

STEP Electronic Treatment E-zine

June 10, 2003

Issue 48



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)

The FDA recommends the approval of Atazanavir, a new *Protease Inhibitor*.

Also: BMS lipid studies on Atazanavir presented to the FDA

Written by Jules Levin of NATAP

The FDA Antiviral Drugs Advisory Committee met on May 13th from 8am to 5pm and voted unanimously 15-0 to recommend that the FDA approve **Atazanavir**. The FDA said that since BMS had provided extensive 48 week data the FDA will provide full traditional approval rather than just accelerated approval, if it agrees with the recommendation from the panel which I presume they will.

Last night I sent out the first report from this very informative hearing and it should be posted and archived on the NATAP website at http://www.natap.org/2003/may/051403_2.htm if you have not seen it.

BMS reported that 1000 antiviral-naive subjects have been studied on Atazanavir (ATV) and over 500 patients treated for over 2 years. 500 antiviral treatment-experienced patients have been studied. 9 phase II/III studies have been conducted. An early access program was provided to 3600 patients.

Two studies were reported yesterday in treatment-experienced patients: ATV 400 mg compared to Kaletra in patients with 1 PI failure and Kaletra performed better; the second study compared once daily ATV 300 mg plus ritonavir booster of 100 mg compared to once daily ATV 400/saquinavir 1200 mg and Kaletra. After 24 weeks ATV 300 mg/RTV 100mg appeared comparable in antiviral efficacy to Kaletra. But ATV 400mg/SQV 1200mg appeared inferior. The details and data were in yesterday's report.

In the phase III study comparing ATV+AZT/3TC to efavirenz+AZT/3TC, subjects in this trial generally were modestly immuno compromised based on CD4 cell count. The median HIV RNA level and CD4 cell count for all treated subjects were 4.88 log₁₀ c/mL and 282 cells/mm³, respectively, and were comparable between regimens. Forty-two percent of all treated subjects had baseline HIV RNA levels greater than 100,000 c/mL.

Comparisons of the treatment regimens within the subsets of baseline HIV RNA levels (< 30,000 c/mL, 30,000 - < 100,000 c/mL, >100,000 c/mL) and CD4 cell counts (< 200 cells/mm³, 200 - < 350 cells/mm³, >350 cells/mm³) were also consistent between treatment regimens, slightly favoring ATV. Apparently, regardless of CD4 count and if viral load was over 100,000 c/ml responses as evaluated by achieving <400 copies/ml were comparable between EFV and ATV. The data reported was that for patients with >100,000 copies/ml of viral load at baseline 61% of patients receiving EFV had had <400 copies/ml and 64% of patients receiving ATV (ITT) had <400 copies/ml. They did not report yesterday the percent of patients for each drug <50 copies/ml for patients with >100,000 copies/ml at baseline nor for patients with <200 CD4s.

BMS reported yesterday that patients who were receiving nelfinavir in study 034 could rollover into substituting ATV in study 044. After 24 weeks total cholesterol declined by 36 mg/dl, LDL-C declined by 27 mg/dl, non-HDL-C by 33 mg/dl, and triglycerides by 37. BMS said lipid returned to baseline levels after switching to ATV.

Atazanavir is a new drug with about 48 weeks of efficacy data and lipid data out as far as 108 weeks. With all new drugs additional safety and efficacy information is revealed after a few years following approval. The benefits of the drug are its once daily, low pill burden (2 pills once daily), it apparently does not raise lipids nor glucose. ATV can cause bilirubin elevations which appear not harmful so far in studies. Experts I have spoken with do not feel it is a problem medically but cosmetically it is an issue as some patients will develop jaundice & yellow eyes. One expert told me by laying in the sun or going under a sun lamp you can prevent the yellowing or get rid of it. One study of patients with lipid elevations on NFV saw reversal of lipid levels to baseline after switching to ATV. The cardiac effects of ATV are for prolongation of PR and QT intervals. Regarding QT intervals at the meeting yesterday it was said that it appears as if ATV has the same effect in this area as other protease inhibitors. It was said that some patients could be at greater risk if for example they had heart disease or were on medications that also effect QT intervals. For them it was suggested they might want to consider an EKG before starting therapy but opinions on the need for an EKG were mixed. As I reported yesterday studies show ATV was comparable antivirally to NFV and to EFV. Since this is a new drug more information will be revealed as doctors start prescribing it.

