

Greetings, and happy new year to everyone!! I'm looking forward to what will certainly be an interesting and productive meeting in Chicago, and I'm also looking forward to passing on the Chair responsibilities to Kathy once the meeting is over! Thanks everyone for all their input and support; I have really enjoyed the information and idea sharing, and am confident that we will all continue to learn and benefit from each other in the future.

## 1. New Members

- Announcing a new (sub-)member of the network: Natalie had a bouncing baby boy, Matthew Francis Webster, on October 5 weighing 8 lb. 8 oz. Both Mom and Baby are doing fine. At almost 9 weeks, he was weighing in at 12lb. 12 oz. and was 24 inches tall - a big baby. Best wishes to Natalie and her family.

## 2. New Resources/Information/Websites, etc.

### a) **Guidelines for Treating and Preventing TB in HIV:**

- Prevention and Treatment of Tuberculosis Among Patients Infected with Human Immunodeficiency Virus: Principles of Therapy and Revised Recommendations. MMWR October 30, 1998/Vol. 47/No. RR-20. Text available at: <http://www.cdc.gov/epo/mmwr/mmwr.html>

### b) **Fourth International Congress on Drug Therapy in HIV Infection (November 8-12, 1998, Glasgow, Scotland)**

- Graeme Moyle, MD, William G. Powderly, MD, Ian G. Williams, MD, Steven Deeks, MD, and others wrote comprehensive summaries each day of the Fourth International Congress on Drug Therapy in HIV Infection in Glasgow. Articles focus on the clinical implications of the materials presented, including treatment following drug failure, virologic monitoring, opportunistic infections, lipodystrophy, and abacavir hypersensitivity. Participants are eligible for up to 7 hours of CME credit. <[www.healthcg.com/hiv/confs/glasgow98/](http://www.healthcg.com/hiv/confs/glasgow98/)>

### c) **Updated Guidelines for the Use of Antiretroviral Agents - 12/01/98**

- The Panel on Clinical Practices for Treatment of HIV Infection has updated the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. This update includes information about the most recently approved HIV drug, Efavirenz. Additional information regarding class adverse events and adherence are included as supplemental links from the guidelines. These guidelines are available at: <http://www.hivatis.org>

### d) **Mexiletine for HIV-peripheral neuropathy: the last chapter?**

- This report of a clinical trial concludes that it does not work in HIV-related PN, and notes that 39% of those on mexiletine had to stop treatment because of side effects.
- Mexiletine for HIV-infected patients with painful peripheral neuropathy: A double-blind, placebo-controlled, crossover treatment trial, Kemper,C.A., Kent,G., Burton,S., Deresinski,S.C. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology,19 (4):367-372 (1998 Dec 1)
- Abstract : Although mexiletine, an antiarrhythmic with local anesthetic properties, has been reported to relieve discomfort in diabetic neuropathy, its usefulness in the treatment of HIV-related painful peripheral neuropathy (PPN) has not been determined. The tolerance and effectiveness of mexiletine in HIV-related PPN were assessed in 22 patients who were randomized to receive mexiletine (maximum dose, 600 mg/day) or placebo for 6 weeks, followed by the alternative intervention for 6 weeks after a 1-week washout period. The daily pain response was assessed using a visual analogue scale card in 19 patients who received at least 2

weeks of the drug. 16 of whom were crossed-over to receive the alternate agent. No statistically significant difference was found between the mean daily pain scores for patients receiving mexiletine versus placebo, irrespective of the order in which the agents were received. Comparing the mean individual daily pain scores for each phase of study, 5 patients (31%) had significantly less pain while receiving mexiletine compared with their response to placebo, 5 patients (31%) had significantly less pain while receiving placebo, and no difference was noted in 6 patients (38%). Crossover and multivariate analyses for repeated measures showed no apparent difference in the response to mexiletine versus placebo. Dose-limiting adverse events occurred in 39% of those receiving mexiletine, but only 1 patient (5%) discontinued placebo. Mexiletine was only modestly well tolerated despite its relatively brief period of administration, and no evidence was found to support its benefit in HIV-related PPN. Although a first-drug effect was not demonstrated, a powerful placebo effect was seen in some patients.

**e) Post-exposure prophylaxis for non-occupational exposure to HIV**

- Well, it was only a matter of time after the guidelines for occupational HIV exposure were developed. A few articles of interest include:
- Centers for Disease Control and Prevention. Management of possible sexual, injecting-drug use, or other nonoccupational exposure to HIV, including considerations related to antiretroviral therapy. MMWR Recommendations and Reports September 25, 1998, Vol. 47, No. RR-17
- Lurie P, Miller S, Hecht F, Chesney M, Lo B. Postexposure prophylaxis after nonoccupational HIV exposure - Clinical, ethical, and policy considerations. JAMA 1998;280(20):1769-1773.

