The 11th Conference on Retroviruses and Opportunistic Infections February 8-11, 2004

Featuring coverage by:

Cal Cohen, M.D., M.S.  Edwin DeJesus, M.D.  Keith Henry, M.D.

Mark Holodniy, M.D., F.A.C.P., C.I.C.  Andrew Pavia, M.D.  Gerald Pierone, Jr., M.D.

Paul Sax, M.D.  Corklin Steinhart, M.D., Ph.D.  Pablo Tebas M.D.

David Wohl M.D.  Ben Young, M.D., Ph.D.

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- Metabolic Complications
- New Antiretroviral Agents
- Side Effects of Antiretroviral Therapy
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The Body Pro
Body Health Resources Corporation
250 West 57 Street
New York, NY 10107-0622
Fax: 212-541-4911

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**Dear Reader,**

We are pleased to provide this abridged version of The Body Pro’s coverage of The 11th Conference on Retroviruses and Opportunistic Infections. Body Health Resources Corporation, which manages The Body Pro, has been providing next-day coverage on the Internet since 1996; from day one, our coverage has been authored by nationally respected HIV specialists and clinicians.

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ABOUT THE AUTHORS

Calvin “Cal” J. Cohen, M.D., M.S.

Dr. Cohen is the research director of the Community Research Initiative of New England and teaches at Harvard Medical School in Boston. In addition, he works as a HIV clinical management consultant and internist at Harvard Pilgrim Health Care, and is affiliated with Harvard Vanguard Medical Associates.

Support for Dr. Cohen’s research and speaking/lecture opportunities has been provided by Abbott Laboratories, Agouron Pharmaceuticals, Inc., Bristol-Myers Squibb Immunology, Chiron Corp., Gilead Sciences, GlaxoSmithKline, Merck & Co., Inc., Pfizer, Roche Labs, Roxane Laboratories and Serono Laboratories, Inc.

Edwin DeJesus, M.D.

Dr. DeJesus is the medical director of Infectious Diseases Consultants Research Initiatives in Florida; in addition to treating HIV and hepatitis patients, he serves as the firm’s principal investigator for several clinical trials. He is also a consultant for the Florida Department of Corrections, where he participated in the prototype HIV Prison Unit currently operating in central Florida.

Dr. DeJesus has served as a consultant to many pharmaceutical companies, including Abbott Laboratories, Agouron Pharmaceuticals, Inc., Bristol-Myers Squibb, GlaxoSmithKline and Merck & Co.

Keith Henry, M.D.

Dr. Henry is Associate Professor of Medicine at the University of Minnesota School of Medicine and Director of HIV Clinical Research at Hennepin County Medical Center in Minneapolis. In addition, he is Medical Director of the AIDS Unit and the Sexually Transmitted Disease Clinic of the St. Paul Department of Public Health.

Dr. Henry receives research support from Boehringer-Ingelheim (BI), Roche, Serono, Bristol-Myers Squibb Immunology (BMS), GlaxoSmithKline (GSK) and Agouron. He is the member of the speaker’s bureau of BI, Roche, BMS, GSK, Gilead Sciences, Agouron and on the advisory boards of Roche, Gilead Sciences, GSK and BMS.

Mark Holodniy, M.D., F.A.C.P., C.I.C.

Dr. Holodniy is Associate Professor of Medicine at Stanford University and Director of the HIV Clinical Program and AIDS Research Center at Veterans Affairs Medical Center in Palo Alto, Calif. He is a fellow of the American College of Physicians and a member of several professional societies, including the International AIDS Society.

Visible Genetics Inc., Bayer Diagnostics, Merck & Co. and HollisEden Pharmaceuticals provide grant support for Dr. Holodniy’s research.

Andrew T. Pavia, M.D.

Dr. Pavia is Chief of Pediatric Infectious Diseases and a Professor of Pediatrics and Medicine at the University of Utah. In 1989 he helped to found the university’s AIDS clinic.

In addition to caring for patients with HIV, he is involved in research on the development of new agents and new strategies for HIV treatment. His other research interests include HIV in children and pregnant women, and the epidemiology of food-borne diseases.

Dr. Pavia receives support for his research from Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences and Roche Laboratories.

Gerald Pierone Jr., M.D.

Dr. Pierone Jr., is Founder and Executive Director of the AIDS Research and Treatment Center of the Treasure Coast in Fort Pierce, Fla., a nonprofit medical clinic with more than 450 HIV-positive patients. He also maintains a private HIV medical practice in Vero Beach, Fla.

Dr. Pierone’s HIV/AIDS research is, or has been, funded by Abbott Laboratories, Agouron Pharmaceuticals, Inc., Barton &

Paul E. Sax, M.D.
Dr. Sax is the clinical director of the HIV Program at Brigham and Women’s Hospital in Boston and the principal investigator in its AIDS Clinical Trial Unit. He is also an Assistant Professor of Medicine at Harvard Medical School, where he has taught for more than nine years, and the Research Notes Editor for AIDS Clinical Care.

Dr. Sax’s dedication and years of service earned him the Edward H. Kass Award in Clinical Excellence in 1993 and the Harvard-Longwood Infectious Disease Fellowship Award in Clinical Teaching in 1997.

Funding for Dr. Sax’s research has been provided by Abbott Laboratories, Agouron Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, NeurogesX, Inc. and Tibotec BVBA. He has also served on the advisory boards and speakers’ bureaus of Gilead, Glaxo, Johnson & Johnson, Merck & Co., Ortho Biotech Products, L.P., Serono Laboratories, Inc., Tibotec, URRMA Biopharma, Inc., Virco and ViroLogic, Inc.

Corklin R. Steinhart, M.D., Ph.D.
Dr. Steinhart is the Medical Director of the Florida/Caribbean AIDS Education and Training Centers and is an Assistant Professor of Medicine at the University of South Florida College of Medicine. He has been in private practice caring for HIV-infected persons since 1989 and has been a principal investigator in many clinical trials of new HIV therapies.

Dr. Steinhart’s research is, or has been, funded by Boehringer Ingelheim, Bristol-Myers Squibb Company, Gilead Sciences, Inc., GlaxoSmithKline, NeurogesX, Inc. and Tibotec BVBA. He has also served on the advisory boards and speakers’ bureaus of Gilead, Glaxo, Johnson & Johnson, Merck & Co., Ortho Biotech Products, L.P., Serono Laboratories, Inc., Tibotec, URRMA Biopharma, Inc., Virco and ViroLogic, Inc.

Pablo Tebas, M.D.
Dr. Tebas is an Associate Professor of Medicine at University of Pennsylvania School of Medicine and principal investigator in the AIDS Clinical Trial Unit at University of Pennsylvania.

In addition to being the primary care provider for more than 100 patients living with HIV, Dr. Tebas is involved in clinical trials evaluating new therapies for HIV infection. His research interests include antiretroviral therapy, treatment of virologic failures, simplification strategies as well studying the metabolic complications associated with antiretroviral treatment.

Support for Dr. Tebas’ research has been provided by Abbott Laboratories, Agouron Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck & Co., the National Institutes of Health, Pfizer and Roche Laboratories.

David Wohl, M.D.
Dr. Wohl is an assistant professor of medicine at the University of North Carolina at Chapel Hill, and co-directs HIV services for the North Carolina Department of Corrections. Dr. Wohl is an investigator in the NIAID-sponsored AIDS Clinical Trials Group (ACTG) and a member of the ACTG Complications of HIV Disease Research Agenda Committee. His research focuses on metabolic and infectious complications of HIV and its therapies, as well as issues related to medication adherence and access to care—particularly among incarcerated inmates with HIV infection.

Dr. Wohl’s research has appeared in a half-dozen peer-reviewed journals and several clinical texts. He has taken part in several major HIV conferences, including the 2001 meeting of the International AIDS Society—U.S.A. and the recently completed International AIDS Conference in Barcelona, where he co-authored a study on risk behaviors among HIV-positive former prisoners.

Dr. Wohl has participated in the speaker’s bureaus of GlaxoSmithKline, Gilead Sciences, Merck and Abbott Laboratories. He has received funding for
his research from Roche Pharmaceuticals and the U.S. National Institutes of Health.

Benjamin Young, M.D., Ph.D.

Dr. Young is Attending Physician at the Rose Medical Center in Denver, Colo. and a clinical instructor in the Department of Medicine at the University of Colorado Health Sciences Center.

Dr. Young is currently serving as an investigator in several clinical trial initiatives, including the HIV Outpatient Study of the Centers for Disease Control and Prevention and the NIAID/NIH's Adult AIDS Clinical Trials Group. He is a member of the American College of Physicians and the Infectious Disease Society of America.

The author of numerous journal articles, reviews and abstracts relating to HIV and its treatment, Dr. Young has most recently received attention for his work on the clinical symptoms of fat redistribution in the HIV Outpatient Study. His findings have been presented at many major AIDS conferences.
Structured Treatment Interruption Overview

STI Background

Strategic or structured treatment interruptions (STIs) are one of the most controversial and interesting topics in HIV medicine. And, whether we like it or not, patients will continue to ask for them even if the data regarding them is unclear. With the life span of someone living with HIV expected to be measured in decades, it is clear that even with once-a-day medications, patients can experience burnout. However, patient burnout is only one of a multitude of reasons for an STI. In order to properly discuss this subject, it helps to differentiate between the general types of STIs. Once the kind of STI is clearly described, the data that support or refute the stratagem may be considered. For the sake of this CME, I have separated STI into the following categories, which I’ll discuss at length later:

1. STI for the evaluation of possible HIV-related side effects.
2. STI on a fixed schedule to purposefully allow cycles of HIV replication and stimulate a heightened immune response against HIV—known as "auto-immunization" or "autovaccination."
3. STI on a fixed schedule (long or short) in order to reduce a patient’s exposure to antiretroviral agents. This will actually be renamed SIT, or structured intermittent therapy, in the discussion.
4. STI on a variable schedule with CD4-count-driven treatment in order to reduce a patient’s exposure to antiretroviral agents.
5. STI in a salvage setting to produce reversion to wild-type virus and enhance the patient’s response to subsequent antiretroviral treatment.
6. STI because of treatment fatigue. This would actually best be described as an unstructured treatment interruption. Many patients facing a lifetime of taking medications may experience treatment burnout and stop medications on their own.

STI for Management of Possible Antiretroviral-Related Toxicity

Many clinicians would not consider this to be an STI. Instead, it would be considered a temporary treatment interruption undertaken with the intention to determine if a patient’s symptoms are related to HIV medications. Some medication-related side effects have an insidious onset and may be quite nonspecific. The only way to determine if troublesome symptoms are
related to an antiretroviral cocktail is to interrupt therapy and see if the symptoms recede or resolve. If a question remains about the relationship between symptoms and medication, some clinicians conduct a re-challenge with the same regimen to see if the symptoms recur (however, an abacavir [ABC, Ziagen] re-challenge is strictly proscribed because of the possibility of hypersensitivity).

The prompt resolution of a patient’s symptoms during this kind of treatment interruption will typically lead to the selection of an alternate medication for the most likely offending agent. Often it’s quite clear which drug is causing all the problems based on the known side effect profiles of certain agents (i.e., nausea from zidovudine [ZDV, Retrovir] or diarrhea from nelfinavir [NFV, Viracept]). On the other hand, if a patient’s symptoms remain unchanged off therapy, then another explanation for these symptoms can be pursued and the identical regimen resumed.

However, it may not be necessary to interrupt treatment in cases of probable medication toxicity. When one agent is highly likely to be causing symptoms (i.e., neuropathy from stavudine [d4T, Zerit]), a single agent switch with continuation of the other medications in the combination, may be the most appropriate course of action.

One of the more common HIV management errors is to continue antiretroviral therapy in the face of medication-related side effects affecting a patient’s quality of life. Given the expansion of treatment options in recent years, there are few patients who must stay on a prescribed treatment course that is causing them distress.

**STI in Acute Infection (Autoimmunization)**

An early pilot study, and one of the most successful in this category, was published in Nature in 2000 by Dr. Eric Rosenberg from Massachusetts General Hospital. It suggested the potential usefulness of an STI with patients experiencing acute HIV infection. In this study, there was evidence of increased virus-specific cytotoxic T lymphocytes and maintained T-helper-cell responses in patients who had one or two STIs after they were treated for acute infection. In this cohort, there also was a suggestion that patients were more likely to maintain lower viral load levels (below 5,000 copies/mL) off therapy and manifested a slower viral rebound after the second STI.

A study with the acronym PRIMSTOP was designed to examine the role of STI in primary HIV infection utilizing hydroxyurea as part of the HAART regimen. In this trial, the combination of nelfinavir, stavudine, didanosine (ddI, Videx) and hydroxyurea was given to 29 patients with primary HIV infection. After 32 weeks of continuous treatment, a series of three STIs of two, four and eight weeks (all separated by 12 weeks) was performed. HAART was stopped 12 weeks after the last STI and patients were followed for an additional 24 weeks. Overall, three patients were lost to follow up, three developed genotypic resistance to nelfinavir, and 52% had hydroxyurea discontinued due to side effects. At the 24-week endpoint, 7/26 patients (27%) had a viral load less than 1,000 copies/mL and one patient had a viral load less than 50 copies/mL. This study suggests that there may be limited benefit in early treatment of primary HIV infection with STI strategy.

Other studies of STI in acute HIV infection have not demonstrated consistent immunologic benefit. These studies utilized different treatment schemes. In one cohort treatment often was begun after seroconversion and in another a therapeutic vaccine was administered in conjunction with one treatment interruption. Significant immune control was not observed in these trials.

Recent reports have shown that even
when favorable short-term outcomes were observed, virologic control eroded with longer-term follow up. In February 2004, at CROI, Bruce Walker presented data from his original Massachusetts General cohort with greater than five-year follow up. There was evidence of immune escape and rising viral loads despite previously well-controlled viremia and only one out of 14 of the patients in the study maintained a viral load below 5,000 copies/mL. Unfortunately, no randomized and controlled trials of STI in primary HIV infection are yet available.

**STI in Chronic Infection (Autoimmunization)**

The great majority of HIV-infected individuals are diagnosed beyond the window of acute infection, so studies of "autoimmunization" in chronic infection have more pragmatic implications. The landmark study that provided a number of important distinctions regarding STIs was the Swiss-Spanish-Intermittent-Treatment-Trial (SSITT). This study included 133 subjects with chronic HIV infection who received antiretroviral treatment on a schedule of eight weeks on therapy, followed by two weeks off. Although there was evidence of an expanded CD8+ lymphocyte response to HIV antigens as a result of the interruptions, this was not associated with viral load reductions. In fact, subjects with higher numbers of HIV-specific CD8+ lymphocytes had higher viral load increases during their interruptions. It is quite possible that during the STI and viral rebound, the destruction of CD4 cells by viral growth was the dominant effect, which overwhelmed any beneficial immune response. As expected, during treatment interruptions, CD4 counts fell. The negative results of this large, carefully performed study, makes a strong case against the "autoimmunization" theory of STI in chronic HIV infection.

Of course, a concern with any STI is the risk of developing viral resistance. However, one of the important findings from the SSITT study was that the risk of developing drug-resistant virus was quite low. In over 500 treatment interruptions, drug-resistant virus developed in only two cases. This low rate of development of viral resistance may largely have been a result of the relatively short two week time period off treatment. Other studies with longer treatment interruption times have been complicated by higher rates of viral resistance.

Another significant finding from a sub-study of the SSITT study was that 14 of the subjects in the study had frequent blood sampling during the 14-day STI in order to determine the tempo and trajectory of viral rebound with the interruption. Viral load testing was performed during the STI at day 4, 8 and 14. There was minimal evidence of viral rebound seen at day 4, with less than 10% of the viral load test results greater than 100 copies/mL. However, by day 8 almost half of the subjects had viral loads above 100 copies/mL and by day 14 all but two subjects consistently had viral loads greater than 100 copies/mL. These data suggest that an STI lasting more than a few days will pose a significant risk for the development of viral resistance with repetitive cycles of replication. In fact, eight of 14 patients in this sub-study were found to have minor variants of the m184v mutation. However, the clinical relevance of these minor populations is of uncertain clinical significance. These findings are quite pertinent to the design of structured intermittent therapy studies, and suggests that with current antiretroviral agents, interruptions of greater than several days may be problematic.

**SIT to Reduce HAART Exposure**

The primary focus of structured intermittent therapy (SIT) is to reduce long-term exposure to antiretroviral therapy, thereby lowering a patient's risk for toxicity as well as reducing medication costs. It is
also hoped that with this strategy patients may experience an improved quality of life as a result of a break from the pressure of daily medications and associated treatment fatigue. The main risk of an SIT is the premature development of drug resistance with the attendant compromise of future treatment options because of cross-resistance.

One of the primary educational messages regarding HIV management has been the importance of a patient’s strict adherence to his or her antiretroviral therapy. The link between missed doses and the development of viral resistance has been well established. Although the following SIT data are interesting, this strategy of purposefully skipping doses on a schedule will require careful study in large, randomized trials.

**Long-Cycle SIT**

Dr. Mark Dybul from the U.S. National Institutes of Health reported the results from a study on long-cycle SIT which was designed to compare eight weeks on therapy followed by four weeks off with a control population on continuous therapy. The results were disappointing; an unacceptable rate of viral resistance occurred in the SIT group (three of eight patients receiving efavirenz [EFV, Sustiva, Stocrin] developed resistance) and so the study was terminated prematurely.

Although this long-cycle SIT study was not designed to test for autoimmunization, there was neither evidence of progressive reduction in viral load during the series of interruptions nor enhancement of HIV-specific CD4 cells in the SIT group. Also, there were no significant differences in lipid levels between the SIT and control groups. As a result of this study, enthusiasm for long-cycle SIT has waned, but short-cycle SIT still beckons.

**Short-Cycle SIT**

In fact, it looks as if short cycles of interruption may still have a future. The first short-cycle SIT report was a pilot study, also by Dr. Dybul, of one week on, one week off therapy with ritonavir (RTV, Norvir)-boosted indinavir (IDV, Crixivan)-based therapy in 10 subjects. This strategy was surprisingly successful, with controlled viral levels seen at 52 weeks of follow up. An additional benefit of this approach was the improvement in patients’ cholesterol and triglyceride levels compared to baseline determinations.

Another small study of week on, week off therapy was also reported by Dr. Dybul -- in this case with eight subjects treated with an efavirenz-based regimen. There was no evidence of viral rebound or viral resistance at more than 52 weeks of follow up. In addition, no overall changes were observed in lipid levels. Of course, this may be due to the fact that efavirenz is known to have less of an impact on lipid levels compared to the boosted indinavir in the first trial.

A failed study of week on, week off SIT was the Staccato study. This study was different from prior studies in that it was performed in Thailand and most of the subjects received ritonavir (100 mg) together with 1,600 mg saquinavir (SQV, Invirase, Fortovase) once daily with two NRTIs. More than half of the subjects (19/36) randomized to week on, week off therapy had virologic failure, most within the first 12 weeks, so this study was terminated prematurely. The PI-treated patients with virologic failure had genotypic testing performed and no PI mutations were noted. All patients, except for one, were re-suppressed after resuming continuous therapy with the same regimen.

Of interest, seven of the eight subjects on the efavirenz-based therapy maintained virologic control (mean 19 weeks). The one person failing had a large body mass and a low efavirenz trough level prior to the change to intermittent therapy.

The results of the Staccato study may curb the interest for this investigational
week on, week off strategy (at least for saquinavir-based therapy) for the management of HIV infection. However, as newer, more potent agents with better pharmacokinetics and longer half lives become available, this situation may change.

The first study utilizing a five-day on, two-day off SIT format was recently reported. In this trial from Uganda, 31 subjects were randomized to either a week on, week off regimen, a five-days on, two-days off schedule or continuous therapy. The majority of subjects received an efavirenz-based combination. There were three cases of virologic failure overall, two in the continuous-therapy group and one in the 5/2 group; all virologic failures were related to non-adherence. Additional studies of this nature are underway and the results will determine if a 5/2 strategy has merit.

The 5/2 stratagem is interesting because it fits with a typical work schedule. This may appeal to some patients who would welcome a weekend free from HIV treatment. It also might reduce one of the logistical obstacles to expanding directly observed therapy (DOT) programs. DOT for HIV infection holds some promise to help difficult-to-reach populations who are at high risk for non-adherence. Weekend coverage by medical staff for DOT is problematic; it would be beneficial if DOT could be accomplished within the confines of a standard Monday through Friday work week.