Here is information from BMS on studies exploring lipids and ATV presented to FDA Committee.

The results of five Phase II/III comparative studies conducted across ARV treatment-naive and treatment experienced individuals consistently demonstrated that ATV treatment, as part of a HAART regimen, resulted in significantly less hyperlipidemia and hypertriglyceridemia as compared with other PIs (eg, NFV, LPV/RTV) and as compared with the NNRTI, EFV. The favorable lipid and triglyceride profile for ATV was consistently demonstrated when ATV was combined with a variety of NRTI backbones (ZDV, d4T, ddI, 3TC, TDF). One study (AI424043) met the co-primary objective to demonstrate superior lipid parameters for ATV compared with the PI LPV/RTV as assessed by low density lipoprotein (LDL-cholesterol) measurements.

Another study (AI424008/44) confirmed the long term durability of achieving lower lipid concentrations with ATV treatment through 108 weeks and demonstrated a regression in hyperlipidemia and hypertriglyceridemia when NFV was switched to ATV. In addition, ATV demonstrated no clinically important effect on insulin/glucose metabolism. The magnitude of the difference between LDL-cholesterol concentrations observed for the population of subjects treated with ATV relative to comparator PIs and to the NNRTI EFV is clinically relevant based upon NCEP criteria. In the short-term, fewer ATV-treated patients meet requirements for lipid lowering interventions. The long-term benefits of avoiding hyperlipidemia have been established in the general population, and current clinical practice for HAART-treated patients presumes a similar association between hyperlipidemia and CV risk. For example, 18-30% of patients treated with PIs have a co-morbidity condition of hyperlipidemia, and 8% of patients initiate a lipid lowering therapy.

Results from three Phase II/III studies conducted in ARV treatment-naive HIV-infected subjects consistently

demonstrated an improved lipid profile for ATV-treated subjects compared to NFV and EFV treated subjects as assessed by total cholesterol, fasting LDL-cholesterol, and fasting triglycerides changes from baseline.

Studies AI424007 and AI424008 were randomized studies comparing ATV regimens to NFV regimens in ARV treatment-naïve subjects. Differences between ATV and comparator regimens were observed by Week 4 and continued throughout the treatment period. Analysis of mean percent changes from baseline indicated that subjects on the NFV treatment regimens had substantial increases in LDL-cholesterol by Week 12 and that these increases were sustained through 72 weeks. ATV-treated subjects experienced little or not increases in LDL-cholesterol. Based on NCEP, 80 - 87% of subjects had baseline LDL-cholesterol in the optimal or near optimal range (< 130 mg/dL). However, at Week 72 the proportion of subjects who achieved LDL-cholesterol concentrations that were classified as high or very high (≥ 160 mg/dL) was greater on NFV compared with ATV (17% vs 5%).

Study AI424034 was randomized blinded Phase III study comparing ATV with EFV, each in combination with fixed dose ZDV. Through 48 weeks of treatment, ATV did not result in increases from baseline in fasting LDL-cholesterol, total cholesterol, or insulin, and resulted in a statistically significant decrease of 9% in fasting triglycerides and a statistically significant increase of 13% in HDL-cholesterol $p < 0.05$ for comparisons to baseline. Baseline LDL-cholesterol values assessed by NCEP categories were comparable for ATV and EFV regimens. At 48 weeks, the proportion of ATV- treated fasting LDL-cholesterol concentrations outside the NCEP-defined desirable range was unchanged from baseline. Among ATV-treated subjects, LDL-cholesterol was >130 mg/dL in 13% of subjects at baseline and 13% at Week 48. LDL-cholesterol was >160 mg/dL in 2% and 3% of ATV-treated subjects at baseline and Week 48, respectively. In comparison, the proportion of EFV-treated subjects with LDL-cholesterol >130 or >160 mg/dL increased from baseline. Nineteen subjects (2%) were administered lipid reduction pharmacological therapy while on-study, five (1%) on ATV and 14 (3%) on EFV.

Long-term lipid benefits were maintained through Week 108 for those subjects who enrolled into Studies AI424041 and AI424044. The following fasting LDL-cholesterol analyses were conducted on the cohort of subjects who were treated on the extended dosing studies that followed completion of Studies AI424007 and AI424008.

