



## CHAP Spring 2002 Newsletter

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## News

### ***New website for Oak Tree Clinic***

Dom/Glenda: Our clinic has just launched our website at [www.oaktreeclinic.bc.ca](http://www.oaktreeclinic.bc.ca) We have included BC's mother-child transmission prevention protocol under clinical guidelines section. Please feel free to forward any feedback/comments to [dkhoo@cw.bc.ca](mailto:dkhoo@cw.bc.ca)

## Communications

### ***New members***

At this time, we would like to say hello to the following pharmacists who have joined CHAP:

- **Miranda Mak.** Miranda is a pharmacist at The Riverdale Hospital, which is a long-term care hospital in Toronto.
- **Junine Toy.** Junine is a pharmacist in the Immunodeficiency Clinic, St. Paul's Hospital.

We would also like to congratulate **Michelle Foisy** on her return to HIV clinical practice. Michelle's new position, as of May 13<sup>th</sup> will be the HIV Pharmacy Specialist, Royal Alexandra Hospital, and DOT for HAART Pharmacist, for the DOT for HAART Inner-city Program, Edmonton, AB.

### ***CHAP meeting - Wed. April 24<sup>th</sup>, Winnipeg***

The annual Canadian HIV/AIDS Research Conference (CAHR) will be held from Thursday, April 25-Sunday April 28th, in Winnipeg, Manitoba. The annual CHAP meeting is scheduled for Wednesday, April 24<sup>th</sup> at the Delta Winnipeg. This will be an all-day meeting, with our network dinner planned for that evening. An agenda is attached. CHAP members are responsible for making their own travel and hotel arrangements.

## Project Updates

### ***Poster for the International AIDS Conference***

An abstract on the development of CHAP has been submitted to the International AIDS Conference. We will find out the status in the middle of April.

### ***Publications/Research***

- a) Pregnancy survey: 12 completed surveys were returned, and the data have been compiled. Laura is in the process of analyzing and summarizing the final results. These results will be presented at the network meeting.
- b) HIV Drug Interactions website paper: Due to ongoing time constraints, this year we will attempt to do a bulk of the website review at the annual CHAP meeting. Time has been set aside in the agenda for this activity, and the meeting room will have internet access for one or more computers. A draft protocol and evaluation tool was distributed for comments.



## **Upcoming Conferences**

### ***XIV International AIDS Conference***

This will be held in Barcelona, Spain, July 7–12, 2002. [http://www.aids2002.org/IE\\_Home.asp](http://www.aids2002.org/IE_Home.asp)

### ***3<sup>rd</sup> International Workshop on Clinical Pharmacology of HIV Therapy***

The 3rd PK Workshop will be held in Washington DC at the Monarch Hotel from Thursday April 11th to Saturday April 13th, 2002. This workshop will again aim at providing a unique opportunity for international interchange on all aspects of clinical pharmacology of HIV therapy by gathering the latest findings in the field. Rolf, Alice, and Lizanne will be attending the workshop, and will give a brief update on the proceedings at the CHAP Network meeting.

## **Drug Updates**

### ***Company Withdraws Nevirapine Drug Application for Preventing MTCT***

Associated Press (03.22.02): Paul Recer Ridgefield, Conn.-based Boehringer Ingelheim Pharmaceuticals announced Friday that it was withdrawing its request that the US Food and Drug Administration approve the drug nevirapine for preventing mother-to-child HIV transmission. John Wecker of Boehringer said the decision came after researchers at the National Institute of Allergy and Infectious Diseases (NIAID) audited a 1999 clinical trial conducted for NIAID in Uganda by Johns Hopkins University researchers. The audit raised questions about the study's supporting documentation, Wecker said, adding that the company will resubmit the application once the issues are resolved. The 1999 study appeared in the *Lancet* (354;9181:795). It concluded that nevirapine was more effective than zidovudine in preventing pregnant women from passing HIV to their babies at birth and through nursing. Wecker said the audit uncovered "no reasons to suspect that there was a problem with the fundamental conclusions." However, FDA spokesperson Jason Brodsky said there are problems with the study that "the agency believes are potentially quite serious." Brodsky declined to identify the problems, but said the FDA is not recommending any change in the approved uses of nevirapine.

