CANADIAN COLLABORATIVE HIV/AIDS NETWORK NEWSLETTER-JULY/AUGUST

HOPE THAT EVERYONE IS ENJOYING THEIR SUMMER !!!!!!!!!

Sorry this newsletter is sooo late. Hmmm I just haven't had enough to do lately. I am hoping to get some vacation in September & then will be going off to ICAAC. I know that Alice is also going anyone else???

Social News

I think that congratulations are in order for several of our members:

First of all Rachel is expecting a wee little baby. Rachel is due in October 4 and is planning to take maternity leave for 5-6 months. Congratulations Rachel!!!

Nicola & Volker got engaged August 7 and will be married the summer of 2000!!!!!!!!! Hurray Niki

I also have some news Michael & I are expected our first baby on December 22 hopefully it won't be late (that millenium thing is kinda scary). Christine has graciously offered to Chair our January meeting. I will be contacting Merck in the next couple weeks to sort out funding issues/hotel & travel grants. I am also going to draft an agenda soon sooo if anyone has anything that they would like to add to the agenda, please let me know ASAP. Also we will still plan to have a speaker address our group, once again if anyone has any ideas or special requests please let me know.

Perhaps someone can be thinking about helping Christine out at the meeting with regards to taking minutes. Any volunteers??? Christine will be chairing so someone helping out would be greatly appreciated.!!!!!!!!!

New Members

I am still waiting to hear from Debbie Harris. Debbie is a MUN Grad (a Newfie!!) who completed her residency at the QE II in Halifax & obtained her PharmD from U of T. As some of you may remember Debbie won the Young Investigator Award at CAHR this year (under the wonderful supervision of Alice Tseng & Sharon Walmsley). Debbie is planning on practicing in the area of HIV/AIDS & she wants to join the committee. Once

she notifies me of her official title, job description I will contact Merck to see if it would be feasible to add her to our group. I think that she would be an outstanding asset.

Also Alice brought to my attention that there are some of her colleagues that would like to expand their resource base & join our network as email members only ie we are proposing that we have 2 email lists one for our official members and one that includes other pharmacists internationally(Europe, Spain etc). It may be kind of neat to have their perspective on things. Could everyone let me know your thoughts on this matter? Alfred what do you think? Could they link up with our Web page?? By the way how is that coming along??

Chicago Meeting- Not!!!!!!! The Retroconference Meeting 2000 is going to be in San Francisco January 30-February 2. Lucky you guys. A little warmer than Chicago. Abstract deadline is October 5, 1999. The call for Abstracts will be posted on the Retroconference web site in late August. Registration opens November 12 for Abstract authors and for others November 30.

Wastage Study

The study ends in a few weeks. If everyone is really keen and gets there data to Christine an abstract could be submitted to the Retroconference.

New Aniretrovirals

1. Abacavir (Ziagen) newly marketed by Glaxo June 15, 1999
monograph can be found at www.glaxowellcome.ca/monogr/
300 mg tablets $6.25/tab, btl of 100
20 mg/mL solution $100/240 mL.

2. Amprenavir is now available through the Glaxo compassionate access program.
3. Ritonavir Availability
New Soft-Gelatin Capsules Offer Non-Refrigerated, Twice-Daily Treatment
Option -

ABBOTT PARK, Ill., June 30 /PRNewswire/ -- Abbott Laboratories (NYSE: ABT - news) announced today it has received U.S. Food and Drug Administration (FDA) approval for Norvir (ritonavir) soft-gelatin capsules. Norvir is a protease inhibitor indicated in combination with other antiretroviral medications for the treatment of HIV infection. Norvir soft-gelatin capsules require refrigerated storage between 36 degrees Fahrenheit to 46 degrees Fahrenheit until dispensed to patients. Refrigeration by patients is recommended, but not required, if used within 30 days and stored below 77 degrees Fahrenheit. Norvir is approved for twice-daily use and should be taken with food, if possible. Norvir soft-gelatin capsules were also approved for marketing in Switzerland in June.

The approval of Norvir soft-gelatin capsules follows intense reformulation work at Abbott after an announcement in July 1998 that a new crystalline structure of ritonavir, which affected how the semi-solid capsule dissolved, would interrupt the production of Norvir semi-solid capsules.

`Bringing Norvir capsules back to patients has been our top priority throughout the past year and we appreciate the patience and understanding we've received from the community as we have worked on the reformulation," said John Leonard, M.D., vice president, pharmaceutical development at Abbott Laboratories. ``We also appreciate the

efforts regulatory agencies worldwide have made in working closely with us on this formulation throughout the past year."

