

ACRIA Update
Spring 1999 - Vol. 8 No. 2

Update from the 6th Annual Retrovirus Conference

Contents

- **Hold the Protease, Please**
- **Evaluating Drug Resistance Tests**
- **Immune-Based Therapies**
- **Vertical Transmission**
- **Intermittent HIV Therapy**
- **HAART-Related Fat Redistribution and Metabolic Complications**
- **New Drug Update**
- **CRIA News - CRIA Trials - Contributions – Masthead**

About This Issue

Our Spring 1999 issue of *ACRIA Update* focuses on reports from the Sixth Retrovirus Conference in Chicago this past February-March, one of the most important annual conferences for the presentation of research related to antiretroviral therapy. Frequent CRIA Update contributor Tim Horn heads up this issue with his look at updates in protease-sparing therapies. Carlos Arboleda and Jill Cadman weigh in with their report on the newest developments on HIV resistance tests. Dr. Shaffik Essajee, a pediatric AIDS doctor at Bellevue Hospital, reports on the latest findings around vertical transmission, and Richard Jeffreys does the same for immune-based therapies. And outgoing CRIA medical director Dr. Marshall Glesby files updates on fat redistribution and metabolic complications, and on intermittent HIV therapy.

We hope you find these updates as enlightening and hopeful as we did...and happy spring!

Hold the Protease, Please

By Tim Horn

Ever since the 12th World AIDS Conference in Geneva, where researchers presented data from a study comparing the non-nucleoside reverse transcriptase inhibitor (NNRTI) Sustiva® (efavirenz) to the protease inhibitor (PI) Crixivan® (indinavir sulfate)-both in combination with two nucleoside analogues -- there has been a great deal of speculation as to whether patients starting highly active antiretroviral therapy (HAART) for the first time necessarily need to take a protease inhibitor. True, PIs have been proven to offer a powerful antiviral punch and have for several years been the gold standard therapy. Yet their side effects -- which may include body composition changes, metabolic complications, and a slew of other problems-have caused many physicians and patients to question their use for long periods of time.

A protease-sparing HAART combination is just that: a drug "cocktail" consisting of an NNRTI with two nucleoside analogues or, perhaps, a combination consisting of three nucleoside analogues. Now-as reported at the [Sixth Conference on Retroviruses and Opportunistic Infections](#) in Chicago this past winter-there are some data suggesting that such combinations may, in fact, be viable options.

NNRTI-Based Combinations

Perhaps the most convincing data come from a DuPont study (with ACRIA as a co-participant) involving the NNRTI Sustiva. Reported at the conference were data involving 450 patients who had been taking one of three combinations for approximately one year (48 weeks). The first combination consisted of Sustiva, AZT (Retrovir®) and 3TC (Epivir®); the second was made up of Sustiva and Crixivan, and the third consisted of Crixivan, AZT, and 3TC. Approximately 98% of the patients who were still taking Sustiva/AZT/3TC after 48 weeks had undetectable viral load (<400 copies/mL), compared to 86% of those who were still taking Crixivan/AZT/3TC. While this doesn't mean we can conclude that Sustiva/AZT/3TC is better than Crixivan/AZT/3TC, we can conclude that the two are equally effective.

Of particular interest are data from an "intent-to-treat" analysis. Such an analysis includes all patients enrolled in the study, even if they weren't taking their designated drugs at the time of the analysis, perhaps due to side effects or poor compliance. Unlike the "on-treatment" analysis reported above, an intent-to-treat analysis is much more accurate in terms of answering how the drug (or combination of drugs) will perform in the real world, as it reflects the total number of patients who started therapy with the intent of being successfully treated. Using this analysis, approximately 71% of patients who were originally randomized to receive Sustiva/AZT/3TC had undetectable viral loads after 48 weeks of therapy. Among those originally given Crixivan/AZT/3TC, however, only 48% had undetectable viral loads after 48 weeks. These data were statistically significant, which lends credence to the suggestion that Sustiva may, in fact, be more effective than Crixivan for patients who are starting HAART for the first time. There was, however, a higher than expected drop-out rate in the Crixivan/AZT/3TC arm of this study, and the fact that drop-outs count as treatment failures in the intent-to-treat analysis accounts for the poorer performance of this regimen compared to previous studies.

Another interesting analysis of this trial suggested that patients who had a viral load of more than 100,000 copies/mL upon entering the study did best if they received Sustiva/AZT/3TC. In terms of side effects, more patients taking Crixivan/AZT/3TC either reported side effects (particularly nausea and vomiting) or discontinued the drugs altogether than patients receiving Sustiva/AZT/3TC or Sustiva/Crixivan. However, more patients (approximately 55%) who received Sustiva/AZT/3TC reported central nervous system (CNS) problems including sleeping troubles, vivid dreams, and muddled thinking.

In a second report at the Chicago conference, preliminary results from the international ATLANTIC study comparing one PI-based combination with two PI-sparing combinations were presented. The specific regimen tested in this open-label randomized trial was the NNRTI Viramune® (nevirapine) in combination with d4T (Zerit®) and ddI (Videx®) (Group 1), Crixivan with d4T and ddI (Group 2), and a triple-nucleoside combination of 3TC, d4T, and ddI (Group 3). Data were presented with respect to the first 234 patients who completed six months (24 weeks) of therapy.

After 24 weeks of therapy, there appear to be some differences between the three groups. Yet, because the study is still in its early stage (the researchers hope to collect three years'-worth of follow-up data), it's still too early to tell if these differences are statistically significant. In the intent-to-treat analysis, approximately 78% of patients in Group 2 had undetectable viral loads (<500 copies/mL), compared with 69% in Group 1 and 71% in Group 3. As for the on-treatment analysis, 91% in Group 2 had undetectable viral loads, compared to 89% in Group 1 and 80% in Group 3.

Even though these results seem to suggest that a Viramune-containing regimen is equally as effective as one that contains Crixivan -- at least for 24 weeks -- it is important to remain cautious. For starters, patients appeared to enter this study with low viral loads. The average viral load before starting the treatment was approximately 15,000 copies/mL, which can often be pushed to undetectable levels for at least 24 weeks using two nucleoside analogues alone. Also, it will be

important to see how well the combinations hold up for a prolonged period of time. It's important to keep in mind that not only do we want to keep viral load as low as possible, but also to keep it low for as long as possible.

Making the Switch

For patients who have already started a protease inhibitor-based combination and are enjoying good viral load and T-cell responses, but are experiencing lipodystrophy, a handful of studies suggest that switching the PI for an NNRTI may be a feasible option. One small study presented at the conference involved 21 HIV-infected patients, all of whom had received at least nine months of Crixivan, d4T, and 3TC, and had both undetectable viral loads and signs of lipodystrophy. The study either maintained them on this regimen or switched the Crixivan for Viramune. The study volunteers were monitored every four weeks using viral load tests, T-cell counts, and a slew of other tests to measure metabolic and body composition changes.

After 12 weeks, all patients -- which includes 10 patients in the Crixivan group and 11 patients in the Viramune group -- still have undetectable viral loads (<50 copies/mL). Among those who were switched to Viramune, cholesterol and triglyceride levels have significantly decreased. This is potentially an important outcome, as high cholesterol and triglyceride levels are associated with a heightened risk of experiencing heart disease or stroke over the long term. While most patients who were switched to Viramune also reported that their body composition has begun to normalize, none of the actual body composition tests have yet been able to detect a difference between the two treatment groups.