**f) Drug interactions with recreational agents**

- Professor David Back (the guest speaker for our annual meeting) and his colleagues at the Pharmacology department, University of Liverpool have put together information on recreational drug interactions in HIV. This important and often hard-to-find information is available on their website at: <http://www.liv.ac.uk/hivgroup>
- Information on this topic can also be found on the TTH website at: [www.tthhivclinic.com](http://www.tthhivclinic.com)

**2. Drug Update**

**i) drugs licensed in Canada**

**a) Combivir® (AZT 300mg/3TC 150 mg tabs):**

- Combivir received its NOC on December 4, 1998. In Ontario, it will NOT be available via the Sunnybrook HIV Project Centre. Glaxo Wellcome is currently applying to ODB for LUP status (which most HIV drugs are under). In the meantime, section 8 applications will need to be filled out. The DIN number is 02239213.

**b) Fortovase® (saquinavir 200mg soft gel capsules)**

- Fortovase received its NOC on November 20, and is now available to pharmacies. The price is \$183.60/180 capsules (200 mg caps), which works out to about \$550/month, for the usual adult dosage of 1200 mg TID. The DIN is 02239083.
- Patients receiving Fortovase through the compassionate release program will continue to receive the drug until it has been approved for the provincial formulary.
- Roche Canada plans on keeping Invirase (saquinavir 200mg hard gel capsules) on the market and will reassess periodically to see if both products are needed. Invirase is still an ODB-LUP drug; it is unknown under which ODB program Fortovase will be covered. Due to better absorption, Fortovase can be used as a sole protease inhibitor as part of a 3 drug regimen. It can also be used in combination with other protease inhibitors (i.e. ritonavir) at a dose of 400mg BID. Invirase should only be used in combination with other protease inhibitors, such as ritonavir.

**ii) drugs from U.S.**

- a) **abacavir (Ziagen®)** - licensed in U.S. December 18, 1998
- Press release: A new drug with proven antiviral activity, which is conveniently dosed with one pill twice daily and easily incorporated into multi-drug regimens, has been granted accelerated approval by the U.S. Food and Drug Administration for use in combination with other drugs to treat HIV and AIDS. Ziagen (abacavir sulfate) becomes the 15th drug approved by the FDA to treat HIV and AIDS and is the first new drug in its class (nucleoside analogue reverse transcriptase inhibitors) to be approved in more than three years.
  - Ziagen has been studied in clinical trials that have included previously untreated patients as well as heavily pre-treated patients -- including a large, well-controlled study in heavily pre-treated children. Studies show that combinations containing Ziagen have proven antiviral activity in patients who have not previously received treatment with antiretroviral drugs. Patients who have had prolonged prior exposure to Retrovir® (zidovudine; AZT) and Epivir® (lamivudine; 3TC) may have a minimal response to combinations containing Ziagen. However, studies have shown some of these patients to have experienced significant antiviral activity as a result of switching to new combinations containing Ziagen.
  - Ziagen in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of surrogate markers in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV-RNA or disease progression with Ziagen.
  - Today's approval of Ziagen is based on results from three phase III studies. In a planned interim analysis at 16 weeks of a study of adults with no previous treatment history, the three drug combination of Ziagen+Epivir+Retrovir was shown to be superior to the combination of Epivir+Retrovir in reducing HIV-1 RNA viral load. In this study, 75 percent of 87 patients on triple combination including Ziagen were at less than 400 copies/mL using the Roche Amplicor HIV MONITOR®Test compared to 35 percent of 86 patients on dual therapy. Through 16 weeks of therapy, the median CD4 changes from baseline were 47 cells/mm<sup>3</sup> in the group receiving Ziagen and 112 cells/mm<sup>3</sup> in the placebo group. This difference was not statistically significant. In a planned interim analysis at 24 weeks of a study of children with extensive prior nucleoside treatment, the three drug combination of Ziagen+Epivir+Retrovir was shown to be superior to the combination of Epivir+Retrovir in reducing HIV-1 RNA viral load. In this study, 13 percent of 102 patients on triple combination including Ziagen were at less than 400 copies/mL using the Roche Amplicor HIV MONITOR®Test compared to 2 percent of 103 patients on dual therapy. After 16 weeks of therapy, the median CD4 increases from baseline were 69 cells/mm<sup>3</sup> in the group receiving Ziagen and 9 cells/mm<sup>3</sup> in the control group.
  - Preliminary findings from a second controlled study in therapy-naïve adults were supportive of the efficacy of Ziagen through 16 weeks of treatment. This study compares Ziagen+Combivir® (lamivudine/zidovudine) with the combination of Crixivan® (indinavir; protease inhibitor; Merck)+Combivir, and is continuing through 48 weeks.
  - "Ziagen appears to be a highly potent drug that will have potential in a variety of drug combinations because of its ease of dosing and the fact that it has a low likelihood of interactions with other antiretroviral drugs that are metabolized by the cytochrome P450 enzyme system," said Robert Schooley, M.D., professor of medicine at the University of Colorado Health Sciences Center.
  - Ziagen will be dosed as one 300-mg tablet twice daily with no food or water restrictions or requirements. It is expected that Ziagen will be available in pharmacies in early January.
  - In clinical trials to date, the most commonly reported adverse events were headache, nausea, vomiting, malaise and diarrhea when Ziagen was taken, primarily with Epivir and Retrovir but also with all marketed and most investigational compounds. Lactic acidosis and severe hepatomegaly with

steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretrovirals.