The soft-gelatin capsule has undergone a number of tests to ensure its stability. Norvir liquid has allowed patients to continue therapy during the period of time when capsules were not available. New Norvir soft-gelatin capsules will be available in U.S. pharmacies beginning next week.

``The availability of the new Norvir soft-gelatin capsules will be welcome news for many patients," said Cal Cohen, M.D., research director, Community Research Initiative of New England. ``The twice-daily dosing with Norvir is important. Also, patients choosing to switch from Norvir liquid to the new capsules should experience a relatively smooth transition."

Clinical Pearls

1. Grapefruit juice hinders uptake of some drugs

NEW YORK, Apr 09 (Reuters Health) -- Many patients take their pills with a glass of grapefruit juice because they believe it raises levels of medication absorption into the bloodstream. However, a new report finds that in some cases, grapefruit juice may actually inhibit drug uptake.

"We now recognize (that) depending on the drug... grapefruit juice may either increase or decrease levels of drug in the blood," explain Dr. Leslie Benet and colleagues at the University of California at San Francisco. The findings are published in the April issue of the journal Pharmaceutical Research.

Previous research has suggested that compounds in grapefruit juice suppress the activity of CYP3A4, an intestinal enzyme that normally breaks down drug molecules before they enter the bloodstream. Those studies have shown that the consumption of grapefruit juice boosts levels of specific medications in the blood.

But the investigators noticed that "the magnitude of (this) increase is often insignificant, unpredictable and highly variable," depending on the drug. With some drugs, grapefruit juice had little or no 'boosting' effect, and, indeed, seemed to suppress medication absorption.

They noticed that absorption of all of these poorly affected drugs was closely related to the activity of another compound, P-glycoprotein.

Based on their experiments in the laboratory, Benet's team say they now have "evidence that grapefruit juice exposure enhances... P-glycoprotein activity" -- thereby inhibiting the absorption of numerous medications. These medications include HIV protease inhibitors, the anti-cancer agent vinblastine, cyclosporine (used in fighting organ rejection after transplant), the antihypertensive losartan, the heart medication digoxin, and the allergy drug fexofenadine.

In a statement from the American Association of Pharmaceutical Scientists, Benet said that "patients already taking grapefruit juice with their medications can continue to do so. However, for certain drugs we studied, such as immunosuppressives and HIV protease

inhibitors, patients may get a further increase in absorption by taking their drugs a couple of hours after a glass of grapefruit juice."

"Patients who have not previously taken their drugs with grapefruit juice should be very cautious in doing so," the California researcher warned. As Benet explained, wide variations in drug absorption -- either too little or too much -- can be dangerous, "leading to potential concerns for toxicity or lack of efficacy."

SOURCE: Pharmaceutical Research 1999;478-485.

2.Protease inhibitors may treat respiratory distress

NEW YORK, Apr 09 (Reuters Health) -- Protease inhibitors -- a class of drugs used to fight HIV -- may also be effective in treating a serious lung condition called acute respiratory distress syndrome (ARDS), researchers report.

A combination of antiprotease therapy and an experimental therapy aimed at replacing surfactant "may improve therapeutic prospects" for ARDS patients, conclude Dr. Patricia Haslam of the National Heart and Lung Institute in London, and colleagues there and at the University of Bristol, UK. Their findings are published in the April 10th issue of the British journal The Lancet.

ARDS can follow severe infection, pneumonia, injury or major surgery, and involves a breakdown in the function of surfactant -- a slippery film that facilitates the expansion of alveoli, tiny air sacks in the lung, during breathing. ARDS is fatal in about 40% of cases. There is currently no effective treatment for the syndrome, apart from supportive measures such as ventilation.

In their study, Haslam's group examined the role of neutrophils -- white blood cells that play a major role in the immune response to infection. Comparing the lung surfactant of 18 ARDS patients with that of 6 healthy people, they found that elastase -- an enzyme produced by neutrophils -- effectively breaks down surfactant, impairing its function. "These changes promote the... (alveoli) collapse characteristic of the syndrome," the authors conclude.

Elastase is a member of the protease family of enzymes -- targets of the protease inhibitor drugs currently used in the suppression of HIV. Based on their findings, Haslam and colleagues now "propose that sustained response to surfactant therapy (in patients with ARDS) might be achieved if such therapy were combined with antiprotease therapy."

SOURCE: The Lancet 1999;353:1232-1237.

3. Pulse therapy: D/C ARV once VL is undetectable, then reinstitute therapy once VL increases significantly

4. Drug holidays: D/C meds to give body a cleansing period from toxicities, and restart either the same meds or new ones.