Marketed as Viramune, nevirapine is approved in the United States to treat HIV in adults and children over age two. Nevirapine continues to be used in dozens of other countries by pregnant women and newborns. Dr. John R. LaMontagne of NIAID said the problems mostly involve differences in record keeping, particularly the FDA's requirement for patients' original records. LaMontagne also said there were "professional differences of opinion" between the Hopkins and Ugandan researchers as to what constitutes a "serious adverse event," each of which must be included in data submitted to the FDA. The drug maker continues to donate nevirapine to programs in some 23 counties to help prevent mother-to-child HIV transmissions. The FDA requires that data from drug trials, regardless of where they are conducted, meet the same standard. Otherwise, they cannot be used to evaluate a drug for use in the United States, Brodsky said.

### ***Revised Labelling for Stavudine***

Changes have been made in the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and PATIENT INFORMATION sections of the ZERIT (stavudine, d4T) label to describe the occurrence of lactic acidosis and neuromuscular toxicity in patients using stavudine.

A total of 25 patients with neuromuscular weakness resembling Guillian-Barre syndrome in association with lactic acidosis were reported to the FDA's Adverse Event Reporting System. In most cases, antiretroviral therapy was continued in the presence of symptoms that might have been due to lactic



acidosis, such as abdominal pain, nausea, and fatigue, leading to death in six of the patients. Most of these patients (22 out of 25) were receiving antiretroviral combinations containing stavudine. Although causality has not been established, these findings were consistent with recent reports in peer-reviewed journals that the use of stavudine in antiretroviral combination therapy may increase the risk of lactic acidosis. Therefore, the stavudine label now includes a warning that its use may increase the risk of lactic acidosis, which represents a rare, but serious adverse event. The label now includes the symptoms of the newly described symptomatic hyperlactemia syndrome, and the recommendation for prompt suspension of all antiretroviral therapy in suspected cases of lactic acidosis with or without neuromuscular weakness. Permanent discontinuation of stavudine should be considered in confirmed cases of lactic acidosis.

Please refer to the Zerit label for full prescribing information. A copy of the revised labeling is available at: <http://www.fda.gov/cder/foi/label/2002/20412S017.pdf>

Bristol-Myers Squibb Company, which makes and markets Zerit is distributing a letter to health care providers giving more detailed information. The letter reads:

February 2002 Dear Healthcare Provider,

Bristol-Myers Squibb Company would like to remind healthcare providers caring for persons with HIV of the potential for lactic acidosis as a complication of therapy with nucleoside analogues, including ZERIT (stavudine), d4T. The early signs and symptoms of clinical events associated with hyperlactatemia should receive careful attention because of the life-threatening potential of the most extreme manifestation, lactic acidosis syndrome (LAS).

Bristol-Myers Squibb has received reports of rare occurrences of rapidly ascending neuromuscular weakness, mimicking the clinical presentation of Guillain-Barré syndrome (including respiratory failure), in HIV-infected patients receiving stavudine in combination with other antiretrovirals. Some cases were fatal. Most of the cases were reported in the setting of lactic acidosis or symptomatic hyperlactatemia and, in most, antiretroviral therapy had been continued in the presence of non-specific signs compatible with early symptomatic hyperlactatemia that preceded the development of neuromuscular signs and symptoms. If motor weakness develops in a patient receiving stavudine, the drug should be discontinued.