### STI on a Variable Schedule With CD4-Count-Driven Treatment

One of the pressing questions in HIV management is what to do about patients who began therapy with lower CD4 counts, but, following immunologic recovery, have CD4 counts now in the normal range. Are these patients obligated to continue lifelong therapy or is it reasonable for them to stop at some point? An additional group to consider is the numerous patients who began antiretroviral therapy when the U.S. government treatment guidelines recommended therapy at higher CD4-count thresholds. Is it safe and advisable to discontinue treatment in these cases?

One of the proposed strategies to deal with this thorny issue is CD4-count-driven therapy. The notion is to start or resume antiretroviral therapy when a patient’s CD4 count falls below a critical threshold and then to interrupt therapy when the patient’s CD4 count rises above a specified point. Depending on the CD4-count parameters selected for starting and stopping therapy, this strategy usually translates into relatively long periods of time off therapy, often months to years.

### BASTA Study

One such trial, BASTA (meaning “stop” or “enough” in Italian), has helped clarify this issue. This is an ongoing, prospective, randomized and controlled trial that originally enrolled subjects with CD4 counts more than 800 cells/mm$^3$ and plasma HIV-RNA less than 50 copies/mL on HAART. Subjects were randomly assigned (2:1) to either interrupt HAART or continue continuous therapy. In the STI arm, the goal was to maintain a CD4 count of greater than 400 cells/mm$^3$. The primary endpoint of the study was the proportion of patients whose CD4 count remained above 400 cells/mm$^3$. Secondary endpoints included predictors of time off therapy, metabolic changes, tolerability, costs and virologic resistance. There were 114 patients enrolled in the study (76 STI, 38 control). After a mean of 18 months of follow up, 21% of the STI group restarted therapy because their CD4 counts fell below 400 cells/mm$^3$. The nadir CD4 count was the only predictor of the need to resume therapy; those with a nadir below 200 CD4 cells/mm$^3$ restarted within 10 months.
BASTA is a proof of concept for CD4-count-driven therapy. Results show that HAART may safely be discontinued in patients with more than 800 CD4 cells/mm³ who show no evidence of the development of virologic resistance. There is a caveat though: Those with nadir CD4 counts below 200 cells/mm³ will likely have to resume sooner rather than later.

SMART Study

Another variable-schedule STI study underway and still enrolling is the "Strategies of Management of Antiretroviral Therapy" (SMART) study. This large CPCRA-sponsored trial is planning to enroll 6,000 subjects and is scheduled to run for nine years. The intention is to compare the maintenance of viral suppression on continuous antiretroviral therapy versus on a CD4-driven STI strategy. Subjects with greater than 350 CD4 cells/mm³ are eligible for enrollment. The study design calls for treatment to be stopped in the STI group and then resumed when CD4 counts dip below 250 cells/mm³. The viral suppression group will be treated with HAART for the duration of the study with the goal to maintain an undetectable viral load. A number of sub-studies in SMART are planned; a partial list includes an evaluation of cardiovascular complications, risk of HIV transmission and neurologic complications.

STI for Multidrug-Resistant Patients to Promote Reversion to "Wild Type" and Improve Virologic Response

Some patients with multidrug-resistant virus have limited or no treatment options. An STI may lead to partial or complete reversion to wild-type virus over the course of weeks or months. The hope is that by allowing this to occur, such patients may have a better response to salvage therapy, even though they have had prior documented virologic resistance to the regimen.

The French GIGAHAART Study suggested that a pre-salvage STI approach had potential merit. This randomized trial with 68 participants looked at patients who had drug-resistant virus and median CD4 counts of 27 cells/mm³. Those who received an eight-week STI prior to restarting an aggressive salvage regimen (with a mean of 7.3 drugs) had a significantly better response to therapy. Patients in the STI group experienced a mean viral load reduction of 1.91 log copies/mL compared to an only 0.37 log copies/mL reduction in the control group of patients who were switched straight off to the salvage regimen.

The much larger CPCRA trial 064 (270 vs. 68 participants) came to a different conclusion. However, the design of this trial was different in a number of ways. Although the subjects had multidrug-resistant virus, their median CD4 count of 144 cells/mm³ was substantially higher than that of the GIGAHAART study. In addition, the STI duration was longer at 16 weeks and the salvage regimen contained fewer medications (mean 3.6). The results were divergent as well; there were no differences in the viral load changes between the STI and immediate therapy groups at 12 weeks of follow up. This study was terminated prematurely due to a higher rate of adverse clinical outcomes in the STI group. There was the same number of deaths in both groups (eight each), but higher rates of opportunistic infections in the STI group. Presumably, the higher rate of infections in the STI group was related to the considerable decline in CD4 counts during the 16-week STI. We still don't understand the underlying reasons for the disparate results of GIGAHAART and CPCRA 064. The differences may be due to the shorter...
time off of therapy in the GIGAHAART study or its more aggressive regimen.

More pre-salvage STI studies are underway or in the planning phase in order to better understand the dynamics of viral rebound and resistance and to clarify the differing results of prior studies. However, based on the negative results of CPCRA 064, this strategy is not recommended outside of research trials unless individual patient considerations require a temporary treatment interruption.

**Treatment Fatigue -- Unstructured Treatment Interruption**

Although the topic of this CME is STI, it must be recognized that in the real world of HIV clinical care, patients are interrupting therapy on their own. These patient-mediated interruptions occur despite strenuous efforts by HIV-treating clinicians to encourage their patients to have a high level of adherence to continuous antiretroviral therapy. Many of these interruptions also happen without the medical team's knowledge and are first recognized when viral breakthrough is noted on a routine follow up of blood testing.

One of the least appreciated factors in patient-driven treatment discontinuation is the influence of medication-related side effects. Although antiretroviral therapy has improved significantly in the last several years, drug-related toxicity is still common. Even in the absence of a definite relationship between symptoms and a medication, some patients will discontinue therapy because of a perceived association. In fact, it may simply be a media report about a newly discovered problem with an antiretroviral agent that will trigger someone to stop therapy.

There are economic factors that also influence treatment interruptions. Even individuals with private health insurance are impacted by financial considerations in HIV treatment. There are considerable costs related to medication co-pays and deductible and non-covered medical fees. There are also travel expenses and time lost from work that have an adverse financial impact. For other patients who access care through the public systems, there are costs involved as well in negotiating the system and sustaining benefits.

Psychological issues also have a dramatic impact on the decision by individuals to remain on or discontinue therapy. Many people with HIV are overwhelmed by the challenges of accessing healthcare, keeping up with doctor visits, blood testing and the necessity to take medications on a daily basis.

Moreover, the warning that viral resistance will be the penalty for missing doses is a major deterrent for those patients that question their ability to stick with a program. As a result of these concerns, some patients simply opt out of treatment for a while in order to take a break from the responsibilities that are required to participate in treatment. These patients are not necessarily nonadherent, in fact some of them never miss a dose of medications while "on treatment." After a period of time off medication in which they have had a chance to enjoy a less regimented life, they are ready to marshal their personal and emotional resources and resume treatment.

**General Precautions With STIs**

There are additional considerations and precautions for STI use in clinical practice and research studies.

**HBV Coinfection**

One important issue is hepatitis B (HBV) coinfection, which occurs in 5 to 10% of patients with HIV infection, depending on the population considered. Several commonly used antiretroviral medications have potent activity against HBV. These include lamivudine (3TC, Epivir), emtricitabine (FTC, Emtriva) and tenofovir (TDF, Viread). Many clinicians select
therapy for coinfected patients with the intention to treat HBV infection as well as HIV. Data are limited, but in one small sub-study the combination of lamivudine and tenofovir in HBV coinfected patients led to an average 4.7 log decline in HBV DNA at 48-weeks follow up.\(^\text{17}\)

The concern is that if a patient coinfected with HBV goes on an STI there will be a spike in HBV replication shortly after treatment is withdrawn. There have been cases of acute hepatitis, even fatal, after the discontinuation of lamivudine in coinfected patients.\(^\text{18}\) Thus, there should be careful consideration of STI in coinfected patients because of the potential for a flare up of HBV upon withdrawal of lamivudine, emtricitabine or tenofovir.

**Increased Risk of Sexual Transmission of HIV**

The public health ramifications represent another dimension that must be considered in the study of STIs. HIV-RNA levels are one of the strongest predictors of the rate of sexual transmission of HIV infection.\(^\text{19, 20}\) Therefore, the risk of HIV transmission would likely be enhanced during an STI, based on increased viral load levels in plasma and genital secretions.

**Conclusion**

Clearly the toxicities of antiretroviral therapy will be the driving desire behind continuing research into STI. But in addition to the potential for life-threatening toxicity from antiretroviral therapy, there are also the financial costs, especially apparent in underdeveloped parts of the world where treatment is not available, even with substantial price reductions.

This past summer at the International AIDS Society conference, Dr. Bernard Hirschel presented this theoretical model to gauge the financial impact of antiretroviral therapy on a modern industrialized country versus a developing country.\(^\text{21}\)

Since a country typically spends about 10% of its Gross National Product (GNP) on total health expenditures, 6.6% for antiretroviral therapy alone is not within the realm of possibility based on historical precedent.

If antiretroviral costs could be reduced further through a SIT program, this would allow more patients to be treated in locales with limited financial resources. This in not only the case in underdeveloped countries; currently in the United States there are financial shortfalls in state Medicaid and ADAP programs and some patients on waiting lists do not have access to medications.

If proven effective, SIT would offer the prospect for reduced antiretroviral toxicity and expansion of treatment slots in financially-challenged regions of the world.

**Take-Home**

In general, STI or SIT should still be considered experimental and not be performed in clinical practice. One exception would include patients who began antiretroviral therapy when treatment was recommended at higher CD4 count cut-offs. These patients may safely discontinue therapy and restart based on contemporary guidelines.

Another group of patients who may consider an STI outside of a trial are those

<table>
<thead>
<tr>
<th></th>
<th>Switzerland</th>
<th>Zimbabwe</th>
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<tr>
<td>Total Population</td>
<td>7 million</td>
<td>12 million</td>
</tr>
<tr>
<td>HIV-Infected</td>
<td>12,000</td>
<td>1.5 million</td>
</tr>
<tr>
<td>Gross National Product</td>
<td>$245 billion</td>
<td>$6.8 billion</td>
</tr>
<tr>
<td>Antiretroviral Therapy Cost/Year/Patient</td>
<td>$12,000</td>
<td>$300</td>
</tr>
<tr>
<td>Antiretroviral Therapy Cost/Year</td>
<td>$144 million</td>
<td>$450 million</td>
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<tr>
<td>% Gross National Product for Antiretroviral Therapy</td>
<td>0.06</td>
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who have immunologic reserve (based on CD4 counts above 350) and who are experiencing medication-related toxicity. Especially if nadir CD4 counts were not below 200 and pre-treatment viral load levels were not high, these patients may be able to safely stop therapy for an extended period of time. The decision to withdraw treatment in this setting depends on the severity of side effects, presence of viral resistance and availability of antiretroviral options. Based on patterns of antiretroviral use from observational cohorts, it appears that more patients are on treatment interruptions. It is likely that many of these patients off therapy fit into one of these categories with higher CD4 counts and/or medication-related side effects.

Summary Regarding STIs in Other Circumstances

- Recent studies have raised serious doubts about the short- and long-term effectiveness of an STI in acute or chronic infection for autoimmunization.
- Only future studies (the SMART and BASTA trials) will give definitive answers regarding whether SIT holds promise utilizing either a fixed schedule with short course (5/2) treatment or a CD4-count-driven treatment approach.
- The bulk of evidence available up until now does not support STI as pre-salvage approach because of clinical progression that may occur in the more advanced patients that this approach focuses on.

And finally, one of the most passionate arguments for STI still will come from HIV-infected patients, many of whom are worried about the long-term toxicities of antiretroviral therapies, or from others who just need a break from daily treatment adherence. Although we do not yet have clear answers, ongoing studies promise to advance our understanding and define the appropriate place for STI in HIV practice.

References

Structured Treatment Interruption Case Studies

Despite their generally experimental nature, structured treatment interruptions (STIs) are fairly common, and there may be a trend for even more STIs in HIV clinical care in the future. For example, the important Swiss HIV observational cohort...
tracks, among other things, HIV treatment status. In this cohort, 7.6% of patients were on HIV treatment interruption in January 1999. However, as of January 2003, 14.8% were in this category.¹

Some STIs are, in fact, patient initiated, and the clinician learns about the situation after the fact. In other cases, the determination to initiate an STI is a shared decision that is often based on an attempt to mitigate medication-related toxicity. The following four case studies represent a variety of STI scenarios that might be encountered in practice. These case presentations should not be construed as an endorsement of STI, but rather as a reflection of some of the reasons for STI and its potential outcomes.

Case Study 1

A 38-year-old, gay male was diagnosed with HIV infection in April 1996. He presented with AIDS dementia complex and was found to have a CD4 count of 61 cells/mm³ and a viral load of 78,000 copies/mL. He was begun on a combination of stavudine (d4T, Zerit), lamivudine (3TC, Epivir) and indinavir (IDV, Crixivan) and demonstrated an excellent virologic and immunologic response. Two months into therapy, his CD4 count increased to 284 and his plasma HIV-RNA was less than 250 copies/mL. The findings of neurocognitive dysfunction gradually improved, eventually resolving completely after several months.

He remained on the same regimen of stavudine, lamivudine and indinavir until January 2000; his CD4 count was 826 cells/mm³ and his plasma HIV-RNA was less than 250 copies/mL. The findings of neurocognitive dysfunction gradually improved, eventually resolving completely after several months.

In August 2001, his viral load was less than 50 copies/mL, his CD4 count was 725 cells/mm³ and his serum testosterone level was normal. Because of complaints of fatigue and malaise, and after discussion with his clinician, he elected to interrupt antiretroviral therapy. Two weeks after he stopped treatment, he developed a sore throat and headaches. Sinusitis was suspected and he was begun on azithromycin (Zithromax). There appeared to be transient improvement, but four weeks after he stopped treatment, he developed fevers accompanied by cervical lymphadenopathy and worsened fatigue. Despite empiric therapy with levofloxacin (Levaquin) for suspected sinusitis, within several days the headaches worsened and he developed encephalopathy along with a high fever and he was admitted to the hospital.

A brain computed tomography (CT) scan was negative for mass lesion. A lumbar puncture was performed and there were 250 white blood cells, 86% of which were lymphocytes. Cerebrospinal fluid protein was 85 mg/dL and glucose 56 mg/dL. He was treated empirically with ceftriaxone (Rocephin) and corticosteroids. The fluid rapid plasma reagin (RPR) was negative as were the bacterial cultures. A diagnosis of aseptic meningitis was made; ceftriaxone treatment was stopped and corticosteroid treatments were tapered off. His CD4 count was 301 cells/mm³ (21%) and his plasma HIV-RNA was 24,800 copies/mL.

After he was discharged from the hospital, he was started on zidovudine (ZDV, Retrovir) + lamivudine (ZDV+3TC, COM, Combivir) and efavirenz (EFV, Sustiva, Stocrin). He developed a rash from the efavirenz and the regimen was changed to zidovudine + lamivudine + abacavir (ABC, Ziagen) (ZDV+3TC+ABC, Trizivir). He tolerated the therapy well and there was hypertension, which was treated with atenolol (Tenoretic, Tenormin) and enalapril (Vasotec).

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a gradual resolution of the headaches and fatigue. In October 2001, his viral load was again undetectable and his CD4 count had increased to 514 cells/mm$^3$. Subsequently, he experienced viral breakthrough with the development of resistance to zidovudine + lamivudine + abacavir. Currently he is on zidovudine + lamivudine + abacavir and tenofovir (TDF, Viread) and is clinically stable.

**Discussion**

This patient had acute retroviral syndrome or retroviral rebound syndrome, a potential complication of a STI.$^2$ Some patients who discontinue therapy will develop a viral-type syndrome that, on occasion, may be quite severe. In this case, the aseptic meningitis was likely related to recrudescent HIV infection following years of quiescence created by effective HAART. Studies of primary HIV infection have shown that approximately one third of patients present with aseptic meningitis as a component of their illness.$^3$

However, the risk of acute retroviral syndrome during an STI appears to be low, generally less than 5%, depending on which study is referenced. In the BASTA study,$^4$ acute retroviral syndrome occurred in two of the 76 subjects in the STI group with the first STI, but not on subsequent interruptions. In the SSITT study, there were two cases of acute retroviral syndrome among the 133 subjects,$^5$ although the short treatment interruption of only two weeks may have reduced the likelihood of this event. Thus, the overall risk of a retroviral rebound is low, but when it occurs, symptoms may be quite severe.

**Case Study 2**

A 58-year-old, male hemophiliac was diagnosed with HIV infection in 1993. His CD4 count was 350 cells/mm$^3$ and therapy was commenced with zidovudine monotherapy. The course was complicated by anemia and treatment was placed on hold.

In 1996, he was given stavudine, lamivudine and indinavir. Subsequent viral load determinations were below the level of

![Figure 1: Plasma Levels of HIV-RNA in Case Study #2](image-url)

Plasma levels of HIV-RNA were measured using a branched-chain DNA assay with a limit of sensitivity of 500 copies per milliliter. Day 0 was the first day of treatment. Shaded areas indicate periods of no treatment.
detection and his CD4 count improved and ranged around 500 cells/mm³ over the next several years. The course was complicated by the development of painful sensory neuropathy and he was treated with amitriptyline (Elavil, Endep).

Despite the use of amitriptyline, his neuropathy worsened and eventually stavudine was stopped and delavirdine (DLV, Rescriptor) was substituted. The neuropathy continued to be poorly controlled and he was begun on controlled release morphine (Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol, Roxanol 100). Because of this chronic pain and the sedation caused by the pain management narcotics, he retired from work.

He developed progressive abdominal protuberance, post-prandial bloating and weight gain in 2001, which responded to neither diet nor exercise. His viral load was undetectable and his CD4 count was 488 cells/mm³. The decision was made to discontinue his antiretroviral medications. Within several weeks his bloating improved and over the next several months his abdominal protuberance began to recede. His plasma HIV-RNA has remained below the level of detection from 2001 to January 2004 and his CD4 count has fluctuated between 300 and 400 cells/mm³. EIA for HIV and Western Blot testing have been repeatedly positive.

Discussion

This unusual case demonstrates that rare patients treated with HAART are able to maintain virologic control even after antiretroviral therapy is withdrawn. This phenomenon was first described in 1999 with the example of the "Berlin" patient, a patient who had been started on antiretrovirals during acute infection and had therapy temporarily stopped on two occasions. When his therapy was stopped altogether, he maintained long-term viral suppression.

In this present case, our hemophiliac patient was probably not treated during acute HIV infection. In addition, we did not have a baseline viral load prior to initiating antiretroviral therapy since he had been started on HAART in 1993 -- before HIV-RNA testing had become commercially available. It is possible that he may have had a favorable prognosis with low viral load prior to starting antiretroviral therapy, although he did have a fairly low CD4 count and percentage reflecting enough viral activity to lead to immune damage.

As mentioned, the impetus for this patient's treatment interruption was directly related to antiretroviral toxicity, including the severe painful peripheral neuropathy from stavudine that had led to his subsequent early retirement. Gastrointestinal side effects and progressive abdominal protuberance also were responsible for his treatment interruption. Once therapy was stopped, all these symptoms significantly improved. An added and unexpected bonus of this STI has been this patient's prolonged time off therapy with an undetectable viral load and stable immunologic function.

It is unclear why the rare patient with HIV infection is able to maintain long-term virologic control after treatment interruption. This case, also atypical, was presented to highlight the fact that unexpected observations may stimulate investigation into new areas and sometimes lead to a better understanding of disease states. Just as the "Berlin" patient led to research interest into STI for acute HIV infection, study of cases like this may clarify the mechanisms of virologic control with STI after long-term treatment in chronically infected patients. Ongoing STI studies such as "SMART" will provide some answers as to the frequency of virologic control after STI in chronic infection. However, at this point, there is no way of predicting which patient will be able to maintain virologic control after stopping. In the meanwhile,
anecdotal cases like this one continue to tantalize clinicians and sustain interest in STI.

**Case Study 3**

In March 2001, a 25-year-old male was diagnosed with AIDS when he was found to have *pneumocystis carinii* pneumonia. At that time, his CD4 count was 43 and his viral load was 280,000. He commenced a regimen of lopinavir/ritonavir (LPV/r, Kaletra), zidovudine and lamivudine. Over the next two years of therapy, his viral load became undetectable and his CD4 count gradually rose to greater than 500 cells/mm³.

In October 2003, he complained of worsening nausea, anorexia, diarrhea and profound fatigue. As a result of these symptoms, he was taken off antiretroviral medications. Within two weeks, his gastrointestinal symptoms largely subsided, but the fatigue continued. A repeat viral load test eight weeks after therapy interruption showed that his viral load had risen to 75,000 copies/mL and, simultaneously, his CD4 count had dropped to 220 cells/mm³.