Research has begun on two new strategies for long-term treatment of HIV disease. Although both theories involve taking people off treatment in some way, they have different goals and expectations. These two strategies are known as pulsed therapy and structured interruptions of treatment (sometimes called drug holidays).

The first approach, best described as a form of pulsed or intermittent therapy, aims at stimulating a stronger immune response against HIV. Researchers speculate that this will empower the person's own immune system sufficiently to control HIV replication without the continual use of anti-HIV drugs.

The second approach, a type of structured interruption of treatment (or drug holiday), can take a number of different forms. On one level, it can be little more than taking people off therapy, after successfully suppressing HIV for a year or more, to simply see what happens. On another level, it assumes that measurable HIV replication will begin again sometime after treatment is stopped but tests whether this is necessarily bad. This kind of therapy interruption compares the benefits and drawbacks of constantly staying on drug therapy against those of
periodically taking time off.

While each approach is getting serious attention as a research project, no one suggests that we know enough to recommend these strategies for anyone's personal use. They are experimental strategies whose overall harm or benefits are simply not yet known.

Pulsed Therapy

The pulsed therapy approach assumes that people should always maintain viral loads below the limit of detection to be healthy. In this approach, a person who has been treated since the earliest stage of HIV infection is taken off all therapy once viral load remains undetectable for some pre-determined length of time, perhaps six months to a year or longer.

While off therapy, the person would be carefully monitored for the return of measurable virus. If and when viral load becomes detectable again, the person would be put back on aggressive antiviral therapy. Typically, this results in the rapid disappearance of measurable viral load for the second time. After another pre-determined period on therapy, the cycle is repeated, taking the person off therapy while monitoring for return of measurable viral load.

An interesting phenomenon has been noted in a few cases of pulsed therapy, either as a structured experiment or simply as a matter of patient choice. The first time a person went off therapy, viral breakthrough (return of measurable levels of viral load) occurred after a relatively short period of time, ranging from a few days to a few weeks. After restarting therapy, viral load plummeted again, below the level of detection. Then after staying on therapy for varying periods, they stopped therapy a second time. This time, viral load remained undetectable for considerably longer than the first time, despite the lack of continued treatment.

A few people who cycled on and off therapy twice now have no return of measurable viral load, while off therapy, for periods ranging from 6 to 21 months. Researchers theorize that each cycle of pulsed therapy led to a progressively longer period for the body to fully control viral replication without the help of anti-HIV drugs. In a few cases, people treated with two or more cycles of pulsed therapy have been able to control viral replication with continued therapy for as long as two years (and still counting).

It is hard to draw any clear conclusions from these observations since nearly every patient involved has done something differently from others. For the most part, they were simply choosing to go on and off therapy for personal reasons. They each had varying times on and off therapy, and varied considerably in how quickly they returned to treatment when viral load reappeared. Researchers carefully studied the consequences of their actions, and were understandably surprised by the results.

What is going on here?

Researchers at the Aaron Diamond AIDS Research Institute and the RIGHT group have proposed a theory: the periods in which a person is taken off therapy and viral replication is allowed to resume may be beneficial. They suspect that the returned viral load is acting somewhat like a vaccination. HIV is aggressively presented to the immune system once again, stimulating a more powerful immune response.

This makes some sense because we know when people use antiviral drugs that work for them, HIV is no longer being presented to the immune system. In theory this might allow the normal immune response against HIV to gradually decline. In turn, occasional interruptions in therapy as proposed here may reintroduce HIV into the immune system, thus stimulating a renewed immune response against the virus.

If this is indeed what is happening and there is promising initial evidence that it is=97this approach might be used to help people become less dependent on anti-HIV drugs and more reliant on their immune systems for control of HIV. Such a response might resemble the tiny percentage of HIV-infected people known as "long-term non-progressors." Such people appear able to control HIV replication without the use of anti-HIV drugs and usually have an abnormally strong immune response against HIV, very similar to that being seen in people who are treated with pulsed therapy.

Still, pulsed therapy is far more theory than reality at this point. The only thing known for sure is that a few people seem to respond in a way that resembles the theory, including the widely discussed "Berlin patient" reported by Dr. Franco Lori's group. Studies of many more people are necessary and already planned.

Even proponents of pulsed therapy warn that there is no evidence so far that this will work in typical, chronically infected people. The case reports noted have all come from people who began anti-HIV treatment extremely early after initial HIV infection. Such people are known to still be able to mount strong HIV-specific immune responses.

In contrast, many people with more typical chronic HIV infection (where treatment began six months or later after initial infection) frequently show no evidence of this kind of immune response. Some researchers believe that the natural capacity for this immune response is lost fairly early in the course of HIV infection. Thus, for now, the only realistic target for pulsed therapy research is in people treated from the earliest or acute stage of HIV infection, also known as primary infection.