In another study, 12 patients who opted to drop their protease inhibitor for Sustiva did not appear to fare as well as those enrolled in the Viramune study. Although nobody who switched to Sustiva experienced an increase in their viral loads after dropping the protease inhibitor, most patients did see a rise in their cholesterol and triglyceride levels after 12 weeks. After 24 weeks of switching, however, the levels began to decrease once again.

These preliminary results--at least those involving Viramune--demonstrate a potential treatment alternative for some patients who are seeing good viral load response while on a PI-containing regimen but are also encountering signs and symptoms of lipodystrophy. Although the follow-up time is extremely short, the initial results in terms of declining triglyceride and cholesterol levels as well as improved patient-reported body image are very promising. Continued follow-up of patients in this trial will confirm whether switching from a protease inhibitor-containing regimen to an NNRTI-containing regimen will be a feasible management strategy for lipodystrophy associated with HAART.

Regimens that use NNRTIs as a foundation are not without their potential concerns. First, the chance of developing resistance to NNRTIs is much higher than with PIs. All three NNRTIs approved to date are associated with relatively high levels of resistance, even after just one mutation in the reverse transcriptase enzyme, as opposed to the PIs, which require multiple mutations in the protease enzyme to confer resistance. While combining NNRTIs with standard nucleoside analogues does appear to delay the onset of resistance, no one knows for how long. At the same time, combinations consisting of one NNRTI and two nucleoside analogues only prevent healthy cells from becoming infected, whereas a protease/nucleoside analogue combination also prevents cells that have already been infected from producing new virus. In turn, an NNRTI-based combination will not be active against long-lived, resting cells that can begin producing new virus if activated. Finally, as mentioned above, these studies have yet to produce long-term data.

PI- and NNRTI-Sparing Combinations

While the ATLANTIC study is in the midst of pitting its own all-nucleoside analogue combination against the PI- and NNRTI-based combinations, another study has demonstrated that a combination of Ziagen™ (abacavir), AZT, and 3TC is equally as effective as a combination of

Crixivan, AZT, and 3TC, at least for 24 weeks. Unlike the ATLANTIC study, the abacavir study enrolled treatment-naive patients with high viral loads; the average viral load upon entering the study was higher than 100,000 copies/mL and the average T-cell count was 360. Using an intent-to-treat analysis, the researchers found that approximately 65% of patients in both groups had undetectable viral load (<400 copies/mL). As for the on-treatment analysis, approximately 85 % in both groups had undetectable viral loads.

Should a combination consisting of three nucleoside analogues prove to be a truly effective option -- which will require follow-up data lasting a few years or more -- the number of treatment options available to patients would greatly expand. Given the lack of cross-resistance between many of the various nucleoside analogues, along with the fact that an all-nucleoside analogue combination will have no impact on the future sensitivity of HIV to both NNRTIs and PIs, future options are undoubtedly preserved. Yet, an all-nucleoside analogue combination is not without its problems, and suffers from many of the same potential drawbacks as NNRTI-based combinations.

Evaluating Drug Resistance Tests

By Carlos Arboleda with Jill Cadman

Almost two years since genotype and phenotype testing have become generally, if not widely, available for the diagnosis and evaluation of HIV drug resistance, there is still much controversy about their accuracy as diagnostic tools and their usefulness as predictors of treatment success. In theory, the likelihood of treatment failure can be minimized by using resistance assays to determine ahead of time which drugs each person's particular strain of HIV is susceptible to, and choosing those drugs for that individual's treatment regimen.

Drug Resistance

Drug resistance could be called the Achilles' heel of the current strategies for the treatment of HIV infection. Resistance results from HIV's tendency to mutate its genetic material (RNA) in a way that impedes one or more of the antiviral drugs from inhibiting viral replication. The virus' genetic material is an instruction manual, telling the virus what to do and how it will look.

In the absence of antiviral treatment, HIV replicates freely in the blood stream, making billions of copies of itself each day. This virus is usually called "wild type" because it has not been exposed to any drugs. Since the virus replicates at such an extraordinarily rapid rate, errors frequently occur during the process of producing new copies. This results in HIV whose genetic material is not identical to the original and is in some way defective. These defective viruses are called mutants and occur at all times during the replication process. However, the mutations remain a relatively small portion of the total viral population, since wild type tends to be the prevalent and stronger strain of virus.

Some of the mutations that do occur make the virus so different from the wild type that one or more of the antiviral drugs are no longer effective, making those mutant versions of HIV resistant to a particular drug or class of drugs. However, not all mutations cause the virus to become resistant to all drugs. In some cases, the presence of a single mutation can confer resistance to a drug, while in other cases a set of mutations is required before a drug becomes ineffective. For example, HIV develops resistance to [3TC](#) (Epivir®) due to the presence of a simple mutation (at position 184), while a complex series of mutations is required for the emergence of resistance to Crixivan® (indinavir) and other protease inhibitors. Each person's mutations are called resistance patterns.

If an antiviral combination is not completely suppressing viral replication, drug-resistant mutations will eventually emerge and become the dominant strain in an individual's viral population. The direct effect of this can be an increase in viral load, which is generally known as virologic failure, and subsequent drug or treatment failure.

Resistance Assays

Currently, there are two methods to determine whether a particular virus is sensitive or resistant to a drug: genotype and phenotype testing. Genotype testing looks for the mutations that make the virus resistant or potentially resistant while phenotype testing measures the potential sensitivity of a cultivated virus to a particular drug. The methods are very different.

Genotyping relies on the amplification of the gene sequence of the reverse transcriptase and protease enzymes of HIV. The net result of the genotype test is a map of the genetic sequence of the virus with its associated mutations. Because researchers have identified some of the mutations associated with certain resistance patterns, they can determine whether the virus being tested is resistant to a particular drug or drugs. The problem with this is that the presence (or absence) of a mutation or set of mutations known to confer resistance in a lab setting does not always correlate with treatment outcomes in a real-world setting. Likewise, drug failure in an HIV-positive person cannot always be explained by genotypic analysis.

Phenotype testing measures the potential sensitivity or resistance of HIV by growing virus in a test tube with genetic characteristics copied from blood samples submitted by individual patients. Cultures in which the virus is growing are then treated with various 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 the virus cannot grow in the presence of a drug, then it is still sensitive to that drug. However, if the virus replicates freely or requires a larger than normal amount of a drug in order to be suppressed, then it is resistant or has a degree of resistance to that drug. The degree of resistance is often expressed in terms of the amount of drug required to suppress replication. Generally, anything above a 10-fold increase in the amount of drug required to inhibit the virus is considered highly resistant and likely to mean that the drugs are no longer capable of blocking the virus from replicating. A finding of a four- to ten-fold increase is considered intermediately resistant. Less than a four-fold increase is considered sensitive.

Because they directly test the patient's virus against the actual drugs used in treatment, phenotypic assays are sometimes considered the gold standard of resistance testing. The test is quite expensive, costing over \$800, and takes 4-6 weeks. Genotyping is a simpler process and typically costs less, between \$300 and \$500, and takes less time. Both assays generally require a minimum viral load of 1,000 to 2,000 copies in order to be accurate.

