S T E P E l e c t r o n i c t r e a t m e n t E z i n e

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The Seattle Treatment Education Project's (STEP) EZINE is an electronic treatment resource distributed bi-monthly to people living with HIV/AIDS, people affected by HIV/AIDS, case managers, front-line workers, physicians, other public health and allied health professionals. STEP's contact information is: Seattle Treatment Education Project, 1123 East John Street, Seattle, WA 98102, (206) 329-4857 or 1-877-597-STEP (WA, OR, AK, HA, ID, MT)

**ANTIRETROVIRAL UPDATE**

# A NEW LOOK AT LIVER TOXICITY DEVELOPMENT DURING ANTIRETROVIRAL THERAPY CONTAINING PROTEASE INHIBITORS IN PATIENTS WITH HIV

Protease inhibitors (PIs), a class of HIV medications, can greatly reduce the number of new, infectious copies of HIV made inside cells. If PIs succeed in slowing down the production of HIV, HIV infection would not spread inside the body as quickly as it does without PIs. PIs can be used safely, but members of healthcare teams should monitor liver enzyme levels for signs of trouble. Liver enzymes should be monitored for all antiretroviral agents (eg. Recent Johns Hopkins manual cites nevirapine/Viramune as the antiretroviral combination that can cause the worst chemical hepatitis but other combinations are not excluded). Although PIs have been key in lengthening survival for people with HIV and delaying full-blown AIDS, some providers have been reluctant to prescribe them because of reported side effects about liver toxicity. Soon after these drugs were released for public use in 1996, several case reports indicated that they could cause liver toxicity, especially in people co-infected with the hepatitis C virus. The mechanism by which they might cause this effect remains unclear.

Findings by Johns Hopkins researchers published in the January 5, 2000, issue of the *Journal of the American Medical Association*, noted that 10 percent of HIV-infected individuals taking antiretroviral therapy experienced liver toxicity at a level high enough to warrant stopping treatment. To identify the risk, the Hopkins researchers analyzed 211 people over a 2-year period who were undergoing treatment with four different PIs: ritonavir, saquinavir, indinavir and nelfinavir, as well as 87 who were undergoing treatment with another category of anti-HIV drugs called nucleoside analogs. Doctors periodically collected information on patients' sex, age, race, social practices (e.g. alcohol and recreational drug use), drug doses and clinical variables such as new illnesses. They also monitored liver enzyme levels using blood tests.

The doctors discovered that 10 percent of the individuals taking PIs experienced severe liver toxicity. The risk was only slightly higher, 12 percent, for those with hepatitis C.

Hepatitis C-infected patients who were not taking ritonavir, however, were more than three times as likely to develop severe liver toxicity, indicating that patients with hepatitis C co-infection may be at a greater risk for medication-related liver damage. This study shows that liver toxicity is fairly high with these drugs and that ritonavir is more toxic than others. These drugs, however, can be used safely if liver enzyme levels are monitored closely.

In a recent report from the "LIVERHAART Group" from Rome who were looking at liver toxicity in PI-based antiretroviral regimens. The group reviewed 1,325 HIV-infected patients who received PI-based HAART regimens for at least 6 months. The purpose was to determine the frequency of liver toxicity, which was categorized as either mild or severe. Mild damage was defined as ALT results (ALT stands for *alanine aminotransferase* which is a measure of liver damage) that were elevated but were less than 5 times upper limit of normal (ULN). Severe damage was defined as ALT results that were over 5 times ULN. The results showed that chronic hepatitis C infection and alcohol abuse were strongly associated with liver toxicity. (Note: Any alcohol use as long as been known to exacerbate the hepatitis so often seen in persons with Hepatitis C virus. Among the PIs, ritonavir was associated with the highest rates of severe liver toxicity when it was used alone or in combination with saquinavir. The results are shown in the following table:

| | No. | Total > ULN | Severe > 5x ULN |
|---|---|---|---|
| Ritonavir | 120 | 21 (17.5%) | 14 (11.7%) |
| Saquinavir | 372 | 47 (12.6%) | 14 (3.7%) |
| Indinavir | 680 | 58 (8.5%) | 9 (1.3%) |
| Nelfinavir | 88 | 10 (11.4%) | 0 (0%) |
| RTV/SQV | 60 | 11 (18.3%) | 7 (11.6%) |

*Source:* Aceti, A., et al. *JAIDS* 2002:29:41

**Editorial Note:** Other reports and research colleagues have additionally showed a risk of liver toxicity that seemed to be substantially higher with ritonavir, but failed to show a strong correlation with chronic hepatitis. An explanation for the association with PIs in the presence of chronic viral hepatitis has been the possibility of immune reconstitution with immune-mediated hepatitis. The results here do not support this thesis because those with liver toxicity generally had poor HIV virologic response.