Confirmed elevations of serum lactate may be associated with a broad spectrum of clinical manifestations, ranging from asymptomatic hyperlactatemia, through symptomatic non-acidotic hyperlactatemia (SHL), to acute severe LAS. Early signs and symptoms associated with a high lactate may be subtle and include generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea), or neurologic symptoms (including motor weakness). Patients with these symptoms should promptly interrupt antiretroviral therapy, and a full medical work-up should be performed rapidly. i Permanent discontinuation of stavudine should be considered for patients with confirmed LAS. It is important to note that symptoms associated with hyperlactatemia may continue or worsen following discontinuation of antiretroviral therapy.

At this time, prospective monitoring of lactate levels does not appear to be helpful in predicting the subsequent occurrence of SHL or LAS. i

Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. ii, iii, iv

See the enclosed full prescribing information for ZERIT(r) for additional information regarding the recommended use of stavudine. If you have any further questions, please contact the Medical Information Department at Bristol-Myers Squibb Company at 1-800-426-7644.

Sincerely, Michael R. Stevens, PharmD Vice President, Medical Affairs, Virology



i. Brinkman K. Management of hyperlactatemia: no need for routine lactate measurements. *AIDS* 2001; 15: 795-797. ii. John M, Moore CB, James IR, et al. Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001; 15: 717-723. iii. Lonergan JT, Havlir D, Barber E, Mathews WC. Incidence and Outcome of Hyperlactatemia Associated with Clinical Manifestations in HIV-Infected Adults Receiving NRTI-Containing Regimens. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, February 2001 [abstract 624]. iv. Gerard Y, Maulin L, et al. Symptomatic hyperlactatemia: an emerging complication of antiretroviral therapy. *AIDS* 2000; 14: 2723-2730.

Richard Klein Office of Special Health Issues Food and Drug Administration  
Kimberly Struble Division of Antiviral Drug Products Food and Drug Administration

### ***Shortage of IV-Cytovene (ganciclovir)***

*The FDA Safety Information and Adverse Event Reporting Program - February 13, 2002*

Healthcare professionals are advised of a critical shortage of Cytovene-IV, indicated for the treatment or prevention of cytomegalovirus (CMV) disease. This shortage in supply is expected to last through the second quarter of 2002. Roche urges physicians to explore alternative treatment therapies or management strategies for their patients. This temporary situation affects only the IV formulation of Cytovene. A copy of the letter from Roche Laboratories follows:

Dear Physician,

A few weeks ago, we advised you of a critical shortage of CYTOVENE-IV (ganciclovir sodium for injection) and asked that you consider alternative therapies or management strategies for your patients in order to avoid a complete out-of-stock situation.

Despite the implementation of a system to manage the available stock, demand exceeds our ability to supply Cytovene IV. Regretfully, we must inform you that you will soon face a complete out-of-stock situation. While we expect to receive periodic shipments of Cytovene IV over the next few months, we may experience intermittent complete out-of-stock situations until the middle of the second quarter. We at Roche urge you to continue to explore alternative treatment therapies or management strategies for your patients.

This temporary situation affects only the IV formulation and not the oral formulation of Cytovene (ganciclovir capsules). Please consider using the oral formulation wherever appropriate. Valcyte tablets (valganciclovir HCl) are also available for the treatment of CMV retinitis in patients with AIDS.

Roche is fully committed to the prevention and treatment of CMV disease and we are working as quickly as possible to resolve the current situation.

We regret any inconvenience this situation may cause and we appreciate your patience and support as we work to meet your needs. If you have any questions or need additional information, please call the Roche professional product information department at 1-800-526-6367, Monday - Friday 8 AM - 6 PM EST.

Please see a complete Cytovene and Valcyte product information enclosed.