- The most serious adverse event associated with Ziagen is a hypersensitivity reaction that can be life threatening and has been fatal in some cases. The hypersensitivity reaction has been observed in approximately 3 to 5 percent of patients receiving Ziagen in clinical trials and is characterized by fever, skin rash, fatigue, and gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain. The symptoms of this reaction get progressively worse if treatment continues. Patients experiencing these symptoms should stop taking Ziagen and contact a physician immediately. Symptoms of this reaction usually occur within the first six weeks of treatment and generally resolve following permanent discontinuation of Ziagen. Patients experiencing this reaction must not take Ziagen again as restarting the drug after a hypersensitivity reaction has resulted in cases of life-threatening and fatal reactions. Glaxo Wellcome will be issuing to patients a Medication Guide for Ziagen to provide further information on optimizing care with this drug. This may be the first such Medication Guide issued under the FDA's new regulations announced on December 1, 1998.
- The Glaxo Wellcome price to wholesalers for Ziagen will be \$9.70/day, or \$3,540 annually, though retail prices paid by patients will be different. However, the price to state ADAP programs is 15 percent less, or approximately \$3,000 annually. This price is expected to enable ADAPs to quickly add Ziagen to state formularies. For complete prescribing information for Ziagen, Efavir, Retrovir and/or Combivir, please call 919-483-2311 or 919-483-8580. Or go to <http://www.glaxowellcome.com>

b) **AZTEC®**

- (Michelle): just a follow-up on the AZTEC AZT. I just received 2 bottles of 100 300mg tablets free of charge from the company to try in one of our patients who had severe nausea on regular AZT. I will keep you posted on the tolerability.
- The name of the contact is Dr. James Dunn: [jmdunn@verex.com](mailto:jmdunn@verex.com); Verex Laboratories, 14 Inverness Dr. East, D-100, P.O. Box 3817, Englewood, Colorado 80112, phone: 303-799-4499
- He said the product costs about \$170 US/100 tabs (300mg), but was willing to let us try it for a couple of months. We were able to order the drug directly from him in the states. The drug is not yet marketed in the States, but is under review.
- (via Glaxo): Glaxo Wellcome and Verex zidovudine row Source: Scrip 2133 p7 Date: 31 May 1996 Text: Glaxo Wellcome's decision not to develop a controlled-release version of zidovudine developed by the US company, Verex, has prompted some highly vocal complaints by the latter. Verex has taken its cause to the media and AIDS groups, warning that "AIDS activists are now assimilating the data, and will be causing quite a public relations issue over the matter".
- Wellcome obtained an option to license worldwide rights to the product, known as Aztec, in 1994, but last December the merged Glaxo Wellcome decided not to go ahead with further development. Verex claims the multinational is depriving patients of a superior formulation. Verex cannot go ahead with the development of the controlled-release formulation on its own or with another partner as Glaxo Wellcome holds patent rights to zidovudine. In 1994, Wellcome won a US patent battle with generics manufacturers, Barr and Novopharm, which prevents other zidovudine products entering the market until the patent expires in 2005. (Barr and Novopharm are challenging the ruling.)
- Verex director Mark Banister told Scrip that the gradual release of zidovudine in Aztec avoids the high drug peaks seen with Glaxo Wellcome's immediate-release formulation, Retrovir, resulting in a significant reduction in side-effects. For example, in the sickest patient group (CD4 counts below 200/mm<sup>3</sup>), headache occurs in 42% of those treated with Retrovir versus 13% with Aztec, fever in 16% vs 0%, nausea in 20% vs 0% and vomiting in 48% vs 0%, he said. This superior side-effect

profile enables more patients to take the drug, and higher doses to be used, he declared. Mr Banister maintains that Glaxo Wellcome is making a mistake in rejecting Aztec: "Although they have to make hard business decisions, this does not give them the right to play God with AIDS patients. They have chosen the wrong issue this time. If they did this with a headache tablet they may have got away with it, but AIDS is different. The patients and the public will demand a very high price for this error of judgement - it will cost senior executives their positions."

- Glaxo Wellcome says the decision not to proceed with development of Aztec was made after a thorough evaluation of data submitted by Verex which showed "no appreciable clinical or commercial benefit". "Having already paid Verex \$1.2 million for the option, we were naturally disappointed when we saw the results", a company spokesman commented to Scrip. However, he noted that Verex had submitted additional data to the company within the past few weeks, adding that if evaluation of these new data shows anything of scientific, clinical or commercial interest, talks may be reopened. © PJB Publications Ltd.

### iii) other news

#### **a) ritonavir liquid - storage, EtOH content**

- (Alfred): Now that ritonavir liquid doesn't have to be refrigerated, has anyone noticed Abbott shipping the liquid with Ice Packs? The last batch we got, Abbott packed the bottles with ice packs.
- (Ann): We get ours in the styrofoam containers but there aren't any cooler packs in them. Also, for everyone's info, it turns out that the ritonavir capsules have dehydrated ethanol in them and we have calculated it to be about 14%. Abbott told us that each capsule contains 136.7mg (or 0.173ml) ethanol. This converts to 0.692ml ethanol for a 400mg dose vs. 2.16ml ethanol in the liquid formulation. Abbott's argument is that if patients who are recovering alcoholics can tolerate the capsules then the liquid should be no problem. However, patients can taste the ethanol and psychologically this may be the difference. Also, the liquid has about 3x more than the capsules.

