



Welcome to the second issue of **Community Conference Watch**, a user-friendly and easy-to-understand newsletter that brings you select samples of clinical trial results of recent studies from major science conferences in HIV and hepatitis diseases. Our goal is to provide helpful insights that will assist our readers in understanding the *ins and outs* of clinical trials with samples from the **12th International Conference on Retroviruses and Opportunistic Infections (CROI)**, which occurred February 22-25, 2005 in Boston, MA.

# Community Conference Watch

  
visionaryhealthconcepts  
[www.freehivinfo.com](http://www.freehivinfo.com)  
[www.freehepatitisinfo.com](http://www.freehepatitisinfo.com)

## Issue 2

**Writer and Editor-in-Chief**  
Lillian Thiemann

**Contributing Editors**  
Charles Gonzales, MD, PhD  
Jay Lalezari, MD  
Krista Martel  
Robert Munk, PhD

## Helpful Tools

**Glossary** Some words in this newsletter may be new to you. If you see a word that is ***“bold italic”*** with quotes, look it up in the Glossary in the middle of the newsletter to see what it means.

### TRIAL **Watch**

In this newsletter, we cover different clinical trials that were presented at conferences. Reading about this new information is one thing, but really understanding the ins and outs of the trial is another. Read the “Trial Watch” section for take-home messages, comments about the trial design, and who this information might be particularly important to. To help guide you, we are also using the following symbols to help you find information quickly about the trial:

**TE** **Treatment experienced** (for those who have taken one or more HIV treatment regimens before)

**ST** **“Salvage therapy”** (for those that are running out of treatment options, and are waiting for much-needed information on new drugs)

**TN** **“Treatment naïve”** (for those who have never taken anti-HIV drugs before)

**LH** **Liver health** (for those who are co-infected with hepatitis (HBV or HCV) or need to pay special attention to their liver because of hepatotoxicity)

**SE** **Side effects** (for those who are concerned about short- or long-term side effects from taking anti-HIV treatment)

**Q: WHY BOTHER to learn about the ins and outs of clinical trials? A:** If you are interested in finding out where the latest news about your HIV and hepatitis healthcare comes from, then this newsletter is for you. Even if you keep up-to-date on new information, you can always increase your skills to better understand what is real in the cutting-edge news from scientific conferences. Even better, it is important to figure out how this information might apply to you.

### The BIG fight

A main goal in medical research is to find cures for diseases. Research scientists work their way to a cure by studying the disease and watching how the body fights back against it. This is done by gathering information and by testing specific questions and approaches in a ***“study”*** or ***“clinical trial.”*** New drugs to fight diseases are also tested in this way.

Sometimes clinical trials are held to find out how effective a new drug is to gain ***“FDA-approval”*** so it can be available to the public as quickly as possible. Sometimes these trials are held to find out if an older drug is causing serious or different side effects in particular groups of people. Whatever the reason, these studies often have an impact on certain groups of people, and we’re here to show you how new studies might affect you, your friends, peers or family. See our Helpful Tools section to read more about how we do this.

### Can ANYONE present at a conference?

**A:** The major HIV and hepatitis science conferences are like big games of medical “show and tell” that happen several times a year. The kinds of people who might attend conferences are: research scientists, people who provide healthcare such as doctors and nurses, ***“patient advocates,”*** and the press. To be able to present the results of their study at a conference, researchers have to submit their results in a form called an ***“abstract”*** to a conference committee to be reviewed. If the committee thinks the research is worthy, it will be approved. Unfortunately, sometimes conference committees are political in their selections. As in life, some researchers and their organizations are more popular than others. Some information presented at conferences (study results) is very important. But some results don’t really mean anything, generally because the clinical trials were poorly designed or worse, nothing more than a dressed-up drug company press-release. There are things to look out for and questions to ask when looking at study results that will tell you how much you can rely on the information. Good, bad, or indifferent, the results from studies need to be looked at carefully so we can pull out the best info and add it to the knowledge we already have. If you take part in the process by regularly reading this newsletter, it may improve your HIV healthcare by helping you enter into a more active relationship with your healthcare provider.

# Research: One Patient at a Time?

There were two presentations at CROI that each focused on ONE patient:

1.