Sincerely,

James Thommes, MD  
Medical Director

### ***Adefovir for Hepatitis B***

*Gilead Initiates Early Access Program for Adefovir Dipivoxil, Investigational Treatment for Chronic Hepatitis B Infection. Program Open for Patients without Treatment Options Due to Lamivudine Resistance*

**Foster City, CA, March 12, 2002** - Gilead Sciences, Inc. today announced the initiation of an Early Access Program (EAP) to provide its investigational agent adefovir dipivoxil 10 mg to people with chronic hepatitis B virus (HBV) infection resistant to the currently available antiviral treatment lamivudine. The program will open initially in the United States, followed by Canada, Australia and countries in Europe as



local regulatory approvals for the program are obtained. Based on positive data from two pivotal Phase III studies, Gilead anticipates submitting applications for marketing approval of adefovir dipivoxil 10 mg in the United States and Europe in the first half of 2002.

Early access programs are part of an effort by the U.S. Food and Drug Administration (FDA), European regulatory agencies and the pharmaceutical industry to make investigational drugs available during the later stages of clinical development for the treatment of serious or life-threatening diseases.

### **Program Design**

The Early Access Program will make adefovir dipivoxil 10 mg available to patients in the United States 16 years or older with chronic HBV resistant to lamivudine and who are at risk for disease progression. Lamivudine resistance is defined as a positive serum HBV DNA greater than or equal to 10<sup>6</sup> copies/mL (PCR assay) and ALT greater than or equal to 1.2 times the upper limit of normal within four weeks of screening despite ongoing treatment with lamivudine. Patients must have received at least 24 cumulative weeks prior treatment with lamivudine and have adequate hematologic and renal function at screening. Those patients co-infected with HIV, HCV or other viral infections will be eligible provided they meet all other entry criteria.

Physicians will be required to evaluate patients at baseline and after one month on therapy, then every two months until drug discontinuation or study termination following the protocol-specified guidelines. Patients enrolled in the U.S. Early Access Program will receive adefovir dipivoxil via their physician until the drug has been licensed for marketing by the U.S. Food and Drug Administration and is commercially available, or until the program is terminated by Gilead Sciences. A similar program was initiated in France in July 2001 and has enrolled 278 patients to date.

"Providing advanced care to patients through improved therapeutics is at the core of the Gilead mission," said John C. Martin, PhD, President and CEO, Gilead Sciences. "Initiating this program is a significant step toward providing early access to adefovir dipivoxil to patients who have become resistant to lamivudine."

### **Physician Registration**

For more information regarding the Adefovir Dipivoxil Chronic Hepatitis B Early Access Program or to request registration materials, physicians may call 1-800-GILEAD-5 or 1-650-574-3000. Parexel is the contract research organization that will manage the program on Gilead's behalf for sites in the United States, Canada, Australia and Europe.

### **About [Adefovir Dipivoxil](#)**

Adefovir dipivoxil belongs to a class of drugs called nucleotide analogues which are designed to work by blocking HBV DNA polymerase, an enzyme involved in the replication of HBV in the body. The investigational drug is dosed as one 10 mg tablet taken once daily.

Data from two pivotal Phase III studies were released in 2001. All primary and secondary efficacy endpoints were achieved, and the safety profile of adefovir dipivoxil 10 mg over 48 weeks of dosing was similar to placebo. Study 437 is a Phase III clinical trial evaluating the safety and efficacy of adefovir dipivoxil once daily as monotherapy compared to placebo in 515 hepatitis B "e" antigen-positive patients with chronic HBV infection and compensated liver function. Results from this study were presented at the 52nd annual meeting of the American Association for the Study of Liver Diseases (AASLD) in November 2001.

Study 438 is an ongoing Phase III clinical trial that enrolled 185 patients with precore mutant HBV, or hepatitis B "e" antigen-negative virus, and compensated liver function. This two-year study is being conducted in Australia, Canada, France, Greece, Israel, Italy and Southeast Asia. Preliminary results were released in September 2001 and will be presented at the 37th annual meeting of the European Association for the Study of the Liver (EASL) in Madrid in April 2002. Data from these studies will comprise the core of the regulatory filing packages in both the United States and Europe. To further evaluate the long-term safety and resistance profiles of adefovir dipivoxil, some patients are continuing on Studies 437 and 438 for an additional three years of treatment.



