healthy anti-HIV functions of the immune system, the primary role of IL-10 is to suppress potentially harmful immune functions. In test tube and human studies, IL-10 has been shown to effectively reduce the levels of the following cytokines: IL-1a and b, IL-6, IL-8, GM-CSF, G-CSF, and TNFa, along with monocytes and other key cells. The reason for wanting to play down these cytokines is simple; they all have been shown to increase HIV production and to cause certain HIV-related symptoms, such as fever, fatigue, diarrhea, and weight loss. IL-10 is still in the early stages of clinical development, thus it has not yet been determined how effective it will be in terms of boosting the immune system, reducing viral load, and delaying disease progression. Results from studies thus far, however, have demonstrated IL-10 to be a relatively safe and well-tolerated regimen.

While there are a number of potentially useful roles of IL-12 therapy, the most plausible in terms of HIV is its ability to promote the growth of "TH1" cells. T-cells generally fall under two

categories: TH1 cells and TH2 cells. The former are typically found in the earlier stages of disease and are synonymous with proper immune function, whereas the latter are frequently associated with disease progression. By stimulating the production of TH1 cells, IL-12 facilitates production of IL-2 and gamma-interferon, two cytokines that aid substantially in the immune response to HIV and other infections. Researchers studying IL-12 are being cautious; previous studies involving non-HIV-infected patients with kidney disease resulted in a high number of hospitalizations and a few deaths. As a result, several small safety studies are now being conducted prior to the development of larger efficacy studies.

HIV-1 Immunogen (Remune®)

Given what is known about the lack of a lymphoproliferative response (LPR) in people infected with HIV, even among those receiving HAART, researchers have been questioning whether or not HIV-1 immunogen (Remune®) can bolster the immune system's response, not only to opportunistic infections, but also to HIV. HIV-1 immunogen is also known as Salk immunogen, in honor of its inventor, Dr. Jonas Salk. Like Dr. Salk's polio vaccine, HIV-1 immunogen consists of whole virus (in this case, HIV) that has been slightly altered and killed. In earlier clinical trials of the compound, it was found to be extremely safe and associated with very few side effects.

Most recently, data from an efficacy study was presented at the 12th World AIDS Conference by Dr. Fred Valentine, an immunologist at New York University Medical Center. Dr. Valentine's study compared HIV-1 immunogen to placebo in 43 HIV positive patients, all of whom received HAART for the study's duration. After five months, patients receiving HIV-1 immunogen had moderately lower viral loads and higher T-cell counts than those receiving placebo. According to Dr. Valentine, patients receiving HIV-1 immunogen also showed "profound" increases in their anti-HIV LPR, a first for any type of anti-HIV or immune-based therapy.

As promising as these data seem, they remain controversial and have been subject to a litany of commentary. According to a powerful article written by treatment advocate Mike Barr in the August/September issue of TAGLine, published by the Treatment Action Group, very few conclusions can be drawn from Dr. Valentine's study. For starters, HIV-1 immunogen proved only to increase the LPR to the immunogen itself, along with a laboratory-derived strain of HIV; there is no evidence to suggest that the immunogen increased the immune system's sensitivity to the actual HIV strains in the patients' bodies. Moreover, it is unclear whether or not the LPR changes associated with HIV-1 immunogen are associated with any sort of clinical benefit (i.e., delayed diseased progression).

Cell Transfer Therapy

While there are many different types of cell transfer therapies being developed and studied, their basic premise is the same: Cells provided by the HIV-infected patient or a donor are collected, allowed to grow (and, sometimes, genetically modified in a laboratory), and then infused into the patient. If the cells are provided by and infused into the same patient, the process is known as an "autologous" infusion. Cells provided by another human or an animal donor are known, respectively, as "allogeneic" and "xenogeneic" infusions.

The intent of this process is to grow and infuse cells that will significantly boost the immune system's response to HIV. Researchers have also found that by genetically altering and infusing immune cells—a process known as gene transfer therapy—it may be possible to restart an immune system that has been altered or weakened due to HIV. Clinical trials of various cell transfer therapy techniques continue to yield promising results.