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He was put back on treatment, with a regimen of once-daily ritonavir (RTV, Norvir), atazanavir (ATV, Reyataz), lamivudine and tenofovir. Eight weeks after resuming therapy, he was tolerating the medications well and a repeat viral load test showed <75 copies/mL and his CD4 count had increased to 350 cells/mm³.

**Discussion**

This case illustrates the point, now observed in multiple cohort studies, that individuals with a low nadir CD4 count and high viral set point are generally not able to stop therapy for long periods.

This patient had a crescendo pattern of worsening gastrointestinal side effects that quickly resolved after treatment interruption. However, virologic and immunologic parameters also quickly deteriorated and led to early resumption of treatment.

This STI provided an opportunity for this patient to change to a new regimen with the hope of better tolerability and continued virologic control. One of the more common errors in the management of HIV is the continuation of an antiretroviral regimen in the presence of ongoing toxicity. Because of the aversive effect of medication-related toxicity, continuation of such treatment increases the likelihood of poor adherence. Clinicians should keep in mind that a patient's quality of life is compromised by forging ahead with a regimen in spite of progressive toxicity, which will certainly affect treatment compliance. There are now more than 17 approved antiretroviral agents, and except for patients who have multidrug-resistant virus, it will almost always be possible to individualize therapy somewhat and construct a well-tolerated regimen.

**Case Study 4**

A 51-year-old male was diagnosed with HIV in 1989. He started antiretroviral therapy in 1992 and received, in sequence, zidovudine monotherapy, dual nucleosides and ultimately a triple combination of zidovudine, lamivudine and indinavir.

In 1998, his regimen was modified to zidovudine + lamivudine, ritonavir and indinavir and this was continued to January 2003. In 1997, his CD4 count was 197 cells/mm³ and by January 2003 had increased to 538 cells/mm³. His plasma HIV-RNA had been consistently below the level of detection for years.

However, this patient was obese, hypertensive and smoked two packs of cigarettes daily. On antiretroviral therapy, his lipid levels had progressively increased:

- September 1998: cholesterol 146 mg/dl, triglyceride 372 mg/dl
- December 2001: cholesterol 290 mg/dl, triglyceride 1049 mg/dl

In June 2002, he had an acute
myocardial infarction that led to an angiogram and the placement of a left anterior descending stent. He was begun on clopidogrel (Plavix), aspirin (Alka-Seltzer, ASA, Ascriptin A/D, Aspergum, Bayer, Bufferin, Easprin, Ecotrin, Empirin), atorvastatin (Lipitor), atenolol and ramipril (Altace), and reduced his smoking to five cigarettes per day. Despite these measures, in January 2003 his cholesterol was 530 mg/dl and his triglycerides 3,180 mg/dl. He was also diagnosed with diabetes mellitus in January 2003, with a fasting blood glucose of 164 mg/dl and a hemoglobin A1C of 7.3 mg/dl. He developed recurrent angina and oral nitrates were added to his regimen.

In February 2003, he moved from Boston to Florida in the hopes a warmer climate would improve his health. On Feb. 27, 2003, his cholesterol was 368 mg/dl and his triglycerides were 2,375 mg/dl. Antiretroviral therapy was discontinued and, with no other changes in the regimen, on March 27, 2003 his cholesterol was 82 mg/dl and his triglycerides were 368 mg/dl. The daily episodes of angina resolved within one week of stopping antiretroviral therapy.

In June 2003, he experienced a cerebellar ischemic stroke related to basilar artery atherosclerosis. The resultant ataxia precluded him from riding his motorcycle for several months. He improved with physical therapy, has quit smoking and is clinically stable. He is currently on an STI with a plasma HIV-RNA in the 100,000 copies/mL range and has a CD4 count in the 250 cells/mm³ range.

**Discussion**

This case provides a rather dramatic example of the potential adverse metabolic effects of antiretroviral therapy in a patient with multiple risk factors.

Protease inhibitors (PIs) in particular have a substantial impact on metabolic parameters. Lipid elevations and insulin resistance are commonly seen, especially with indinavir and lopinavir/ritonavir-based therapy. One of the advantages of the newly released PI, atazanavir, is its neutral effects on lipids.

However, NRTIs also influence lipids. Recent studies have shown that stavudine increases cholesterol and triglycerides much more than tenofovir. Nonnucleosides also demonstrate differences in lipid effects; nevirapine increases high-density lipoprotein (HDL) cholesterol more than efavirenz and produces a more favorable total cholesterol:HDL cholesterol ratio.

We now know that the metabolic impact of therapy should always be considered when making treatment decisions for an individual patient. In this case, despite multiple risk factors and demonstrated severe hyperlipidemia, this patient had never been treated with an NNRTI-based regimen. Several recent studies demonstrate the safety and effectiveness of switching from PI-based regimens to either NRTIs or NNRTIs in order to improve lipids. A PI to NNRTI switch strategy may also lead to improvements in insulin resistance and diabetes control. When patients develop significant hyperlipidemia or diabetes on PI-based therapy, it is appropriate to switch to a different regimen with less potential for metabolic side effects.

We are still learning about the adverse metabolic effects associated with antiretroviral therapy, which appear to be associated with higher rates of atherosclerosis and adverse cardiovascular outcomes. The D:A:D study, a large, prospective cohort of over 23,000 HIV-infected patients, demonstrated a 26% increased risk of myocardial infarction per year of exposure to antiretroviral therapy. And since many patients with HIV also have risk factors for heart disease, like obesity, smoking, family history of heart disease, this will be a continuing problem.
previous negative HIV tests went on vacation and, during a weekend of heavy cocaine use, had unprotected intercourse with multiple partners. Two weeks later, he developed a severe viral type illness characterized by headache, conjunctivitis, fever, anorexia and diarrhea. He promptly sought medical attention. An HIV antibody test was negative, but a quantitative plasma HIV-RNA came back positive at >500,000 copies/mL and he had a CD4 count of 489 cells/mm³.

Several weeks later he visited an HIV specialist and the decision was made to initiate antiretroviral therapy. Immediately prior to starting treatment, his plasma HIV-RNA was 57,000 copies/mL, his CD4 count was 460 cells/mm³, and an HIV genotype showed wild-type virus. A regimen of tenofovir, lamivudine and efavirenz, with all medications taken together at bedtime, was commenced. He tolerated the medications well except for morning dizziness and a "hung over" feeling that gradually improved and, after two weeks, resolved completely.

Follow-up testing at week 4 showed that his viral load had dropped to 640 copies/mL and his CD4 count was 610 cells/mm³. By week 8 his plasma HIV-RNA level was undetectable and his CD4 count was 723 cells/mm³. A repeat HIV EIA and a Western Blot confirmatory test were positive. At this time, he had unprotected intercourse with an HIV-positive individual who was on antiretroviral therapy, but with incomplete viral suppression. The new sexual contact had a plasma HIV-RNA that had recently been measured at 1,000 copies/mL, but no resistance testing was available. Because of this second exposure, the original plan to stop HAART was postponed, and therapy was continued for an additional month before it was discontinued.

He had received a total of 12 weeks of continuous antiretroviral therapy before the discontinuation. Four weeks after stopping treatment, his plasma HIV-RNA remained undetectable, although eight weeks later it rebounded to 1,200 copies/mL. From a clinical perspective, he was asymptomatic. After an additional eight weeks, his viral load was 800 copies/mL and, during this time off medications, his CD4 count ranged from 600 to 750 copies/mL. The patient and his clinician planned to monitor his course off antiretroviral therapy and consider restarting if his viral load showed a consistent increase above 5,000 copies/mL.

**Discussion**

In this case, prompt diagnosis of HIV infection in a patient at high risk led to early treatment with HAART. Notably, even before initiation of antiretroviral therapy, there was a reduction in viral load from >500,000 copies/mL to 57,000 copies/mL. This aspect of the case highlights the ability of HIV-specific immune responses to gain some measure of control over viral replication. For this patient, commencement of combination antiretroviral therapy led to rapid virologic control and improvement in his CD4 count.

After three months of HAART, treatment was suspended as part of a planned STI strategy. In the short term, this patient has done well with plasma HIV-RNA levels remaining relatively low off therapy. Of course, it is impossible to know whether this patient would have ended up with a similarly low viral load had he not initiated HAART early.

Much of the interest in STI was generated from early positive results found in observational case studies in patients with primary HIV infection. Although it is estimated that about 40,000 new cases of HIV infection occur in the United States each year, the great majority are not diagnosed during the early acute phase. Some patients are not diagnosed early because the infection is silent, but the non-specific nature of findings in those with symptomatic infection and a low index of suspicion among front-line clinicians also
contribute to misdiagnosis.

Also, the shift in the epidemic towards the heterosexual and minority populations accounts for some of the challenges in establishing an early diagnosis. Many of those currently at risk for HIV infection do not perceive themselves to be at risk, and present to emergency departments or urgent care centers that are not equipped for HIV counseling and testing. Moreover, sometimes when HIV is considered in the differential diagnosis and testing is ordered, only an antibody test is performed and not a test to measure viral replication and thus the diagnosis may be missed. As this case illustrates, the early diagnosis of primary HIV infection before seroconversion depends on measuring HIV-RNA.

For the rare few who are diagnosed with primary HIV infection there are no clear answers on the most appropriate management. Based on positive reports from early STI studies in primary HIV infection, some clinicians will recommend a similar approach. The hope is that prompt treatment may curtail widespread dissemination of HIV and that STI may lead to some degree of autoimmunization. However, recent reports have shown that despite positive initial results with this approach, the majority of patients have loss of virologic control due to viral escape mutants. It is time for randomized, controlled trials of a variety of early treatment strategies in patients with primary HIV infection to help guide clinical management.

References


Little Benefit Seen for Treatment During Acute Infection

Coverage provided by Keith Henry, M.D.

Keith Henry, M.D., is Associate Professor of Medicine at the University of Minnesota School of Medicine and Director of HIV Clinical Research at Hennepin County Medical Center in Minneapolis. In addition, he is Medical Director of the AIDS Unit and the Sexually Transmitted Disease Clinic of the St. Paul Department of Public Health.

Bruce Walker walked across the hall from the immune response session (featuring four Walker-linked studies) to present an update on his highly visible and often-presented small study of patients treated during primary infection who subsequently underwent several sequential treatment interruptions (STIs). The initial results from the study (3/8 maintained <5,000 copies HIV RNA after the first STI and 5/8 maintained <5,000 copies/mL after the second STI), suggested that very early antiretroviral therapy during primary infection, followed by a series of brief treatment interruptions, could lead to improved immune control of HIV off therapy. Those results (discussed in further detail on page 46) have stimulated the practice of treating primary infection and spawned enthusiasm that immunologic interventions (such as therapeutic vaccination) could also be utilized in chronic infection.

Dr. Walker then presented the longitudinal data for a total of 14 patients (all had acute retroviral syndrome) followed for an average of 5.3 years including for up to 3 years after the last STI. Only 1/14 of the patients has maintained control of viremia (defined as <5,000 copies RNA/mL). The second and third STI failed more quickly, with the fourth STI providing no observable benefit.

The rate of CD4 count loss when antiretroviral therapy was stopped was quite high and it was not much different from the CD4 loss observed when stopping antiretroviral therapy in the setting of chronic infection. Dr. Walker then discussed what factors could be identified that could predict the control of viremia. They had looked at HLA type, CCR5 status, GBV-C infection, time of treatment since onset of ARS symptoms, viral load at seroconversion, and anti-HIV immunity from CD4+ or CD8+ T-cells. None of those factors predicted control of viral rebound.

Particularly disappointing was the observation that, although anti-HIV immunity appeared to be enhanced with the STIs, this did not translate into observable clinical benefit. These results were interpreted to indicate that durable maintenance of low-level viremia may be difficult to achieve. The CD4 declines were substantial with immune escape at even low viral loads sufficient to be a problem.

In a question to Dr. Walker, Joe Eron made the comment that the window to perhaps protect anti-HIV immunity during

Abstract:
Limited Durability of Immune Control Following Treated Acute HIV Infection (Oral 24: www.retroconference.org/2004/cd/Abstract/24.htm)

Authored by:

Affiliations:
primary infection may be vanishingly short. Another questioner pointed out that the definition of failure (confirmed viral load >5,000 copies/mL or one level >50,000) made it difficult to perhaps see some attenuation in the true magnitude of viral rebound. Although Dr. Walker stated that randomized clinical trials of early treatment and immune interventions are needed, the enthusiasm about the potential for this to achieve much has waned.

In all, the different presentations on acute infection suggested that we can do much better in finding and preventing recent infections. Although discussed a lot, superinfections still seem to be relatively unusual but are a growing problem. And it’s still unclear how helpful treatment during acute infection is.
Boosted Atazanavir Similar to Boosted Lopinavir in Treatment-Experienced Patients

Coverage provided by Calvin J. Cohen, M.D., M.S.

Cal Cohen, M.D., M.S., is Research Director of the Community Research Initiative of New England and a clinical instructor at Harvard Medical School in Boston.

Data from a study called BMS 045 was first presented in July 2003 at the International AIDS Society (IAS) meeting in Paris. This study (further details on which are available at www.thebodypro.com/confs/ias2003/cohen2.html) involved 358 participants who had triple-class experience and resistance, and were randomized to receive a combination of either standard dose lopinavir/ritonavir (LPV/r, Kaletra), atazanavir (ATV, Reyataz) 300 mg/ritonavir (RTV, Norvir) 100 mg, or unboosted atazanavir with saquinavir (SQV, Invirase, Fortovase) at 1,200 mg once daily. All participants were on one of these protease inhibitor (PI) regimens in combination with tenofovir (TDF, Viread) plus a third NRTI selected by the investigator. This presentation further defines the longer-term outcome of this study, presenting results from week 48.

At study entry, the baseline RNA was about 4.4 logs, and CD4 counts were about 300 cells/mm³. Most patients (about 60%) were on an NNRTI regimen at study entry, limiting the power of this study to define specific baseline PI mutations and their impact on each of the arms of this study. Nonetheless, the overall results give a general idea of the relative potency of each of these approaches. Similar to the week 24 results, both boosted atazanavir and lopinavir/ritonavir provided a 1.9 log drop sustained to week 48, while the unboosted dual-PI regimen had a 1.55 log drop.

The two boosted regimens can be considered similar, with statistics suggesting that these two regimens differ by no more than 0.4 log (97.5% confidence interval). When looking at the more standard measurement of performance, viral load percent “below cutoff,” and using the 400-copy cutoff, both boosted regimens had about 53% below 400, while the dual unboosted arm showed only 37% suppression. With the 50-copy cutoff, there was an 8% difference favoring lopinavir/ritonavir. Lopinavir/ritonavir showed 46% suppression, atazanavir/ritonavir had 38%, while the dual-unboosted arm was only 26% successful, demonstrating some evidence that lopinavir may retain more activity than atazanavir, especially when dealing with highly PI-resistant virus.
CD4 counts were similar in the two boosted-PI arms, showing about 115 cell increases at one year, while the non-boosted arm showed a 72-cell increase.

As with the 24-week analysis, there were differences in the lipid fractions over time. Overall, the two atazanavir arms show less changes to these lipid fractions, with the biggest difference seen in the mean percent change in triglycerides, showing a 30% increase in those on lopinavir/ritonavir, and a fall in those starting on either atazanavir arm.

Similarly, the total cholesterol falls a small amount in both atazanavir arms, with a small 6% increase in the lopinavir/ritonavir arm. Accordingly, fewer patients on the atazanavir arms were started on lipid lowering therapy during the trial. Adverse events continued overall to be low in all three arms, although 11% did report grade 2 or greater diarrhea on lopinavir/ritonavir, while only 3% noted this adverse effect on boosted atazanavir/ritonavir. Supporting this is the observation that 24% required antidiarrheal treatment on the lopinavir regimen, and only 6% did so while on the boosted atazanavir. As expected, 6% did have jaundice on the boosted atazanavir arm, with none on the lopinavir/ritonavir arm.

Overall, these results are similar to what was seen at week 24. The overall potency is similar in the two boosted regimens, while the unboosted dual-PI approach is clearly less successful than either one. The percent with suppression using a 400-copy cutoff confirms the similar response in these two regimens, although there is a small difference noted in the 50-copy cutoff, consistent with earlier reports that in highly PI-resistant virus, there may be some advantage to lopinavir/ritonavir over atazanavir/ritonavir.

The safety and tolerability profile also confirm earlier findings showing less gastrointestinal toxicity in terms of diarrhea on atazanavir/ritonavir versus lopinavir/ritonavir. In addition, there were fewer lipid disturbances on boosted atazanavir. These data continue to provide support to patients and clinicians facing choices about treatment options after prior regimen failure, and allow continued insights about the role of boosted atazanavir as an alternative to the current “gold standard” lopinavir/ritonavir.
Dual-PI Regimen Preferred Over Single-PI Regimen After Initial PI Failure

Coverage provided by Edwin DeJesus, M.D.

Edwin DeJesus, M.D., is the medical director of Infectious Diseases Consultants Research Initiatives in Florida; in addition to treating HIV and hepatitis patients, he serves as the firm’s principal investigator for several clinical trials.

The selection of a second treatment regimen after an initial treatment failure is becoming easier as our armamentarium of antiretroviral agents expands. Currently, for patients failing an initial NNRTI-based regimen, the decision for a second regimen is pretty straightforward: either switch to a protease inhibitor (PI)-based regimen or a boosted PI-based regimen.

On the other hand, for patients failing an initial PI regimen, we have several treatment options, including the use of an NNRTI-based regimen, another PI-based regimen or potentially a combination of both.

This was the rationale behind the poster presented by Dr. Kostman from the University of Pennsylvania. This was a government-funded, open-label study (CPCRA 057) in which patients were randomized to receive one or two protease inhibitors in combination with an NNRTI and background therapy consisting of one or more nucleosides. The study was initially designed to enroll 400 patients, but due to slow accrual enrollment, the study was closed after 68 patients were randomized.

This study enrolled NNRTI-naive patients who were failing their first regimen with an unboosted PI: nelfinavir (NFV, Viracept), ritonavir (RTV, Norvir) or indinavir (IDV, Crixivan). Randomization was stratified by the PI in the failing regimen (nelfinavir, indinavir or ritonavir), baseline HIV RNA and whether the patient had previously achieved an undetectable HIV RNA (less than 500 copies/mL). The treatment arms included one new PI versus two new PIs, both in combination with an NNRTI and one or more nucleosides.

At 12 months, the percentage of patients achieving an undetectable viral load (<400 copies/mL) was significantly higher in the dual-PI group (61%) compared to the single-PI group (36%). The same trend was observed in the change in log HIV RNA, with a p-value of 0.05 at 12 months. The changes in CD4 counts were also higher in the dual-PI group. There were no significant differences between the treatment groups for HIV RNA greater than 10,000 copies/mL. Unfortunately, the study population is too small to draw any trends or conclusions regarding the stratification groups or the incidence of adverse events.

The investigators concluded that patients who experienced virologic failure on their
first PI regimen may benefit from a combination of one NNRTI and two PIs. The suboptimal performance of the single-PI group may be due to the lack of pharmacological boosting or to pre-existing resistance.

It is very hard to draw a take-home message from this study. First, the study was too small and did not take into consideration the pharmacological boosting of the second PI. There is also no mention about the pharmacokinetic interactions of efavirenz (EFV, Sustiva) and PIs, and whether a dose adjustment was performed, for example, in patients taking efavirenz and amprenavir (APV, Agenerase) as part of their new regimen.

What is clear is that this study showed more evidence that using an unboosted PI for second-line therapy after failing a first PI is probably not adequate. But, with the availability of more antiretroviral agents in today’s treatment paradigms and the widespread use of boosted regimens, most physicians will probably feel more comfortable using a boosted PI before selecting a dual-PI/NNRTI regimen after initial failure.
Substudy of 2NN Shows Nevirapine and Efavirenz to Be Equal in Potency

Coverage provided by Gerald Pierone Jr., M.D.

Gerald Pierone Jr., M.D., is Founder and Executive Director of the AIDS Research and Treatment Center of the Treasure Coast in Fort Pierce, Fla., a nonprofit medical clinic with more than 600 HIV-positive patients. He also maintains a private HIV medical practice in Vero Beach, Fla.

The 2NN study was first presented at the Retrovirus meeting last year, and it generated much excitement at the time. It was a large (1,216 participants), randomized study of treatment-naive subjects who received either nevirapine (NVP, Viramune), efavirenz (EFV, Sustiva), or both NNRTIs together with a nucleoside backbone of lamivudine (3TC, Epivir) and stavudine (d4T, Zerit). The nevirapine arm was also divided into once-daily and twice-daily groups.