Structured Interruptions of Treatment

The second strategy, structured interruptions of treatment, responds to a different set of goals and concerns. It assumes that people taken off therapy are likely to see a rebound of measurable viral load. What's not clear is how high the rebound will go and whether it will initially shoot up and then fall back to some lower "set point" level (a viral load level lower than that seen before the person began therapy).

In this approach, people are not automatically put back on antiviral therapy the minute viral load becomes detectable again. Instead, a per-son stays off drugs for awhile despite the presence of detectable viral load. So then a question begs to be asked: "Is the harm caused by a return of measurable viral load a greater or lesser danger than constant therapy, and all the attendant side effects and development of resistance to treatment?"

What is the harm of constant therapy? Even if viral load remains undetectable for long periods, there are many possible long-term consequences to constant therapy. The risks of cumulative side effects and tissue damage are perhaps the greatest concerns. This encompasses problems such as fat redistribution (lipodystrophy), high cholesterol and triglycerides, diabetes, heart disease and liver problems. These come in addition to the side effects of the older generation of drugs, such as pain in the feet, legs, and/or hands (peripheral neuropathy), red and white blood cell suppression (anemia), pancreatitis, rash, etc.

Suppression of viral load through anti-HIV drug therapy can produce improvements in overall health and prolonged survival. The challenge is to find the best possible balance to get the most from therapy without experiencing its down sides which includes the emergence of possible long-term negative effects. For some, this might mean periodically structuring time away from the drugs, for the body to recover from side effects. Some researchers believe that periodic interruptions of therapy may not only be possible, but necessary to help people live out a normal lifetime with HIV disease.

Since we only have about three years of experience treating people with today's potent three- and four-drug combinations, it remains highly uncertain just how long people will tolerate constant use of the drugs. Few researchers, however, have enough confidence in the drugs to believe that people could use them continually for the 20 to 50 years needed to live a normal life span.

In contrast, we have long known that most people can tolerate long periods of untreated HIV infection without irreparable harm. On the average, people using no treatment at all can usually go for roughly ten years without progression to AIDS. For some, this period is longer, for others it's shorter. Part of the goal of treatment interruptions is to give some of this time back to people, in effect letting them coast along with the virus for awhile. They then return to medication only when signs of disease progression become apparent. Similar strategies employing periodic interruptions of treatments are routinely used for other chronic illnesses that require long-term therapy.

Another concern caused by constant therapy is simply the weariness it causes people. The longer many people remain on constant therapy the more likely they begin to miss doses or take short unstructured drug holidays. That can do harm by encouraging development of viral resistance. If structured interruptions of treatment can be offered to people in ways that are unlikely to hasten resistance, with little or no downside, commitment to proper use of therapy may increase during those periods when people use the drugs. This approach offers a compromise, but hopefully one that will provide long-term benefits.

Since we know that short or frequently repeated drug holidays speed the development of viral resistance, the model here focuses not on casual weekend holidays but rather on carefully planned, structured interruptions. An additional benefit already demonstrated in initial studies is that the break from drugs may help a person's virus increase its sensitivity to some previously used drugs. In theory, this might restore their ability to use drugs to which they had developed resistance. This would greatly enhance their options for future therapy.

Structured Treatment Interruption Research Programs

Treatment interruption programs are just beginning and plan to start with people who have undetectable levels of HIV for six months to a year or more (though this may change after more experience is gained). After that, the approaches vary. Four are outlined below.

1. Some plan to take people off therapy and monitor them to measure the immune and viral responses when therapy is stopped. Here, a person will usually restart anti-HIV therapy as soon as viral load again becomes measurable. The hope is that this may identify the people in whom this approach would be safest and most productive. Such a study is underway at the National Institutes of Health (NIH).

2. Some plan to take people off therapy and monitor them, but not immediately restart therapy if viral load reappears. These seek to determine whether viral load will rise to and maintain a high level peak, perhaps even higher than before the person started therapy. Or they may find that such a peak is followed by a gradual reduction back to a lower and stable level (a set point). If viral load comes back down to a modest set point, researchers may choose to withhold therapy as long as viral load remains stable with no major decline in CD4+ cell counts. Such a study is planned at the NIH.

3. Still another approach, perhaps targeted to people with more advanced disease or those who have developed resistance to most available drugs, will keep people off therapy, regardless of viral load, for a period of a few to several months. At some fixed point, anti-HIV therapy will be restarted. The hope of this approach sometimes called a washout period is to see if the time off allows the virus to return to its natural state (often called wild-type virus) and regain sensitivity to previously used drugs. Restarting therapy with a mix of old and new drugs might then kick off another long period of effective viral control.