AI424007/041 provided long term lipid data for subjects treated with ATV+ddI+d4T versus a NFV comparator. Through Week 108, subjects treated with the NFV regimen show substantially higher mean fasting LDL-cholesterol levels compared to ATV-treated subjects, who show no substantial mean increase from baseline. The ATV regimen was associated with a minimal mean percent increase from baseline in fasting LDL-cholesterol of 1% whereas, the NFV regimen was associated with a 22% increase from baseline.

AI424008/44 provided long term lipid data (108 weeks) for subjects continuing on treatment with ATV +d4T+3TC and demonstrated that after prolonged therapy (median 76 weeks) with another PI (NFV), reduction in serum lipid and triglyceride concentrations to pre-ARV levels was achieved within four weeks of the switch to ATV and sustained for 24 weeks following the switch.

Subjects who enrolled into AI424044 and were initially treated with NFV maintained an increase from baseline in fasting LDL-cholesterol of approximately 30% through the time they rolled over. Changes from baseline for the corresponding subjects treated with ATV were minimal through Week 108 (ATV 400, 7%; ATV 600, 8%).

Study AI424044 had a specific objective to assess changes in serum lipid concentrations associated with a switch from NFV to ATV. The sample size had sufficient statistical power to detect a mean decrease of 15% or greater in total cholesterol after 12 weeks of therapy. The 12-week endpoint was selected based on data from previous Phase II studies (AI424007 and AI424008) that showed ARV associated dyslipidemia can be detected as early as Week 4 after the start of HAART therapy. The mean time on NFV prior to a switch to ATV was 76 weeks. The mean time on ATV in Study AI424044 was 38 weeks among the 63 subjects switching from NFV to ATV. The aggregate time on ATV for those subjects continuing ATV from AI424008 was approximately 108 weeks. At the Week 12

endpoint, significant differences were observed for the mean percent change from entry in total cholesterol (-16%), HDL-cholesterol (+5%), fasting LDL-cholesterol (-21%), and fasting triglycerides (-28%) (Table 7.1.4). For all lipid parameters except HDL-cholesterol, these statistically significant differences were maintained through Week 24. Median Week 12 levels of total cholesterol (165 mg/dL), fasting LDL-cholesterol (94 mg/dL), and fasting triglycerides (86 mg/dL) in this cohort were comparable to median baseline levels in Study AI424008 (168 mg/dL, 91 mg/dL, and 93 mg/dL, respectively). Additionally, more than half of subjects in the NFV _ ATV cohort who entered AI424044 with borderline high or high LDL-cholesterol no longer met these criteria by Week 12 (LDL-cholesterol >130 mg/dL in 55% at entry vs 22% at Week 12; LDL-cholesterol >160 mg/dL in 27% at entry vs 10% at Week 12).

LIPIDS IN TREATMENT-EXPERIENCED STUDIES

Results in treatment-experienced HIV-infected subjects demonstrated a favorable lipid profile for ATV-treated subjects compared to RTV/SQV and LPV/RTV-treated subjects, as assessed by changes in total cholesterol, LDL-cholesterol, and fasting triglycerides.

Study AI424009 was a pilot study conducted in 85 ARV treatment-experienced subjects. At Week 72 on Study AI424009, the mean change in LDL-cholesterol for RTV/SQV treated subjects was 8% compared to a mean decrease of 2% for ATV 400/SQV and 30% for ATV 600/SQV-treated subjects. While the mean change in serum triglycerides for RTV/SQV-treated subjects was 95% compared to 27% for ATV 400/SQV-treated subjects and a decrease of 15% for ATV 600/SQV-treated subjects.

Study AI424043 was a randomized, open-label, study in ARV treatment-experienced subjects comparing ATV with LPV/RTV, each in combination with two nucleosides selected on the basis of resistance testing. In Study AI424043, the co-primary objective was to compare the magnitude of change in LDL-cholesterol at Week 24. The magnitude of changes in total cholesterol, HDL-cholesterol, glucose, and fasting triglycerides through Week 24 were analyzed as secondary study objectives. The ATV-containing treatment regimen was associated with a decrease from baseline in fasting LDL-cholesterol (6%), whereas LPV/RTV was associated with an increase from baseline (8%) at Week 24. The superior fasting LDL-cholesterol levels for ATV compared with LPV/RTV were demonstrated by comparing the mean percent change from baseline in fasting LDL-cholesterol (-14.2%, 97.5% CI: -23.0%, -5.4%, nominal $p < 0.0001$).