The overall results showed similar outcomes in the efavirenz and nevirapine groups, but more toxicity and poorer results in the arm that received both NNRTIs. Overall, there was also more liver toxicity associated with nevirapine compared to efavirenz. (Further details of this study are available at: www.retroconference.org/2003/Abstract/Abstract.aspx?AbstractID=947)

This current poster presentation involved a breakdown of data obtained from the 2NN study. Since the study was presented last year, there continue to be questions regarding the relative potencies of efavirenz and nevirapine, and this analysis attempts to shed some light on this issue.

Subjects were divided into different strata based on their CD4 counts and viral loads. The CD4 count stratum were <25 cells/mm³, 25-199 cells/mm³ and >200 cells/mm³. For viral load, the groupings were less than or greater than 100,000 copies/mL.

For each stratum, the risk of virologic failure was estimated. Virologic failure was defined as never reaching a viral load of <400 copies/mL or a rebound to two consecutive viral loads >400 copies/mL. The proportion of subjects with virologic failure was compared for the nevirapine and efavirenz arm using Kaplan Meier analysis.

There were several significant findings in this investigation. The first was that subjects with a baseline CD4 count <25 cells/mm³ had a 25% rate of virologic failure compared to 17% for those with CD4 counts of more than 200 cells/mm³ (p=0.04). This is consistent with other trials that have shown patients with extremely low CD4+ counts have greater challenges with therapy and may require a more potent regimen.
Another result was that 23% of the subjects with a viral load exceeding 100,000 copies/mL had virologic failure compared with 16% for those with less than 100,000 copies/mL (p = 0.004). Other studies have shown mixed results with regard to high viral load levels and rate of virologic failure in treatment-naive patients. There has been a tendency, though, for less-potent regimens (such as unboosted protease inhibitors) to perform less well than highly potent regimens in this higher-risk group.

There were no differences in the rate of virologic failure in any of the CD4 count and viral load stratum between nevirapine and efavirenz. These observations should help dispel some of the folklore that efavirenz is intrinsically a more potent NNRTI than nevirapine.

However, this does not negate the issue of higher rates of liver toxicity seen with nevirapine in 2NN and other trials. To that point, Boehringer-Ingelheim, the maker of nevirapine, has recently updated its recommendations (available at www.thebodypro.com/treat/pdfs/nevirapine_risk.pdf) to HIV providers about the risk of nevirapine hepatotoxicity, particularly in women with a CD4+ cell count greater than 250. For any patient who is treated with nevirapine, there must be heightened vigilance for clinical and laboratory evidence of hepatitis.
Virologic Failure Analyzed in a Trial of Once-Daily Versus Twice-Daily Abacavir With 3TC and Efavirenz

Coverage provided by Andrew T. Pavia, M.D.

Andrew T. Pavia, M.D., is Chief of Pediatric Infectious Diseases and a Professor of Pediatrics and Medicine at the University of Utah. In 1989 he helped to found the university’s AIDS clinic.

The Zodiac study (otherwise known as CNA30021) was a 48-week, randomized clinical trial comparing efavirenz (EFV, Sustiva, Stocrin) given with abacavir (ABC, Ziagen) 600 mg and lamivudine (3TC, Epivir) 300 mg once daily or abacavir 300 mg and lamivudine 150 mg twice daily in 770 antiretroviral-naive persons. The reasons for doing this trial were two-fold: to determine whether abacavir and lamivudine can really be given once daily as suggested by their intracellular half life, and to prepare the way for the new co-formulation of abacavir and lamivudine that GlaxoSmithKline is bringing to market.

Brian Gazzard presented the primary results of this trial in September 2003 at ICAAC (the details of which are available at www.thebodypro.com/confs/icaac2003/youn g3.html). This presentation presented new data on the resistance profile among those patients who experienced viral failure. It used the U.S. Food and Drug Administration (FDA)-mandated TLOVR (time to loss of virologic response) analysis, which gives fairly similar results to the more familiar intent-to-treat, missing-equals-failure analysis. As we have come to expect from a regimen that uses efavirenz, lamivudine and a third drug, the response was excellent, with 68% achieving a viral load of less than 50 copies/mL.

The various virologic and CD4 outcomes were essentially identical for the once-daily and twice-daily regimens. Virologic failure occurred in only 8% of those on the twice-daily regimen and 10% of those on the once-daily regimen. Many of those classified as virologic failures maintained viral loads of less than 400 copies/mL, although follow up was limited. Thus, only 31 patients out of the 770 had a sample that was suitable for determining resistance.

Phenotypic testing at baseline (using the Virologic phenosense assay) showed reduced susceptibility to at least one drug in 1/15 (7%) of the patients in the twice-daily group, compared to 5/16 (31%) in the once-daily group, but the details were not given. At treatment failure, efavirenz resistance was seen in about 60% of the twice-daily group and about 80% of those in the once-daily group. Lamivudine resistance was detected at failure in 30% of the twice-daily group and 60% of the once-daily group. Resistance to abacavir was unusual at about 15%. Zidovudine (ZDV, Retrovir)/stavudine (d4T, Zerit) resistance was not seen.

Were there any surprises in the

Abstract:
Analysis of Virologic Failure in a Clinical Trial of Abacavir Once Daily Versus Twice Daily With Lamivudine and Efavirenz
(Poster 551: www.retroconference.org/2004/cd/Abstract/551.htm)

Authored by:
C. Craig, C. Stone, T. Bonny, H. Zhao, D. Gordon, S. Castillo, D. Faes

Affiliations:
GlaxoSmithKline, Stevenage, UK;
GlaxoSmithKline, Research Triangle Park, NC; GlaxoSmithKline, Greenford, UK
genotypic studies? In a word, no. Somewhat more patients in the once-daily group had baseline mutations (5/16 compared to 2/15). Resistance mutations to lamivudine at M184 were also common (5/16 and 2/15, respectively). Only one subject developed the K65R mutation.

So what did we learn from this analysis? Virologic failure is uncommon in efavirenz-containing regimens, but, when it occurs, it usually involves efavirenz resistance with or without lamivudine resistance. That is not new, but confirms several other studies, including the original efavirenz studies (DMP 006) and the more recent GS 903 study. There did not appear to be any significant difference in resistance between once-daily and twice-daily abacavir and lamivudine, but that conclusion has to be tempered by the small number of patients

At failure, the majority of patients had efavirenz-resistance mutations (14/15 in the twice-daily group and 12/16 in the once-and the difference at baseline. Eliminating zidovudine from the regimen did not lead to new or surprising patterns of abacavir resistance, but as with the tenofovir (TDF, Viread), 3TC and efavirenz regimen used in GS 903, the overall potency and success of the regimen might have masked subtle differences in patterns that may come out with widespread use.

Are we ready to use abacavir and lamivudine once daily? So far, the data are consistent and encouraging, but the FDA will have to review the complete data set before they can decide on whether to approve the lamivudine/abacavir combo as a once-daily regimen.
Triple-PI Regimens for Rescue Treatment

Coverage provided by Benjamin Young, M.D., Ph.D.

Benjamin Young, M.D., is Attending Physician at the Rose Medical Center in Denver, Colo. and a clinical instructor in the Department of Medicine at the University of Colorado Health Sciences Center.

There is an ever-growing appreciation for just how complicated combining some HIV medications can be. Certain medications alter the way that the body processes other medications, at times accelerating the metabolism, at other times blocking the metabolism. Sometimes, the interactions can be complex and difficult to predict.

These interactions are the very basis for the use of ritonavir (RTV, Norvir) boosting. Ritonavir blocks the metabolism of other protease inhibitors (PIs), enabling them to be used with fewer doses and fewer pills.

An additional potential consequence of boosting is the ability to boost, or increase the drug levels of PIs. These higher drug levels can translate into increased potency of the drugs, a critically important issue for the treatment of persons with drug-resistant HIV. For these persons, the use of ritonavir-boosted PIs has offered hope of achieving the grail of an undetectable viral load, and immune system health. Unfortunately, some patients have virus that is so resistant to PIs, that the conventional use of boosted PIs is insufficiently potent. This is often the case in my clinic, where I take care of a number of people with highly-resistant virus. Having as potent a combination as possible is essential for these persons, particularly, if we’re thinking about using the new fusion inhibitor drug called enfuvirtide (T-20, Fuzeon).

This is where the concept of dual-boosted PIs comes in. We’ve had experience using two full-dose PIs in the past, with regimens that were composed of ritonavir and saquinavir (SQV, Invirase, Fortovase), but these regimens were difficult to take because of high pill burden and side effects. The availability of ritonavir coformulated with the PI lopinavir (LPV) as Kaletra, and the recent approval of the newer, very low pill count PIs—atazanavir (ATV, Reyataz) and fosamprenavir (908, Lexiva)—provides an opportunity to construct low pill count, and potentially very potent, dual-boosted PIs. This promise is particularly important for some drug-resistant patients who have a glint of drug sensitivity to amprenavir (APV, Agenerase).

The two studies discussed here address issues related to the administration of fosamprenavir with lopinavir/ritonavir.
Normally, two pills of fosamprenavir are combined with ritonavir once- or twice-daily for boosting; lopinavir/ritonavir’s dose is normally three pills twice-daily. If everything were simple, we’d expect that patients would simply take two pills of fosamprenavir with three pills of lopinavir/ritonavir, right? Unfortunately, it turns out that all three PIs appear to interact with one another. In a study presented by the AIDS Clinical Trials Group last fall at the ICAAC meeting (the details of which are available at www.thebody.com/confs/icaac2003/dejesus1.html), it was found that the drug levels of fosamprenavir and lopinavir were unexpectedly and dramatically reduced—meaning that there wouldn’t be enough of the drugs in the blood to be effective in stopping HIV. These studies explore ways to figure out just how to adjust the doses of these PIs.

The first study, by Corbett and colleagues from the University of North Carolina (Poster 611: www.retroconference.org/2004/cd/Abstract/611.htm) examined the strategy of separating the dose of the two medications. Study subjects either took the medications at the same time or separated by four or 12 hours (the later with an extra 200 mg of ritonavir). The results of this study showed that the dose separation strategy corrected the drug levels of lopinavir, but, unfortunately, did not improve the levels of amprenavir in the dual-boosted regimen.

The second report, from Wire and colleagues from GlaxoSmithKline, the makers of fosamprenavir (Poster 612: www.retroconference.org/2004/cd/Abstract/612.htm), looked at the use of different doses of fosamprenavir and lopinavir/ritonavir as a way to offset the metabolism issues. In this study, two new doses of the two medications were compared to the typical dose (and drug levels) of ritonavir-boosted fosamprenavir. The first regimen looked at 1,400-mg fosamprenavir (two pills) with 533/133 mg of lopinavir/ritonavir (four pills), all taken twice a day. The second evaluated 1,400-mg fosamprenavir (two pills) with 400/100 mg of lopinavir/ritonavir (three pills) with an additional 100 mg of ritonavir (one pill), all taken twice a day. Overall, the regimens were poorly tolerated, even in these healthy, HIV-negative persons. Elevations in cholesterol and triglyceride (lipid) levels were frequent.

After all of the blood sampling and analysis, the authors concluded that the increased doses of pills did increase the amprenavir levels, but the levels were still lower than had been seen in previous boosted studies; the lopinavir levels were maintained at their expected levels. They concluded that no specific recommendations about the dosing of fosamprenavir and lopinavir/ritonavir could be made.

So where does this leave us? The answer, I think depends on the patient. For those who have HIV with only limited drug resistance, there are a number of well-defined treatment options, with well-defined drug interactions (or lack thereof). For these persons, I would definitely not recommend the use of unproven dual-boosted PIs.

For persons with highly drug-resistant virus, the story, and the stakes are enormously different. In these circumstances, we sometimes cannot wait for the optimal scientific data sets to guide treatment—doctors and patients are forced to make the best educated guesses, based on the best available studies. The later study, by Wire, provides a framework for thinking about how to use fosamprenavir with lopinavir/ritonavir, even if it is not an optimal regimen for patients. It is clear that the combination is not great with regards to side effects and its effect on lipid levels, but it might be essential, or even immune system saving, for the person whose virus only has some susceptibility to fosamprenavir and/or lopinavir, when combined with enfuvirtide. Because of the uncertain and uncharted waters of these regimens, I would request therapeutic drug monitoring tests to make sure that the drugs the patient was taking were achieving sufficient blood levels.
Single-Drug Interruption May Be Useful in Identifying Still-Active Drugs in Heavily Treated Patients

Coverage provided by Gerald Pierone Jr., M.D.

Gerald Pierone Jr., M.D., is Founder and Executive Director of the AIDS Research and Treatment Center of the Treasure Coast in Fort Pierce, Fla., a nonprofit medical clinic with more than 600 HIV-positive patients. He also maintains a private HIV medical practice in Vero Beach, Fla.

This small pilot study of only six patients was notable because it advanced a new concept that might turn out to be useful in the management of patients on a failing antiretroviral regimen.

From a practical viewpoint, in patients with virologic failure on antiretroviral therapy, it would be advantageous to know if an agent in the regimen still possessed significant activity, or was just taking up space. In this setting, genotypic and phenotypic resistance assays are certainly helpful, but not always predictive of clinical response to therapy. Genotypic testing has limitations because some mutational patterns are complex and difficult to interpret. Phenotypic analysis does not entirely correlate with clinical outcomes and minor variants may be missed. For both tests, an intermediate range sensitivity of an antiretroviral agent selection.

The clever idea put forth in this study was that a short, single-agent, discontinuation in a failing regimen might quickly determine if that medication was contributing to the antiretroviral activity of the regimen.

In this trial, subjects with a viral load of more than 5,000 copies/mL on a standard antiretroviral regimen stopped one antiretroviral and continued the remainder of the regimen. Resistance testing was done prior to discontinuation and frequent viral load testing was done in the period immediately after the patient stopped a medication in order to determine the dynamics of viral load changes.

Interestingly, three of the subjects had stavudine (d4T, Zerit) discontinued for two weeks and during this time interval there was a significant increase in viral load. Of note, two of these three patients had multiple reverse transcriptase mutations that predicted probable stavudine resistance. Two of these three subjects elected to restart stavudine and viral load levels promptly returned to baseline.

In a similar manner, one subject discontinued didanosine (ddI, Videx) and two stopped efavirenz (EFV, Sustiva). All had baseline genotypic mutations suggesting viral resistance and there were no significant changes in viral load during the short treatment interruption. So with
these agents and typical mutations (K103N and Y188L for efavirenz; M41L, L210W and T215Y for didanosine), the short, single-agent interruption confirmed a lack of activity.

The authors’ main conclusion was that a single drug interruption might be useful for identifying combinations of agents that maintain activity in heavily treated patients.

The results of this pilot study are quite interesting and will likely be expanded to test other agents in a comparable manner. The frequency of viral load testing over a short period of time represents a practical limitation, but as more experience with this approach accumulates, it may turn out that less intense testing may be possible. Although this pioneering strategy is clearly in the experimental realm at this time, it may have important implications for the clinic once it is tested further.
Little Difference Between Resistance Testing Methods in Treatment-Experienced Patients

Coverage provided by Mark Holodniy, M.D., F.A.C.P., C.I.C.

Mark Holodniy, M.D., is Associate Professor of Medicine at Stanford University. He is Director of the HIV Clinical Program and AIDS Research Center at Veterans Affairs Medical Center in Palo Alto, Calif.

How useful are the available resistance tests for choosing appropriate treatment? Studies done so far have been split. In this Spanish study, genotypic and phenotypic resistance testing (with expert advice in the interpretations) was compared to see which was more clinically useful at helping doctors choose a HAART regimen that would most effectively reduce a patient’s viral load or CD4 cell increase after 48 weeks. Blanco and colleagues looked at heavily treatment-experienced patients who required a new salvage HIV regimen. This Spanish study looked at heavily treatment-experienced patients who required a new salvage HIV regimen. In order to qualify for the study, patients needed to have failed more than two previous HAART regimens and have a viral load more than 5,000 copies/mL.

The study enrolled 137 patients, 78 in the genotype arm (using the Viroseq HIV-1 genotyping assay) and 58 in the phenotype arm (using the Antivirogram). The average patient age was about 40, and the average CD4 count and viral load was about 230 cells/mm³ and 4.6 log/ml, respectively. The two groups were fairly evenly matched with respect to the number of previous HAART regimens, and specific HIV drugs or classes that each had previously received. Expert advice was defined as an independent committee composed of a virologist, a clinician expert in interpreting resistance tests and the treating physician who decided on the most appropriate regimen for the patient.

The data was analyzed by intent-to-treat (ITT) analysis—in which dropouts were considered failures—and by the less rigorous on-treatment (OT) analysis, in which these dropouts were not included in the final analysis. Viral load and CD4 count were measured at 12, 24, 36 and 48 weeks. At week 48, the average drop in viral load was just over a 1.5-log/ml reduction for both the genotype and phenotype arms. This was not significantly different. In terms of the number of patients who achieved an undetectable viral load (<200 copies/mL), the phenotype group was slightly better (38% versus 28%, P = NS) than the genotype group in the ITT analysis, and about equal in the OT analysis (44% versus 41%, P = NS). There was a slight advantage for genotyping with respect to CD4 cell

Abstract:
Genotypic vs. Real Phenotypic Tests to Guide Salvage Antiretroviral Therapy in Heavily Pretreated Patients With Virological Failure: A 48 Weeks Prospective, Randomized Study (VIHRES Study) (Poster 675: www.retroconference.org/2004/cd/Abstract/675.htm)

Authored by:

Affiliations:
Hosp. Clin., Barcelona, Spain; Hosp. del Mar, Barcelona, Spain; Hosp. Santa Creu i San Pau, Barcelona, Spain
increase (88 versus 69 cells/mm³, P = NS).

This study demonstrates—in a very treatment-experienced group of patients—that there does not appear to be any advantage to using one type of resistance test over another when expert advice is available for interpretation of the test result and a suggested new regimen. It is often thought the genotypic resistance tests may be somewhat harder to interpret, given the numerous genetic sequence changes conferring HIV drug resistance that must be remembered and applied to the interpretation of genotypic tests. Even when algorithms are provided and used in the interpretation of these tests, differences exist as to the significance of some sequence changes among these algorithms and the experts who develop them.

Phenotypic tests are thought to be more easily interpretable by practicing clinicians, since the reports indicate whether a patient’s viral strain is susceptible or not to a particular drug based on growth characteristics in the presence of HIV drugs.

Several studies have determined that either genotypic or phenotypic resistance testing is superior to standard of care (SOC) alone without the benefit of resistance test results. Studies are split on the superiority of one technology over the other in conferring a better virologic outcome. One previous study (the Havana trial, an abstract of which is available at www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&elist_uids=11807305&dopt=Abstract) indicated that expert opinion associated with genotypic resistance testing resulted in better virologic outcome, when compared to genotypic results alone used by the treating physician. Phenotyping was not assessed in that study.

The current study further indicates no superiority of either technology even when expert opinion is provided for interpretation. One thing to keep in mind is that there is a cost differential between these two types of resistance tests. Phenotypic resistance testing is more expensive and can require more time to produce results when compared to genotypic testing.

In any case, these studies still have not answered the basic question concerning whether there is any advantage of one testing method over the other, or the use of expert advice in less advanced or less heavily treatment-experienced patients.
CARDIOVASCULAR COMPLICATIONS OF HIV/HAART

Review of Cardiovascular Complications of HIV/HAART

Coverage provided by Corklin R. Steinhart, M.D., Ph.D.

Corklin R. Steinhart, M.D., is the Medical Director of the Florida/Caribbean AIDS Education and Training Centers and is an Assistant Professor of Medicine at the University of South Florida College of Medicine.

As morbidity and mortality due to HIV/AIDS have dramatically decreased over the past eight years, the focus of clinical management concerns have shifted to non-opportunistic diseases.

A number of studies over the past few years, for example, have strongly suggested that there is an increased risk of cardiovascular disease in HIV-infected patients compared with age-matched controls.

Moreover, it appears that this risk is further increased for patients taking protease inhibitor (PI)-containing HAART, although there is controversy regarding this point. Several reports at this meeting continue to provide us with more information regarding the cardiovascular complications of HIV/AIDS in the third decade of the epidemic.