Studies of Resistance Testing

While there has not been definitive proof that either test can predict whether a particular combination therapy will be successful, a number of recent reports have suggested that resistance assay results may reliably predict response to therapy. In a study presented at the Resistance Workshop in Italy last summer, indinavir failures whose HIV was sensitive to two or three of the drugs in their salvage combinations experienced a dramatic and sustained reduction in viral load through the 16 week study period. In comparison, patients with HIV sensitive to zero or one drug in their salvage regimen only experienced a transient drop in viral load in the first 4 weeks that rapidly returned to baseline.

Another study presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego last fall demonstrated that patients with phenotypically or genotypically sensitive virus to [ritonavir](#) (Norvir®) with saquinavir (Invirase®) before therapy were

4- to 12-fold more likely to achieve a viral load below 500 copies/ml using this double protease inhibitor combination. However, patients whose tests showed sensitivity to both drugs were not always successfully treated. This correlates with information collected in databases that indicates that about 15% of HIV isolates without known protease-inhibitor mutations are still protease-inhibitor resistant.

At the [International Congress on Drug Therapy and HIV Infection](#) in Glasgow in November, preliminary results from the French VIRADAPT study were presented. This study looked at the value of genotyping in selecting salvage regimens. The 108 participants had previously experienced treatment failure and were divided into two groups. One group switched regimens based on physician judgment and treatment guidelines. The other group used genotypic testing to select a new regimen. Those in the group using genotyping were more likely to have a viral load below the limit of detection at both month three and month six.

At the recent Sixth Conference on Retroviruses and Opportunistic Infections held in Chicago, a similar study on genotype testing was presented. This study enrolled 153 volunteers with evidence of viral load rebound on a triple combination regimen. The participants were randomized either to receive a genotype with expert guidance on its interpretation (GART), or the current standard of care in which the clinician chose the next regimen based on the patient's treatment history. Overall, there was a significant difference in the viral loads in the two groups, with a lower viral load in the group using GART. In both arms, the viral load decline was transient and viral load rebound was noted by week 12. Nonetheless, these results suggest that there is likely to be a role for genotypic testing in the selection of antiviral medications for patients experiencing treatment failure.

The Role of Resistance Testing in Clinical Practice Due to the growing body of data on resistance patterns in the context of scientific and clinical research, there is a better understanding of how the presence of HIV mutations in an individual impacts his or her treatment options. Genotypic and phenotypic analysis could be used as diagnostic tools to predict the success of initial therapy, to evaluate and perhaps measure the onset of resistant patterns, to determine salvage therapies and to follow the spread of multi-drug resistant virus.

Supporters of the use of resistance testing in treatment-naïve patients maintain that prior knowledge of pre-existing resistance patterns would enable the selection of an initial therapy with the greatest chance of success. The problem with this approach is that most people who are treatment naïve have wild type virus, making these tests an unnecessary expense. However, there is evidence that strains of drug-resistant virus are being transmitted. It has been reported that AZT (Retrovir®)-resistant virus is present in 10% of new infections. There was also a report of a virus resistant to all commercially-available HIV drugs being transmitted in San Francisco.

Genotypic and phenotypic analysis could be used to track the spread of drug-resistant HIV. A presentation in Chicago focused on the resistance profiles of HIV isolated from 114 treatment-naïve people with documented infection within the last three years. Using genotype and phenotype testing, the researchers found that the prevalence of resistance to two different classes of drugs was 3.2% by genotype and 2.2% by phenotype, and the prevalence of resistance to all three classes of drugs was 2.1% by genotype and 3.3% by phenotype. Although the investigators suggested that based on these data, "resistance testing prior to starting therapy may be useful to optimize initial therapy," it would be hard to recommend general resistance testing based on such low levels of resistance in treatment-naïve patients. These data could be used to monitor the spread of drug-resistant HIV for both epidemiological and prevention purposes and, in some cases, to recommend a more widespread use of resistance testing.

The value of genotype and phenotype testing is more evident in the diagnosis of resistance in treatment-experienced patients and in the development of strategies for treatment failure. Up to now, the most reliable method of determining drug resistance and treatment and virologic failure

is testing viral load. An increase in viral load from below the level of detection may be an indicator of the onset of viral resistance and drug failure. One possible use for the phenotype and genotype assays is to catch the development of resistance early so that a change in treatment can be made before a complex pattern of resistance evolves. In fact, there is some evidence to suggest that a virus that shows early evidence of resistance to one protease inhibitor may still be sensitive to other PIs if a switch is made quickly enough. This would prevent the development of cross-resistance within a class. If this is proven to be true, then genotype and phenotype testing will have an important role in monitoring the efficacy of treatment.

The use of genotype and phenotype testing in designing salvage-therapy regimens is clearly the most compelling at this point. Both tests have shown some promise in improving the odds for success in salvage therapy, although the clinical benefit has yet to be definitively demonstrated. A presentation at the Retrovirus conference showed that evaluating failure with genotype and phenotype testing can help make an informed decision without sacrificing treatment options. In this case, the researchers looked at patients failing therapies that included indinavir and two nucleoside analogs. They concluded that the patients failing these regimens had virus more likely to present resistance to the nucleoside analogs than to the protease inhibitor, therefore allowing the change of the ineffective portion of the regimen only. Without resistance testing, the protease inhibitor might have been replaced as well, even though it was still effective.

While both methods need to be further fine-tuned and researched, the ability to use resistance assays to pinpoint which drugs in a failing combination are not working would allow only the problem drugs to be replaced and retain the benefit of any drugs that are still working. This would greatly increase treatment options.

Another example of the use of this new technology was presented at the Retrovirus conference. Baseline resistance testing was used to evaluate virologic response to a salvage protocol using Mega-HAART (more than six antiviral drugs). This study looked at 37 patients failing therapy, with phenotyping available for 24. The results of treating with Mega-HAART were given in terms of response (achieving and sustaining a viral load below 500 copies) and failure (never achieving a viral load below 500 copies).

The correlation between baseline resistance and response or failure was evident. While two out of the ten responders had virus resistant to some protease inhibitors, four out of six failures had viral isolates resistant to all protease inhibitors. Of the ten responders, seven had virus sensitive to three or four protease inhibitors, while only one of the six failures had virus sensitive to three or four protease inhibitors. The aim of this study was to measure the Mega-HAART response by baseline resistance and not the predictive value of genotype testing, but it is clear that such information is relevant in the management of heavily-pretreated patients.

While genotypic analysis points to specific mutation patterns that can be associated with resistance to a drug or combination of drugs, phenotypic analysis can help gauge the degree of resistance. Several studies have found a correlation between phenotypic and genotypic resistance. Perhaps an approach using both methods could provide the best results for predicting success or failure of salvage regimens, especially in heavily-pretreated patients.

Carlos Arboleda coordinates treatment education at GMHC. ACRIA Board member Jill Cadman is a research associate and medical writer at the Bentley-Salick Medical Practice.