4. Another approach takes people off therapy for a fixed period, such as two to six months or longer. This is done to let the body heal from drug side effects and rest from the constant rigor of daily therapy. Either at a fixed point in time, or after some permissible level of CD4+ cell count decreases and/or viral load increases occur, the person may be put back on anti-HIV therapy. If successful, this could theoretically be repeated over many years or even throughout a normal lifetime. The hope is that the mix of time on and off therapy might lead to the increased tolerance of therapy and the longest possible life expectancy for
HIV-infected people, short of an outright cure.

Commentary

Many important new strategies for the use of anti-HIV therapy must be tested. Until recently, most research focused only on how well individual drugs worked over a period of a few months to a few years. Many people are already coming to the end of the hope offered by such narrowly defined, product-driven strategies.

Today, new strategy research on pulsed therapy or structured interruptions of treatment may well be what's needed. Such research may extend our knowledge of how to best get HIV-infected people through a lifetime, or at least well into the new millenium and not just the next few years. These strategies should not yet be considered recommendations for medical practice, nor should the fact that they are being tested encourage people to try them on their own.

We don't have enough information to know whether these procedures will help people live longer or instead cut precious time off what a person has left. If we knew, there would be no need for the research. The right approach is in the context of well-designed studies. Self experimentation seldom leads to knowledge, since there is never a way to know whether what happens to an individual is due to the strategy or drugs used, or whether it is a mere coincidence.

The next several months will see a rash of new strategy studies asking whether and how it might be possible for people to get off therapy, at least temporarily. The more people who volunteer to participate in these studies, the sooner we will know what is and isn't possible.

5. (Kathy) Stability of Antiretrovirals Abroad

Does anyone have any data/ experience with stability of antiretrovirals at high temperatures??? We are sending over some medical students to Africa with a month's supply of AZT,3TC,nelfinavir. (potentail PEP) It is usually over 90 degrees celcius there . The drug companies won;t give us any data on stability. Any thoughts???

(Pierre)Not really. However, I would avoid capsules as a general rule. Use of AZT 300mg tablets or Combivir could be an option.

(Ann)- We have had lots of medical workers go to Africa and Central America without any problems- Not that anyone used them. I think that having them at those temps is better than nothing at all!!

(Helene) What about using a wide mouth Thermos to store the medications? The glass container inside will act as an insulator.

6. Amprenavir & Efavirenz

Now that amprenavir is available through expanded access, does anyone have any thoughts regarding the interaction of amprenavir and efavirenz? I was looking at Alice's drug interaction table and efavirenz decreases the AUC, Cmin and Cmax of amprenavir although the clinical significance is unknown. Are any of you recommending or thinking of recommending a dosage increase?

Part II I just wanted to see if any of you have any experience in combining amprenavir and efavirenz. Due to the decrease in amprenavir AUC caused by efavirenz, I have come across several possible recommendations: changing amprenavir to TID dosing, or adding ritonavir 200mg po bid. I have not seen any good exact data to support these recommendations, though the idea could make sense. Have you tried anything like this? What would be your suggestions?

(Pierre)
We have not used amprenavir yet in Ottawa. We do not believe it brings something new to the actual agents available. However, there is an abstract presented at Chicago this year on ABC+APV+EFV (see below). Hope it might help you.

[133] HIV-1 Baseline Genotype/Phenotype and Virological Response Following Salvage Therapy with Ziagen (Abacavir, ABC), Amprenavir (APV), and Sustiva^{(TM)} (Efavirenz, EFV).

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Objective: To relate baseline HIV-1 genotype and phenotype to viral load (VL) response to salvage therapy in ART experienced adults, and assess development of genotypic and phenotypic resistance following VL rebounds.

Methods and results: Phase II, open label, single arm; ABC (300mg BID), APV (1200mg BID) and EFV (600mg QD). The HIV-1 gag cleavages sites, protease, and reverse transcriptase genotyping and resistance phenotyping at baseline and following VL rebounds at 8 weeks of therapy and thereafter was determined. The relationship between baseline resistance and Wk 16 VL response was determined for subjects who completed 16 weeks of all 3 study drugs (Virology Sub-population, n=65). In this heavily pretreated

population, although most baseline isolates contained >=4 RTI and >=5 PI resistance associated mutations, 55% of baseline isolates were susceptible to APV, 42% to ABC and 75% to EFV. Association between specific baseline mutations and resistance phenotype will be presented. 50% and 56% of subjects experienced a VL decrease from baseline of >= 1 log_{10} copies/mL or a VL < 2.6 log_{10} copies/mL if their baseline isolates were sensitive to 2 (n=14) and 3 (n=9) of the study drugs respectively. Only 18% of subjects with isolates sensitive to only 1 drug (n=17) responded. Subjects responding to the regimen were more likely to harbor baseline viral isolates susceptible to at least 1 of 3 study drugs (60% to APV, 63% to ABC, and 87% to EFV). There was a trend (two-sided p= 0.1) towards higher baseline resistance phenotype to the 3 study drugs in the non-responders. Data on the emergence of resistance following VL rebounds will be presented.