At last year’s CROI meeting, results from the D:A:D cohort (The Data Collection on Adverse Events of Anti-HIV Drugs)—which is a large, prospective, international, observational database of more than 23,000 HIV-positive patients—demonstrated that the incidence of myocardial infarction increased by 26% per year of exposure to combination antiretroviral therapy (ART).1

At this year’s CROI meeting, additional analyses on these more than 23,000 patients were presented. The first study2 presented determined whether this 26% rate pertained to cardiovascular events other than myocardial infarctions, and looked at whether the previous rate of myocardial infarction was similar to predictions based on the Framingham cohort. (The Framingham study is a landmark, ongoing prospective study of risk factors for cardiovascular disease in the general, HIV-negative population. It began in 1948.)

Two analyses were performed in this study. In the first analysis, the rate of the first cardiovascular event (myocardial infarction, invasive cardiovascular procedure, stroke or death from cardiovascular events other than a myocardial infarction) was found to be 5.5/1000 person years in 35,151 person years of follow up: 199 cardiovascular events occurred, including 121 myocardial infarctions and 30 strokes.

The results confirmed that the longer the exposure to ART, the more a patient was at risk for a cardiovascular event, and that this rate was similar to using myocardial infarction as a single endpoint, which confirms the D:A:D results reported at
CROI last year.

In the second part of this study, the Framingham model was used to determine the expected rate of myocardial infarction during the D:A:D follow up, and to ascertain whether the increased rate seen with increased exposure to ART was due to conventional cardiac risk factors.

Those patients not receiving ART had an observed rate of myocardial infarction of 3/1000 person years compared to the predicted rate of 7/1000 person years. In patients receiving ART, the number of myocardial infarctions was slightly higher than what is predicted by the Framingham equation, although they were still within the 95% confidence limits.

Because the D:A:D cohort included patients from Europe, the United States and Australia, the Framingham equation was controlled for differences in cardiovascular events in different countries by using data from the World Health Organization.

The trends seen with the increased rate of myocardial infarction with a longer duration of exposure to ART were similar to those expected on the basis of a change in known cardiovascular risk factors. The authors concluded that the increase was due to ART-induced changes in conventional risk factors.

The results of this study, then, extend the previous findings suggesting that the longer someone is exposed to ART, the greater their risk of a cardiovascular event occurring.

However, it must be kept in mind that the risk remains small compared with aged-matched controls based on the Framingham study. Whether ART causes the increased risk remains to be determined.

In the meantime, aggressive modification of known coronary risk factors needs to be a mainstay of our treatment strategies, with selection of treatment individualized and drugs that are known to raise lipids avoided for patients with known coronary risks.

**Hypertension in HIV-Infected Men and Women**

The second study\(^3\) presented from the D:A:D cohort examined the factors affecting blood pressure in HIV-infected patients, since very little data exists in the HIV-positive patient population. Here again two different analyses were performed in order to determine both the incidence of hypertension and the factors that may affect both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients in the D:A:D cohort.

During a median follow-up period of 1.5 years, more than 43,000 blood pressure measurements were obtained in over 16,000 patients. The median number of measurements for each patient was three. At baseline, more than half the patients were found to be normotensive (SBP <140 and/or DBP <90 mmHg).

During the evaluation period, 487 of the 8,341 normotensive patients developed hypertension with an incidence of 35.8/1000 person years. This incidence is at the upper limit of normal in HIV-negative patients.

Risk factors for the development of hypertension were as follows: male gender (hazard ratio, HR=1.69), higher body mass index or BMI (HR=2.20 for BMI >30 kg/m\(^2\) vs. <18), older age (HR=2.08 for age group 43-83 years versus 17-33), and a higher blood pressure at baseline (HR=2.40 for SBP 130-139 mmHg versus <120).

Further analysis attempted to elucidate those factors associated with an increase in systolic blood pressure compared to a reference group. Those factors that were associated with a higher predicted systolic blood pressure were the same as those mentioned above: male gender (+7 mmHg and +6 mmHg at baseline and 24 months versus female), higher BMI (+16.4 mmHg and +15.6 at baseline and 24 months for BMI>30 kg/m\(^2\) versus <18), and older age (+12.8 mmHg and 14.5 mmHg at baseline and 24 months for 60 years old versus 30).
In addition, the use of blood pressure-lowering medications at baseline was also associated with the increase (+8.3 mmHg at baseline and 24 months for those being treated). However, neither cumulative exposure to each class of antiretrovirals, nor the type of treatment at baseline, were associated with the development of hypertension. The authors concluded that hypertension in HIV-infected persons is associated with the same risk factors as those in the general population. In addition, the results do not support an association of antiretroviral medicine with an increase in blood pressure in HIV-infected persons.

**Hypertension in HIV-Infected Women**

Conversely, a study presented from the Women’s Interagency HIV Study (WIHS) reported the opposite results. WIHS is an on-going, prospective cohort study being conducted at six U.S. sites and involving 2,057 HIV-positive women and 569 demographically similar HIV-negative women. Enrollment began between 1994-1995. As part of an attempt to determine the relationship, if any, between hypertension and lipodystrophy, this study determined the occurrence of hypertension in the large women’s cohort in a similar fashion to what has previously been reported for men in the large Multi-Center AIDS Cohort Study. Both univariate and multivariate analyses were performed; however, only the more important multivariate analysis will be discussed here.

The prevalence of hypertension at baseline was defined as having one of the following: diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg or current use of anti-hypertensive medication or a self-reported history of hypertension. The incident rate of hypertension was defined as any of the first three criteria present in at least two six-month intervals, one of which must have occurred after the introduction of HAART in April 1996. The results reported here demonstrated that neither the incidence nor the incidence rate of hypertension were different between the HIV-positive and HIV-negative cohorts.

Risk factors determined to be significantly associated with the development of hypertension were: increasing age, African-American race, less education, increasing duration of smoking and a higher BMI (≥30 kg/m²). Being pregnant had a protective effect. In addition, the use of HAART and increasing duration of time on HAART were independently associated with developing hypertension. Interestingly, zidovudine (ZDV, Retrovir) monotherapy was protective.

As a result of these conflicting results, we are again left wondering whether the use of ART does in fact increase the risk of developing hypertension. The discordant results presented here undoubtedly are the result of the different demographics that exist in large observational cohorts.

Moreover, methods for assessing blood pressure can be highly variable depending upon who is doing the measurement, the number of times the reading is done at each visit, how many readings are taken at each visit, as well as other factors that have been determined to influence blood pressure in the general population.

It is this author’s own observation that, indeed, there may be an increased rate of hypertension in both HIV-infected patients in general, as well as those on ART. Additional studies are required in order to elucidate whether there is truly an increased rate of hypertension.

**Cardiovascular Risk of PI-Containing HAART**

Lastly, another study attempted to determine whether PI-containing HAART increases the risk of cardiovascular disease. HIV Insight is a prospective, observational cohort comprised of the 10 sites from the HIV Outpatient Study cohort and another nine from primary healthcare providers. There were 7,542 patients eligible for evaluation between January 1, 1996 and
June 30, 2003. The median duration of follow up for the PI-containing group was 3.5 years (mean 3.5 years; maximum 7.4 years) and 2 years (mean 2.5 years; maximum 7.4 years) for the non-PI group.

Median PI-use was 1.7 years, with more than 95% of patients having been exposed to a PI for more than one month and 75% of patients for more than six months. Cardiovascular disease events were defined as any one of the following: acute myocardial infarction, angina pectoris, coronary artery disease, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, cerebrovascular accident, transient ischemic attack and peripheral vascular disease.

During the study period, 127 events occurred: 112 in the PI-group (incidence rate of 9.8/1000 patient years of follow up (PYFU), and 15 in the non-PI group (incidence rate of 6.5/1000 PYFU). In the subset of patients ages 35-65, there was also a higher incidence rate of 11.5 vs. 7.9/1000 PYFU.

There were a number of significant differences in the demographics of the two groups: In the PI-group, there was a longer time of follow up, plus, overall, the group was older, more male, more white, and also included more patients with hyperlipidemia at baseline and fewer smokers and African-Americans. These differences were, however, relatively small. By both uni- and multivariate analyses, the risk factors for the development of cardiovascular disease included older age, smoking, diabetes mellitus, hypertension, hyperlipidemia, pre-existing coronary artery disease and PI use for more than 60 days.

Sensitivity analyses performed in which all risk factors were controlled for, were also associated with more than 60 days of PI use in both the entire cohort, as well as the 35-65 age group. The duration of PI use was further subdivided into time periods: PI use for 1-179 days, 180-364 days, and more than 365 days. Applying this in a multivariate analysis demonstrated that only those patients who had used PIs for more than 365 days, as well as the subset of patients ages 35-65, had an increased risk of cardiovascular disease.

The results of this study are in agreement with those of the D:A:D study and suggest that indeed there is an increased incidence of cardiovascular events the longer someone is exposed to antiretroviral therapy. The nature and type of ART need to be "teased out," if possible, in order to more fully elucidate which type of ART—PI-containing or non-PI-containing—may be most causative.

At the present time, we are still left with trying to do what is best for our patients by weighing the pros and cons of which ART to recommend for each individual patient. Moreover, as in the general population, aggressive interventions aimed at reducing known cardiovascular risk factors need to be an integral part of patient management in those deemed to be at risk.

References


HIV-Infected Patients Have Multiple Risk Factors for Cardiovascular Disease

Coverage provided by Pablo Tebas, M.D.

Pablo Tebas, M.D., is an Associate Professor of Medicine at University of Pennsylvania School of Medicine and principal investigator in the AIDS Clinical Trial Unit at University of Pennsylvania.

It is difficult to ignore data from prospective studies that involve over 1,000 patients. Some of the data might already be known, but having such a large sample size makes any conclusion almost definitive.

CPCRA is one of the large National Institutes of Health (NIH)-sponsored networks conducting clinical studies related to HIV and its treatment. The main study this network is currently running is called the SMART study. They even have a Web site, www.smart-trial.org, if you are interested in learning more about it.

The SMART trial, which has already enrolled more than 1,300 patients, will compare two strategies for the long-term management of antiretroviral therapy:

- The drug conservation (DC) strategy, a strategy aimed at conserving drugs through the episodic use of antiretroviral treatment for the minimum amount of time required to maintain a CD4+ cell count of 250 cells/mm³,

  versus

- The viral suppression (VS) strategy is aimed at suppressing viral load as much as possible immediately following randomization and throughout follow up, irrespective of a patient's CD4+ cell count.

In the study Drummond et al. presented today, they examined some of the baseline lipid data, as well as the predictors for a low HDL level, which is a known cardiovascular risk factor. They performed a multivariate analysis to try and identify factors that would be associated with a low HDL level, both in the patients not on therapy and in the patients receiving antiretroviral therapy.

In general, being on therapy was associated with having a higher HDL cholesterol level. (It is well known that patients with advanced HIV infection have low HDL levels, as well as high triglyceride levels.) Among patients on treatment, those receiving NNRTIs were more likely to have higher HDL levels. Higher HIV RNA viral load numbers and high triglyceride levels were also associated with low HDL levels intreatment-naive patients. In patients on treatment, high triglyceride levels and diabetes were associated with low HDL levels.

The results are not earth shattering, but confirm the prevailing wisdom in the field. The bottom line is that it is quite common for patients with HIV infection to have multiple risk factors for cardiovascular disease. Data recently published in the New England Journal of Medicine¹ suggest that

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¹ Dr. Tebas noted that the SMART-4 study is an ongoing trial that is specifically examining cardiovascular outcomes in HIV-infected patients.
HIV-positive patients on treatment have a higher incidence of cardiovascular events.

Clearly, it is important both for patients and physicians to be aware of this fact. Clinicians should review each patient’s individual risk factors in order to intervene if necessary. Cardiovascular risk is an important variable to take into consideration when selecting antiretroviral therapy, since currently available treatments for HAART-associated hyperlipidemia have limited efficacy. Several studies presented at this meeting looked at possible treatments: ACTG 5087 looked at the efficacy of pravastatin, fenofibrate or both (Poster 723: www.retroconference.org/2004/cd/Abstract/723.htm), and another study from the University of North Carolina examined the use of fish oil (Poster 724: www.retroconference.org/2004/cd/Abstract/724.htm). However, both showed only partial effectiveness.

Footnote:
here was not much news this year in the arena of metabolic complications. In fact, the one big news item during this meeting did not even take place in the conference (the Abbott price increase and the resulting activism by doctors and patients). Other big news at this meeting included the failure of the first large vaccine trials run in Thailand. Although most everyone had heard the news before the conference, this did not make the presentation of the study more palatable. Everybody has a different take on it, but, in the end, everyone seems to be asking for more money—obviously the vaccine researchers are asking for more money for more trials, basic scientists are asking for more money to continue HIV basic science research and microbicide researchers are asking for more money to try to get a microbicide to market. Everybody is right in a different way.

The other important (and extremely sad) news was the data presented regarding the price that African women and women from other developing world countries are paying when they use single-dose nevirapine (NVP, Viramune) as a way to prevent maternal-fetal transmission of HIV infection. The response rate of subsequent NNRTI-containing regimens for these women is at least 20% less potent. All this made the general tone of the meeting pretty somber.

Regarding metabolic studies, although some interesting data were presented, unfortunately, none of it was encouraging. From a clinical perspective, the metabolic presentations that I think were the most important included the following:

**ACTG 5005**

Michael Dube presented data from ACTG 5005, the metabolic substudy of ACTG 384. In this study, patients were randomized to receive zidovudine (ZDV, Retrovir) plus lamivudine (3TC, Epivir) or stavudine (d4T, Zerit) plus didanosine (ddI, Videx) with efavirenz (EFV, Sustiva), nelfinavir (NFV, Viracept) or both. The original study was published in the New England Journal of Medicine.

The hypothesis of ACTG 5005 was that regimens containing the protease inhibitor (PI) nelfinavir would cause hyperlipidemia and insulin resistance, as compared to regimens containing efavirenz. This did not happen, and it is this which makes the results interesting.

The primary analysis was performed after 16 and 32 weeks of treatment, but data up to 64 weeks was presented. A summary of the conclusions discussed lipid metabolism: All regimens were associated with increases in fasting lipids. Regimens containing efavirenz or nelfinavir were
associated with similar increases. Changes in HDL-C and total HDL-C ratio were more favorable with efavirenz, but small in magnitude. Zidovudine/lamivudine tended to have more favorable changes in total-C and non-HDL-C than did didanosine/stavudine; didanosine/stavudine had a more favorable effect on HDL-C.

With regards to glucose metabolism, insulin resistance, as estimated by homeostasis model assessment (HOMA-IR), increased modestly in the group as a whole; regimens containing efavirenz and nelfinavir affected HOMA-IR in a similar manner, with no early increases with either agent. The lack of an early increase in HOMA-IR with nelfinavir suggests that acute insulin resistance is not a PI-drug-class effect (which is something that had been long assumed).

Indinavir (IDV, Crixivan) is the PI that produces the most insulin resistance, and it does so really quickly. Zidovudine/lamivudine and didanosine/stavudine-containing regimens affect insulin resistance in a similar manner.

In summary, this study challenges the common belief that all PIs—that is until atazanavir (ATV, Reyataz) was approved last year—have similar metabolic effects. It also challenges the idea that these metabolic side effects are mainly mediated through increasing insulin resistance and that NNRTIs are metabolically neutral. None of these assumptions turn out to be completely true.

The ROSEY Study

Lipoatrophy is the most difficult to treat of the metabolic complications associated with HIV and HIV treatment. Nothing seems to work well except switching off some of the antiretrovirals most commonly associated with its development—stavudine, and, to a lesser degree, zidovudine. Unfortunately, not all patients can switch antiretrovirals easily. The other alternative is an expensive surgical procedure which can produce an aesthetically acceptable result in some patients, but ignores the root of the problem.

Rosiglitazone, a drug used for the treatment of type II diabetes, has been suggested as a possible therapeutic agent to treat lipoatrophy in HIV-infected individuals. Rosiglitazone belongs to a family of drugs called glitazones. The glitazones are insulin-sensitizing drugs, which tend to increase the storage of fatty acids in peripheral fat tissue and to stimulate a receptor called PPAR-gamma in multiple types of cells (including fat cells).

Two small studies on rosiglitazone use have been presented so far:

At the 2002 Retrovirus conference, Sutinen, et al from Finland presented a small study of 30 lipoatrophic patients randomized to receive 8 mg a day of rosiglitazone or placebo. The drug did not seem to work at all, to the point that, based on this data, the ACTG stopped an ongoing trial of rosiglitazone.

During the 2003 IAS conference, Steve Grinspoon presented a small study of patients with insulin resistance that suggested they had an increase in subcutaneous fat after being treated with 4 mg a day of rosiglitazone.

As usually happens in medicine, a positive study gets more publicity than a negative one. Both studies were too small and underpowered to provide any definitive answer regarding how useful this drug is for the treatment of lipoatrophy.

During this conference, Andrew Carr from Australia presented the results of the ROSEY study. This study evaluated the use of rosiglitazone for the treatment of lipoatrophy. One hundred and eight HIV-1-infected lipoatrophic adults on antiretroviral therapy were randomized to rosiglitazone 4 mg twice daily (n=53) or matching placebo (n=55) for 48 weeks.

Limb fat increased by 0.14 kg in the rosiglitazone group and 0.18 kg ”0.18 kg” in the placebo group. Rosiglitazone had no significant benefit on any other measure of lipodystrophy.
So, clearly, 48 weeks of rosiglitazone use did not improve lipoatrophy in HIV-1-infected adults receiving antiretroviral therapy.

However, one issue with this study is that patients were allowed to switch off stavudine and PIs, which the same authors have already demonstrated increases peripheral fat in patients with lipoatrophy. That could have significantly contaminated the results of this trial, although I do not think it would have affected the main results.

Thus the bad news regarding lipoatrophy treatment continues, with yet another possible intervention that does not work very well, and so lipoatrophy remains a critical concern for patients.

The study is important because it dramatically demonstrates that the best way to treat lipoatrophy now is by preventing it through prescribing HIV medications that do not produce it.

ACTG 5087

Interventions for hyperlipidemia do not seem to do much better than those for lipoatrophy. Judy Aberg presented the follow-up data for ACTG 5087 (originally presented in Paris) that compared the administration of fenofibrate, pravastatin or both for the treatment of patients with hyperlipidemia. The benefits were as expected. Fenofibrate is good for patients with hypertriglyceridemia, pravastatin better for hypercholesterolemia and the combination a little bit better for the most severe cases.

The problem was that in most of the cases, the patients did not reach National Cholesterol Education Program (NCEP) goals. The message here is similar to that of the Andrew Carr paper—prevention is critical because, when someone develops these antiretroviral therapy-associated problems (hyperlipidemia or lipoatrophy), it is quite difficult to get rid of them with treatment. So far, switching antiretrovirals seems to be the best option, although sometimes this is not possible.

Supplementation With Fish Oil

Fish oil supplementation also only had modest effects on high triglyceride levels in a randomized trial by the University of North Carolina. David Wohl presented this randomized trial of patients with high triglycerides (200 to 2,000 mg/dL) on HAART and no history of diabetes mellitus. Patients were randomized to receive a nutritionist-administered AHA-based diet and exercise counseling (week 0 and 4) alone, versus with 3 g of fish oil daily (1,150 mg DHA, 1,750 mg EPA, Coromega Inc) for 16 weeks. Fish oil seemed to have modest effects (17% decrease in triglycerides), which in patients with triglyceride increases of 300 to 400% of the normal values, is probably not clinically useful. Again, prevention and a medication switch have been the most effective approaches to this problem.

Wasting

Although HIV-associated wasting has become a rare complication in the era of HAART, at least in the developed world, it still affects a significant number of patients. Hengge and colleagues presented a study evaluating oxymetholone for the treatment of this complication. In this randomized trial, 89 patients were randomized to receive two different doses of oxymetholone (50 mg two times a day or 50 mg three times a day) or placebo. Patients in the oxymetholone group gained more weight than the patients that received placebo (a couple of kg, or 4 pounds). However, this beneficial effect came at a price: an increased frequency of liver abnormalities and a suppression of pituitary gonadotropins (basically making patients decrease the endogenous production of testosterone). Both are well know side effects of anabolic steroids, as many players in major league baseball can testify to themselves.

The efficacy of this drug is similar to other known interventions for the treatment
of this kind of wasting—like growth hormone—and the cost is probably lower. Anabolic steroids are an alternative for the patient with wasting in whom HAART and nutritional supplementation do not work, fortunately, in a small number of individuals, since frequently these medicines have side effects.

**Osteopenia and Osteoporosis**

During the last couple of years, osteopenia and osteoporosis have become recognized metabolic complications associated with HIV or its treatment. There were only a few presentations related to this topic during this year’s conference. There was a poster10 from an Italian group showing improvements of bone turnover with the use of alendronate. However, surprisingly, the investigators did not see clear improvements in DEXA bone mineral density. This study confirms previous results presented last year in Boston11 by the Washington University group and solidifies the evidence that alendronate is a reasonable option for patients who have evidence of osteoporosis that warrants treatment.