Data from additional studies of adefovir dipivoxil in a variety of patient populations, including those with lamivudine-resistant HBV, patients with compensated and decompensated liver disease, post-liver transplant patients and patients co-infected with HBV and HIV, also were presented at AASLD in November 2001, and further data will be presented at EASL in April 2002. To date, Gilead has provided access to adefovir dipivoxil through Study 435 to approximately 400 patients with lamivudine-resistant chronic HBV infection who are wait listed for or have received a liver transplant. Adefovir dipivoxil is an investigational compound and has not yet been determined safe or efficacious in humans for its ultimate intended use.

Gilead Web site: <http://www.gilead.com/wt/sec/news>

## Clinical Pearls

### ***Perinatal Kits***

Jeff: I'm wondering about your perinatal kits vs. what other provinces are doing..... does anybody else provide the 6 week course of AZT for the babe in a kit? In Calgary, the babe wards have the AZT liquid as wardstock for inpatient use, and on discharge a script is given to get filled at the Outpatient Pharmacy so the prescription gets screened by a pharmacist. In the past two years we have had one instance where the pediatrician made a 10X dosing error which was also missed by Nursing (and unfortunately by the Outpatient Pharmacist as well) until our clinic pharmacists caught the error (luckily) three or four days later. The kid was OK, but six weeks of that much too much AZT couldn't be too good for anyone..... how is everyone else managing newborns?

Dom: Glenda and I follow up on all the kits that are used in the province...checking dose, bloodwork (serology/PCR), etc. in conjunction with our peds ID doc. Here at Children's Hospital, we dispense the AZT and NVP liquids specific for each baby so that the doses can be checked by a pharmacist. The dose of AZT is labelled on each bottle (in English) for the caregivers to take home with them (if necessary). For the positive moms whom we follow prenatally, we do some peripartum teaching regarding IV AZT during the delivery and postpartum AZT liquid for baby. We're in the process of collating our data on the number of kits used and follow up data since the program was started early last year. We'd be interested to hear what other in the group are doing.

Kathy: Who pays for it???

Linda: In British Columbia the MTCT kits are included as part of the CFE's formulary. We have kits at most of the major hospitals, but we also provide kits for situations in which the GP is aware of the potential for a high-risk delivery. In this case, we refer the GP to the specialists at the Oaktree clinic for further advice and if appropriate, a kit is released to either the physician or more usually to the hospital pharmacy where the baby is to be delivered.

Kathy: So does this mean that the government pays ie the CFE's?? Wondering as no one is covering the cost in Nova Scotia.

Jeff: Hi Kathy... in Southern Alberta the hospital budget is covering the expense for inpatient prophylaxis, and our province-wide services division for high-cost drugs is picking up the tab for outpatient newborn prophylaxis. Fortunately our numbers are reasonably low, as we have in each hospital access to the rapid point-of-care HIV tests to check out moms with unknown status.

Linda: Yes, The cost is part of the CFE drug budget, (which comes from the provincial Pharmacare budget.)



### **Tenofovir dosing in hemodialysis**

*Linda: Does anyone out there have experience with dosing tenofovir in hemodialysis patients? We have a patient that we want to try this on and we are not getting anywhere with getting information from the company. Dialysis is 3x/week and the dosing interval that we are guesstimating for this patient.*

Rolf: I am not aware of any data on tenofovir during hemodialysis, so it may be interesting to collect blood samples from this patient between and during dialysis sessions for analysis of tenofovir concentrations. We currently don't have an assay for analysis of tenofovir in plasma but I could try to develop one if you are interested.

Kathy: The company may even analyze the samples for you. We had a similar situation with abacavir when it was new. We sent the levels off to the company (GSK) they analyzed them and then we presented our data at CAHR. So it could answer both a clinical & research question.