Conclusion: Results of this study showed that APV, ABC and EFV may be used as components of multi-drug salvage therapy in a subset of ART experienced subjects failing their current PI containing regimen.

7. Access to Sustiva in BC

FYI to the group: BC is refusing to bring efavirenz onto formulary due to the high cost of the drug (51% higher than any other NNRTI). A formal presentation and complaint has gone into the National Price Review Board who has not made any decision yet as the company has not received the patent yet. The pricing issue is major as Glaxo_Wellcome is hoping to price abacavir as a PI as well. Don't know about the rest of the group, but we don't have the funding for this and there really is no good data to support either of these drugs being classed as PIs. Apparently, sales of efavirenz are slower than expected in the US and this is compounding the major push by the company in Canada. In BC, only patients already on the EAP program will continue on the drug. New requests (unless there is a very specific and urgent reason) are not being approved at this time until the pricing issue is resolved.

8.. Sustiva & Food

(Pierre) You can take SUSTIVA with or without food. However, SUSTIVA should not be taken with a high fat meal. What are the instructions you give to the patients in regard to the diet they should follow? Have you seen more side effects in patients taking a full meal with their drug ? I am not sure of the significance of that drug interaction. I was told AUC was increased by 50%. Are CNS side effects dose dependant?

(Michelle)The CNS S/E are not dose-dependent (info from Jan Sahai). The company has put this statement in the monograph for their protection, as the safety of higher doses has not been studied. Personally, I am not strict about this recommendation, unless the patient chronically takes it with very high fat foods.

9. Sustiva in UK Guidelines

The British HIV Association's latest guidelines on antiretroviral therapy recommend regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) as first-line therapy. NNRTIs are preferred because of problems with toxicity, patient adherence and pharmacokinetics with protease inhibitors, say the draft 1999 guidelines, which were distributed at the 5th annual meeting of the BHIVA, in Cambridge on March 26th-28th. This is in stark contrast to the 1998 BHIVA guidelines, which recommended two nucleosides plus either an NNRTI or a protease inhibitor for patients with blood virus levels of less than 50,000 copies/mL. For patients with higher viral loads, two nucleosides plus one or two protease inhibitors were advised. Last year, revised US

guidelines included for the first time an NNRTI (DuPont's efavirenz (Sustiva)) as a choice for first-line therapy. However, this was one option, along with protease inhibitors, not a direct replacement of protease inhibitors (Scrip No 2395, p 20). Protease inhibitors have been linked with various lipid metabolism disorders over the past eighteen months. These have ranged from the more cosmetic problems of local fat depletion and accumulation - leading to "buffalo humps" and "Crixbellies" - to potentially fatal raised blood lipid levels. The frequency of the body fat disorder, termed lipodystrophy syndrome, has varied widely in different research, from 16% to 65%, the new guidelines note. The rise in blood lipid levels occurs to some extent in nearly all individuals, and in a small proportion of patients very large increases have been observed. The hyperlipidaemia "might belife-threatening" the authors of the new guidelines say, because of an increased risk of pancreatitis and coronary artery disease. They state the rises in blood lipid levels are likely to produce only a "relatively modest" increase of coronary artery disease. But they also point out this may have synergistic effects on cardiovascular risk associated with HIV itself. Research presented at the BHIVA meeting confirmed that lipid metabolism disorders were not confined to protease-inhibitor-based antiretroviral regimens, but have also been seen with NNRTI-based combinations. But most delegates thought the syndrome was more prevalent with protease inhibitors. Professor Brian Gazzard, chairman of BHIVA and a clinical research director at Chelsea and Westminster Hospital in London, said: "The lipodystrophy syndrome is clearly commoner with protease inhibitors. And NNRTIs seem to be as good as protease inhibitors in trials that have lasted for at least a year."

The 1999 guidelines say another problem with protease inhibitors is that of patient compliance, because of gastrointestinal side-effects, dietary restrictions, pill burden or size, or the need for strict timing of doses. And even in some individuals who adhere fully to therapy, drug serum levels are not maintained throughout the day in excess of the viral IC90, due to "considerable intersubject" variability of protease inhibitor pharmacokinetics.