#### **b) ritonavir liquid - placing into gel capsules**

- (Michelle): Has anyone heard of injecting the ritonavir solution into gel capsules? I wonder how much would fit in a gel cap. I'm sure stability is an issue, but she's asking about a patient doing it prior to taking the dose.
- (Nikola): I have also been asked this question by a patient. It would appear to be a lot of work considering the amount of liquid needed; and there is no data on stability that I have come across. Additionally, most of our patients not only complain of the immediate taste, but mostly of the aftertaste for hours post-dose.
- (Alice): I've heard of this suggestion as well. You can buy empty gelatin capsules from certain independent drugstores (usually those that deal with Drug Trading). Frankly, I think it would be a lot of hassle and a lot of capsules to swallow (assuming each RTV dose is 5 to 7.5 mL). Patients would probably still be able to taste the ritonavir liquid, since those taking the regular RTV capsules still complain about the taste. BTW, another suggested use for these empty gelatin capsules is to place the (powdery) nelfinavir tablets inside each one, to make them easier to swallow.
- (Lori Esch, Buffalo): It doesn't work! We obtained vegetable based (as opposed to gelatin based) capsules and tried filling them. Each capsule only held 0.6 mL and they only last 5-15 minutes before beginning to melt.
- (Ann): We have been using the 00 size- 1ml/capsule. There have been no problems as long as the patient takes the cap right away. We give them a syringe to measure the liquid. We have kept alot of patients on the drug by doing this.
- (Michelle Diment, SK): We've experimented filling a clear hard capsule size 000 (there is a bit more room than size 00 which is easier for patients to fill). The capsule has been sitting on my counter for a week now and is still intact (a bit greasy on the outside). We will likely teach patients to do this

themselves, just prior to ingestion. We are talking about getting a baseline viral load, then doing more frequent monitoring of viral load thereafter.

**c) ritonavir liquid - instability in amber, plastic bottles**

- (Nikola): I have contacted Abbott to see if they can supply empty Ritonavir bottles since most amounts we dispense are not in multiples of 240ml. We cannot dispense glass bottles. Has anyone found any solution for this? And what are community pharmacies doing in those provinces where RTV is supplied through them?
- (Christine): I do not work in the dispensary however as far as I know, we typically dispense the entire bottle of ritonavir.

**3. Professional News Updates**

a) Update on Canadian Cardiovascular Pharmacists Network

- Can. Cardiovas. Pharmacists Network (CCPN or "cardiopigs"), are planning a draft document on the relationship of the group with industry. They are interested in seeking funding from other sources in the industry. They are also planning other initiatives that we may be interested in.

b) Update on U.S. National HIV Pharmacotherapy Network.

- Colleagues in the U.S. (including Lori Esch, Mark Shelton, et al. in Buffalo, NY) have put together a national HIV pharmacotherapy network.
- The network will have multiple functions. Clinical pearls, case reporting, etc. Also, they (Buffalo) are enrolling people into their PI-PK service and will be offering to do levels for sites (real time).
- The network currently has the website in operation but have not placed anything of significance on it at this time. They are currently asking people to "enroll" ie. identify themselves and be placed on a server. There is a national advisory board, contributing editors and an editorial board. At the moment, the network is funded by pharmaceutical sponsorship and are not officially affiliated with any group (although SIDP and ACCP are interested).
- The network is certainly interested in "linking" the american and canadian groups via cyberspace.

c) 1999-2000 HIV Pharmacy Residency

- St. Michael's Hospital & The Toronto Hospital are accepting applications for next year's HIV specialty residency program. This specialty residency is a joint program involving two of the largest, university-affiliated, outpatient HIV clinics in Canada. An interdisciplinary approach is used to provide primary and specialty care and outreach programs. This 12-month program will provide the resident with experience in a variety of HIV clinical settings, with a focus on ambulatory care. The resident will be expected to initiate and complete a research project, and will also have teaching responsibilities. Preference will be given to applicants who have completed a one-year general clinical hospital residency. A stipend of \$25,000 is offered, along with funding to attend and present at a national or international HIV conference. The desired starting date is July-August 1999. Interested applicants may contact either Michelle Foisy or Alice Tseng. The deadline for applications is March 1, 1998.

d) Infectious Diseases Residency (U.S.)