The first ("**poster**" # 310) reported on a patient who was diagnosed with HIV in 1995 when he went to donate blood and was given routine HIV "**antibody tests**". His infection was confirmed in two different labs. After about two years, when his "**viral load**" had reached about 29,000 copies and his "**CD4+ T-cell count**" was 856 "**cells/ml**", he started HIV treatment ("**HAART**"). Within four months his viral load was "**undetectable**" but his CD4+ T-cell count didn't change much. Three years after starting treatment, he went to enroll in a clinical trial. All clinical trials or studies run routine lab tests on a person before accepting or denying their participation in the trial. The result of the HIV antibody tests they ran on him were negative—meaning that HIV was not showing up in his blood. They then stopped his HIV treatment for a "**structured treatment interruption**" study. They have observed him for the past 4 years. In that time, the patient has not received any anti-HIV treatment. His anti-HIV antibody tests have remained negative and his viral load has remained undetectable. They also looked in his semen and found no HIV. This is the first report of such an occurrence. The "problem" with this very fortunate turn of events is when you are infected with any microbe (HIV or not, CMV, Influenza A etc) you should still retain your antibodies to the microbe even if you "cure" the disease.

2.

The second presentation was given in a special "**symposium**" (Session 31b) by David Ho, MD, In his talk, he discussed a case that has recently made international headlines and is referred to in the press as the "New York patient". In his update, Dr. Ho described a man in his late forties who had tested negative for HIV several times between 2000 and his last negative HIV test in May 2003.

The man had anal sex without using condoms with "countless" partners over the years, often while high on methamphetamine (crystal meth). When he was diagnosed in January 2005, his HIV infection was already well past the "**acute**" stage. Within a month, he lost almost 10-lbs of body weight. The researchers looked closely at the man's HIV using both "**genotype**" and "**phenotype**" tests. Results of these tests suggested that the man's HIV is "**resistant**" to most anti-HIV treatment. Only two of all "**FDA-approved**" anti-HIV drugs, Fuzeon® and Sustiva®, were considered active against his HIV. What's more, tests found that his virus was much more able to make copies of itself than common multi-drug resistant ("**MDR**") virus.

Most resistant virus does not make copies of itself as well as "**wild-type**" HIV. Dr. Ho said that he found that this person's virus had a different make-up than any other HIV they have recorded in their database or in the Los Alamos National Laboratory. He ended by stating that they will be looking into this "disease-accelerating" virus further.

However, on occasion something so unusual occurs that researchers decide not to keep it to themselves.

## TRIAL Watch

**TE** So far, this data relates to no one else but the individual patients described in each study above. As a rule of thumb, "**data**" presented about small numbers of patients are not considered anything but interesting. A **TN** presentation about a single case is rarely taken seriously at all. Reliable results are usually produced by testing a question or drug in a well-designed trial that includes large numbers of people observed over a long period of time. However, on occasion something so

unusual occurs that researchers decide not to keep it to themselves. That was the situation in both of these cases. Trying to find out if--and how--the man described in poster 310 possibly cleared his HIV virus are important questions to study. Answers to these questions might lead to a research breakthrough. As to the "New York patient," more investigation is needed. Some researchers at CROI commented that the fast disease progression may have been caused by factors that relate

to the man's immune system rather than to a unique HIV virus. It will be necessary to find out if there are more people out there with similar virus that have a faster-than-normal disease process. In the least, even the prospect of such a virus should inspire people to practice safer sex, using latex condoms, on every occasion. The development of new treatments capable of fighting resistant virus also remains a real priority.

## Research: Observing many people for a long time COHORT studies

Every big HIV conference usually has its fair share of reports from the large "**cohort**" studies. Large cohort studies observe, question or study many people over a number of years and try to answer questions that can only be answered over the long haul.

**Cohort studies (T-cell response to HAART):** There were four poster presentations at CROI (poster #'s 609, 610, 611, 612) that looked at the "**immune recovery**" of thousands of patients staying on "**HAART**" for periods of between three and seven years. These poster presentations were from cohort studies from Spain (PISCIS study), France (APROCO study), Switzerland (The Swiss HIV Cohort Study) and the U.S. ("**AACTG**" 384). They all generally found that the average increase in CD4 T-cells that can be expected for a person taking HAART may be around 350 (cells/ml). The study with the longest follow-up period of all, The Swiss HIV Cohort, found a T-cell count increase of 349 in patients they studied for seven years. But this increase was only seen in those who had never interrupted therapy. For patients whose therapy had ever been interrupted, even if only for a month, they saw a T-cell count increase of only 153. It was also noted by many (during the discussion portion of the presentation) that there seems to be a ceiling in the amount of CD4 increase that is possible and that it occurs after 3-4 years. This may fuel the continuing debate about when anti-HIV treatment should be initiated.