Conclusion

It is clear that many of the recent IBT research findings will provide research teams with a reinforced foundation from which to build new eradication and immune reconstitution models. Perhaps there is something good to be said for the controversy and confusion surrounding IBT

research after all. as new avenues of research-any of which may result in ground-breaking results-are being generated.

Tim Horn is the Executive Editor of The PRN Notebook, published by Physicians' Research Network in New York.

What is Post-Exposure Prophylaxis (PEP)?

By Mike Barr

Why PEP Now?

There is no cure for AIDS. And there is no proof that post-exposure prophylaxis (PEP) can actually work as a so-called "morning after" pill in humans exposed to HIV through sex or injection drug use (IDU). Avoiding internal exposure to HIV-infected blood, semen and vaginal fluids still remains the most effective way to remain HIV-negative. However, for HIV-uninfected persons who are exposed to HIV, there may be a window of opportunity in the first few hours or days after exposure in which antiretroviral combination therapy may be able to prevent established infection. The idea of providing potent anti-HIV drugs to prevent infection makes sense biologically, but some people believe the results from post-exposure studies to date (primarily using AZT in occupational exposures among healthcare workers) are far from definitive, and there have been no studies yet on the efficacy of PEP for sexual or injection exposure. The potency of the new anti-HIV drugs, however, is a compelling, if unproven, reason to offer PEP treatment after exposure to this life-threatening infection.

What is Known About PEP?

There is currently information from three different settings that suggests that PEP might be an effective strategy in reducing-but not entirely preventing-new HIV infections.

Most of the information regarding PEP comes from healthcare workers. Several years ago, a comprehensive strategy was developed to identify and reduce occupational risk behaviors among healthcare workers. Those who had been exposed to HIV through occupational hazards such as needle-stick injuries (occupational exposure) were offered AZT. Recent analysis of data comparing the rate of infection in those who took AZT with the rate of infection in those who did not receive treatment suggests that AZT is very effective in preventing HIV infection in this setting (79% reduction). The second set of information about PEP comes from studies of AZT in HIV-positive pregnant women and their newborns. Recent analysis of viral load data from the largest study to date suggests that AZT's usefulness in preventing HIV infection in the newborns of HIV-infected mothers (67% reduction) is due in part to prevention of the establishment of HIV infection in the exposed infant. Reduction in the mother's viral load, and thus the fetus' exposure to HIV, also plays some role.

Finally, studies in macaque (Simian) monkeys who were exposed to SIV (the simian immunodeficiency virus) intravenously and were then treated with an experimental antiretroviral agent called PMPA have demonstrated a reduction in the rate of SIV infection. Other animal studies suggest that it is important to treat as soon as possible after exposure to prevent infection.

What is Not Known About PEP?

These data suggest-but do not prove-that taking antiretroviral medications after a sexual or injection drug use exposure may reduce the rate of new HIV infections. It is important to generate data that demonstrate whether PEP is an effective strategy because there are potential risks associated with providing anti-HIV drugs to people after these types of exposures. All anti-HIV drugs have toxicities associated with them. There is also likely to be some emotional distress

associated with taking powerful anti-HIV medications for a period of time after a high-risk exposure. Thus, careful counseling would need to be included in PEP programs. The costs of the medications and the necessary counseling would be significant, underscoring the need for research prior to providing PEP as a service.

We do not know what effect the availability of potentially effective medications will have on people's choices and behaviors. One overriding concern is that even the act of developing a study would convey to people that it is thought PEP will work- and, consequently, that people will believe that they can engage in high-risk behaviors safely if PEP is available. Such a belief could undermine years of prevention work that have been crucial to reducing the rate of new infections in the communities at risk. We hope, but do not know, that a combination of medications and prevention techniques could result in a significant reduction in new HIV infections.

It is also not known how PEP might affect HIV drug resistance patterns. There may also be unexpected adverse effects such as birth defects, increased risk of tumors, and negative impact on the quality of life. Concerns about confidentiality and partner notification may present significant obstacles. These issues must be addressed before a study is initiated.

What Are Components of PEP?

