

# STEP Electronic Treatment E-zine

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### Issue 45



The Seattle Treatment Education Project's (STEP) EZINE is an electronic treatment resource newsletter distributed monthly to case Managers, front-line workers, people affected by HIV/AIDS, physicians, other public health and allied health professionals and people living with HIV/AIDS. STEP's contact information is: Seattle Treatment Education Project, PMB 998, 1122 East Pike Street, Seattle, WA 98122-3934, (206) 329-4857 or 1-877-597-STEP (WA, OR, AK, HA, ID, MT)

## Retrovirus Conference 2003 Update; New Antiretroviral Drugs: Atazanavir, T-1249, plus more

### **NATAP report *By Jules Levin***

There are some interesting stories from today's opening sessions. In the morning oral session on "New Antiretrovirals" for HIV there were presentations on ten new drugs at various stages of development: 2 protease inhibitors for individuals with protease inhibitor resistant virus (one from Roche in very early development and TMC-114 for use in PI resistant patients); and some new NNRTIs in early development from GlaxoSmithKline; 5 entry inhibitors at various stages of development including the presentation I will highlight on T-1249 for T-20 resistant virus; an anti-CD4 monoclonal antibody; the first "maturation" inhibitor; a new class of integrase inhibitors. These talks offered a lot of promise as we see a bunch of new drugs being developed. All of the drugs appear promising, although most are in early development.

An interesting presentation was on UK-427, 857, which is a new CCR5 (entry inhibitor) from Pfizer-Agouron. Early study results show it to be safe, tolerable, and does not have the QT prolongation problem that the Schering C CCR5 inhibitor has. Although it was not presented I hear that it UK-427, 857 shows good antiviral activity, which should be presented at the IAS Conference this July. More details to come. This drug appears to be a promising new CCR5 inhibitor, but this is based on preliminary data and we must wait for more data.

Another interesting story is regarding the new protease inhibitor Atazanavir. BMS reported that patients who developed viral failure on Atazanavir were sensitive or hypersensitive to the currently available protease inhibitors. Details below.

## T-1249, A fusion Inhibitor Against T-20 Resistance

"T-1249 Demonstrates Potent Antiviral Activity over 10 Day Dosing in Most Patients who Have Failed a Regimen Containing Enfuvirtide or T-20 (ENF): Planned Interim Analysis of T1249-102, a Phase I/II Study"

T-1249 is a peptide fusion inhibitor that has shown potent antiviral activity over 14 days of administration in fusion inhibitor naive HIV-infected adults. In vitro (test tube) studies suggest that T-1249 is active against most HIV isolates resistant to enfuvirtide (ENF). This study evaluated the short-term safety and antiretroviral activity of T- (T-20) 1249 in 54 patients failing a regimen containing ENF. 53 patients were dosed, with no discontinuations after dosing began.

Patients were HIV-1 infected adults participating in a phase II or III ENF study who were receiving ENF and a stable background antiretroviral regimen and demonstrated two consecutive plasma HIV RNA values between 5,000 and 500,000 copies/ml, viral failures. Patients discontinued ENF after the evening dose and the next morning added 192 mg/day of T-1249 subcutaneously to the unchanged background regimen for 10 days. The data presented here reflect the results of the planned interim analysis of the first 25 patients. Enrollment into the study has now been completed. Patients rolled over to chronic T-1249 in a separate study.

The 25 patients were mostly men (88%) and averaged 42 yrs old. The average T-20 exposure was 70 weeks. The average time from having virally failed T-20 was 60 weeks. The average viral load was 100,000 copies/ml. Six patients enrolled from T-20 phase II studies and 19 patients from the TORO 1 study. All 25 patients completed the 10-day dosing. One patient died for reasons unrelated to the study drugs (pneumonia).