Continued

(continued) **Cohort studies (Update on long-term side effects of HIV treatment):** In another type of presentation called an **"oral presentation"** (**"abstract"** 42), Dr. Wafaa El-Sadr gave an updated report from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D). It is called an **"update"** because the topic she presented on, **"myocardial infarction"** (MI), had been looked at before and presented at previous conferences. This update covers 6 years of follow-up of the D:A:D cohort, which analyzed data from over 20,000 people with HIV from Europe, Australia, and the US. It showed less risk of MI than an earlier published report<sup>(1)</sup> (from 26% to 17%). Dr. El-Sadr stated that there are many factors besides being on anti-HIV treatment that cause MIs to occur. For example, 47% of the people in the D:A:D cohort smoke, 42% have higher than normal "lipid" levels, and 23% have **"lipodystrophy."** After the researchers accounted for these risk factors (and others such as sex, age, family history), the overall MI risk still proved 1.17 times higher per year on HAART when compared with no treatment. So while the risk of MI remains small for patients receiving HAART, it increases the longer a person takes it.

Updates of long-term cohort studies are necessary because as time goes on, the amount of data grows and the results and conclusions can shift. Often, different cohort studies that are studying similar things disagree in their results! When this happens, we need not be too discouraged because this is part of the long-term cohort process. Some questions need a really long time and a lot of people to answer. In cardiac (heart) research, there are cohort studies that have gone on for 20 to 30 years! So the updates from large HIV cohorts can agree as they did in the posters mentioned above, or provide us with updated data as the D:A:D analysis did. There can be weaknesses in such studies of very complex health issues though. D:A:D could not account for every possible thing that might lead to heart disease. For example, researchers did not collect data on insulin resistance. Nor did they know how many heart attack victims may have used cocaine or anabolic steroids. Still, the D:A:D researchers urged the conference attendees to monitor people with MI risk factors more closely and to work towards helping patients with the risk factors they have the power to change: stopping smoking, eating better and getting exercise. One thing that would be of value that D:A:D has not done so far, is an analysis of risk according to anti-HIV drug class.

TN

TE

SE

## New HIV Drugs

Almost every conference has a session on the anti-HIV drug **"pipeline,"** which is of particular importance to people who are running out of anti-HIV drugs (see **"salvage therapy"**). The FDA has standards that the drug companies have to meet to get their new drug approved for sale in the US. This means trials are designed so the results are reliable enough to assure an FDA approval. The two examples of such trials we'll use here were presented on new drugs that offer the hope of controlling HIV that is already resistant to the existing **"protease inhibitors" (PIs)**. Both of the new PIs described below use small doses of the PI Norvir<sup>®</sup> to boost their effectiveness (as do most currently available PIs).

**TIPRANAVIR:** As tipranavir, a new protease inhibitor, gets closer to FDA approval, more and more detailed study results are released. In our last issue of *Community Conference Watch*<sup>®</sup> we discussed a presentation on one of two RESIST trials: "RESIST-1" took place in North America. In Europe and Latin America, it was called "RESIST-2." Both were designed alike to compare the safety and effectiveness of tipranavir + Norvir versus the **"control group"** who received any of 4 standard PIs (already approved by the FDA) plus Norvir. New results from a RESIST **"sub-study"** were presented by Dr. Shapiro of Stanford University (Abstract 104). The sub-study looked at how the amount and type of resistance the study participants had when they started the trial affected the success (or failure) of tipranavir + Norvir-based therapy. Remember, only very HIV **"treatment experienced"** people with some resistance to PIs took part in this trial. Drugs were not chosen for people in the control group until a resistance test of the HIV in their blood was done. This

helped the researchers know which PI might be a participant's best shot at success. The people in the trial could also start using the drug Fuzeon<sup>®</sup> (T-20), a **"fusion inhibitor"**, along with tipranavir. Results showed that tipranavir + Norvir-based regimens worked better at fighting very resistant HIV than the treatments taken by the control group.

**TMC114:** This new protease inhibitor under investigation is in **"phase II"** of its development. Dr. Richard Haubrich of the University of California, San Diego, reported the 24-week **"interim analysis"** of two 96-week **"dose-finding"** trials (abstract 164LB). The patients in this study were very HIV treatment experienced with some resistance to PIs. Their viral loads were high (100,000 copies/mL or more) when they started the trial. The researchers boosted the four different doses of TMC114 they were testing with a small amount of Norvir (each given twice daily). Some (47%) of the 497 participants received the fusion inhibitor, Fuzeon<sup>®</sup> (T-20) and all were selected by chance (randomized) to receive regimens that included one of four doses of TMC + Norvir + two **"nukes"** or they received a currently available protease inhibitor of choice + two nukes. The results have people talking because they were very good and fairly dramatic. At the highest dose of TMC114 + Norvir, viral loads dropped to undetectable (below 50 copies/mL), even in five of 13 people with HIV that was resistant to ALL other anti-HIV drugs. Very few people dropped out of the trial because of bad side effects. The researchers will go ahead with the highest dose in a **"phase III"** trial. This study will also include people who have never received any anti-HIV treatment before.