- The Department of Pharmacy practice has an infectious disease position available in Tulsa, Oklahoma, at St. John's Hospital and OUHSC-Tulsa Campus. If you are interested in interviewing for this ID position please contact Michael E. Burton, Pharm.D., Assoc. Prof. And Interim Chair, University of Oklahoma, College of Pharmacy to make an appointment for an interview. Interviews will be held at the Annual ACCP Meeting with recruitment on Nov. 8, 12:30-6:00 p.m. at Table 43 in

Room 230/244, and at the ASHP Midyear Clinical Meeting Personnel Placement Service December 6-9. Please respond via email to set an appointment time: michael-burton@ouhsc.edu

#### 4. Clinical Pearls

##### *Part I: Novel Adverse Drug Reactions*

##### a) Urticarial rash with HAART (Michelle):

- It is a bit complex, but we have a guy who developed a fairly severe urticarial rash 3 weeks after starting indinavir, d4t, 3TC 1.5 years ago. The drugs were D/C and he was never put on anything else. Based on this, we think it may have been indinavir related. He now wants to go on therapy, and maybe even have a rechallenge with the same meds. We have done a complete literature search, etc. and think it may not be immune based, but perhaps a toxic metabolite. We are exploring skin testing, but I doubt that we can get this. In addition, the chemical structures of the PI's seem different enough, that we might be able to try a different one. There is a nelfinavir desensitization protocol from the Geneva abstracts. Any other thoughts?
- P.S. I had a case last year of a man who had a similar reaction on d4t, 3tc and saquinavir- he successfully started on indinavir, ddI and AZT after. The AZT was D/C due to severe anemia and replaced with nevirapine.

##### b) Alopecia with indinavir

- (Kathy): I have a male patient who just started indinavir, ddc and nevirapine. He feels that his hair is falling out more than usual. (he is a drag queen who colors his hair a lot anyhow) I know that fluconazole can cause alopecia.
- (Hélène): I have quite a few patients (male and female) who did complaint of alopecia after starting indinavir. Most of them reported the side effect within the month after starting indinavir. The majority of patients were also on d4T and 3TC, but other were also on different combinations. Some patients had to stop taking indinavir and noticed that alopecia decreased or stopped. Case reports have been submitted to Merck.
- (Alice): We've definitely seen alopecia with 3TC (sometimes with d4T); with indinavir, a lot of the time the complaints we hear are about loss of body hair, not necessarily just the scalp.
- (Nikola): We have also had a few patients complain of hair loss, both body and scalp hair; they were also on 3TC; when I called Merck, it was mentioned that they have received several such reports, which may have been secondary to Indinavir use.

##### c) CNS side effects with efavirenz

- (Michelle): For the Sustiva CNS side-effects, what types of clinical tips have people been giving to their patients? Have any of them actually worked?
- (Christine): We have been suggesting to split the dose (200 mg q am, 400 mg q hs). It does appear to help with the "hangover" feeling and nightmares in a lot of our patients.
- (Tom): If patient still can't tolerate efavirenz, I have them go down to 400 mg hs for 1-2 week, then go up to full dose as soon as tolerate. Those who already have prior c/o dizziness or those who "freak out at the thought of a new, strong medication", I may start off at 400mg, then go up to full dose.

##### *Part II: New dosing regimens, protocols, etc.*

##### a) More on BID nelfinavir

- (Nikola): We are using Nelfinavir 750mg TID regularly. We are just starting the first patient on 1250mg BID, so I have no results to share yet.
- (Ann): We have patients on both and no problems with either. However, in the wake of the indinavir fiasco, Dr. Montaner and the BC Centre for Excellence are NOT recommending BID nelfinavir unless there is a second PI combined with it.
- (Glenda): We are using Nelfinavir 1250 BID in patients who have trouble being adherent with 750 TID. I have found that when I offer patients the choice- some jump at the chance for a BID regimen, while others couldn't possibly manage 5 pills each dose. Some people have a "ceiling" for the number of pills they can take at each dose. We haven't seen any differences to date in viral load in the patients on BID vs TID. We are less comfortable about using BID dosing in the pediatric patients, although we have some kids on BID for adherence reasons. In kids, we only do it if we have to- if they are on nelfinavir powder the volume of food that you have to mix it in becomes a problem, especially with infants who don't have that many food options yet. We also have a couple of patients on Saquinavir 1000 BID/Nelfinavir 1250 BID as a dual PI regimen (in combination with 2 NRTI's).

b) Stopping PCP prophylaxis

- (Linda): Is anyone stopping Septra once CD4 counts increase & remain relatively high? -- >350 or so. If so, after how long? This is in patients who did not have PCP, but whose counts were <200 at one point & so prophylaxis was started.
- (Kathy): In some patients we are stopping primary prophylaxis, based on data from Geneva & ICAAC . It is not a universal thing in our clinic though especially if the patients aren't having any troubles with the Septra.
- (Nikola): yes we are stopping Septra used for primary prophylaxis in patients who have had an increased CD4 (>200) for several months, who have an undetectable viral load and are otherwise stable on their antiretroviral therapy. Other things we also take into consideration are presence other infections. If a patient has problems tolerating Septra, we might consider stopping it sooner if the above criteria are met, rather than waiting several months.

c) Treatment of CMV Retinitis

- (Hélène): We don't use implants at Ottawa Hospital- General Campus, but the intravitreal injections are very popular.
- (Alice): We rarely use implants. Our ophthalmologist is quite comfortable with intravitreal injections. Most physicians here would still go with intravenous therapy for the systemic effect. Sharon Walmsley was part of the International Panel that developed the consensus guidelines (Arch Intern Med 1998;158:957-69) and they are pretty reflective of what goes on here in terms of ganciclovir and foscarnet use.

d) Ritonavir/saquinavir combinations: food requirements, dosing, etc.