24 patients had baseline genotype or phenotype resistance tests results available. All 24 patients had genotypic resistance mutations associated with T-20. Fifteen patients had paired phenotypic results available prior to starting T-20 and at baseline before starting T-1249 in this study. The average increase in phenotypic resistance to T-20 was 77 fold compared to 2 fold for T-1249.

Three patients reported serious adverse events: grade 4 elevated ALT, bronchitis, and respiratory failure. In addition, 1 patient with a history of neutropenia developed transient grade 3 neutropenia. There was a possible allergic reaction: adverse event of rash (grade 2) associated with fever observed after completion of dosing which resolved without treatment in 48 hours. And I think the speaker said this person is now backing on T-1249 therapy.

The median HIV RNA viral load reduction was from baseline at Day 11 was -1.12 log. 63% of the patients had 1 log or greater reduction in viral load on day 11.

Here's an interesting point. All patients (7/7) had >1 log viral load reduction if they were on T-20 with viral failure for 24-48 weeks and the median drop in viral load was -1.6. For patients on T-20 with viral failure for >48 weeks the average drop was 0.94 log.

The study authors concluded that T-1249 demonstrates potent short-term antiviral activity in most patients failing a T-20 regimen. (Editorial note: to maintain this activity it's important to make sure additional active drugs are in the regimen). The safety and efficacy of T-1249 remain to be tested in clinical trials during chronic administration.

#### Atazanavir Resistance Study Suggests Sensitivity to Other Protease Inhibitors

"Emergence of Atazanavir Resistance and Maintenance of Susceptibility to Other PIs is Associated with an I50L Substitution in HIV Protease Emergence of Atazanavir Resistance and Maintenance of Susceptibility to Other PIs is Associated with an I50L Substitution in HIV Protease"

Researchers from Bristol Myers Squibb, the maker of atazanavir (ATZ), reported that I50L is the signature mutation for this new once daily protease inhibitor and poster 597 today reported findings from by BMS on the significance of this mutation in their studies. Recently, the FDA granted priority review for ATZ, which means that it may receive FDA approval in June. Studies of ATZ for 48 weeks show no or little increase in tryglycerides, cholesterol, as well as glucose. These studies were reported at ICAAC in September 2002 and can be found on the NATAP website in the ICAAC Conference reports and the Lipodystrophy workshop reports.

The emergence of ATV resistance was monitored in clinical studies AI424-007, -008/044, -009, -034, -043, -045 and ACTG P1020. The phenotype and/or genotype of >70 clinical isolates, designated as virologic failures on ATV containing regimens and who displayed reduced susceptibility to ATV, were determined for ATV, APV, indinavir (IDV), lopinavir (LPV), ritonavir (RTV) and saquinavir (SQV) and evaluated.

When viral failure to atazanavir occurs and this mutation emerges patients are still sensitive or hypersensitive to currently approved protease inhibitors. BMS reported on clinical or patient isolates (blood samples) from 26 patients, from a large number of study participants, who were treatment-naive, received atazanavir in a study, and were viral failures. Atazanavir was the only protease inhibitor they received in their regimen, as opposed to a different group of patients who received atazanavir plus saquinavir in a regimen. These patients were sensitive (<2 fold change) to ATZ before the study and developed ATZ resistance. After developing the I50L these patients were remained fully sensitive or hypersensitive to approved protease inhibitors even if they had additional mutations. These patients's viral load stayed constant, it did not continue to increase. They tested amprenavir, nelfinavir, ritonavir, saquinavir, lopinavir (Kaletra), and indinavir. Hypersensitivity suggests patients were more sensitive to other protease inhibitors when the I50L mutation was present than without it. In vitro, this sensitivity and hypersensitivity was lost when the I50L mutation was removed. So perhaps the I50L mutation needs to be maintained by keeping a patient on ATZ while adding another PI. This remains to be further researched. This study was performed with clinical patient isolates in the lab, but needs to be studied in patients.