Immune-Based Therapies

By Richard Jeffreys

"Immune-based therapy" (IBT) has long been a buzzphrase among HIV researchers. Now that stronger anti-HIV drugs are available, the idea behind IBTs is to improve the function of the immune system. Although there was little new data on IBTs at the Sixth Conference on Retroviruses and Opportunistic Infections, currently available candidates break down into two categories. Non-specific IBTs attempt to improve the immune system's overall health. The best known example is interleukin-2 (IL-2). HIV-Specific IBTs try to improve the immune response to HIV specifically. Therapeutic vaccines like Remune® (HIV-1 immunogen) fall into this category.

Non-specific IBTs

There were many presentations on the cytokine IL-2 in Chicago. Cytokines are a group of chemicals released by immune system cells that carry messages between the cells. When IL-2 is released, it carries a message telling T-cells to copy themselves -- a process known as "proliferation." Researchers have long hoped that giving synthetic versions of IL-2 might increase T-cell counts in people with HIV.

The two major problems with IL-2 are how it is given (by either intravenous or subcutaneous injection) and its severe, flu-like side effects. Several studies at the Retrovirus conference tried different doses, dosing schedules and routes of administration for IL-2.

One research team looked at HAART with or without subcutaneous IL-2 at a dose of 7.5 million units (MU) twice daily for five days every eight weeks. Dose reductions of IL-2 were allowed if side-effects were problematic. The average T-cell count of study participants was 345. The average T-cell count increase was over 400 cells in the HAART + IL-2 group and 60 cells in the HAART-only group. However, since everyone had T-cell counts above 200 to start with, it is not known if the extra T-cells produced due to IL-2 will actually improve long-term health. IL-2 also produced significant side effects. Over half the IL-2 recipients experienced serious toxicities, compared to 16% of the HAART-only group.

Another study found that a lower dose given more regularly may cause less side effects. Three different dose schedules were tried, all given along with HAART: a) continuous intravenous infusion of 12 MU daily for five days every eight weeks (for two cycles) followed by subcutaneous (SC) 7.5 MU twice-daily for five days every eight weeks (for 4 cycles); b) 7.5 MU SC twice-daily for five days every eight weeks (for six cycles); and c) 3 MU SC twice-daily for five days every four weeks (for six cycles). T-cell increases of 600-700 cells were seen in the three groups, but side effects were only half as common in group C compared to groups A and B.

Perhaps the most widely publicized IL-2 presentation in Chicago was a case-control study. This study compared the results of 12 people taking HAART to 14 taking HAART + IL-2. The idea was to see if IL-2 helps eliminate HIV-infected cells that HAART can't get at. HIV-infected cells could be found in all 12 people taking HAART. In contrast, six of the 14 taking HAART + IL2 did not show evidence of HIV-infected cells.

The researchers looked at samples of up to 330 million cells in one of these individuals. It has been previously reported that long-lived memory T-cells may harbor HIV. The researcher presenting this study suggested that IL-2 may reduce the numbers of these HIV-infected memory cells, but couldn't explain how. Test tube studies have shown that IL-2 can interfere with the development of memory T-cells, but whether this explains these results is unknown.

Two of the people in the IL-2 cohort were reported to have stopped treatment, and after three weeks their HIV viral load remains undetectable. It is not yet clear if their immune systems are effectively suppressing any remnants of HIV, or if HIV has indeed been eradicated.

HIV-Specific IBTs

Several presentations focused on the importance of HIV-specific T-cell responses in controlling

HIV replication. However, there were only two poster presentations on immune-based therapies designed to induce new HIV-specific T-cell responses. One poster was a further follow-up on a small 42-person study of HAART given along with a therapeutic vaccine called Remune, which is whole-killed HIV with the outer coat (envelope) stripped off. Removing the envelope means the vaccine induces immune responses to the core proteins of HIV. This may be important for stimulating antiviral immune responses.

The study found evidence of strong HIV-specific memory T-cell responses after just two vaccinations. No such T-cell responses were found in a control group of people taking HAART alone. Study leader Fred Valentine, MD, reported that he has received permission to stop HAART in willing study participants that have received Remune. This will hopefully show if their HIV-specific T-cell responses can control viral replication without any help from the drugs.

The only other HIV-specific IBT presentation used a new type of "naked DNA" vaccine. This vaccine uses bacterial DNA to produce dummy HIV proteins in the body. Unlike Remune, this vaccine uses both envelope and core HIV proteins. There was only a few weeks of follow-up of participants in this study. Most had evidence of some new memory T-cell responses to HIV. It was too soon to tell if these responses were helping their immune systems fight the virus.

Conclusion

Although there was no dramatic new information on IBTs at the Chicago conference, there is little doubt that this research will eventually bear fruit. In his state-of-the-art conference lecture on antiretroviral therapy, Italian expert Stefano Vella noted "it is important that we investigate all potential anti-HIV immune-based approaches." The focus seems to be turning towards the HIV-specific strategies, but there may still be room for combinations of non-specific and specific approaches.

Several studies of IL-2 combined with Remune® are ongoing, for example. A smattering of presentations at the conference did at least show that the immune system can be a potent weapon against HIV. Two individuals from an early David Ho study have now been off HAART for one to two years. Both have viral loads that remain below 500 copies, without any help from the drugs. With this kind of encouragement, the pace of research into immune-based therapies is likely to pick up significantly.

Richard Jeffries oversees the Access Project, a national database of AIDS drug assistance programs at the AIDS Treatment Data Network.

Vertical Transmission

By Dr. Shaffik Essajee

Ever since the results of the ACTG 076 trial were published in 1993, AZT (Retrovir®) has been administered to HIV-infected pregnant women and their infants to reduce the rate of mother-to-child transmission. In the era of HAART, many doctors and scientists are asking whether combination therapies might not prove to be even more effective than AZT alone, but without reliable safety data on protease inhibitor use in pregnancy, some practitioners have been reluctant to advocate HAART for pregnant women.

At the 12th World AIDS Conference last year, a Swiss trial reported that there was a 33% risk of premature birth in pregnant women taking protease inhibitors (PIs), and a small but significant risk of brain hemorrhage in their infants. These findings led to a temporary freeze on all U.S. government-sponsored trials of HAART during pregnancy, but at the recent Sixth Retrovirus

Conference in Chicago, several studies were presented which challenge the findings of the Swiss group.

Presented in Chicago

A large survey of 85 pregnant women across the country who were treated with various protease inhibitors reported a 20% premature birth rate. This is higher than for uninfected women, but the majority of those women who delivered prematurely had other risk factors, such as smoking, twin pregnancy, and previous premature deliveries. There were no significant adverse events in the infants, and, remarkably, no instances of transmission -- although to date, only half of the infants have been adequately evaluated.

Another survey from the University of Southern California reported on 64 women who took HAART during their pregnancies. Some of these women were on non-PI-containing regimens, and the overall risk of premature delivery was only 13%. To date, 47 of these mothers have delivered, and although four infants had birth defects, these defects were associated with other conditions such as Down syndrome or inherited disorders. More than half of the newborns had transient liver abnormalities, but once again there were no cases of HIV transmission.

Interim data from an ongoing French study in which both mothers and babies were treated with AZT and 3TC (Epivir®) were presented by Dr. Sebastian Blanche from the Hospital Necker in Paris. Their analysis of the first 200 women enrolled in the study showed an overall transmission rate of 2.6% compared with 6.5% for mothers and infants taking AZT alone. The combination was well tolerated, but almost 40% of the women developed 3TC-resistant virus after only a month of dual therapy.