Linda: Thanks Kathryn and Rolf, Our own PK lab guys are looking at a way to assay the samples for us. We have already approached the company to see if they would do the work for us, but they declined. Apparently, they have had a number of requests already to analyze samples, but they are only doing 'in house' work for now.

### **Voriconazole-antiretroviral interactions**

Alfred: We have a patient who's was admitted on Kaletra, Combivir, phenytoin and dapsone. He's been treated a couple of times for cryptococcal meningitis but his kidneys lately have grown adverse to ampho b and ablc. To date he is receiving eod ablc + 5FC. The service would like to start voriconazole. Has anyone had any experience with managing potential interactions between voriconazole and his ARTs?

Pierre: We had the exact same situation 3 months ago. We had a gentleman with crypto resistant to fluconazole & being adequately treated on ampho B+ flucytosine for the induction then ampho B for maintenance (had a breakthrough while on Itraconazole maintenance dose). He developed nephrotoxicity on ampho B. Then we switched to lipid complex formulation knowing it was going to be a matter of time before creat started to climb again.

We switched to VCZ 200mg po BID. Other meds include Kaletra, 3TC, AZT. I suspected drug interaction between VCZ - Kaletra. So we did Kaletra serum level pre-VCZ (trough). Then we did VCZ + Kaletra(trough) levels 2 weeks and 4 weeks post VCZ. Essentially, we found no change in VCZ levels compared to population data. Kaletra was also unaffected by the addition of VCZ.

Clinically, the patient had increased N/V starting 4 days post VCZ that went away in 2-3 weeks. He had a very significant exacerbation of his neuropathy which we don't know if it is related to VCZ. We decreased the dose to 150mg BID for better GI tolerance. In term of his meningitis, he is doing very well.

I don't know if you would like to check the levels the same way we did. We could try to publish a case series. Rolf did the kaletra level here and Pfizer did the VCZ (was done in UK). The contact persons in Pfizer are Jacqueline Atallah (514 426-2052) or Candice Taylor.

Rolf: Sure we can measure LPV concentrations pre- and post VCZ. Alfred, if you want to proceed with this, please send an email to me at: [rvanheeswijk@ottawahospital.on.ca](mailto:rvanheeswijk@ottawahospital.on.ca) so we can make arrangements

### **ESPRIT Trial**

*Linda: I have a patient who indicates he was in the CTN 124 or ESPRIT trial with interferon (He was going to Dr. Conway in Vancouver). He says the interferon part of this study has been dropped b/c of*



*limited success and now says the same study # will be a trial out of Montreal using a vaccine??? This sounds very strange. Does anyone have more info re: this.*

Marie: I have just received the news that this trial will replace the IL2 portion with the vaccine ALVAC 1452 and dendritic cells in a few months. I do not yet have a copy of this amendment. Just in case, this is an open label multi center trial comparing the efficacy of a protease sparing regimen ( d4t /ddiEC /efavirenz vs d4t /ddiEC/IDV/RTV) and the ability of IL2 to purge HIV from latent stores. Hope this is useful.

## **New references**

### ***New Treatment Guidelines***

Amazingly, there have been NO NEW treatment guidelines posted on the web ([www.hivatis.org](http://www.hivatis.org)) during the time since the last newsletter was published.

There is one new development of interest, though:

The Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents and the PHS Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the U.S. are **now available for download onto a Personal Digital Assistant (PDA).**

The download instructions can be found at <http://www.hivatis.org/ AcrobatDownloadGuidelines.htm> for both Palm and Pocket PC operating systems.

### ***Updated Glossary of HIV/AIDS-Related Terms***

The 4th edition of the Glossary of HIV/AIDS-Related Terms is now available in a searchable database and in PDF format on the ATIS web site, <http://glossary.hivatis.org/index.asp>.

Developed by the HIV/AIDS Treatment Information Service (ATIS), the 4<sup>th</sup> edition of the Glossary contains new and updated terms and definitions. A hardcopy version of the updated Glossary is planned for release in Spring 2002.