- (Michelle): When saquinavir (Invirase product) and ritonavir are used in combination, I was always under the impression that higher fat food still needed to be given to enhance the saquinavir gastric absorption. For ritonavir, the food is only to help minimize the GI upset (not to enhance absorption). Then once the drugs were in the system, ritonavir would increase saquinavir levels through inhibition of hepatic metabolism. As such, I was always recommending that the combo be taken with food (and high fat food if possible to enhance saquinavir absorption).
- I was surprised to see the exact opposite in a patient brochure written by Nancy-Hawley Foss/ Bill Cameron of the Ottawa General Hospital, which was sponsored by Abbott. In the brochure, they mention the following: "When saquinavir is taken in combination with ritonavir, a greater amount of saquinavir remains active, making its bioavailability very high. As a result, saquinavir may be



taken twice a day instead of three times a day and taken with or without food". Any information, suggestions, insights on this issue?

- (Christine): I can't add much to the above question; however, Bill Cameron provided us with the same information when he did a presentation here in Edmonton a little while back. I can't really remember his explanation of the mechanism.
- (Alice): I believe that RTV increases SQV concentrations not only through hepatic inhibition, but also via inhibition of gut CYP3A4 enzymes (inhibition of P-glycoprotein is also another postulated mechanism of RTV's effects on SQV); inhibiting GI enzymes may help to improve SQV bioavailability, which is maybe the reason that Abbott feels that food is no longer as important. I don't know if this is correct or not. My limited understanding is that the presence of food can improve drug bioavailability via different mechanisms (i.e., improved solubility in a fat-rich environment for lipophilic drugs, slowing GI intestinal motility, changing pH, as well as interfering with gut metabolism). So, maybe these food effects would be additive/complementary to ritonavir's effects - in which case the food recommendation should still stand. On the other hand, maybe these food effects are minor players compared to ritonavir's effects on saquinavir disposition - so with this assumption, saquinavir no longer needs to be taken with food in the presence of ritonavir. I have no clue which (if any) of these ideas is correct. I've always still recommended to people to take RTV/SQV with food to improve absorption (to be on the safe side) and more importantly, to decrease GI intolerance. Most people do anyways just so they can tolerate RTV.
- (Yasmin): Alice is right about ritonavir inhibiting gut 3A4 as well as hepatic inhibition. Also P-glycoprotein is a gut player. David Back will elaborate on that at the Chicago meeting. The result is that SQV levels achieved with RTV are basically 100% bioavailability. This is an AUC of about 30 ug-h/mL. This is achieved with 4/4 BID of RTV-SQV HGC in healthy volunteers +HIV pts and RTV-SQV SGC 4/4 BID in healthy volunteers only. The assumption is the HIV pts will be about the same with the SGC + RTV. For this reason food is not necessary, but at the same time I think improving tolerance is an issue so this approach is continued. Fortovase alone does not achieve the same AUC as with RTV - AUC only 20 ug-h/mL in healthy volunteers.
- (Ann): We have been told that food is less of an issue with combination RTC and SQV. However, we still do recommend a fatter meal with taking the drugs to ensure less GI upset. We routinely use BID dosing with SQV 400mg bid but increase to 600mg bid if the patient had a rising VL on a PI-including regimen before. It also depends whether an NNRTI is included in the regimen- we have a lot of patients on 5-9 drug regimens!!!!
- (Nikola): I don't have much further to add to the other comments already provided. I take the same approach as Alice, in that I still recommend that RTV/SQV be taken with food, just to be on the safe side, although I am not sure of its importance. Good question.

e) Role of Fortovase in ritonavir/saquinavir combinations

- (Christine): Since Fortovase is now available, how is everyone handling the issue of ritonavir/saquinavir combinations? Given the improved bioavailability with the soft gel formulation I was wondering how many people will convert patients from RTV/SQV to SQV alone.
- (Alice): We haven't done much of this yet, I think because of concerns about efficacy. Even though the SQV-*sgc* bioavailability is much improved, it still doesn't compare to levels achieved when RTV is on board. (by the way, in Ontario anyways, using RTV 400/SQV 400 BID is actually cheaper with the soft gel vs. hard gel forms - \$442.30 vs. \$538.80 per month). We've switched a lot of people from Invirase to Fortovase as the sole PI, just to give us a better margin of comfort.
- (Ann): We are continuing stable patients on their original combination. Fortovase will be considered on a patient-to-patient basis, primarily where SQV is wanted as a mono-PI in a combination. The feeling here is that SQV is still a second or third-line choice and not really

recommended for mono-PI combination therapy except in exceptional circumstances. The group still feels that the RTV-SQV combos are much better.