A Disturbing Addendum

In a controversial and unexpected addition to their published abstract, Blanche and colleagues also reported the finding that two uninfected infants developed neurodegenerative disorders at four months of life. Both babies died a few months later, and muscle biopsies suggested that their mitochondria (cellular energy-making machinery) had been poisoned. In spite of an exhaustive investigation, no known disorders were identified to explain these two deaths, and they questioned whether this was a side effect of the AZT/3TC combination which the newborns had taken for six weeks. Other researchers cautioned against making such an assumption, pointing out that the same combination has been extensively used in young children and infants without this phenomenon having been observed before.

Overall, despite lingering concerns over the long-term safety of in utero exposure to antiretrovirals, with reported transmission rates consistently below 2%, it seems likely that combination therapy during pregnancy will become the rule rather than the exception. Will we ever be able to eradicate vertical transmission in the U.S.? Dr. Lynn Mofensen from the National Institutes of Health thinks not. Nationwide, about 15% of HIV-infected women receive no prenatal care. Most of these are young, minority women-the same group with the fastest-growing rate of new HIV infections. Without improvements in the delivery of care to these women, transmission rates will remain much higher in this segment of the population.

Furthermore, as the prevalence of multidrug-resistant virus rises in this community, HAART may become less effective at preventing vertical transmission, and those infants that do become infected will be more likely to harbor hard-to-treat resistant viruses themselves. It would certainly be premature to suggest that these potential downsides may outweigh the remarkable benefits of HAART, but one group from North Carolina has already identified a baby who acquired multidrug-resistant virus from his mother and continued to develop more resistance mutations despite aggressive antiviral treatment. Is this a sign of things to come? ACRIA Update will continue to follow this area.

The Role of Caesarean Section

In contrast to the Geneva AIDS Conference, there were few abstracts presented in Chicago that addressed the role of Caesarean section in reducing the rate of vertical transmission. However, the consensus appears to be that elective C-section is undoubtedly beneficial if AZT monotherapy is used as prophylaxis, or if the prenatal viral load is high. In these situations, elective C-section may reduce the transmission rate by more than 50%. However, the efficacy of C-section has not been proven in pregnant women who are well-controlled on HAART. These mothers already have a very low risk of transmission and it is not clear that a C-section would lower the risk further.

Two studies presented data on the complication rates of elective C-section in HIV-infected women. The first, a survey of modes of delivery among 1,112 women enrolled into the Women and Infant Transmission Study, found that women who had C-sections stayed twice as long in the hospital and had three to four times the post-delivery complications than did the women who gave birth vaginally. The second study-of 497 HIV-infected pregnant women with CD4 counts below 500-showed an equally striking difference between surgical and natural childbirth. There were almost four times as many uterine infections in the mothers who had C-sections than in those who did not. If the number of HIV-infected pregnant women having elective C-sections increases, then there is likely to be an increase in the number of post-operative complications. The study authors highlighted the importance of evaluating every patient individually to determine the balance of risk and benefit in each case, rather than performing C-sections on all mothers as a matter of routine.

Many Interventions, Little Access

An HIV-infected pregnant woman in the developed world can access a range of interventions to ensure that her child has a minimal risk of becoming infected. With some exceptions, most developing countries can offer none of these costly measures. In some parts of sub-Saharan Africa, where almost one quarter of all women of child-bearing age are HIV-positive, transmission rates are still in the range of 20-25%.

Research to find alternative therapeutic options in these countries has been slow coming, but Dr. Joseph Saba of the UNAIDS presented preliminary results from PETRA, a large trial of AZT and 3TC to prevent vertical transmission. The placebo-controlled study, which enrolled almost 1,800 pregnant women in South Africa, Tanzania and Uganda, evaluated three different therapeutic options against placebo-AZT/3TC given to mothers and babies from 36 weeks gestation to one week after delivery; AZT/3TC given to mothers and babies from the onset of labor to a week after delivery; and AZT/3TC given only during labor.

The placebo group transmission rate was 17.2% -- no different than that for mothers receiving treatment only during the labor. The most intensive regimen was most effective, producing a transmission rate of 8.6%, but a course of only one week of treatment to mother and child from the onset of labor produced a rate of 10.8% -- a significant 37% reduction in the risk of transmission. The study had previously come under much criticism from consumer advocacy groups that had challenged the rationale for inclusion of a placebo group, arguing that since the benefits of therapy are well established, it was unethical to treat patients with placebos. Dr. Saba pointed out that without a placebo group, it would have been impossible to determine that treatment during labor alone was ineffective.

These transmission results were based on samples taken at six weeks of life, and might not include some of the infants infected after birth by breast feeding. The completed analysis will provide a more accurate measure of the usefulness of this short-course regimen as a relatively cost-effective method of reducing transmission in breastfeeding HIV-positive mothers.

Balancing Research and Ethics

Another study from Thailand using monotherapy with Norvir® (ritonavir) from the 36th week of

pregnancy also reduced the transmission rate to just below 10 percent. However, even the proponents of these short-course regimens concede that, for the most part, they are economically unfeasible in the developing world. Dr. Catherine Wilfert from Duke University addressed the need to test alternative modalities in an appropriate ethical context. She presented the consensus of an international group that was convened to discuss the ethical principles which should govern such research in the developing world. Their guidelines boiled down to four essentials:

- that the treatment should be safe and effective
- that there should be no obligation to provide the highest standard of care which is available anywhere in the world
- that it is acceptable to have a placebo group, provided the therapeutic modality being tested is other than an antiviral
- and that if an intervention is found to be effective, it should be implemented in that country on a wide scale as soon as possible.

Hopefully these guidelines will provide a boost to scientists and governments to investigate viable options such as protective vaccination of exposed newborns, cheaper antivirals, nutritional agents such as vitamin A and methods to cut down the risk of breastfeeding.

Dr. Shaffik Essajee is a pediatrician specializing in infectious diseases. He works in the pediatric HIV/AIDS clinic of Bellevue Hospital.

Intermittent HIV Therapy

By Marshall J. Glesby, MD, Ph.D.

Temporary discontinuation of antiretroviral therapy under the guidance of a health care provider is sometimes necessary due to severe side effects or other quality of life issues. Because viral loads generally rebound rapidly, such discontinuations -- sometimes called "drug holidays" -- are often felt to be a last resort. But could such temporary rebounds in viral load in other settings have beneficial effects?

The impetus to explore the potential utility of intermittent HIV therapy stems from observations made by Dr. Franco Lori and colleagues involving a person now commonly referred to as the "Berlin patient". This 29-year-old man began treatment with ddI (Videx®), hydroxyurea, and Crixivan® within about a month of presumed initial infection with HIV. He suspended therapy on two occasions due to other concurrent infections, and while he had a rebound in viral load after the first treatment interruption, his viral load remained "undetectable" (less than 500 copies/ml) during the second interruption, which lasted 16 days. He stopped treatment completely after 176 days, and his viral load has remained undetectable for over 18 months.