Atazanavir treatment was also associated with small decreases from baseline in total cholesterol (2%) and fasting triglycerides (2%) through 24 weeks. In contrast, at 24 weeks LPV/RTV was associated with substantial increases from baseline in total cholesterol (18%) and fasting triglycerides (57%). Mean percent changes from baseline were statistically superior for ATV for total cholesterol (-18.1%, 95% CI: -23.4%, -12.9%; $p < 0.0001$) and fasting triglycerides (-36.1%, 95% CI: -46.7%, -25.5%, $p < 0.0001$). The differences in LDL-cholesterol, total cholesterol, and fasting triglyceride levels were observed for ATV-treated subjects within four weeks of beginning therapy and persisted through Week 24. HDL-cholesterol increased for both treatment regimens, with slightly greater increases on the LPV/RTV treatment regimen. As a result, the use of serum lipid reducing agents was less common on the ATV treatment regimen (5%) than on the LPV/RTV treatment regimen (18%).

In the highly treatment-experienced population (AI424045), both ATV-containing regimens were associated with superior lipid parameters compared to LPV/RTV, as assessed by the mean percent change from baseline at Week 16 in total cholesterol (ATV/RTV: -7%; ATV/SQV: -10%; LPV/RTV: +5%) and fasting triglycerides (ATV/RTV: 2%; ATV/SQV: -15%; LPV/RTV: +34%). Mean percent changes from baseline in fasting LDL-cholesterol at Week 16 for ATV 400/SQV were superior compared to LPV/RTV (ATV/SQV: -10%; LPV/RTV: +1%). At Week 16, fasting LDL-cholesterol concentrations outside the desirable range (values >130 mg/dL) were comparable across the three treatment regimens. Thirty-eight subjects (11%) took serum lipid reduction therapy while on study, 7% on ATV 300/RTV, 12% on ATV 400/SQV, and 14% on LPV/RTV. More importantly, 3% of subjects each on ATV

300/RTV and ATV 400/SQV and 8% of subjects on LPV/RTV initiated serum lipid reduction therapy while on study.

Thank you to NATAP for the privilege of posting this article on our Ezine.

What is CMV?

A 'BABES' Perspective by Nancy Somes (from the BABES Network)

Cytomegalovirus (CMV) is a member of the herpes virus group, which includes the viruses that causes chicken pox, mononucleosis (“mono”) and herpes simplex 1 and 2. The viruses all share the ability to remain dormant in the body for a long time.

How Is CMV Spread?

CMV can be spread through bodily fluids such as urine, saliva, blood, tears, semen, vaginal fluids and breast milk. CMV is spread from person to person and has been known to spread in households with children or in daycare centers.

How Does CMV Affect The HIV Infected?

CMV in the immuno-compromised person can cause serious disease. It has been a major cause of death among people living with HIV/AIDS. Pneumonia Retinitis (infection in the eyes) and gastrointestinal disease are the most common problems associated with CMV. CMV can also cause blindness. So, for those of us living with HIV and AIDS we should be particularly careful to avoid contact with an infected individual as much as possible.

How Can You Prevent Transmission?

Wash your hands often. Since CMV is spread from person to person, using condoms would protect you from sexual transmission. It's also a good idea to talk to your doctor if you are going to be receiving a blood transfusion because they don't check the blood for CMV. If you work in a daycare center you need to be extra cautious.

Diagnosis of CMV

CMV infections are rarely diagnosed because the virus produces few, if any symptoms. As with HIV, the body develops antibodies to the virus and there are a number of lab tests that can detect the antibodies. Also the virus can be cultured from urine, throat swabs, and tissue samples. Some of the most common symptoms are symptoms that would occur if you had mononucleosis or hepatitis. If a person tests negative for mono or hepatitis then a costly CMV test should be done.