- (Lori Esch): We have had Fortovase available in the US for some time now and very few patients are able to handle the pill burden associated with the recommended dose of Fortovase (18 vs 4 if combined with ritonavir). In addition, the BID advantage of combining with RTV is also preferable to most. We are currently looking at saquinavir plasma levels in patients on RTV/SQV versus Fortovase alone (all in combo with NRTIs) so will get back to you with that data!

f) Role of Fortovase in nelfinavir-saquinavir combinations

- (Alice): A quick question regarding the combination of nelfinavir-saquinavir. This has become the dual PI of choice around here because of the inavailability of RTV capsules. Previously, we had always used the doses: NFV 1250 mg BID + SQV-hgc 1g BID, based on a couple of PK and preliminary clinical studies. Now that the soft-gel formulation of saquinavir is out, have people been using Fortovase in combination with nelfinavir? I know that with the RTV-SQV combo, you could use either formulation of SQV at the same dose (400 mg BID) since RTV is such a potent inhibitor. But I'm not sure if this translates to NFV-SQV. If people are using NFV + fortovase, at what (BID) dose? There was a PK study that suggested you could use 800 mg Fortovase TID with the usual nelfinavir dose (i.e., 750 mg BID). But I'm wondering how or if this translates to a BID regimen, since it seems the kinetics of BID Fortovase are slightly different from TID (i.e., similar AUC achieved with 1600 mg BID and 1200 mg TID).
- (Michelle): We are not using much Fortovase (Section 8, ugh!), but if I did the BID dose I would use is 1200mg BID of Fortovase with 1250mg BID of nelfinavir.

g) Zyban (bupropion) interactions with antiretrovirals

- (Nikola): The monograph states that it is affected by the CYP450 2B6 enzyme, however we found another reference (for Wellbutrin) mentioning the 2D6 enzyme instead. What have people been suggesting?
- (Christine): We have had a few patients interested in starting Zyban. I agree with you that the product monograph indicates it is primarily metabolized by CYP 2B6. The only "documented" drug interaction I could find with antiretrovirals was ritonavir which could potentially increase the toxicity of bupropion (Medical Letter August 15, 1997). I am not really sure of the significance of this drug interaction. I also looked in the AHFS under bupropion drug interactions and found a paragraph mentioning possible metabolism by CYP2D6 (under hepatic microsomal enzyme induction). This was based on limited data that "bupropion decreases the clearance of imipramine however further data is needed to determine whether specific cytochrome P-450 isoenzymes (e.g. CYP 2D6) are involved".
- Thus, I have recommended that for patients who are on indinavir or nelfinavir it is okay to be given a trial of Zyban. Given the possible interaction with ritonavir, I would not recommend this combination, however fortunately none of our patients so far have been taking ritonavir. We have seen a couple of patients in follow-up and they are doing fine. I would be interested in hearing others experience. Good question!
- (Alice): This is a very confusing issue, with a lot of incomplete and sometimes conflicting data around. I called Abbott about this a few months ago, and was told the following: As stated, bupropion is primarily metabolized by CYP2B6, which apparently is not significantly affected by ritonavir. However, the medical information pharmacist at Abbott confirmed that ritonavir and bupropion are contraindicated, for the following reasons: (a) bupropion undergoes extensive first-pass metabolism; (b) ritonavir significantly increases concentrations of drugs that undergo first-pass metabolism, and this may occur regardless of what specific CYP enzymes are involved; (c) thus, there is the potential for bupropion levels to be significantly increased by ritonavir; (d) higher concentrations of bupropion are associated with increased risk of toxicity, including seizures.

- Therefore, Abbott feels strongly that these two drugs should not be co-administered. This was from a few months ago, so Abbott may have looked into this a bit more and come up with a more solid opinion or recommendation since then. Anyone??
- (Rachel): When we talked with Glaxo they said that it's a theoretical drug interaction, when we look closely at the drug metabolism. May be we can use this combination with close monitoring. We had one patient we really wanted to use it. Half of the dose can be started at the beginning. But I agree if we don't have to use it may be is better to wait when we will have more information

h) Carbamazepine-antiretroviral interactions

- (Christine): One of our physicians was asking me about an inpatient who was admitted for septic shock and advanced HIV disease. She is taking carbamazepine for a seizure disorder (he is not sure what type) with good effect. He has talked to her about antiretroviral therapy however she is not keen on switching her anticonvulsant as she did not tolerate valproic acid in the past. The physician asked me if there is any antiretroviral combination we can give her with carbamazepine. I know carbamazepine can interact with all of the NNRTIs and protease inhibitors and I have not seen anything regarding how to adjust the dose of the antiretrovirals when used with this agent. In the past, if I had a patient on carbamazepine for neuropathy, I recommended switching to something else. I had another patient with epilepsy who was on phenytoin that I switched to valproic acid and he is doing well. Have any of you used carbamazepine with any of the antiretroviral combinations or do you always recommend switching to valproic acid or one of the newer anti-epileptics?
- (Kathy): There is some preliminary data looking at using 3 NRTIs ie AZT, 3TC & abacavir. We did this for a patient that we have on rifampin.
- (Michelle): I try to avoid the use of CBZ if possible. Other agents are of course valproate and gabapentin. Some of the newer anticonvulsants (vigabatrin [mostly renally eliminated], lamotrigine [substrate and inducer of GT]) may be worth looking into as well. If they are to remain on CBZ, other options are to try ARV TDM on patients and to increase the AVR dose accordingly (expensive, and still not that well studied). The Ottawa General have some ARV assays (ie. nelfinavir). In fact our resident is doing a study on TDM dose adjustments for nelfinavir. I had a patient on phenobarb and indinavir and did not feel comfortable with the standard indinavir dose, so we increased it to 1gTID-1200mg TID.