HIV, however, has been found in his lymph nodes and at a low frequency in his circulating T-cells. This patient has had evidence of vigorous immune responses to HIV. Taken together, it is not clear whether the control of HIV replication in this patient is due to one or more of the following factors: his very early treatment after initial infection, the specific antiretroviral regimen used, and/or intermittent therapy. Perhaps intermittent exposure to HIV antigens during dose interruptions could act like a vaccine and stimulate the body's immune response to the virus, enabling the immune system to control viral replication.

At the Chicago conference, Dr. Lori's group reported preliminary findings which hinted that intermittent therapy may be worthy of further exploration. The researchers treated three patients with stable baseline viral loads ranging from about 23,000 to over 700,000 copies/ml with HAART regimens containing hydroxyurea.

Treatment was given for three weeks, followed by a one-week interruption, and then for two cycles of three months of treatment followed by interruption until viral load rebounded to over 5,000 at which time treatment was reintroduced. Viral load fell back to less than 400 each time treatment was re-started. Interestingly, the time to rebound of viral load to over 5,000 increased with each dose interruption. Rebound time lasted an average of seven days during the first interruption and increased to 14 days and 37 days for the second and third. Parallel studies in rhesus monkeys acutely infected with the related simian immunodeficiency virus (SIV) yielded similar results.

These very preliminary results in only a few patients must be interpreted with caution. In no way do they prove that intermittent therapy or drug holidays are beneficial. Randomized, controlled clinical trials to compare continuous with intermittent therapy are needed and are being planned.

HAART-Related Fat Redistribution and Metabolic Complications

By Marshall J. Glesby, MD, Ph.D.

The phenomenon of fat redistribution (lipodystrophy) and metabolic complications of HIV infection or its therapy have received considerable attention in the past 18 months (see ACRIA Update, Summer 1998). Over 30 original research studies on these topics were presented at the recent Sixth Conference on Retroviruses and Opportunistic Infections in Chicago. Although fundamental issues remain unresolved regarding the terminology and classification of the various clinical manifestations, this article will treat fat redistribution, abnormalities of glucose metabolism, lipid abnormalities, and coronary artery disease as separate entities, though they certainly overlap in many people.

Fat Redistribution

The seemingly straightforward question of how frequently fat redistribution occurs has been difficult to answer. The lack of an agreed-upon case definition for diagnosis is a key reason for the discrepancies in reported prevalence of fat redistribution. Many investigators describe fat wasting and fat accumulation as components of fat redistribution which may occur separately or co-exist in some people. Fat wasting (lipodystrophy) generally refers to loss of the fatty layer beneath the skin which may lead to a prominent appearance of veins and a thinning of the arms and legs and hollowed-out appearance of the face. The fat accumulation aspect refers to increased abdominal fat (truncal obesity or adiposity), [buffalo hump](#), and lipomas (fatty tumors beneath the skin).

A large study of the prevalence of body shape changes in persons receiving protease inhibitor therapy was reported at the Retrovirus conference by a group from France. Seventy-eight percent of nearly 500 consecutively evaluated patients had body shape changes, of whom 20% had fat wasting, 16% fat accumulation, and 42% a mix of fat wasting and accumulation. Patients in this study had received protease inhibitor therapy for an average of about 18 months. This high prevalence of fat redistribution was similar to that reported previously by an Australian group led by Dr. Andrew Carr and updated at the conference.

Other researchers described cases of fat redistribution in persons who had never received protease inhibitor therapy, most of whom were receiving d4T (Zerit®) and/or 3TC (Epivir®). These reports, along with others previously published or presented, imply that fat redistribution is not caused exclusively by protease inhibitor therapy, though use of this class of drugs appears to be a significant risk factor.

Several studies focused on potential causal mechanisms of fat redistribution. A leading hypothesis on the mechanism by which protease inhibitors may cause fat redistribution was

published last year in the British medical journal The Lancet by Carr and colleagues. They theorized that protease inhibitors bind to human proteins involved in fat metabolism and inhibit their function, leading to inappropriate deposition of fat in some regions of the body and death of fat cells (fat wasting) in other regions. Investigators from Glaxo Wellcome studied some of the key steps in pathways related to fat metabolism in test tube studies with cell culture systems and found that different protease inhibitors either enhanced or inhibited steps in the pathways. While intriguing, these findings did not definitively support Carr's elegant hypothesis. Further work is clearly needed to sort out the mechanism(s) of fat redistribution.

Despite the lack of understanding of the mechanism of fat redistribution, several potential treatments are under study, and preliminary results were reported at the conference. Drs. Gabriel Torres, Kenneth Unger, and colleagues from New York updated a prior presentation of their series of patients with fat redistribution who have been treated with recombinant human growth hormone (Serostim®). They concluded that growth hormone at 5 or 6 mg/day was effective in reducing truncal obesity and buffalo humps but not peripheral fat wasting. Of note are their observations of a relatively rapid re-accumulation of fat after cessation of growth hormone therapy in one patient and the failure of a lower dose of drug (4 mg/day) in another. ACRIA's study of growth hormone for truncal obesity, led by Dr. Donald Kotler, is fully enrolled and preliminary results are anticipated in the coming months.

Because insulin resistance is felt by some to contribute to or cause fat redistribution, investigators have begun to study the effects of diabetes drugs which combat insulin resistance as possible treatment. French researchers studied the effects of metformin, a drug which improves sensitivity to insulin, in 16 patients with truncal obesity and insulin resistance. Insulin resistance improved and visceral fat -- that is, fat which accumulates internally as opposed to beneath the skin -- was reduced by 38% at 16 weeks in the group receiving metformin compared with controls who had an average increase in visceral fat of ten percent.

Another European group studied troglitazone, an insulin-sensitizing agent, in a pilot study of six diabetic patients on protease inhibitors. While glucose levels decreased in these patients, effects on insulin resistance and fat distribution were mixed. Although no liver toxicity was seen in this small study, troglitazone has been associated with liver failure in HIV-negative diabetic patients, so potential safety concerns remain.

Several studies explored the effects on body composition of changing from a protease inhibitor-containing regimen to a protease inhibitor-sparing regimen. These studies are summarized in [Tim Horn's article](#) on the front page of this issue of ACRIA Update.

Glucose Metabolism

Prior to the Retrovirus Conference, a number of research groups demonstrated an association between protease inhibitor use and insulin resistance. The body's resistance to the actions of insulin may result in elevated blood glucose levels (hyperglycemia), impaired glucose tolerance (often assessed by the body's ability to metabolize ingested glucose in an oral glucose tolerance test) and, in a small subset of patients, the development of diabetes.

Like the data on fat redistribution, there has been some variability in the reported prevalence of hyperglycemia and impaired glucose tolerance in patients on protease inhibitors. Behrens and colleagues reported that 62% of 98 patients on protease inhibitors had impaired glucose tolerance by an oral glucose tolerance test. Preliminary findings from ACRIA's ongoing [glucose tolerance study](#) were reported and notable for the finding of glucose intolerance in four of 16 patients who had not yet started protease inhibitor therapy.

The significance of this result is the implication that some HIV-infected patients may be predisposed to altered glucose metabolism in the absence of protease inhibitor therapy and that

these drugs may not be the sole cause of insulin resistance and hyperglycemia in the HIV-infected patient population. Walli and colleagues also described insulin resistance in about one-quarter of patients on nucleoside analogs but no protease inhibitors compared with 55% of patients on protease inhibitors.