In a similar way that the development of hyperlipidemia is a risk factor for cardiovascular disease, osteopenia and osteoporosis predispose one to fragility fractures. Although several studies have shown that osteopenia and osteoporosis are frequent among HIV-infected individuals, there have been no studies demonstrating an increased risk of fractures among these patients.

Grace McComsey presented data12 on the frequency of fragility fractures among HIV-infected patients, a potential sign that the elevated prevalence of osteoporosis might have significant clinical implications. Fragility fractures appear to be under-reported. McComsey identified 49 fractures among almost 9,000 patients followed in several clinics in the U.S. There is always the potential for recall bias in this type of study, but it looks like fragility fractures might be a problem.

**Connection of Obesity and HIV**

New data13 was presented regarding the high frequency of obesity in four clinics in Philadelphia, especially among African-American women. Obesity is much more frequent than wasting among American HIV-infected individuals. Although the prevalence of obesity is lower than in the general population, the numbers are quite concerning—HIV-infected women and men were equally likely to be overweight (30% versus 31%), however, women were significantly more likely than men to be obese (29% versus 11%). African Americans were more likely to be overweight or obese than non-African Americans.

In a logistic regression model, female sex (RR 2.0), African-American race (RR 1.3), smoking (RR 0.6), and current CD4 (for each 100 cells/μL increment, RR 1.11) were independent predictors of obesity. Obesity is a well-known risk factor for hyperlipidemia, diabetes and the metabolic syndrome. Obesity present at baseline or acquired during treatment of HIV might be a significant contributor to the metabolic abnormalities associated with HIV or its treatment.

**Conclusion**

The studies presented at CROI 2004 have not brought us any closer to understanding the metabolic side effects of HIV and its treatment. At this point, the best we can do to avoid these problems is simply avoid the drugs that cause the most metabolic side effects.

As a start, clinicians should always individualize HIV treatment for their particular patient. For patients who already have significant cardiovascular risk factors before they begin treatment (such as obesity, smoking or a family history of heart disease), the preferred choice should be NNRTI-based therapies. The drug regimens to be avoided, if at all possible, are those more commonly associated with the
development of hyperlipidemia (such as boosted PIs, perhaps with the exception of atazanavir). For patients concerned about the stigmatization of lipoatrophy, stavudine should be avoided.

Footnotes:


Osteopenia and Osteoporosis in HIV-Infected Adults and Children

Coverage provided by Pablo Tebas, M.D.

Pablo Tebas, M.D., is an Associate Professor of Medicine at University of Pennsylvania School of Medicine and principal investigator in the AIDS Clinical Trial Unit at University of Pennsylvania.

Stephano Mora from Milan gave us a good introduction this afternoon to the problem of bone metabolism in HIV-infected children.

As most of you know, osteopenia and osteoporosis are frequent among HIV-infected patients. It is still not clear if this problem is related to HIV infection itself, its treatment or both. It is easy to imagine that if this is a serious problem in adults with HIV, because there is a potential risk of increasing fractures in the future, it is even more serious in children with HIV. Children are in a period of development before they reach their peak bone mass, which occurs when they are approximately 25 years old.

Mora’s summary was taped and can be heard in webcast. You may want to consider listening to the talk, since it was a nice introduction to the current issues in the field. (For audio and slides, visit www.thebodypro.com/confs/retro2004/redirect/webcast0209e.html; for video and slides, visit www.thebodypro.com/confs/retro2004/redirect/webcast0209ev.html.)

Dr. Mora started with an overall introduction to the topic. He defined osteoporosis as a problem of bone mineralization and architecture that predisposes one to fractures. The World Health Organization (WHO) defines osteoporosis as based in bone mineral density (BMD) as measured by DEXA. The bone mineral density of a given individual is compared to the bone mineral density of an average 30-year-old. The result is expressed as the number of standard deviations from that measurement (the t score). A t score of less than -1 and greater than -2.5 defines osteopenia and a t score of less than -2.5 defines osteoporosis.

BMD can be measured using different techniques. The most popular of them is the already mentioned DEXA, but using plain XR, QCT scan or Q ultrasound are alternative ways to look at bone mineralization.

Each technique has its advantages and disadvantages. There are normalized data for adults using these techniques, so it is easy to calculate t scores. However, it is much more difficult with children because there are no normalized data for children since they grow so rapidly. Children’s bone mineral density cannot be expressed by comparison to the typical adult, who at 30 years old has reached his or her peak bone mass. This markedly complicates any type of study in this population.

Although there are multiple predictors for a person’s final bone mass, genetics is by far the most important factor and explains probably more than 75% of an individual’s final bone mass. Other factors that are associated with low BMD include: chronic diseases such as celiac, renal, and now, HIV

Abstract:
Disorders of Bone Mass and Bone Metabolism (Symposium 47: www.retroconference.org/2004/cd/Abstract/47.htm)

Authored by:
S. Mora, I. Zamproni, M. Sciannamblo, V. Giacomet, A. Viganò

Affiliations:
Sci. Inst. H. S. Raffaele, Milan, Italy; Univ. of Milan, Hosp. L. Sacco, Italy
infection; hormones (testosterone, estrogen, growth hormone, thyroid, etc.); behavioral factors such as exercise, alcohol abuse and tobacco use; and, finally, the use of certain drugs such as diuretics, anticonvulsants and maybe antiretrovirals.

The most classic approach to learn what is happening to the bone is to perform bone biopsies. But the use of biopsies is complicated for the study of bone metabolism, especially in children.

Nowadays, if we want to know the status of the bone, we tend to use markers of bone metabolism. The bone is a live tissue in a continuous status of remodeling, with a delicate equilibrium between bone formation (done by a particular group of cells in the bone called osteoblasts) and resorption (done by a different group of cells called osteoclasts).

Osteocalcin and bone alkaline phosphatase are used to measure the activity of osteoblasts, and pyridinolines and telopeptides are used for the measurement of bone destruction. HIV infection, in the absence of treatment, is characterized by a status of low bone turnover (especially in advanced disease).

After the initiation of antiretroviral therapy, there is a switch to a state of high bone turnover that is maintained over time. This has been well characterized in adults over the last few years. Dr. Mora presented data suggesting that the same phenomenon is going on in children. He also presented data suggesting that the use of antiretroviral therapy is associated with an increase in RANK-L, a cytokine that increases the activity of osteoclasts, and a decrease in osteopetregin, a cytokine responsible for osteoblast activity.

In summary, deficits of bone mineralization are quite common in children with HIV, especially if they are on antiretroviral treatment, and this is an important issue that clinicians taking care of these patients will have to face. What about treatment? In adults who have developed this problem, we recommend supp-lementation with vitamin D and calcium as well as lifestyle changes that tend to improve bone mineralization (such as regular exercise and discontinuing tobacco and alcohol use).

If the osteoporosis is severe enough to warrant treatment, then alendronate is a potential option. During last year’s Retrovirus conference, my colleagues and I presented data on the use of alendronate in patients with HIV infection. During this meeting, Guraladi (Poster 742: www.retroconference.org/2004/cd/Abstract/742.htm) presented some preliminary data with similar (but less dramatic results). The ACTG is currently performing a larger study called A5163 that will also evaluate the utility of this drug, focusing especially on women.

Unfortunately, the use of alendronate in children cannot be recommended because it might increase the fragility of bone. So, for the treatment of children with deficits in bone mineralization, we are left with “classic measures” such as adequate intake of calcium and vitamin D and adequate exercise and sun exposure (to increase the synthesis of endogenous vitamin D).

Footnote:
No Lipodystrophy Yet Seen With Regimens Including Enfuvirtide

Coverage provided by Calvin J. Cohen, M.D., M.S.

Cal Cohen, M.D., M.S., is Research Director of the Community Research Initiative of New England and a clinical instructor at Harvard Medical School in Boston.

There has been a lot of concern regarding the contribution of many antivirals to changes in body shape—specifically the changes in body fat called lipodystrophy. While enfuvirtide (T-20, Fuzeon) is an antiviral, it works by a completely different mechanism, specifically blocking the attachment of HIV to human cells. Given this difference, it is important to assess whether enfuvirtide has any impact on body composition or other metabolic toxicities such as lipid disturbances.

These results come from an analysis of the “TORO” studies, which compared a standard regimen of antivirals versus the addition of enfuvirtide to a standard combination for patients with multidrug-resistant HIV. Measures of fat distribution were done by DEXA scanning and CT scans in a subset of about 150 people in these studies. In addition, all participants had body shape and blood chemistry measurements done.

The results were quite clear. Over the 48 weeks of the study, there was no negative impact—and perhaps a trend actually favoring the arm containing enfuvirtide for less fat redistribution and other adverse effects. Specifically, the rate was 11.7% for all adverse events of this type (lipodystrophy, diabetes, heart disease and lipid abnormalities) for the control arm, and 9.2% for the enfuvirtide arm. There were no differences seen in patients’ waist/hip measurements in either arm over time.

There was a suggestion from the DEXA scans for recovery of subcutaneous fat on the enfuvirtide arm, and this was also seen on the CT scan. An increase in visceral fat was seen more in the enfuvirtide arm than the control arm, although the authors noted that this might, in part, reflect the changes associated with recovery from HIV wasting. Finally, neither lipid differences nor changes in blood glucose were seen.

Overall, the authors conclude that there were no adverse events related to these troubling metabolic changes associated with the use of enfuvirtide. Specifically, there were trends favoring improvements in terms of fewer reports of lipodystrophy, and evidence of recovery of limb fat on the enfuvirtide arm.

Abstract:
The Effects of Enfuvirtide Therapy on Body Composition and Serum Lipids Through 48 Weeks in the TORO Trials (Poster 715: www.retroconference.org/2004/cd/Abstract/715.htm)

Authored by:

Affiliations:
These results support that the unique mechanism of action of enfuvirtide is also distinct with regard to the side effects we see with the other classes of antivirals. While improvements continue to be explored in these other classes as well, it appears from studies of enfuvirtide that the drug doesn't add any significant additional risk for the metabolic disturbances that complicate the treatment of HIV.
Predicting Lipoatrophy After Treatment Initiation

Coverage provided by Pablo Tebas, M.D.

Pablo Tebas, M.D., is an Associate Professor of Medicine at University of Pennsylvania School of Medicine and principal investigator in the AIDS Clinical Trial Unit at University of Pennsylvania.

I liked this study. Mustafa Noor and the Bristol-Myers Squibb (BMS) group did a post-hoc analysis of a recent, large, randomized trial that compared the use of the currently available formulation of stavudine (d4T, Zerit) and stavudine extended release (XR), a once-a-day formulation that has been approved by the U.S. Food and Drug Administration (FDA) but has not made it to the market yet. Stavudine XR/PRC (prolonged release capsules) provides equivalent 24-hour exposure to stavudine IR (immediate release; the current formulation), but has one half the peak and two- to three-fold higher trough plasma levels.

Week 48 efficacy and safety data demonstrated comparability, but the differing pharmacokinetics could result in clinically relevant differences in outcomes with longer dosing. The two-year follow-up data was presented recently during the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) conference in September 2003.1

The body of literature that points to stavudine as causing lipoatrophy has dramatically decreased its use and has made many people forget that it is actually a well-tolerated drug (at least in the short-term administration), and that when it was approved, clinicians tended to use it instead of zidovudine (ZDV, Retrovir), which had caused a lot of nausea and headaches as frequent side effects.

The question BMS was asking in this study is an important one: Is there any way to predict who is going to develop lipoatrophy after treatment is initiated? If we were able to do that, we could potentially use this drug in patients who are most likely to tolerate it well and who will benefit more from it.

These two studies (096 and its rollover 099) were large, randomized trials that involved almost 900 patients. They randomized the patients to receive the old formulation of stavudine or the new XR formulation in addition to lamivudine (3TC, Epivir) and efavirenz (EFV, Sustiva). Both arms were similarly potent. The stavudine XR arm might be slightly less toxic.

In this study, BMS identified patients who had developed lipoatrophy using a definition created by the investigator, so there was no objective data used from DEXAs or anything like that.

BMS looked at multiple baseline variables and their association with the development of lipoatrophy. At the end of the game (a multiple regression model), the

Abstract:
Baseline Triglyceride Levels Predict Development of Lipoatrophy in Patients Treated With Stavudine Extended-Release/Prolonged-Release Capsules or Stavudine Immediate-Release (Poster 722: www.retroconference.org/2004/cd/Abstract/722.htm)

Authored by:
M. Noor, C. Dezii, C. McLaren, V. Wirtz, J. Maa, L. Bessen, S. Hodder

Affiliations:
following variables were associated with the development of lipoatrophy: having a triglyceride level above 200 mg/dl, being older than 40 years of age and taking stavudine IR rather than the new formulation.

If you had triglycerides >200 mg/dl, were older than 40 and were taking stavudine IR, the probability of developing lipoatrophy was 33% compared to only 10% if you were younger than 40 and your baseline triglycerides were less than 200 mg/dl.

The study has several limitations (the main one was the already mentioned lack of an objective measurement of fat) and will have to be confirmed in other trials with more objective measures of body fat distribution, but this is an important first step. The ultimate goal is to try to identify predisposing factors and predictors that would help tailor antiretroviral therapy to each individual patient, not only for successful viral suppression, but also to minimize toxicity.

Footnote:
An Update on the Diagnosis and Management of HIV-Associated Peripheral Neuropathy

Coverage provided by Keith Henry, M.D.

Keith Henry, M.D., is Associate Professor of Medicine at the University of Minnesota School of Medicine and Director of HIV Clinical Research at Hennepin County Medical Center in Minneapolis. In addition, he is Medical Director of the AIDS Unit and the Sexually Transmitted Disease Clinic of the St. Paul Department of Public Health.

A tired but proud David Simpson (his wife just had a baby!) provided an update on this important topic. Clinical data from the pre-HAART era document that one third of HIV-infected persons experienced peripheral neuropathy (PN). Perhaps the most important point of the whole presentation was not only that the diagnosis of PN is frequently missed, but that the type of PN is often misdiagnosed. The two key types of HIV-related peripheral sensory neuropathy (HIV-SN) are distal sensory polyneuropathy (DSP), which is caused by a direct effect of HIV, and peripheral nerve injury, which is caused by specific HIV drugs (known as antiretroviral toxic neuropathy or ATN).

Clinical evaluation of a patient is crucial for diagnosing PN. The specific location of the PN provides the best clue as to the diagnosis. (For example, dideoxy-nucleoside-associated ATN due to didanosine [ddI, Videx], stavudine [d4T, Zerit] or zalcitabine [ddC, Hivid] usually involves the feet/ankles and then the hands in a symmetrical manner.)

Dr. Simpson referenced Poster 493,1 which is a study by the Adult AIDS Clinical Trials Group comparing the usefulness of a brief neurologic assessment evaluation (focusing on a patient’s vibration sense in his or her feet, as well as ankle reflexes) to a more comprehensive examination. The brief examination was not very sensitive for PN (meaning it would miss many cases that a neurologist would identify with a more thorough examination) but had a high specificity (meaning that when a diagnosis was made it was almost always accurate).

An important point worth repeating is the importance of a good examination by an HIV-experienced neurologist. In one study cited by Dr. Simpson, 71% of the study patients with neurologist-confirmed PN had not been identified by the HIV clinician. Patients with undiagnosed PN may have an increased risk for worsening PN if neurotoxic drugs are then utilized.

There are risk factors clinicians can take into consideration as signs that a patient should be monitored for PN. For example,
the lower a patient’s CD4 count, the greater the PN risk.

In addition, Dr. Simpson noted that the rate of PN increases over time. In one study, for example, after two years of living with a CD4 count of less than 200, 50% of the study patients experienced PN. Higher HIV RNA levels are also associated with an increased risk for PN. It is important to emphasize that although the “D” drugs mentioned above can aggravate or cause HIV-related peripheral sensory neuropathy, the use of HAART has been associated with the reversal or protection against PN.

In another poster presented at this meeting, clinical improvement of PN was associated with the use of HAART and/or the alteration of the dose of the offending D-drugs. Because D-drug-related PN can occur fairly quickly after the initiation of HAART, Dr. Simpson suggested careful monitoring during this period so that early PN can be more easily addressed.

Dr. Simpson also discussed the pathogenesis of HIV-associated PN, with two possible mechanisms being the deposition of tumor necrosis factor-alpha or a direct toxic effect of gp120.

For drug-related sensory neuropathy (ATN), a likely cause is considered to be a direct toxic effect of dideoxynucleoside on mitochondria. Other neurotoxic agents (such as dapsone, metronidazole, INH and many others) can further aggravate HIV-related peripheral sensory neuropathy. Stopping the offending drug usually results in an improvement in distal sensory polyneuropathy over 8-16 weeks.

The recently described HIV-associated neuromuscular weakness syndrome (NMWS) looks like Guillain-Barre syndrome and is often associated with some degree of lactic acidosis.

To sum up, Dr. Simpson pointed out that the management of PN involves numerous approaches. Correcting metabolic (diabetes, thyroid abnormalities, or alcoholism) or nutritional causes (such as vitamin B12 deficiency), optimizing virologic control and stopping any neurotoxic agents are the cornerstones of PN treatment.

In addition, when necessary, pain management is crucial. For patients, PN is often the most physically painful part of their experience of living with HIV. The pathophysiology of HIV neuropathic pain involves enormously complex pathways of pain perception that allow for numerous areas for intervention. However, many patients are undertreated for pain in general, as well as specifically for HIV neuropathic pain.

Barriers to the optimal management of PN often involve the patient, provider as well as general health system issues. Adequate use of analgesics (including narcotics), as well as such newer drugs like gabepentin, lamotrigene, topical capsaicin, or prospatide (under study by the AACTG), may offer improved treatment options in the future.

Footnotes:
Deaths Down for People With AIDS; Causes Shift From AIDS- to Age-Related Diseases

Coverage provided by Corklin R. Steinhart, M.D., Ph.D.

Corklin R. Steinhart, M.D., is the Medical Director of the Florida/Caribbean AIDS Education and Training Centers and is an Assistant Professor of Medicine at the University of South Florida College of Medicine.

On Mar. 26, 1998, the first of a number of important observational database studies was published in the New England Journal of Medicine. This study by Palella et al.1 was the first to report a marked reduction of morbidity and mortality as the era of protease inhibitors, or HAART, began.

Information derived from this large cohort of HIV-infected patients (HOPS or HIV Outpatient Study) regarding the trends in both the death rate and the causes of death among HIV-infected persons has been regularly updated.

The data is presented from the HOPS cohort, in which 5,561 participants, treated at two public, four university and two private clinics, have been followed from Jan. 1, 1996 to Dec. 31, 2002 for a median follow-up period of more than 35 months. In this most recent analysis, the rate of death, opportunistic disease (OD) and non-opportunistic diseases (NODs), determined to be the cause of death by disease category, have been evaluated. This latest analysis also looked at CD4 cell counts and time spent on antiretroviral therapy (ART).

As previously reported (as of June 2003), the death rate fell from 6.3 deaths per 100 person-years (PYs) of observation to 2.2 in 2002, stabilizing at ~2 deaths/100 PYs from 1998 on. Some of us have been concerned that the death rate has hit a plateau; however, in discussing the results with the lead author, Dr. Frank Palella, since the rate is so low, it may be difficult to demonstrate any further reductions. Similarly, the death rate due to ODs has declined from 23 deaths/100 PYs in 1996 to 6 deaths/100 PYs in 2002. In contrast, the death rate from NODs increased over the time period and depended upon the length of time the patient was on ART: 45% for patients on ART for two years to 70.2% for those on ART for seven years.

The percentage of patients on ART rose overall from 48% in 1996 to 80% in 2002. However, the particular types of ART used have not been able to be determined. The increased use of ART was associated with an increase in the mean CD4 cell count and the level within six months of death increased from 65.6 cells/mm³ in 1996 to almost 150 cells/mm³ (148.4) in 2002. However, viral loads were not reported. For the three-year period 2000-2002, the most frequent NOD causes of death were hepatic (35.6%), pulmonary (22.7%), cardiovascular (17.2%) and renal (9.8%).

The conclusions drawn from this paper are quite simple: The overall death rate and
deaths due to ODs have continued to remain low over the past several years, while the rate due to NODs has increased. These changes have been associated with an increasing time on ART and have occurred at significantly higher CD4 cell counts. However, Dr. Palella commented that the “real” take-home message from the data analyzed is as follows: “If someone takes ART, they will live longer and when death occurs, it will not be due to an AIDS-related condition.”