Since July 1997, when a panel of experts convened by the U.S. Centers for Disease Control and Prevention (CDC) to discuss HIV prophylaxis for non-occupational exposures urged that "caution be used in future decision making until more data are available", many physicians and clinics across the country currently have been offering PEP in widely varying forms. Most forms of PEP involve providing one or several anti-HIV drugs-most commonly either Combivir® (AZT and 3TC in one pill) or Combivir® plus Crixivan® - within 72 hours of possible exposure. These drugs are then taken for a four- to six-week period. The average cost of PEP for a four-week treatment-including AZT, 3TC, a protease inhibitor, medical care and tests-ranges from \$1,300 to \$1,800.

Before PEP is implemented, a thorough risk assessment is usually conducted to determine an individual's level and frequency of risk-taking, as well as the HIV status of the partner. Individuals should be informed of the potential side effects and difficulty taking the drugs and should be assisted in developing strategies to successfully take the drugs as prescribed.

One of the potential benefits of PEP is the opportunity to reach and counsel people at high risk for HIV. PEP programs should include a counseling component to help patients deal with the fear of becoming infected and develop skills for avoiding future exposure to HIV. Referrals to HIV prevention, substance abuse, medical, mental health and housing programs can also be included to help high-risk individuals to address important risk factors. The best PEP programs will also offer testing and treatment for other STDs and testing for pregnancy.

Does PEP Work?

No one knows for sure. Researchers from the Centers for Disease Control and Prevention (CDC) reported at the 12th World AIDS Conference that over 30 percent of healthcare workers who received post-exposure prophylaxis (PEP) to lower the risk of HIV infection did not complete the recommended drug regimen. About three-quarters of those who did not complete the regimen said that the side effects associated with the drugs-including fatigue and nausea-caused them to stop the treatment. Dr. Helene Gayle, director of the CDC's National Center for HIV, STD, and TB Prevention, noted that the study shows that anti-HIV efforts must focus more on prevention. "The most effective way to protect healthcare workers is to prevent exposure in the first place," Gayle said. The researchers involved in the study analyzed information collected by the National Surveillance System for Hospital Healthcare Workers from June 1995 to December 1997. Of 114 healthcare workers who were occupationally exposed to HIV, 58 decided to start PEP. Seventy-one percent of these workers reported side effects and 36 percent stopped treatment.

Latest Data on Post-Exposure Prophylaxis

The latest word on PEP following sex and/or injection drug use was heard at the 12th World AIDS Conference. Researchers from UCSF presented preliminary data from the Post-Exposure Prevention Project, a collaborative effort between UCSF, San Francisco General Hospital and the San Francisco Department of Public Health. From October 1997 to May 1998, 151 individuals reporting unprotected sexual activity or needle-sharing within the previous 72 hours participated in the project. Of the participants, 127 (84%) were male, 71% white, 16% Latino and 10% African-American.

Ninety percent of the participants reported sexual exposure as the event leading to enrollment, with receptive anal intercourse the risk activity in almost half. The source individual was known to be HIV-positive in 48% of cases, and to have HIV risk factors in 44%. All participants were offered PEP and only six declined. Of those receiving PEP, 84% were prescribed Combivir®, 11% ddI + d4T, 2% Combivir® + nelfinavir and 1% ddI + d4T + nelfinavir. Remarkably, 80% of the participants completed the four-week course of therapy and only two of those who discontinued treatment early did so because of adverse effects. This is a fraction of the number of healthcare workers who stop PEP with AZT alone following exposure.

The researchers concluded that their preference for dual therapy was based on the better tolerability of two agents and that such combinations are sufficiently potent for PEP—hardly a universal opinion. Dr. James Kahn of UCSF believes the high tolerance of antiretrovirals is due to the close follow-up of participants in the project and the dispensation of medication at weekly intervals for the first two weeks.

What are the Potential Disadvantages of PEP?

Two of the biggest fears are, as mentioned earlier, possibly encouraging a return to unsafe sex practices and the development of drug-resistant HIV strains due to misuse of PEP drug therapies. If PEP drug therapy is unsuccessful and a person does develop a drug-resistant virus, the new anti-HIV drugs may not be as effective for treating that person. This can occur not only with PEP, but with any combination therapy.