In terms of which NNRTI-based regimen to choose, the authors say there are insufficient data to be able to recommend any particular NNRTI. But they add: "Some clinicians would be positively influenced by the potency of efavirenz-containing regimens, which has been compared head-to-head with a protease-inhibitor-containing regimen. A recent study ... has shown similar results with nevirapine (Boehringer Ingelheim's Viramune) ... (but this excluded) patients with a viral load greater than 100,000 copes per mL." After failure of first-line therapy of two nucleosides and an NNRTI, the authors recommend changing both nucleosides and adding a protease inhibitor. This should probably be "a combination of ritonavir (Abbott's Norvir)/saquinavir (Roche's Invirase) or ritonavir/indinavir (Merck & Co's Crixivan)".

The guidelines also address the issue of when to start therapy. In asymptomatic patients, treatment should be offered before patients develop clinical progression and irreversible damage to the immune system, at about 350 CD4+ cells/mm3, they say. However patients with a rapidly falling CD4+ count, rapidly rising viral load, or those with a viral load of over 100,000 copies/mL may require earlier treatment. Professor Gazzard said there was increasing evidence that for the majority of patients, therapy was not urgent, and good long-term adherence was more likely when both clinicians and patients saw the need to begin treatment. "Unless patients take the tablets absolutely regularly, the results aren't very good, but how can you expect them to take them for years and years? And data show that even in very late disease, the immune system can recover," he commented.

HIV antenatal screening

Meanwhile, researchers at the conference suggested that routine antenatal testing for HIV infection should be offered much more widely than currently recommended by national guidelines. The UK Department of Health has advised that routine testing be carried out in London, which has a higher incidence of HIV infection, but in the rest of the country only selective testing to women considered at high-risk should be offered. But a pharmacoeconomic study by the Medical Research Council Clinical Trials Unit showed that routine testing across the UK would be cost-effective, as it would lower vertical transmission. The use of antiretroviral therapy, Caesarian delivery, and formula feeding can cut the rate of HIV transmission from 30% down to about 2%. Even current national guidance is not yet implemented, however, with only about half of London maternity units offering routine screening in 1997, and half of hospitals outside London testing women only at their own request.

10. Viagra & Testosterone

(Michelle) Have you heard anything about using 1/4 Viagra dose with people on testosterone? Although I don't think there is a kinetic interaction, there may be a dynamic one (ie. priapism with testosterone potentiated by Viagra)... Any thoughts?

(Pierre)
I have never heard about that drug interaction. I am surprised to read that. At the latest Update conference in Ottawa, I had the chance to talk with one of the DI pharmacists working at Pfizer. I was told (unofficially) that Viagra has a wide therapeutic index. Healthy subjects received more than 5 times the usual dose without serious adverse effects. The dosage adjustment when Viagra is administered concomitantly with other P450 inhibitor drugs seems to be based on pharmacokinetic data only. I agree that the interaction might be a dynamic one. I have not found anything on Medline & Aidsline. In our clinic, I don't remember having seen that combination but I would not be surprise to see patients using both drugs. I am not too concern. hope it helps you.

11. Effects of Viagra (sildenafil citrate) on Fortovase (saquinavir)

Pfizer and Roche have recently collaborated on a study to investigate the possible pharmacokinetic interaction between Viagra and Fortovase. In addition Pfizer has also investigated the potential pharmacokinetic interaction between Norvir (ritonavir) and Viagra in a separate study. The results of these studies have prompted Pfizer to consider a revision to the Viagra prescribing information to include these new data.

Due to the strong interest in information on drug interactions in the field of anti-HIV medications we feel that it is very important to share this information with prescribers, advisors and consumers of our anti-HIV products and their care givers.

Study results

The coadministration of Fortovase at steady state (1200 mg tid) with Viagra (100 mg single dose) resulted in a 140% increase in sildenafil Cmax and a 210% increase in sildenafil AUC. Viagra had no effect on saquinavir pharmacokinetics.

Coadministration of the protease inhibitor Norvir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with Viagra (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of sildenafil were still approximately 200

ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. Viagra had no effect on ritonavir pharmacokinetics.

The magnitude of the effect of Fortovase on Viagra is comparable to that reported in the current Viagra package insert for the effect of erythromycin. Therefore the current Viagra dosing advice for patients receiving CYP3A4 inhibitors, including erythromycin, can be applied to patients receiving Fortovase. As such physicians should consider a 25mg starting dose of Viagra when administered to patients also taking Fortovase.