Indeed, this is consistent with what many of us are seeing in our patients. As this occurs, age-related diseases (e.g., cardiovascular disease, diabetes mellitus, etc.) begin to play an ever-increasing cause of both morbidity and mortality. However, the current analysis does not provide us with the influence of age on any of the NODs. The HOPS database (in addition to other large cohorts; e.g., MACS, EuroSIDA, etc.) continues to provide us with important information regarding the natural history of HIV/AIDS. As is true for all observational databases, they do not give us “cause and effect” relationships, merely associations. However, these associations often lead to clinical trials that do attempt to evaluate the possible cause and effect relationships that are so necessary to make further advances in the management of HIV/AIDS.

Footnote:
Quality of Life Impact of Non-AIDS-Related Serious Adverse Events Versus AIDS-Related Events

Coverage provided by Corklin R. Steinhart, M.D., Ph.D.

Corklin R. Steinhart, M.D., is the Medical Director of the Florida/Caribbean AIDS Education and Training Centers and is an Assistant Professor of Medicine at the University of South Florida College of Medicine.

For patients with advanced HIV disease, the fear of AIDS-related complications and death continues to play an ever-increasing role in their lives. This is particularly important for the many patients who have failed ART and have multidrug-resistant virus.

The use of the usual treatment strategies involving standard three- to four-drug HAART or mega-HAART inevitably can affect the quality of life of these patients and may add to the uncertainties of what may lie ahead. In this regard, quality-of-life assessment (QOL) tools have been developed to objectively quantify quality of life parameters that are then able to be evaluated in the same fashion as the usual “hard” variables such as CD4 cell count, viral load, death rate, etc.

The OPTIMA trial is an ongoing multinational study of alternative treatment strategies in patients with more advanced HIV disease (CD4 cell counts <300 cells/mm³ and demonstrated resistance to three classes of ARVs). In the current presentation, the effect of both AIDS and non-AIDS diseases on quality of life in such patients, who are taking either “standard” HAART or mega-HAART, are being evaluated. In speaking with the lead author, Dr. Sheldon Brown of the Bronx VA Hospital, the important question of trying to develop a broader definition of “burden of disease” and its effect on quality of life should be paid more attention to in patients with advanced HIV.

In this study, three groups of patients were identified: those experiencing AIDS-related events (AREs), non-AIDS-related serious events (non-AIDS SAEs) and a control group not having an event (Non-E). The MOS-HIV quality of life instrument (a well-studied and validated quality of life tool) was used to compare patients’ physical and mental health statuses at baseline, pre-event and post-event in these three groups. If an ARE and a non-AIDS SAE occurred at the same time, they were excluded from the analysis.

As of September 2003, 235 patients (median CD4 cell count = 115 cells/mm³),

Abstract:
The Effect of Non-AIDS Serious Adverse Events Equals or Exceeds That of AIDS Outcomes in Patients With Advanced Multi-Drug Resistant HIV Disease (Poster 874: www.retroconference.org/2004/cd/Abstract/874.htm)

Authored by:
S. T. Brown, J. Singer, A. Anis, H. Sun, T. C. Kyriakides, B. J. Angus, K. Swanson, W. Cameron, A. Babiker, M. Holodniy, The OPTIMA Study Team

Affiliations:
having a median duration of follow-up of 11 months, have been enrolled and evaluated. Complete accrual is not expected until December 2005.

Six of the eight deaths that have occurred thus far have been due to AIDS. Sixty-six events were able to be evaluated (104 non-AIDS SAEs that occurred in 56 patients and 45 AREs in 35 patients). At baseline, there were no differences between the three groups with respect to either physical health (PHS) or mental health (MHS) scores.

Compared to the non-E group, physical health scores declined in the non-SAE group and both physical health and mental health declined in both the non-SAE and ARE groups. Although both physical health and mental health scores declined from pre-event to post-event in the two event groups, there were no differences between them. However, and most interestingly, there was a significant decline in physical health in the non-SAE group and a significant decrease in the mental health in the ARE group.

In summary, non-AIDS related serious adverse events occurred more frequently than did AIDS-related events. In addition, the effect of the particular type of event had differing impacts on quality of life indices between the two event groups.

What does this all mean? In advanced HIV disease, the type of adverse event that occurs is perceived differently by the patient. According to Dr. Brown, the results demonstrated in the analysis thus far suggest that, when confronted with an AIDS-defining event, the impact on quality of life is psychological; this may be due to the fact that the patient is now confronted with the realization that the end may be near.

Conversely, when the patient with advanced HIV disease suffers a non-AIDS related serious event (e.g., infection, cardiovascular event, etc.) the impact on quality of life is only physical. This may signify that he/she is only suffering from any serious medical condition that a non-HIV patient sustains and does not indicate a worsening of the HIV/AIDS.

The results of this interim analysis are important in that they help to better define the impact of serious events on patients with more advanced HIV disease.

However, this physician remains a bit confused as to how this information relates to the alternative treatment strategies (standard HAART vs. mega-HAART) that are being prospectively evaluated in the OPTIMA study. Information thus far has not been provided regarding whether or not there is a relationship between the two treatment strategies being evaluated and the important quality of life data presented here.

Nevertheless, the inclusion of quality of life evaluations in many studies (not only observational cohort studies but clinical treatment trials as well) is now increasing and suggests that it is not only the impact of treatment regimens on “numbers” that is important to be determined but quality of life issues as well.

Data from studies such as this one will help us better define what impact various treatments may have (not presented here) on the patient as an individual. This may lead to better interventions when a patient with advancing or advanced HIV disease sustains some type of serious adverse event, whether or not it is AIDS- or non-AIDS related. We should look forward to further updates from this trial that hopefully will also include information that has not been included thus far.
New Antiretroviral Drugs in Development

Coverage provided by David Wohl, M.D.

David Wohl, M.D. is an assistant professor of medicine at the University of North Carolina at Chapel Hill, and co-directs HIV services for the North Carolina Department of Corrections.

The need for potent new antiretrovirals is obvious to anyone who treats people living with HIV infection. Drug resistance and intolerance limit the benefits of the current slate of HIV medications. As the long-term consequences of HIV therapy manifests itself in vanishing facial fat and elongating lines of resistance-red ink on genotype reports, clinicians are hard-pressed to craft yet another salvage regimen with whatever leftover antiretrovirals remain.

Fortunately, therapies that are less toxic, more convenient and active against drug-resistant virus are in early development stages in each of the major drug treatment classes: entry inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Results from several of these efforts were reported at the 11th CROI.

New NRTIs

NRTIs are considered the backbone of combination HIV therapies. However, extensive use of these agents has led to increased rates of NRTI resistance among not only treatment-experienced patients but also those naïve to treatment. Development of NRTIs that can suppress virus resistant to the currently available nucleosides and that are free of the mitochondrial toxicity associated with most members of this antiretroviral class would be a major advance in HIV care.

Data from studies of two promising new cytidine analogues SPD-754 and Reverset were presented at CROI. They offer a glimpse at what the NRTI of the future will look like.

SPD-754

SPD-754 is an (-) enantiomer of a previously studied compound, dOTC, which had unacceptable rates of toxicity, halting its further study. SPD-754 appears to be much better tolerated and in vitro data suggest the drug is active against NRTI-resistant HIV-1, including virus resistant to another cytidine analogue, lamivudine (3TC, Epivir).

A dose-ranging study$^1$ of SPD-754 was conducted in 63 HIV-infected, treatment-naïve (<7 days) individuals (43% of whom were women) randomized to one of six doses of SPD-754 or placebo. The study found a respectable reduction in HIV viremia following 10 days of monotherapy. The median baseline plasma HIV RNA level was 4.3 log10 copies/mL and the median CD4+ cell count was 450 cells/uL. The lowest dose of SPD-754, 400 mg, produced a 1.18 log10 decline in viral load. The 1,200-mg and 1,600-mg arms experienced a greater than 1.5 log10 reduction.

SPD-754 had significant antiviral activity even among the four participants who had baseline NRTI resistance. On therapy, no new NRTI mutations emerged in these patients.

Safety data from this trial, which was conducted in South Africa, Thailand and Argentina, were not presented. An
accompanying oral presentation of the in vitro and in vivo investigations of the co-administration of SPD-754 and lamivudine demonstrated no pharmacokinetic interaction between these analogues. However, lamivudine markedly reduced the intracellular concentration of phosphorylated SPD-754, indicating co-administration will likely not be feasible.²

Reverset (D-D4FC)

Another cytidine analogue, Reverset or D-D4FC, was studied in a similar small pilot study of 30 HIV-infected subjects. Prior studies of Reverset have demonstrated activity against wild-type HIV-1 and HIV-2 as well as virus resistant to lamivudine, zidovudine (ZDV, Retrovir) and other NRTIs.

However, in vitro, the multi-drug resistant Q151M mutation and the 69 insertion produce highly reduced susceptibility to Reverset, while the K65R mutation leads to a three-fold reduction in susceptibility. Reverset’s long intracellular half-life (more than 17 hours) bodes well for once-daily administration.

In this 10-day, dose-escalation trial, subjects with a viral load of more than 5,000 copies/mL and a CD4+ cell count of more than 50 cells/μL were randomized to 50 mg, 100 mg or 200 mg of active drug or placebo. At baseline, the median plasma HIV RNA levels among the arms were between 4.24 and 4.81 log10 copies/mL. The median CD4+ cell counts were between 353 and 645 cells/μL. All viral genotypes had wild-type patterns at entry.

After 10 days, viral load declined by 1.67, 1.74 and 1.77 log10 copies/mL in the 50-mg, 100-mg and 200-mg arms, respectively. CD4+ cell counts climbed in the active-treatment arms. There were no significant clinical or laboratory adverse events reported.

Discussion

SPD-754 and Reverset may be a boon to future salvage therapy. Importantly, neither agents has in vitro evidence of mitochondrial toxicity. In addition, with the current heavy reliance on zidovudine + lamivudine + efavirenz (EFV, Sustiva) as initial therapy, subsequent salvage regimens must often contend with a lamivudine-associated M184V mutation, the NNRTI class killing mutations (e.g., K103N) and sometimes thymidine analogue mutations.

Salvage therapy needs NRTIs that can be used against NRTI-resistant virus. Both of these new agents seem to fit this role and may be ideal second-line agents. Their adoption as first-line antiretrovirals hinges on their comparative potencies, resistance patterns, long-term tolerabilities and cost.

As an intracellular interaction between lamivudine and SPD-754 has been demonstrated, extensive future study of antagonism between lamivudine and, by extension, emtricitabine (FTC, Emtriva) and Reverset and between Reverset and SPD-754 will also be required.

New NNRTIs

Arguably, there is no antiretroviral class more in need of a new and improved addition than the NNRTIs. Among the most potent antiretrovirals, the vulnerability of NNRTIs to resistance leads to rapid development of resistance mutations that cripple the class and complicate salvage regimens. Therefore, a Holy Grail of drug development has been the creation of an NNRTI with activity against K103N mutant virus.

TMC-125

TMC-125 is the leading contender to be the first of the next generation of NNRTIs. Previous studies have demonstrated that this compound is active against NNRTI-resistant strains of HIV-1. It has a novel structure that is relatively flexible, allowing for adjustment in shape to mutational changes in its target and avid binding to the site. Initial clinical investigation demonstrates its overall potency; however,
this may be attenuated in patients with significant NNRTI resistance.3

There was not much new data about TMC-125 presented in San Francisco. A poster4 detailing an in vitro investigation of the activity of TMC-125 against increasingly NNRTI-resistant virus was presented.

By first examining the phenotypic susceptibility of TMC-125 among over 5,600 clinical isolates, the investigators identified mutations associated with resistance to the drug and, along with other resistance data, constructed isolates containing single, double and triple TMC-125 mutations.

The panel of single mutants contained known NNRTI mutations, such as K103N, as well as mutations that have been selected for in vitro by TMC-125 and mutations identified among clinical isolates (i.e., K101P and Y181I).

Of the 59 single mutants created and tested, four demonstrated a greater than 10-fold reduction in susceptibility to TMC-125: Y181I, Y181V, F227C and M230L. These mutations were observed to be relatively rare (<2%) in a database of over 7,000 isolates known to be resistant to NNRTIs.

Accumulated resistance, as expected, led to reduced antiretroviral activity. Double mutant constructs containing V179F and Y181C conferred over 100-fold resistance to TMC-125. Again, this mutational duo is rare (<1%) among isolates resistant to the current crop of NNRTIs, although Y181C itself is common—observed in 37% of the NNRTI-resistant clinical isolates. A number of triple-mutant strains containing at least K103N and L100I were also evaluated and several conferred high-level resistance to TMC-125.

These data demonstrate that this new NNRTI may be bulletproof, but it is hardly bomb proof against some of the resistance mutations that are seen in NNRTI-experienced patients, particularly when select mutations are present in combination. Fortunately, these mutations are relatively rare at this point. Phase II trials of TMC-125 are underway.

Discussion

Preclinical data5 from a number of different pharmaceutical companies indicate the hunt for a better NNRTI continues. Whether any of these will advance to clinical testing, as TMC-125 has, remains to be seen.

Certainly, as mentioned previously, the potency of NNRTIs is clear. These are the most popular drugs used in first-line therapies today. Their Achilles’ heel, of course, is their low genetic barrier to resistance. The significance of agents that are active against NNRTI-resistant virus, less susceptible to rapid resistance and well tolerated should not be underestimated. Such drugs may herald a new era in HIV therapy. Can there be any finer lure to entice pharma?

New PIs

The supremacy of PIs as the anchor of initial combination HIV therapy has faded in the face of the well-demonstrated potency of NNRTIs, adverse effects associated with the PI class and the popularity of triple nucleoside therapy. However, PIs have made a resurgence. Last year, lopinavir/ritonavir (LPV/r, Kaletra) earned a coveted spot on the U.S. Department of Health and Human Services’ short list of recommended first line therapies.6 In addition, over the past few months, atazanavir has become the hit antiretroviral sensation of the year.

As is the case for the other classes of HIV therapy, though, there is a need for PIs that are more convenient, less toxic and active against resistant virus.

TMC-114

Another drug being developed by Tibotec, the maker of TMC-125, is TMC-114. This PI has been studied in HIV-infected persons during a two-week, dose-ranging trial in which patients failing PI-based therapy either substituted their current PI
for TMC-114 along with 100 mg of ritonavir (RTV, Norvir) or continued their PI (IAS 2003, abstract LB16). An average decline in viral load of 1.35 log10 was observed in the TMC-114/ritonavir arm, demonstrating the efficacy of this boosted PI.

A follow-up study7, presented at CROI, examined the influence of baseline genotypic and phenotypic PI resistance and response to TMC-114/ritonavir among 38 subjects randomized to receive the compound. Whether a subject had a single-PI mutation, phenotypic resistance to all current PIs except atazanavir (ATV, Reyataz) (which had not been approved at the time this study was performed), or high-grade lopinavir (LPV) resistance by phenotype at baseline, the median change in viral load at day 14 was -1.4 to -1.5 log10 copies/mL.

In another study much like the one presented on TMC-125, the activity of TMC-114 against a host of resistant viral isolates was reported8. A data set of 5,601 isolates, of which 2,202 were known to be PI resistant (greater than four-fold decreased susceptibility), were tested and TMC-114 appeared to be active against strains resistant to anywhere from one to seven PIs and those containing one to three primary PI-resistance mutations. Activity here was defined as having a less than four-fold decrease in susceptibility.

Discussion

Overall, TMC-114 appears promising. However, its current liquid formulation, which contains polyethylene glycol (PEG) to increase bioavailability, may be associated with a high rate of gastrointestinal adverse effects. Data on lipids and glucose will need to be evaluated during long-term studies. In addition, how this boosted PI will stack up clinically against lopinavir/ritonavir (LPV/r, Kaletra)—a drug whose activity is measured in terms of having a less than 10-fold reduction in susceptibility—remains to be seen.

There were no new data on tipranavir, which is likely to be the next approved antiretroviral agent.

New Entry Inhibitors

The most exciting compounds in development are those that inhibit HIV entry into the cell. These agents can be categorized according to the specific point in the process of HIV entry where the agent interferes: i.e., attachment inhibitors, chemokine receptor antagonists and fusion inhibitors.

BMS-488043

BMS-488043 is an oral attachment inhibitor that prevents the binding of the viral envelope protein gp120 to cellular CD4+ receptors, an initial step in the chain of events leading to viral fusion and entry. The safety and antiretroviral activity of the compound was studied at two twice-daily doses, 800 mg and 1,800 mg, in HIV-infected men and women who were either treatment naive or off of HIV therapy for at least four months and had a CD4+ cell count of at least 250 cells/uL and a plasma viral load of 5,000-500,000 copies/mL.9 (In the interest of full disclosure, this author was a participating investigator in this study.)

Two groups of 15 subjects (12 active/three placebo per group) received 800-mg or 1,800-mg doses of BMS-488043 or placebo exactly every 12 hours for eight days with a high-fat meal. At baseline, the median viral load was 4.77 and 4.65 log10 copies/mL in the 800-mg BID and the 1,800-mg BID cohorts, respectively. The median baseline CD4+ cell count was 413 cells/uL and 372 cells/uL, respectively.

After eight days of therapy, viral load dropped by a median of 0.72 log10 copies/mL in the 800-mg BID arm and 0.96 log10 copies/mL in the 1,800-mg BID arm. There was no change in the viral load among patients who received placebo. The agent was well tolerated with no treatment-limiting toxicity observed. Despite the respectable median virologic responses, the
range in the degree of viral decay during the short study was relatively wide. This finding may spell the end of the road in the development for this particular compound, one of several in this class the company is considering.

**TNX-355**

There was new data on another attachment inhibitor, TNX-355, a humanized anti-CD4 antibody, engineered by grafting murine proteins onto a human IgG4 antibody construct and then mutating amino acids in the framework to produce a structure that is 95% human. This compound received attention at last year’s CROI\(^{10}\) and updated clinical data from HIV-infected patients receiving the compound were presented during a poster\(^{11}\) session at this year’s CROI.

In this study, three doses of TNX-355 were administered for nine weeks to 22 subjects who were either off antiretroviral therapy or failing their regimen. In various doses and frequencies, TNX-355 produced about a 1 log\(_{10}\) drop in viral load. However, by week nine, plasma HIV RNA levels returned to baseline and resistance to the compound was detected. CD4+ cell counts, as has been seen in results from earlier studies on this agent, rose and tended to remain elevated. No drug-related serious adverse events were seen.

This is a very novel agent that if found to be effective and well tolerated in larger trials, may usher in a new approach for the engineering of HIV therapeutics. Using antibodies to interrupt the HIV lifecycle was one of the first strategies to be considered early in the epidemic. However, prior attempts at virus-directed antibody therapy were failures. This agent has proven its ability to reduce HIV viremia, and that is a significant first step. TNX-355 is sure to be subjected to more investigation.

**SCH-D**

Along with the CD4 receptor, HIV uses the CCR5 receptor to gain entry into the host cell. Blocking of this so-called co-receptor interferes with virus-cell interface and aborts cellular infection. SCH-D is an oral CCR5 receptor antagonist that was studied in 48 HIV-infected individuals who had not received antiretroviral therapy within two months of study entry and had a CD4+ cell count of at least 200 cells/µL.\(^{12}\)

Subjects entered three different dosing cohorts: group 1: SCH-D 10 mg twice daily for 14 days (12 on drug, 4 on placebo), group 2: SCH-D 25 mg twice daily for 14 days (12 on drug, 4 on placebo), and group 3: SCH-D 50 mg twice daily for 14 days (12 on drug, 4 on placebo).

The subjects were randomized 3:1 to drug or placebo for 14 days. A dose-related increase in antiretroviral activity was seen with mean log\(_{10}\) reductions in viral load of -1.08, -1.56 and -1.62 in the 10-mg, 25-mg and 50-mg BID arms, respectively.

CCR5 antagonists may select for CXCR4 virus, which has been associated with a more rapid decline in CD4+ cell counts and progression to AIDS. Indeed, in this study, a subject with a mixed viral population had his predominantly CCR5 virus replaced by CXCR4 variants, although he did enjoy a 0.5-log\(_{10}\) decrease in his viral load. (This is in contrast to a subject—in the study of a different CCR5 receptor antagonist, UK-427, 857—who had a mixed CCR5 and CXCR4 population while on treatment, but whose viral load did not drop and had a reversible predominance of CXCR4 virus\(^{13}\).)