Lipid Abnormalities

Abnormalities in lipid metabolism have been well-documented in HIV-infected patients since the early years of the epidemic. Protease inhibitor therapy appears to exacerbate some of these abnormalities, specifically triglyceride elevations, and often results in elevations in total and LDL cholesterol and reductions in HDL cholesterol. These prior-recognized findings were confirmed by several groups of investigators at the Retrovirus conference.

Unfortunately, there was a paucity of data on the management of lipid abnormalities in these patients. Dr. Keith Henry of Minnesota updated his previously reported treatment data which demonstrated limited effects of a dietary and exercise intervention but clinically significant lowering of cholesterol and triglyceride levels with gemfibrozil and atorvastatin. Many of the so-called "statin" drugs have the potential to interact with protease inhibitors since they are metabolized by the same liver enzymes. Hopefully drug interaction studies and further safety data on mixing these classes of drugs will be forthcoming.

Coronary Artery Disease

One of the main concerns about the metabolic complications and fat redistribution phenomena relates to the theoretical increased risk of accelerated atherosclerosis (hardening of the arteries) which can lead to heart attacks and strokes. A handful of cases of premature coronary artery disease has been previously reported in relatively young HIV-infected persons on PI therapy, many of whom have had co-existing risk factors like cigarette smoking.

In an insightful talk, Dr. Carl Grunfeld of San Francisco discussed the theoretical impact of protease inhibitor-induced lipid abnormalities on the rate of heart attacks based on data from the classic Framingham heart study. In the absence of other risk factors, average protease inhibitor-induced elevations of cholesterol had minimal impact on the risk of heart attack for a 44-year-old man (1.4 additional cases per 100 men over ten years). Throwing in other risk factors such as high blood pressure and smoking, however, significantly increased the impact of the cholesterol elevations in the model. Dr. Grunfeld emphasized the importance of low HDL cholesterol as a risk factor for coronary artery disease.

Three studies examined the rates of heart attacks in patients on protease inhibitors. In one study, the rate of heart attacks was increased by five-fold in the era of protease inhibitors compared to the era prior to their availability; this difference, however, was not statistically significant. A larger study from Kaiser Permanente's database found no increased rate of heart attacks attributable to protease inhibitor use at one year of follow-up. Similarly, an analysis by Merck of their data from clinical trials of Crixivan® (indinavir) found no increased risk of heart attacks in patients receiving this PI compared with controls who did not receive protease inhibitors. Since the rate of heart attacks in these patient populations is relatively low, very large studies with longer follow-up might be needed to demonstrate or refute a higher risk attributable to protease inhibitors. Nonetheless, the data available to date seem to rule out a significant effect of protease inhibitors on risk of coronary artery disease in the relatively short term.

Conclusions

Studies of fat redistribution and metabolic complications presented at the Retrovirus conference have added some pieces to the puzzle but much remains to be solved. Vast ongoing interest in this field of investigation is evidenced by the announcement at the conference of the First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, to be held in San Diego in June, 1999. Hopefully, our limited knowledge base in this area will have greatly expanded by next year's Retrovirus conference.

Marshall Glesby is co-director of the Cornell Clinical Trials Unit and asst. professor of medicine at Cornell University Medical College.

New Drug Update

There were several reports regarding new antivirals at the 6th Conference on Retroviruses and Opportunistic Infections this winter in Chicago, many of which seem to suggest that progress is being made in terms of developing compounds with unique resistance profiles. Some of the most promising drugs in the pre-clinical (test tube and animal) stages of development include two new protease inhibitors from Agouron Pharmaceuticals (AG-1770 and AG-1776) and two new NNRTIs from DuPont Pharma (DMP-961 and DMP-963). New data from clinical trials were studies involving Abbott Laboratories' new protease inhibitor ABT 378 and Trimeris Pharmaceuticals' novel compound [pentafuside \(T-20\)](#).

In the study of ABT-378, data were available on 101 patients who received six months (24 weeks) of the drug at a dose of either 200 or 400 mg twice daily in combination with a low dose of ritonavir (100 or 200 mg twice daily), d4T, and 3TC. After 24 weeks, more than 90% had undetectable viral loads using the first-generation PCR test (<400 copies/mL). Using the ultra-sensitive PCR test, approximately 89% had levels of HIV below the level of detection (<50 copies/mL). As for T-cell counts, the average increase was 160 cells, with several patients experiencing an increase above 200 cells. To date, no patient has discontinued trials of ritonavir. Abbott Laboratories has also reported previously that ABT-378 is active against strains of HIV resistant to currently available protease inhibitors.

New results also come from a study of pentafuside, the first fusion inhibitor to enter clinical trials. The drug -- also known as T-20 -- interferes with the ways in which HIV binds to T-cells, thereby preventing healthy cells from becoming infected with the virus without causing any damage to the cell or the way it functions. But because it is a peptide, the only way it can be administered is by an injection; an oral form of the drug would not be absorbed properly.

For those who do not fear needles, pentafuside is likely to be developed in the future using a form of the drug that will require twice-daily injections. Several doses of the drug were also examined in the study presented. At the time of study entry, the average viral load was 100,000 copies and a T-cell count of 100 cells. Using the highest dose of the drug studied, which would be 50 mg twice daily, patients' viral loads dropped 1.6 logs at first but began to increase once again during the four-week study period. Now that a formulation has been determined, additional studies can be implemented and, hopefully, yield fruitful results.

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

CRIA NEWS

ACRIA Website Begins New HIV Treatment Education Service

With a start-up grant from the Bell Atlantic Foundation, we will now include on our Website summaries of the monthly Community Treatment Forums at St. Vincent's Hospital we co-sponsor with [AIDS Treatment Data Network](#), [Gay Men's Health Crisis](#), and [Treatment Action Group \(TAG\)](#).

For the past seven years, people living with AIDS (PWLAs) and care providers throughout New York City have come to these forums to hear leading experts in research and healthcare present unique perspectives on emerging HIV treatment issues and advances. Now this information will be available to interested individuals worldwide via the Internet. We hope you find this new treatment education resource both interesting and useful.

CRIA Presents at 11th National HIV/AIDS Update Conference

At the [National HIV/AIDS Update Conference](#), ACRIA's Treatment Education Department presented workshops focusing on the barriers to the dissemination of treatment information in affected communities. The Conference, held March 23-26 in San Francisco, informed people involved in HIV/AIDS treatment and care about the latest developments in HIV treatment.

Guide to Lab Results Now Available

ACRIA has published its first topic-specific treatment education brochure for national distribution. Produced with the support of an unrestricted educational grant from Ortho Biotech, the brochure, entitled Understanding Your Lab Results, explains in simple, straightforward language what each laboratory test is used for, so that PWAs can work with their physician to monitor their course of treatment.

CRIA's brochures are already available at AIDS service organizations in major cities in 22 states, and soon will be available on ACRIA's website. To find out which agencies in your community carry the brochure, call Meredith Snow at (212) 924-3934.