**5. Upcoming Events of Interest**

a) 8th Annual Canadian Conference on HIV/AIDS Research (CAHR)

- This will be held in Victoria, B.C. May 1-4 1999. The theme is "The Shifting Epidemic: Research Directions for the New Millennium". A 2<sup>nd</sup> announcement and call for abstracts will be issued in December, 1998. The abstract deadline is January 31, 1999. For more information, contact the Conference Secretariat: CAHR Conference, c/o BC Centre for Excellence in HIV/AIDS, 6<sup>th</sup> floor Burrard Building, St. Paul's Hospital, 1081 Burrard Street, Vancouver BC V6Z 1Y6.

b) Drug Information Association 1998 Symposium on Drug Interactions.

- Yasmin Khaliq and Keith Gallicano (also from OGH) will be co-chairing the DIA 1998 symposium on drug interactions. This 2-day symposium will be in Philadelphia on December 7-8, and looks excellent. The overview is as follows:
- "Presentations will have a scientific and clinical approach to understanding and managing drug interactions. The FDA's latest clinical guidance on drug interactions will be presented. Scientific information will be geared toward in vitro systems and their relevance in the clinical setting. Clinical information will focus on management and types of drug interactions in selected therapeutic areas - anti-infective chemotherapy, cardiovascular, HIV, organ transplantation, psychopharmacology, and tuberculosis. Issues such as P450 metabolism, gender differences, time course of interactions, timing of medications, effects of disease and age on interactions, and the role of therapeutic drug monitoring will be addressed where possible and particular to each topic." HIV-related lectures include:
- Drug interactions in the HIV-infected patient: lessons we have learned. Charles Flexner, M.D.
- Drug interactions of HIV protease inhibitors. David Back, Ph.D.
- Registration is \$650 members/\$715 US for non-members. For additional registration, contact the Drug Information Association at: (215) 628-2288 (or speak to Yasmin for the inside scoop!)

## **6. Update on Group Projects**

### **a) *ALFRED: Communications***

- Alfred has submitted a proposal to create and maintain a website for us to Merck Frosst. Alfred has very kindly offered to volunteer his own time for this.
- Alfred has also been busy coming up with some proposed acronyms for our group (although it will be tough to beat the cardiovascular network's pet name of "cardiopigs"):
  - CPHiN or CPHN (Can. Pharmacists HIV Network)
  - CHiPN or CHPN (Can. HIV Pharmacists Network)
- A contribution from Nikola: CHAPLIN - Canadian HIV/AIDS Pharmacy Liaison and Information Network
- Anyone else care to make some suggestions?

### **b) *NIKOLA/YASMIN: Research***

- Some of the activities this group is working on include the following:
  - prepare an annual report of research in Canada (to be done for the next Chicago meeting)
  - provide conference summaries (Geneva - Nikola; Glasgow - Yasmin)
  - coordinate group research efforts

## **Final Thoughts: Economic and Political Theory...with Cows**

### **FEUDALISM**

You have two cows. Your lord takes some of the milk.

### **PURE SOCIALISM**

You have two cows. The government takes them and puts them in a barn with everyone else's cows. You have to take care of all the cows. The government gives you as much milk as you need.

### **BUREAUCRATIC SOCIALISM**

You have two cows. The government takes them and puts them in a barn with everyone else's cows. They are cared for by ex-chicken farmers. You have to take care of the chickens the government took from the chicken farmers. The government gives you as much milk and eggs the regulations say you should need.

### **FASCISM**

You have two cows. The government takes both, hires you to take care of them, and sells you the milk.

### **PURE COMMUNISM**

You have two cows. Your neighbors help you take care of them, and you all share the milk.

### **RUSSIAN COMMUNISM**

You have two cows. You have to take care of them, but the government takes all the milk.

### **CAMBODIAN COMMUNISM**

You have two cows. The government takes both and shoots you.

### **DICTATORSHIP**

You have two cows. The government takes both and drafts you.

### **PURE DEMOCRACY**

You have two cows. Your neighbors decide who gets the milk.

#### REPRESENTATIVE DEMOCRACY

You have two cows. Your neighbors pick someone to tell you who gets the milk.

#### BUREAUCRACY

You have two cows. At first the government regulates what you can feed them and when you can milk them. Then it pays you not to milk them. Then it takes both, shoots one, milks the other and pours the milk down the drain. Then it requires you to fill out forms accounting for the missing cows.

#### PURE ANARCHY

You have two cows. Either you sell the milk at a fair price or your neighbors try to take the cows and kill you.

#### LIBERTARIAN: ANARCHO-CAPITALISM

You have two cows. You sell one and buy a bull.

#### SURREALISM

You have two giraffes. The government requires you to take harmonica lessons.