Treatment for CMV

There is currently no cure for CMV. However there are several therapies available for CMV treatment, including:

- ◆ Daily intravenous (directly into the vein) infusions of ganciclovir (Cytovene®)

- ◆ Foscarnet (Foscavir®)
- ◆ Ganciclovir implant (Vitrasert®), a device containing Ganciclovir that is surgically implanted inside the eye and lasts for about 6-12 months)
- ◆ Intravenous cidofovir (Vistide®)
- ◆ Fomivirsen (Vitravene®), a product designed to be injected directly into the eye
- ◆ Valganciclovir, which is a new version of oral Ganciclovir that is far better absorbed into the bloodstream than Ganciclovir.

Clinical Trials

Swedish Research Center

Study #1

The Swedish Research Center is currently studying the safety and efficacy of an investigational formulation of marketed HIV drugs when given in combination with other HIV drugs to people who are HIV positive. To qualify you must be 18 years of age or older, HIV positive, but have not taken anti-HIV medications before.

Qualified participants will receive all study-related care at no cost, including:

- Study medications
- Lab tests
- Physical exams

Reimbursement for childcare and transportation is also available. For more information and/or to find out if you qualify for this study, **please contact Janice Price, R.N., at (206) 386-2523.**

Study# 2

The Swedish Research Center is conducting a clinical research study to test investigational medications for people who are HIV positive. To qualify you must be HIV positive and currently using 3TC and AZT or d4T and have a viral load greater than 400 copies/ ml.

Qualified participants will receive all study-related care at no cost, including:

- Study medications
- Lab tests
- Physical exams

Reimbursement for childcare and transportation is also available. For more information and/or to find out if you qualify for this clinical research study, **please contact Heather Algren, R.N., at (206) 386-2820.**

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Latest HIV/AIDS Clinical Trials

Neuropathy Study

Open-label, Dose-escalation, Dideoxynucleoside-Associated Distal Symmetric Peripheral Neuropathy Pilot Study

Purpose: to see if taking acetyl-L-carnitine (ALC), an investigational substance, reduces neuropathy (numbness, pain, or tingling in legs and feet) in people who are taking anti-HIV drugs ddC, or ddI or d4T.

Length: 24 weeks

Reimbursement: exams, acetyl-L-carnitine, and lab tests given at no cost. Reimbursement of \$20 per visit plus \$50 for each visit when skin biopsies are done.

Contact: Alyssa Spingola or Lori Cray at (206) 731-3184 (spingola@u.washington.edu)

Semen Study

Crossover trial of valganciclovir in persons with HIV-1 infection and HIV and CMV co-shedding in semen

Purpose: to evaluate the effectiveness of oral valganciclovir in decreasing the shedding of HIV in semen.

Length: 12 weeks after entry

Reimbursement: Semen samples are reimbursed at the following rates: \$15 for screening samples, \$25 for each of the three samples at weeks 2-4, and \$40 for each of the samples at weeks 8, 10, 11, and 12.

Contact: Leslie Deutsch (206) 543-8299 (leslie@u.washington.edu)

Center for Health Studies, *at* Group Health Cooperative

Project Plus

Purpose: The Center for Health Studies is now enrolling community participants for a research study to develop an **HIV health management program** specifically for people aged 50 and older.

To qualify, you must be aged 50 years or older and currently be prescribed antiretroviral medication to treat HIV. **Study volunteers do not have to be GHC members.**

What does the study involve?

- Complete one 30-40 minute survey interview about your health, medications and attitudes and get \$25.
- If you are eligible and interested, we'll ask you to visit the Center for Health Studies Research Clinic for 6 free 60-minute **individual or group** sessions. Session topics will match your individual interests and could include: treatment information, keeping track of your health and medications, communicating with medical providers, and setting personal health goals.
- Get another \$25, if you attend a second 30-40 minute interview and tell us what you liked and didn't like about the individual or group counseling sessions.

For more information about PROJECT PLUS, call Christine at (206) 287-2701.
The Center for Health Studies is located in downtown Seattle (1730 Minor Avenue).

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 ezine@stepproject.org.

Special thanks to the following for contributing written material or editing this publication

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Jeffrey Schouten, M.D., J.D. – Chair, Lyndsey Davis, Boyd Kravenas,
Jon Hubert, D.D.S., Janice Price, R.N., M.Ed.

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