CRIA Co-Sponsors Brooklyn Forum

On April 27 from 8:30am to 4pm, in conjunction with Bedford-Stuyvesant/Crown Heights HIV CARE Network and the HIV Center for Women and Children at SUNY Downstate Medical Center, ACRIA will present a day of lectures, workshops and panel discussions on families and HIV. The conference will be held in the main auditorium at the SUNY Downstate Medical Center at 395 Lenox Road in Brooklyn, and requires advance registration. For information, please call 718-270-2301 or 718-270-4736.

Breakfast and lunch will be provided.

Adieu to ACRIA's Medical Director

Marshall Glesby, MD, Ph.D., has resigned as ACRIA's medical director to become director of the Cornell Clinical Trials Unit in Chelsea. We very much appreciate Dr. Glesby's contribution to ACRIA over these past two-and-a-half years. He has been instrumental in conducting an extensive roster of studies which have benefited PLWAs nationwide, and has provided invaluable guidance to our Treatment Education Department staff for their important programs. We will miss Dr. Glesby's regular continued involvement in our agency's important research agenda.

We are actively recruiting a candidate who will aggressively pursue independent protocols of immediate interest to the PLWA community. Our Search Committee has already interviewed candidates who can fulfill the position's essential requirements. Dr. Glesby will remain principal investigator on all ongoing studies until a suitable replacement has been hired.

Good luck, Marshall, in all your future endeavors!

New Staffers Come Aboard at ACRIA

ACRIA is happy to welcome new staff members to help strengthen the administration of our multiple initiatives. Meredith Snow has joined ACRIA's Treatment Education Department. Mark Condon will work with our research staff and Institutional Review Board. And last but not least, Joe Schaller will assist in the Administration/Finance department.

CRIA Welcomes New Board Member

Tiffany Dubin, head of Sotheby's fashion department, was elected to ACRIA's Board of Directors on March 17, 1999. Ms. Dubin has been a strong advocate for ACRIA's HIV research and treatment education mission. Most recently, she ensured that items from prominent ACRIA donors could be included in a major auction of handbags and fashion accessories with the goal of supporting our Capital Campaign. This event raised over \$40,000 in much-needed funds to help pay for constructing our new clinic. ACRIA's Board, staff and clients look forward to Ms. Dubin's increased involvement in promoting the agency's critical programs during the coming years.

CRIA TRIALS

Weekly Procrit® for Anemia

Procrit is a synthetic form of a natural hormone (erythropoietin) involved in red blood cell production which is approved for treatment of anemia in HIV-infected persons on AZT who have low blood levels of the hormone. This 16-week study will look at whether weekly injections of Procrit can improve quality of life and effectively treat anemia in HIV-infected persons receiving antiretroviral therapy. To be eligible, you must have a hemoglobin of 11 g/dL or below, a low erythropoietin level, and be on stable antiretroviral therapy for at least 4 weeks. Study visits are weekly and participants will be reimbursed \$15 at the week 2, 4, 8, 12 and 16 visits.

Ultrase® for Diarrhea

ACRIA is participating in a study of Ultrase (pancreatic enzymes) for diarrhea due to the protease inhibitor nelfinavir (Viracept®). The 12-week study, which is being conducted along with CRI New England and CRI South Florida, is open to HIV-infected persons who have been taking nelfinavir at a dose of 1250 mg twice a day for at least two weeks and who have three or more stools per day not due to any other cause. Participants will be reimbursed \$20 per visit after enrollment.

Protease Inhibitor and Blood Sugar Study

ACRIA 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

ACRIA 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 Mark Condon at 212-924-3934.

Testosterone and MET-Rx™

ACRIA 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.

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

Editor's Notes

- All material in ACRIA Update is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one's personal treatment and therapy choices should be made in consultation with a physician.
 - From this issue forward, ACRIA Update will refer to all drugs by both their commercial and scientific names upon their first reference in an article. Thereafter in the article, they will be referred to by the name by which we feel they are most commonly known, either commercial or scientific.
-

Acknowledging our Friends...

Generous Contributors

The following persons, corporations and organizations made major donations between December 16, 1998 and March 15, 1999 to support ACRIA's search for effective AIDS treatments:

Agouron Pharmaceuticals, Inc.	Michael Goff	Terrence Riley
Bell Atlantic Foundation	Agnes Gund and Daniel	Khalil Rizk
Broadway Cares/Equity Fights AIDS Inc.	Shapiro	RLS Project Management LTD
Caribou Club, Ltd.	H. van Ameringen Foundation	Roche Laboratories
Charles Klein Design, Inc.	Mr. Fredric Hanson	Royal S. Marks Foundation Fund
Bob Colacello	Heinz Family Foundation	Roger E. Schechter
Conde Nast Publications	Carolina & Reinaldo Herrera	Jeffrey B. Soref
Cowles Charitable Trust	Isidore Stern Foundation	Sotheby's
Randall G. Drain	Robert A. Landau	Polo-Ralph Lauren
DuPont Pharmaceuticals	Mr. and Mrs. Ronald S. Lauder	J Daniel Stricker
Mr. and Mrs. Jose Fanjul	Saul H. Magram	Studio 19 Salon & Spa
Gagosian Gallery Inc.	Merck Company Foundation	Richard S. Swenson
Mr. Stephane Gerson & Ms. Alison B. Gerson	Phillip B. Miller and Edward P. Dullea	Telebeam
Dana C. Giacchetto	Steven Neckman	Traditional Home
The Howard Gilman Foundation	Ortho Biotech	United Way NYC
Gilman Family Foundation	Pfizer, Inc.	Diane von Furstenberg
Glaxo Wellcome	Philip Morris Companies, Inc.	Yves Saint Laurent America
	Isabel Rattazzi	

Thoughtful donations in memory of the following people remind us of what is at stake in the fight against AIDS:

Barry Binkowitz, MD · Jon Greenberg · Edward Hansen · Timothy Layton · Peter Surbeck · Joseph P. Wells

Contributions in support of ACRIA's vital research initiatives were made in honor of the following individuals:

Ellen Alpert · Ross Bleckner · Douglas Dietrich, MD · Adam Lippes · Brian Smith · J Daniel Stricker

CRIA UPDATE
Medical Director
Jerome A. Ernst, MD

Executive Director
J Daniel Stricker

Editor in Chief
J Daniel Stricker

Managing Editor
David L. Pieribone

Guest Editor
Pamela Miles

Production Editor
Timothy Murphy

CRIA Board of Directors

Ross Bleckner, President
Donald Kotler, MD, Vice
President

Carlos J. Sandoval, Esq.,
Secretary
Charles Franchino, DC,
Treasurer

Jill A. Cadman
Marisa Cardinale
Bob Colacello

Douglas Dieterich, MD
Tiffany Dubin

Michael Goff

Reinaldo Herrera

Brian L. Heyman

Judith Rabkin, PhD, MPH

George N. Stathakis

In Memoriam

Kiki Mason
David Seidner

CRIA is an independent, non-profit, community-based AIDS research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. ACRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of ACRIA Update are available free to agencies that provide services to people living with HIV/AIDS. For more information call Meredith Snow at 212-924-3934.

Copyright © 1999 ACRIA
230 W. 38th St., 17th Floor
New York, NY 10018
Phone: (212) 924-3934
FAX: (212) 924-3936