There were 42 clinical or patient isolates with ATZ failure that did not develop the I50L mutation and this included 18 patients who received the double Pi combination of ATZ/saquinavir. These patients had decreased susceptibility at baseline to ATZ at

baseline (fold change >2) with >3 key Substitutions. They experienced multiple changes, including primary and secondary PI resistance substitutions observed for other protease inhibitors, and developed high level cross-resistance to other protease inhibitors.

Summary from poster: Atazanavir (ATV, BMS-232632) is a once daily protease inhibitor (PI) currently in late stage clinical development. Characterization of ATV-resistant viruses selected in vitro indicated that N88S, I84V and I50L substitutions may play an important role in ATV resistance and that multiple pathways to resistance are possible.<sup>1</sup> Analysis of a panel of 950 clinical isolates showed that ATV had a distinct resistance profile relative to other PIs.<sup>2</sup> In general, reductions in ATV susceptibility required several amino acid changes, were modest in degree and susceptibility was retained among isolates resistant to one or two of the currently approved PIs. There was a clear trend toward loss of susceptibility to ATV as isolates exhibited increasing levels of cross- resistance to multiple PIs. A genotypic characterization of this panel of isolates demonstrated a correlation between the accumulation of 5 or more changes at 14 key amino acids (L10I/V/F, K K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, I84V and L90M) and reduced susceptibility to ATV. Here, we confirm the identity of a unique I50L substitution as the signature change for ATV and show that isolates harboring the I50L substitution exhibit ATV-specific resistance and increased susceptibility to other PIs. This unique phenotypic pattern appears to be distinct from that observed in the presence of the I50V and 30N substitutions induced by amprenavir (APV) and nelfinavir (NFV), respectively.

## EIP Medical Interpretation Services Available

EIP (Early Intervention Program) offers medical interpretation services in contract with Universal Language Services for in-person medical office interpretation. The process is as follows:

### **Medical provider will:**

Call EIP to request service

### **HIV Client Service staff will:**

- Check that provider is contracted with EIP and confirm that the client has EIP eligibility
- Take the date of the interpretation service request and the date and time of the client's appointment
- Take the provider name as well as the client ID number
- Give interpretation access numbers to the provider
- Confirm with the provider that the interpretation service provided is authorized for the one confirmed appointment only (if further interpretation is desired for other office visits the process will need to be repeated)

**Medical provider will:**

-Contact Universal Language Services to schedule interpreter.

-If the provider has any questions their office can be contacted at:

Monique Ossa McLeod  
HIV Early Intervention Program  
Washington State Department of Health  
PO Box 47841  
Olympia, WA 98504-7841  
Phone:(360) 236-3493  
Fax:(360) 664-2216

## New Clinical Studies

### Swedish Medical Center HIV Research Study

**Purpose: HIV therapy for people who are failing their current regimen**

Study Treatment: Fixed dose tablet of Abacavir/3TC once daily or Abacavir twice daily and 3TC once daily in combination with Tenofovir and a new PI or NNRTI.

This study involves an investigational combination of drugs.

Length: 48 weeks

Study related lab tests, including genotyping and physical exams are free. Study medications, except the new PI or NNRTI are provided at no cost.

Reimbursement for childcare and transportation are possible. Will work around your schedule (evenings, weekends, etc.)

Please contact Heather Algren for more details at:

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### The University of Washington Virology Research Clinic

The University of Washington Virology Research Clinic is initiating studies investigating the epidemiology of Human herpesvirus 8 (HHV-8). This virus has recently been implicated as an important factor in the development of Kaposi's Sarcoma (KS) as well as other malignancies. At present, the mode of transmission and risk factors for

acquisition of this virus are unknown. Preliminary evidence suggests that the virus is sexually transmitted. Data shows that infections are rising and that men that have sex with men are especially at risk for HHV-8.