## TRIAL **Watch**

Drugs that help people fight resistant virus are really needed, and the results from these studies show that tipranavir will probably soon be a welcome addition and that TMC114 is also really on its way. Results from RESIST 1 & 2 included data from a large number of patients from different parts of the world. It is really good to have as many people as possible in a trial so that the results from the trial are more reliable. A question that was not answered by the RESIST sub-study was how to predict how well tipranavir will work for a person who has particular resistance mutations. Knowing which resistant HIV tipranavir

works best against will help guide when and in which patients to use this very promising new drug. Finding the right dose of TMC114, or any drug, is key to moving it through the pipeline. What is also of note is that the patients in this study had no signs of virus coming back during the 24 weeks the researchers looked at. A comment by one famous researcher, Dr. John Mellors, summed it up; He said that overall, the responses in these patients "approach the results of initial HAART regimens" meaning that TMC114 + Norvir may be a important option for people with HIV resistant to more than one anti-HIV drug class.

## Your opinion counts!

If you like this issue of *Community Conference Watch*® and would like to be on our mailing list to receive future issues, check the box on the attached registration form and send it back to us!

# Liver Issues

About one quarter of HIV-infected persons in the U.S. are also infected with "**hepatitis**" C virus (HCV). Most of these people develop "**chronic**" liver disease that gets worse over time. Liver problems are difficult to treat and can be very serious. In some groups of HIV-positive people, liver problems are the leading cause of death. As it stands today, treatment of HCV in HIV-positive patients is usually held off if the first "**liver biopsy**" shows little liver damage. But the big question is how long can we wait?

Dr. Mark Sulkowski from the Center for Viral Hepatitis at Johns Hopkins University presented unexpected results of a clinical trial (67 co-infected participants) exploring how fast liver damage ("**fibrosis**") occurs (Abstract 121) in HIV/HCV co-infected individuals. Many of the participants had CD4+ T-cell counts less than 200 and were on anti-HIV therapy (86%), and 27% abused alcohol. Two liver biopsies were performed on each participant, one at the start of the study and another around 3 years later. On the second biopsy, the researchers found that fibrosis increased quite a bit in a short time. Of the patients with mild fibrosis in the first biopsy, 26% had progressed in their liver damage by two-stages! And these people also had some similar things going on: they were more likely to have had an HIV viral load over 10,000 at the first biopsy and higher than normal liver enzymes (AST levels) throughout the trial. The researchers were able to rule out age, sex, alcohol, antiretroviral therapy, or CD4+ cell count as causes of the faster-than-expected liver damage in these people. The researchers said that more trials are urgently needed.



## TRIAL **Watch**

**LH** Healthcare providers that treat HIV/HCV-positive people have been relying on lab tests and biopsies to tell them how well a person's liver is doing and when to recommend HCV treatment. This small study had unexpected results that (if true) could change how HIV/HCV co-infected people receive treatment for HCV. Unfortunately, it did not have enough people in it to answer certain vital questions: Does liver damage progress more quickly in HIV/HCV co-infected people than was previously thought? Which persons will progress more quickly than others? Should the livers of such people be checked out more often to catch the window of opportunity to start HCV treatment before the liver is so damaged that treatment has little chance of working? A large, well-designed study (or two!) will be needed to answer these questions.

Please consult the product package insert from the drug's manufacturer regarding the efficacy, toxicities, and side effects of each drug discussed in this newsletter. The package insert is available from your pharmacist. Although every effort has been made to ensure the scientific accuracy of the information contained in this document, Visionary Health Concepts assumes no responsibility for any errors contained herein or from clinical outcomes.

Duplication of any part of this newsletter is prohibited without the written permission of the publisher. Brief sections may be photocopied for personal use without the written permission. Reprints may be obtained online at [www.freehivinfo.com](http://www.freehivinfo.com) or by e-mailing [edu@vhconcepts.com](mailto:edu@vhconcepts.com).

#### References:

1. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 349:1993-2003, 2003.

All references not otherwise noted are from the 12th Conference on Retroviruses and Opportunistic Infections, Feb 22-25, 2005.