PEP regimens can be both complicated and prohibitively expensive to follow. PEP drugs need to be taken at specific times of the day on a regular schedule. About one-third of the healthcare workers who received PEP never finished the regimen because of difficulty taking the drugs. Side effects of the drugs can be severe, and long-term effects are still unknown.

Prescribing PEP can be a tough decision. Many clinicians believe that a person with a single case of exposure to an HIV-infected partner would be a good candidate for PEP. Others worry that providing PEP repeatedly to a person with ongoing high-risk behavior may promote unsafe sex and could also be toxic.

What Programs Exist?

San Francisco General Hospital has recently implemented a project to determine the safety and feasibility of PEP rather than its effectiveness. The study offers intensive behavioral counseling, HIV testing and anti-HIV medication to persons who have been exposed within the last 72 hours. In Boston, the Fenway Community Clinic has been offering PEP to walk-in clients for the past 12 months. And in New York, Dr. Gabriel Torres of the Bentley-Salick Medical Practice is currently in the final planning stages of a large 24-hour PEP clinic which is expected to give patients and their primary care providers a menu of experimental PEP combination therapies from which to choose. Internationally, many countries are moving ahead with PEP.

Mike Barr has been a clinical research assistant at St. Vincent's Hospital since 1990. He is also editor of the monthly newsletter of the [Treatment Action Group \(TAG\)](#) in New York.

CRIA TRIALS NOW ENROLLING

For more information on any of these studies, please call Dr. Avinash Desai or Dr. Douglas Mendez at (212) 924-3934.

Fat Accumulation in the Belly (FAB) Study

Fat buildup in the abdomen may be a complication of protease inhibitor use. ACRIA is studying the safety of daily human growth hormone injections as a possible treatment for this complication. To be eligible for this 24-week study, you must be HIV-infected, on stable antiretroviral therapy, and have noticed increasing abdominal size.

Oxandrolone for Women with Weight Loss

Oxandrolone is BTG's anabolic steroid hormone which has shown promise as a treatment for AIDS-related wasting in small, preliminary studies and, unlike testosterone, can be taken as a pill. ACRIA is participating in a multicenter study of oxandrolone for AIDS-related wasting in women. In this study, different doses of oxandrolone will be compared with inactive pills (placebo) for 12 weeks, followed by a 24 week period during which all participants will receive oxandrolone. Participants must be HIV-positive with unintentional weight loss of 10-20% of their usual body weight. Participants will be reimbursed \$15 per scheduled study visit after enrollment.

Protease Inhibitor and Blood Sugar Study

CRIA is conducting a study to examine the effects of protease inhibitor use on responses to the oral glucose tolerance test (measurement of blood sugar levels after taking a drink with a high sugar content). To be eligible, participants must be about to start treatment with a protease inhibitor drug for the first time. Participants will be reimbursed \$30 for each of the first two visits and \$50 for the final visit.

SMART/EST Women's Project

CRIA is participating in a multicenter study to test a 10-week stress management program to teach women how to cope more effectively with their illness and everyday problems. Two approaches -individual and group relaxation training- are being compared. Women 18 years of age and older with a diagnosis of AIDS may be eligible. Participants will be reimbursed \$25 per visit after enrollment (up to \$575). Free child care and refreshments will be provided. For more information, call Debra Munger at 212- 924-3934.

Testosterone and MET-Rx™

CRIA is sponsoring a study of testosterone and MET-Rx™, a high protein nutritional supplement for treatment of AIDS-related wasting. Participants will receive testosterone or placebo injections in combination with MET-Rx™ or standard nutritional supplement. Participants must be HIV-positive men with T-cell counts of less than 400, low testosterone levels, and weight loss or loss of lean body mass. For information, call Dr. Judith Rabkin at 212-543-5762.

SALSATM Questionnaire for Lipodystrophy

CRIA is participating in a multicenter information-gathering study sponsored by Serono Laboratories with the goal of better defining the features of lipodystrophy syndrome. Persons who think they have features of the syndrome, which include thinning of the arms and legs, fat redistribution to the abdomen, and buffalo hump are encouraged to schedule a one-time visit to complete the questionnaire. Eligible participants will be reimbursed \$10 for their time.