Another individual who was receiving SCH-D had CXCR4 virus detected transiently during the study. SCH-D was reportedly well tolerated, though it should be recalled that SCH-C, a previously studied compound, had worrisome cardiac toxicity. To date, however, this has not been observed with SCH-D. This study also elucidated the metabolic pathway for SCH-D and it appears that there is potential for drug-drug interactions, since this drug is metabolized via pathways other HIV medications also use.
GW-873140

GW-873140 is another CCR5 receptor antagonist that is orally bioavailable and potent \textit{in vitro}. It was administered to 70 healthy, HIV-negative volunteers (57 males, 13 females) at a variety of doses in a double blind, randomized, placebo-controlled study\textsuperscript{14}. No serious adverse events and no cardiac-related abnormalities were seen. Co-administration with food increased drug exposure. There is potential for this agent to be administered once a day.

\section*{Discussion}

As is obvious, all of these compounds are in their developmental infancy. It will take years for even the most promising of these drugs to be considered for FDA approval. However, it is a good sign that there are a continuing number of HIV drugs in their early stages of development, particularly in novel areas, such as entry inhibition, which are needed the most by patients who are running out of options.

\section*{Conclusions}

While the pipeline may at times sputter, it is encouraging that many candidate compounds are being investigated. Some of these agents we may never hear of again. Others will enter large-scale clinical study. A couple of drugs may make it to the point where they even get names instead of numbers.

At CROI 2004 we saw potential. However, we also saw that for that potential to be realized, it will take even more time. For now, we wait.

\section*{Footnotes:}


14. J. Demarest, K. Adkison, S. Sparks, et al. Single and Multiple Dose Escalation Study to Investigate the Safety, Pharmacokinetics, and Receptor Binding of GW873140, a Novel CCR5 Receptor Antagonist, in Healthy Subjects. 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, California. Abstract 139. (www.retroconference.org/2004/cd/Abstract/139.htm)
GW873140, a Promising CCR5 Inhibitor Candidate

Coverage provided by Benjamin Young, M.D., Ph.D.

Benjamin Young, M.D., Ph.D. is Attending Physician at the Rose Medical Center in Denver, Colo. and a clinical instructor in the Department of Medicine at the University of Colorado Health Sciences Center.

The search for new categories of HIV medications continues. The need for new HIV medications is obvious, given the increasing rates of HIV resistant to current medications and the need to improve the convenience and potency of HIV treatments. Last year, we welcomed the arrival of drugs called entry inhibitors which target viral entry. This class of medications prevents HIV from gaining access to the human CD4 cell.

There are multiple steps to viral entry which involve the binding of the virus to specific human cell receptor molecules (called co-receptors, either “CXCR4” or “CCR5”), followed by the virus fusing to a human cell. Enfuvirtide (T-20, Fuzeon) is the first FDA-approved drug to block the entry process; it works by preventing fusion.

Another way to stop HIV should be by using drugs that block the attachment of HIV to any of the cell receptors. These drugs are called CCR5 receptor inhibitors and several candidates are currently the subjects of intense investigation.

As opposed to the subcutaneous injection of enfuvirtide, all CCR5 inhibitors under development can be taken orally. An interesting feature of this class of compounds is that they appear to stick to the receptor for a very long time, suggesting once-daily, or perhaps even less frequent dosing. Two CCR5 inhibitors under investigation are Schering-Plough’s SCH-C and SCH-D (Oral 140LB: www.retroconference.org/2004/cd/Abstract/140LB.htm). The SCH compounds appear to work best when taken without food.

GlaxoSmithKline (GSK) has been working on a different CCR5 inhibitor called GW873140 (or “140”). Dr. Michelle Berrey, Director of GSK’s Viral Disease-Discovery Medicine, characterized preliminary studies, saying that GW140 has an “unprecedented interaction with CCR5.”

In this report, Dr. Steve Piscitelli, also from GSK, shared the preliminary experience of GW140 in 70 HIV-negative persons. The objective of these studies was to evaluate the safety and pharmacokinetics of GW140.

Another objective was to see just how GW140 interacted with the CCR5 receptor on CD4 cells in the study subjects. GW140 appears to be well tolerated, with no serious side effects or laboratory toxicities. The drug levels are improved about two-fold when taken with food and there are no apparent differences in drug levels between men and women. The chemical caused mild cramps, nausea and diarrhea in a limited number of study participants.

Abstract:
Single and Multiple Dose Escalation Study to Investigate the Safety, Pharmacokinetics, and Receptor Binding of GW873140, a Novel CCR5 Receptor Antagonist, in Healthy Subjects (Oral 139: www.retroconference.org/2004/cd/Abstract/139.htm)

Authored by:
J. Demarest, K. Adkison, S. Sparks, A. Shachoy-Clark, K. Schell, S. Reddy, L. Fang, K. O’Mara, S. Shibayama, S. Piscitelli

Affiliations:
GlaxoSmithKline, Research Triangle Park, NC; Univ. of Wisconsin, Madison, WI; ONO Pharm. Ltd., Osaka, Japan

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subjects. After the dosing of GW140, the CCR5 receptor was completely blocked—even when the blood level of the drug was undetectable. This means that GW140 should be able to be administered once-daily.

So overall, GW140 looks like an enormously promising candidate CCR5 inhibitor. Dr. Berrey stated that the compound “appears to be very safe in short-term studies.” The next critical steps are to evaluate how well the compound works in blocking HIV in infected persons—a key step in the development of any investigational agent for treating HIV. These studies should commence this year. Stay tuned.
Nevirapine (NVP, Viramune) has come to be an essential drug in the treatment of HIV-infected pregnant women. In addition to the use of single-dose nevirapine to prevent mother-to-child transmission in women in resource-poor settings, nevirapine is frequently prescribed to women of childbearing age as part of HAART, and as part of HAART during pregnancy.

The well-understood pharmacokinetics in pregnancy and in infants, the efficacy, and the apparent safety are attractive features. However, a rare but concerning side effect of nevirapine is a syndrome of severe hepatic injury, often with rash, that occurs early after the beginning of treatment. It can be life threatening and a few deaths have occurred. Recent studies have identified a high CD4 count and being a woman as risk factors for this syndrome, and this new information has been incorporated into the package insert (available at www.bidocs.com/renetnt/: Prescribing+Information/PIs/Viramune/Viramune.pdf). Stevens-Johnson syndrome is another rare, but serious side effect.

Against this background, it is clear we need to know more about the safety of nevirapine in different groups of women, especially those who are pregnant. Two studies provided some reassuring data. Kramer and colleagues from the University of Southern California reviewed all pregnant HIV-positive women cared for at L.A. County USC Medical Center and identified 117 women who had used nevirapine in 125 pregnancies. Most were non-white with 61% Latina and 29% black.

HIV had been diagnosed during pregnancy in 43% of the women. Since a high CD4 count is a predictor of nevirapine toxicities, it is important that 80% of the women had more than 250 CD4 cells/mL and 34% had more than 500 cells. Overall, 19/117 stopped nevirapine at some point, although three women successfully restarted. There were seven significant
reactions among the 117 women. Rash occurred in three women, elevated liver enzymes occurred in three women and one woman had nausea and vomiting. None of the rashes were severe. Only one woman had grade 3 elevations of liver function tests (LFTs) and there were no episodes of severe hepatitis. Toxicity of any grade was more common among those with more than 500 CD4 cells than those with lower counts.

But are these numbers higher or lower than among non-pregnant women? We do not have a clear-cut answer, but another study, from Bersoff-Matcha at Kaiser Permanente in Washington D.C., compared 43 pregnant women treated with nevirapine with 227 non-pregnant women. The two groups were relatively comparable in everything except age (median 28 years versus 38 for the non-pregnant women). CD4 counts higher than 500 were slightly more common in the non-pregnant women (31% compared to 26%, although this was not statistically significant).

Overall, significantly fewer pregnant women had adverse events after starting nevirapine than non-pregnant women. The rates were 1/43 (2.3%) compared to 43/227 (18.9%, \( P = 0.007 \)). This remained significant when controlling for age, CD4 count and race. There was also a significant difference in more serious adverse events (grade 3-4), with 0 among 43 pregnant women compared to 20 among 227 (8.8%, \( P = 0.05 \)).

Rash was the most common side effect. Only one pregnant woman had a rash compared to 23 mild rashes and 17 grade 3-4 rashes among the non-pregnant group. Hepatitis occurred in five non-pregnant women; two had hepatitis with rash, which may be the most worrisome syndrome.

So, what does this mean in daily practice? In the only comparative data we have, pregnancy is not a risk factor for nevirapine toxicity among women. This needs to be confirmed in larger studies. Women are, however, at increased risk of the more severe types of nevirapine toxicity compared to men, and the women with the highest CD4 counts are at the greatest risk

(for more information, see Boehringer Ingelheim’s letter to healthcare professionals at www.bidocs.com/renetnt/Notifications/Dear+HCP+litr+Feb+2004.pdf).

We continue to need to focus on the health of women, pregnant or not, and not just on the prevention of mother-to-child transmission.

I think we can continue to use nevirapine in pregnancy, but we should be careful to warn women to be alert to rashes, abdominal pain, fever and jaundice during the first 6 weeks after beginning therapy. We must educate women to contact their healthcare provider if any of these symptoms occur. We also should remember that the combination of stavudine (d4T, Zerit) and didanosine (ddI, Videx) should not be used in pregnancy because of the risk of severe lactic acidosis.
Hepatitis C May Negatively Impact Neurocognitive Function

Coverage provided by Gerald Pierone Jr., M.D.

Gerald Pierone Jr., M.D., is Founder and Executive Director of the AIDS Research and Treatment Center of the Treasure Coast in Fort Pierce, Fla., a nonprofit medical clinic with more than 600 HIV-positive patients. He also maintains a private HIV medical practice in Vero Beach, Fla.

One of the unresolved issues of hepatitis C (HCV) infection is the potential role of this virus with regard to neurocognitive dysfunction. Some patients with HCV infection report “brain fog” and it has been debated whether this symptom is more frequent in HCV-infected patients, and if so, what causes it.

Previous studies have shown that HCV is able to replicate in the brain (Laskus, 9th CROI, Abstract 649: www.retroconference.org /2002/Abstract/13652.htm). Patients with viremic HCV infection have been shown to have a higher rate of impairment in neurocognitive tasks together with abnormalities on cerebral proton magnetic resonance spectroscopy compared with successfully treated HCV-infected patients (Forton, Hepatology, 2002: www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retriev e&db=PubMed&list_uids=11826420&dopt=Abstract).

This present study was a sub-study of ACTG 5095 and focused on 235 treatment-naive HIV-infected patients, of whom 25 were co-infected with HCV antibody positive. All patients had neuropsychological performance testing at study entry which consisted of the Trailmaking Test (parts A and B), the WAIS Digit Symbol task, and the Center for Epidemiologic Studies-Depression Scale (CES-D).

With regard to baseline characteristics, the HCV-infected patients were similar to the uninfected patients. Differences included a lower educational level among the HCV-positive group (mean of 11.8 years) versus the HCV-negative group (mean 13.8 years), and a higher prevalence of intravenous drug use in the HCV-positive group.

The results of testing showed that HCV-positive patients had poorer overall neuropsychological performance. They also performed less well on the Digit Symbol task and these differences persisted after controlling for confounding variables with multivariate regression analysis.

Significant depression was noted in 52% of the HCV-positive patients compared with 33% in HCV-negative patients (p=0.055). Utilizing subscales of depression, most of the differences were related to the

Abstract:

Authored by:
Y. Yang, S. Evans, R. Gulick, D. Clifford, AIDS Clinical Trials Group A5097s Team

Affiliations:
“somatic complaint” portion of the CES-D scale.

The authors concluded that this data was consistent with the hypothesis that HCV has a negative impact on neurocognitive function. They did concede however, that this study was limited by the potential influence of multiple potential confounding factors.

Following presentation of the data, a comment from the audience raised the point that the poorer neuropsychological performance might be partly related to cerebral damage from intravenous drug use which was more prevalent in HCV-positive patients.

Another member of the audience pointed out that no data was presented regarding hepatic synthetic function in the two groups. The implication of this comment was that some of the HCV-positive patients may have had cirrhosis and varying degrees of hepatic encephalopathy which may have skewed the results.

The most significant limitation of the study seems to have been the relatively small number of HCV-positive patients. There are challenges associated with the use of multivariate regression in small data sets which restricts the ability to control for potential confounders. For example, just a few patients with hepatic encephalopathy could have influenced the results of the HCV-positive group.

In summary, this interesting study adds to the growing body of information that suggests HCV may negatively impact neurocognitive function.
Nelfinavir, Lopinavir/Ritonavir Appear Safe for Hepatitis C Patients

Coverage provided by Paul E. Sax, M.D.

Paul E. Sax, M.D., is the clinical director of the HIV Program at Brigham and Women’s Hospital in Boston and the principal investigator in its AIDS Clinical Trial Unit. He is also an Assistant Professor of Medicine at Harvard Medical School, where he has taught for more than nine years, and the Research Notes Editor for AIDS Clinical Care.

Multiple studies have shown that patients with HIV/hepatitis C (HCV) coinfection are at greater risk for liver toxicity from antiretroviral therapy. This is usually manifested as an increase in liver enzymes and, sometimes, HCV RNA levels.

While the direct effect of HIV medications versus augmented immune response to HCV are often difficult to sort out, apparent hepatotoxicity after starting treatment is a common clinical problem. This abstract is an analysis of nelfinavir (NFV, Viracept)- and lopinavir/ritonavir (LPV/r, Kaletra)-treated patients with HIV/HCV from the Abbott 863 study, with particular attention paid to HCV RNA and alanine aminotransferase (ALT) levels.

A subset of 70 HCV-infected patients from the study were retrospectively evaluated. All patients received stavudine (d4T, Zerit) and lamivudine (3TC, Epivir) with randomization to either nelfinavir or lopinavir/ritonavir. At baseline, 57 of 70 patients (81%) were positive for HCV RNA, and 68% had genotype 1. There were no significant differences between the nelfinavir and the lopinavir/ritonavir arms in terms of baseline demographics, HIV-related clinical and laboratory characteristics, HCV RNA levels or ALT levels.

As has been reported in previous studies, the initiation of antiretroviral therapy was associated with a significant increase in HCV RNA levels. The increases were generally similar in both treatment arms, with the exception of the subgroup of patients with CD4 counts below 100 cells/mm³, for whom HCV RNA levels increased more in the nelfinavir than in the lopinavir/ritonavir arm. Although early in the study greater ALT increases occurred in the nelfinavir arm than the lopinavir/ritonavir arm, by week 48 the difference was not statistically significant. There were no patients who discontinued therapy due to liver toxicity.

Importantly, both study arms had good CD4 count responses (234 cells/mm³ with lopinavir/ritonavir and 184 cells/mm³ with nelfinavir), contrary to some studies that have shown a lesser degree of immune reconstitution among HCV-infected patients.

This study supports the safety of both the lopinavir/ritonavir and the nelfinavir-based regimens in HCV-infected patients—at least those who were stable enough to enroll in this treatment-naive study, which is encouraging. The increases in HCV RNA

Abstract:

Authored by:
K. E. Sherman, N. J. Shire, P. Cernohous, S. D. Rouster, B. Da Silva, J. Moseley, S. Brun

Affiliations:
Univ. of Cincinnati, OH; Abbott Labs, Abbott Park, IL. View poster at: www.thebodypro.com/conf/retro2004/pdfs/811/pdf
levels are of unclear clinical significance, especially given that no patient required cessation of therapy for liver-related issues.

While the results of this analysis are encouraging, a far more vexing problem for clinical practice is that of HIV/HCV coinfection. Patients with advanced liver disease, as they often tolerate any antiretroviral therapy very poorly. Further study of the predictors of antiretroviral-associated hepatotoxicity in this more tenuous group is warranted.
HIV PREVENTION/TESTING

Unique HIV Testing Program in North Carolina

Coverage provided by Keith Henry, M.D.

Keith Henry, M.D., is Associate Professor of Medicine at the University of Minnesota School of Medicine and Director of HIV Clinical Research at Hennepin County Medical Center in Minneapolis. In addition, he is Medical Director of the AIDS Unit and the Sexually Transmitted Disease Clinic of the St. Paul Department of Public Health.

Dr. Pilcher, et al. presented the updated experience with the North Carolina screening and tracing active transmission program (STAT) which was first published in JAMA (2002; 288; 216-221—abstract available at http://jama.ama-assn.org/cgi/content/abstract/288/2/216). A key feature of the approach is to screen HIV antibody negative samples with a pooled RNA approach that efficiently allows for the identification of HIV RNA positive samples at a cost of about $2 per test. This approach allows for the identification of persons who are in the process of seroconverting. From the epidemiologic perspective, it is important to recognize incident HIV, and from the prevention standpoint, the approach allows for access to sexual networks and the potential to interrupt transmission at a time when the risk is highest.

Over 12 months, 117,000 samples were tested for HIV antibodies. Seven hundred fifty-five were HIV Ab positive, with 130 identified to be recent infection (more likely white men who have sex with men [MSM]). Twenty-three samples (4%) were Ab negative RNA positive (picked up by the STAT program), of which 22/23 patients started antiretroviral therapy (ART), with 12 of these patients entering clinical trials. Forty-one at-risk partners received HIV testing and five were found to be HIV positive (four acutely).

The overall cost was $1,500 per case diagnosed. Thirteen of the 23 people who tested positive had experienced acute retroviral syndrome (seven of the people already had symptoms when they tested and six later developed symptoms). Eight of the people who tested positive had additional symptoms due to sexually transmitted disease (STD). The median HIV level at initial screening was 209,000 copies/mL. Overall, an additional 4% of the HIV antibody negative samples were actually HIV positive, with a rate of 6% for samples originating from STD clinics. This approach provides information about where to target resources by geographic technology monitoring. The new cases were
noted to have a limited distribution in rural areas, mostly along trucking/interstate routes. This allowed the identification of contact networks.

Risk associations included: MSM (11), anonymous partner (4), sex work (5), crack cocaine (8), prison release (5), with a small number of college students (black MSM). Eleven of the subjects were likely transmitters (three perhaps to two or more other persons), with 10 involved with previously diagnosed HIV-positive persons and nine in long-term relationships.

A key take-home lesson was that, in some high-risk populations, HIV antibody testing may be inadequate to confidently rule out HIV infection (in STD clinic settings and prisons the additional testing picked up 6% more HIV+ cases). Although resource intensive, the costs pale in comparison to the costs of HIV care/year, so an expanded use of this innovative approach may be warranted. However, this seems unlikely to occur considering the overall poor state of public health funding in the U.S.
HIV Superinfection 5% in Newly Infected Gay Men

Coverage provided by Keith Henry, M.D.

Keith Henry, M.D., is Associate Professor of Medicine at the University of Minnesota School of Medicine and Director of HIV Clinical Research at Hennepin County Medical Center in Minneapolis. In addition, he is Medical Director of the AIDS Unit and the Sexually Transmitted Disease Clinic of the St. Paul Department of Public Health.

The topic of superinfection is important for several reasons. First, it provides important insight into protective anti-HIV immunity. The issue is whether the innate anti-HIV immunity that evolves in an infected person can prevent infection with a second strain of HIV.

That is important clinically since a few anecdotal reports have suggested that superinfection can lead to more rapid deterioration of a patient’s immune status. It is also important from the public health perspective with implications for the potential efficacy of a vaccine to prevent infection.

Several definitions need to be clarified. Co-infection describes when someone is initially infected with two strains, while with superinfection a patient is infected with one strain and then with another strain. Superinfection has been observed in some chimpanzee models and has been inferred from recombination analysis but is still a rarely documented clinical event.

Smith reported the results of a retrospective analysis of trials of primary infection in a cohort of 78 men who have sex with men (MSM) during their first six months living with HIV infection. These men were not yet on antiretroviral therapy. Samples of virus underwent pol gene sequencing and if isolates didn’t cluster then env sequencing was done.

Three cases of possible superinfection with another type B virus were identified and then confirmed by clonal sequencing of env and pol sequences. All three men had a change in the reverse transcriptase sequence that could impact drug sensitivity. When those three patients were evaluated six months after acquiring the second strain, a negative impact on the CD4 count and RNA level was seen.

The 5% rate of superinfection is about the same rate as at risk infection initial infection in high-risk populations in the U.S. The interpretation was that there was no protection afforded by the initial HIV infection against superinfection. Dr. Smith said that the lab approach may underestimate the true rate of superinfection due to sensitivity issues with the assays used.

It seems to me that a group of MSM with fairly recent HIV infection may represent a group with a higher than average risk for acquiring additional HIV, so that extrapolation to the general MSM population may overestimate the overall risk.

Whatever the actual rate is, these data add to the literature about superinfection.
and support enhanced emphasis on harm reduction counseling. A question from the audience highlighted that of the three cases reported, two had been previously reported in other reports. Clearly the topic is of interest and more studies looking at the rate and impact of superinfection are needed.