## STD AND HIV PREVENTION CHALLENGES

## CHALLENGES IN PREVENTION: SHOULD STD AND HIV PREVENTION BE INTEGRATED?

Last week marked the sixth year since the Institute of Medicine, in its landmark report, **"The Hidden Epidemic: Confronting Sexually Transmitted Diseases"**, challenged the sexually transmitted disease (STD) prevention community and its multiple partners to take new steps to address STDs in the United States. While many efforts to address these challenges have been undertaken and much progress has been made, much work remains. For example, efforts to eliminate syphilis from the United States have prompted the need for enhanced community involvement in STD prevention.

Likewise, the emergence of increasing rates of STDs among men who have sex with men (MSM) causes concern not only about the impact of STDs on this population, but also the potential impact on HIV transmission. An additional challenge is the development of effective interventions for viral STDs. In the ever-changing societal and political context within which STDs exist, we must constantly explore these trends in order to build healthy communities that are not burdened by STDs.

The National STD Prevention Conference, sponsored by the Centers for Disease Control, highlighted new research that may underscore significant challenges in reducing the toll of STDs. Among the most pressing challenges are signs of emerging resistance to a common gonorrhea treatment, and gaps in STD screening, counseling, and care in some healthcare settings. Addressing these and other challenges must be a priority in order to make further progress in preventing and treating STDs. The CDC believes that will provide an opportunity to discuss these challenges through exploration of the latest science, the best practices, and how science and practice interface.

**For more information on the STD Prevention Conference, please view:**
http://www.cdc.gov/nchstp/dstd/dstdp.html

# VACCINE NEWS

## NIAID PHASE III HIV VACCINE TRIAL IN THE UNITED STATES WILL NOT PROCEED

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), supports HIV/AIDS research and development. In the past few weeks, several decisions will substantially contribute to a federal effort to develop preventive HIV vaccines in the future.

NIAID states they have a common goal: “to prevent the further spread of HIV/AIDS by developing safe and effective vaccines, other prevention strategies and innovative HIV treatments.” One of the more promising vaccine development programs that is being led

out of the NIAID is the HIV Vaccine Trials Network (HVTN). HVTN was established by NIAID in 1999 to foster the development of HIV vaccines through testing and evaluating candidate vaccines in clinical trials. The network spans four continents and has the capacity to conduct all phases of clinical trials, from evaluating candidate vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy.

Until recently, NIAID and the U.S. Army had proposals under way to begin large-scale, Phase III HIV vaccine efficacy trials in the near future. Both trials were to test similar "prime-boost" vaccine combinations (a canarypox-virus-based primer vaccine followed by a "gp120" subunit booster vaccine). The canarypox vaccine combinations that the NIAID and U.S. Army were going to use were slightly different and answer different important scientific questions surrounding HIV vaccines. The main difference between these trials was that the U.S. Army trial was going to be tested mainly in Thailand and the NIAID trails was going to be tested primarily in the United States.

However, NIAID has decided not to proceed with a three-arm Phase III HIV vaccine efficacy trial, (also known as HVTN 501). That decision, made by NIAID and HVTN leadership, in consultation with other vaccine developers and the manufacturers of the vaccine candidates, was based on recently learned preliminary immunogenicity results of a Phase II trial (HVTN 203) of its canarypox prime-boost candidates.

The decision not to proceed with HVTN 501 does not mean the vaccine products are not efficacious. Several different immune tests are being developed and tested with the vaccine product to help determine which immune test and vaccine candidate will correlate with HIV protection in humans. For this reason, the Thailand study will continue. Aventis Pasteur and VaxGen have made efforts in the development of an HIV vaccine and they will continue to have involvement in the Thailand trial to assess the efficacy of their prime-boost vaccine.

NIAID will continue to support research and development to advance vaccine products. In the next few years, further studies and discussions with stakeholders at domestic and international sites will help guide decisions regarding the future development and testing of canarypox HIV vaccine candidates.

In the future, HVTN's network experience in conducting international vaccine development and testing and its collaborative ties in many parts of the world will enhance global efforts to develop an effective AIDS vaccine.

**For more information on NIAID, please contact:**
**http://www.niaid.nih.gov/daids/vaccine/default.htm**

**For more information on the HIV Vaccine Trials Network (HVTN) and their current vaccine efforts, please contact: http://www.hvtn.org/**

## ACKNOWLEDGEMENTS

- Please note that this is not a complete list of all HIV-related treatment information. STEP strives to provide the very latest in HIV treatment information, research and drug development information. The most current research directions and antiretroviral drug data are provided throughout the Ezine publications. You will find highlight reports as well as extensive follow-up reports from many of the AIDS research and science conferences on the Ezine. In addition, all STEP quarterly treatment journals are available on our Web site at http://www.thebody.com/step/steppage.html or by calling our Talkline at 1-877-597-STEP. STEP works hard to give unbiased treatment information to all interested parties. If you have comments, questions, suggestions or grievances, please contact adimikam@stepproject.org or ezine@stepproject.org.

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