## Study: Human Herpesvirus 8 (HHV-8)

### The Epidemiology of HHV-8

**Purpose:** To determine if HHV-8 DNA can be detected in different sites of the body. We hope to increase understanding about where the virus resides and how it is transmitted. HHV-8, also known as Kaposi's Sarcoma Associated Herpesvirus, is thought to cause Kaposi's Sarcoma (KS) and other tumors in patients with AIDS.

**Study Visits and Procedures:** Participants, who qualify for the study after a screening visit, will be asked to return to the clinic for 4 visits on a weekly basis to donate samples of blood, saliva, tears, urine and nasal secretions.

<i>We Need:</i>	<i>We Provide:</i>
<ul style="list-style-type: none"> <li>Men and women over age 18</li> <li>HIV+ or HIV-</li> </ul>	<ul style="list-style-type: none"> <li>HHV-8, HIV and HSV antibody tests</li> <li>\$60 for study completion or a prorated amount</li> </ul>

### Behavioral and Biological Risk Factors for HHV-8 Transmission and Acquisition

**Purpose:** To determine how HHV-8, the cause of Kaposi's Sarcoma in people who have AIDS, is transmitted between men who have sex with men.

**Study Visits and Procedures:** Participants and their partner are screened for HHV-8 at the initial appointment. If you qualify and choose to participate, the study lasts for 2 years. Participants are asked to come in for regular follow-up visits, where blood will be drawn every 3 months, a soft swab will be used to collect samples from the mouth and rectum and questionnaires will be completed. Some participants will keep a daily symptom diary.

<i>We Need:</i>	<i>We Provide:</i>
<ul style="list-style-type: none"> <li>Men who have sex with men and are in a steady relationship with one partner</li> <li>HIV+ or HIV-</li> <li>Age 18 or older</li> </ul>	<ul style="list-style-type: none"> <li>HHV-8, HIV and HSV antibody tests</li> <li>A physical examination</li> <li>\$100/person for study completion or a prorated amount</li> </ul>

# Governor's Advisory Council on HIV/AIDS (GACHA) Press Release on the Smallpox Vaccine

## **Governor's Advisory Council on HIV/AIDS (GACHA) says HIV infected persons, as well as others with immune system problems should not get the smallpox vaccine, and should be cautious of those who do.**

As public health officials in the state prepare to begin vaccinating perhaps thousands of 'first-responders,' the Governor's Advisory Council on HIV/AIDS (GACHA) is warning thousands more in the state to stay away from the smallpox vaccine.

"While GACHA is very concerned about the use by terrorists of any biologic agent, such as smallpox, we believe more than a half-million persons in our state need also to be warned that the vaccine itself is potentially very risky to some of them," said Judith Billings, chair of GACHA. "We are concerned not just for those with HIV, but for others with weakened immune systems, including transplant patients, and people receiving chemotherapy or immune-suppressing steroid treatment, and for people with certain very common skin conditions (eczema, atopic dermatitis), as well as pregnant women, and infants under the age of one. Even if these persons don't receive the vaccine themselves, they can still be put at serious risk by coming into direct contact with someone who was recently vaccinated. There is absolutely no reason for these people to panic, no need for them to avoid those places where vaccinated workers might be present such as hospitals or medical clinics. But those at risk should be cautious and those who are vaccinated should be careful," said Billings.

To help mitigate any complications, GACHA is issuing the following recommendations and concerns:

-HIV infected, and other immune-compromised people should not receive the smallpox vaccine, even if their T cell counts are high, unless they are actually exposed to a person with smallpox in which case they should seek medical advice before receiving the vaccination.

-HIV infected, and other immune-compromised people should be aware that coming into direct contact (skin-to-skin), or direct household contact (from bedding, towels, or clothing) with a recently vaccinated person does put them at risk for contracting contact vaccinia, which can pose serious health risks. If they are unsure HIV infected and other immune-compromised people should ask people with whom they have direct skin-to-skin or direct household contact with if they have had a recent smallpox vaccination.

-HIV infected and other immune-compromised people should not stay away from health care, but they should ask their health care provider or organization what the institution's policy is for recently vaccinated health care workers working with immune-compromised people.

-At institutions where workers have been recently vaccinated, those institutions

should take prudent measures to protect potentially vulnerable patients.

-All people considering receiving the smallpox vaccine should be encouraged to first learn their HIV status, and have the opportunity for an anonymous, voluntary HIV test. This recommendation applies to everyone to be vaccinated, even if they do not perceive themselves to be at risk of HIV infection, unless they are certain that they are not infected with HIV. (The newly approved OraQuick. HIV test allows for the result in 20 minutes, should be available in early 2003, and should facilitate HIV testing.)

-All potential smallpox vaccination candidates must be fully informed about the risk of spreading vaccinia through direct contact to other persons. Examples include bed partners and other close household contacts.

-Smallpox vaccination should be completely voluntary and no health care worker should be forced to receive the vaccine or be identified to colleagues as someone who refused the vaccine. This is to protect people's job security, confidential medical history, and that of their partners and close household contacts.

-The State Department of Health, and local health departments, in consultation with the Centers for Disease Control and Prevention, should work with local hospitals and health care organizations to ensure that policies are in place and standardized to minimize the risk of transmission of vaccinia virus from a health care worker to an immune-compromised patient and vice-versa.

## Community Announcements

### **An announcement from Lifelong AIDS Alliance and Public Health King County**

Lifelong AIDS Alliance in collaboration with Public Health King County is opening Seattle's First Transgender Resource Center. The Resource Center will be a dedicated space for transgender individuals to gather for social HIV prevention events and to address the unique needs of the transgender community.

Project volunteers are needed to conduct street outreach, recruit volunteers to assist with the development of center activities, materials and events developed specifically with transgenders at heart. The following is one of the events coming up:

#### **Catch the T - The Series**

Transgender Leadership

February 27th 2003. 7-9PM

1415 10th Avenue Studio 5 (up the Ramp to the Right)

206-860-2191

Topics Addressed:

-Introduction of Transgender Resource Center

-Results of the Lifelong AIDS Alliance Transgender Needs Assessment



-New service provisions

RSVP requested but not required. Food and Refreshments will be provided.

## A Message from Building Bridges Coalition

We would like to thank everyone who participated in the cultural competency trainings, helping to make our project a success. We especially appreciate the valuable contribution of all the facilitators and panelists, who shared their knowledge and skills with us. Thanks to everyone for supporting our mission of increasing access for people of color in HIV/AIDS care and prevention. Look for more Building Bridges Coalition events in the future!

(If you would like information about Building Bridges Coalition, contact Jed Lin at 206-329-0064 ext. 102)

## Community Meeting / HIV Medication Update

**Doctor William O'Brien; Chief, AIDS Pathogenesis Research Program from the Division of Infectious Diseases of the University of Texas will be in Seattle on Tuesday, February 25<sup>th</sup> for an update and discussion on recent information about HIV medications.**

**When? Tuesday, February 25<sup>th</sup>, 2003 from 10am-11:30am**

**Where? Lifelong AIDS Alliance 1002 East Seneca  
Downstairs Conference Room, off the main parking lot**

**Please RSVP to: 206-328-8979**

***DON'T MISS THIS OPPORTUNITY TO ASK YOUR QUESTIONS AND EXPRESS YOUR CONCERNS ABOUT HIV MEDICATIONS.***

***Seattle Treatment Education Project is co-sponsoring this event***

## New Issue of *STEP Perspective* Available Online Now

The new Winter 2003 issue of the STEP Perspective has not shipped yet, but you can already view it online. Visit our webpage link at [thebody.com](http://www.thebody.com) (also available in PDF form):

<http://www.thebody.com/step/winter03/contents.html>

## 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 [betsyd@stepproject.org](mailto:betsyd@stepproject.org) or [ezine@stepproject.org](mailto:ezine@stepproject.org).

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