12. Indinavir Syrup

The composition and preparation method of the indinavir syrup as described in the manuscript 'Development of an oral liquid indinavir formulation to treat HIV infected children' by PWH Hugen et al. The manuscript is send to Pediatrics.

The solution is applicable in adults as well. The amount for 800 mg tid is 80 ml per ingestion, because the strength is 10mg/ml.

The solution has to be stored in the refrigerator and is chemically stable during 2 weeks, which is the shelf life. This shelf life is chosen based on microbiological considerations valid for unpreserved oral solutions.

13. Malaria ARV Interaction

(Nikola)I just wanted to check what you anticipate and recommend in terms of drug interactions between antiretrovirals and antimalerials. We have a patient on Indinavir, Efavirenz, AZT and 3TC going to Tanzania, requiring antimalerial prophylaxis. The travel clinic is wishing to start her on Mefloquine. Its pharmacokinetic parameters in question and other interactions appear not to be very well defined. I have called the company (Roche) who cannot comment on the possibility of such an interaction. What do you think? Have you come across this? Thanks for your help!

(Christopher Holtzer) To my knowledge there have not been any direct pharmacokinetic interaction studies involving d4T, ddI, NLF or SQV and eitherhalofantrine and mefloquine. But, Mefloquine and halofantrine are eliminated primarily by biliary excretion and are therefore unlikely to have any interaction with the above mentioned drugs as they are metabolized by different mechanisms. This is nothing but an educated guess, so use the information appropriately within that context.

(Yasmin)We have done an interaction study in healthy volunteers with ritonavir and mefloquine (there is some indication that mefloquine is a 3A4 or 2D6 substrate by in vitro studies). In the first 6 of 12 pts analyzed we have seen no change in mefloquine parent drug levels but a decrease in ritonavir by 30-40%. The MFQ carboxy metabolite may be slightly decreased but we haven't got that far yet. If you wish to extrapolate at this point - maybe use of mefloquine is ok (we loaded for 3 days then once a week for 4 wks) but consider the RTV may be a problem. Whether you want to increase or not - that's a judgement call for your pt.

Someone I think recently asked about rifabutin? We have data suggesting rifabutin 150 mg Mon, Thurs with R/S 400 mg bid each is reasonable.

(Linda)We had this come up a couple years ago -- I think the person was on RTV & SQV & AZT & 3TC -- We used the suggested alternative, doxycycline as prophylaxis because of the potential for DIs with mefloquine. One of the doctors involved spends 3-4months each year in Africa so is quite familiar with malaria tx/prophylaxis.

14. Place of Sustiva in First Line Therapy

(Kathy)Given the recommendations for the use of NNRTIs first line in the New Draft British Guidelines and Sustiva being first line (along with the PIs) in the May IDSA Guidelines it would be interesting to see if your clinics have seen a change in prescribing practices ie are you seeing more use of the NNRTIs as first line agents. All of them or simply Sustiva??

(Alice)
We had an interesting chat about this at the clinic a few weeks ago, when Dr. Graeme Moyle was in town. He felt that we got a blown-up impression of the British guidelines, and his interpretation was that NNRTIs could be considered as a first line option along with PIs (similar to USPHS draft guidelines). Here there is more interest among patients for PI-sparing regimens; efavirenz seems to be the NNRTI of choice among the popular consensus, with a few also opting for nevirapine, especially if patient has prior psych. history. Not many takers for delavirdine due to pill burden. The MDs here have not quite jumped on the bandwagon; many feel that the Pis are still more potent, especially in dual combos, and some are worried about the baseline viral load thing. In addition, David Ho was in town a few weeks ago as well, and his concern/theory was that NNRTIs might not do as good a job as the PIs of clearing virus from lymph node sites.

Our new HIV resident, Mary Nguyen, will be looking at this issue in her research project; specifically, to assess trends of ARV regimens being prescribed to naive patients in Toronto, and to look for any correlating factors as to whether people are given PI vs NNRTI vs triple nuke regimens.

(Pierre)I think the OGH clinic MDs share Alice's opinion. For sure, we are NOT using nevirapine + delavirdine at all for 1st line therapy. Lack of efficacy (or should I say lack of evidence) is the reason why. I have seen some interest (we have started 10 patients max [I have to check the number]on EFV 1st line therapy) for EFV and we clearly think it appears to be the most effective NNRTI. That explains as well why we do not favor the use of other NNRTIs (re:cross-resistance). We think that double PI (RTV-SQV; RTV-IDV) is still the most powerful HAART and that it should be prefered in pts with initial VL>100 000 copies/mL.

(Ann) As usual, B.C. is "different" than most other places. Here, the general feeling is that Sustiva is probably not as good as the company would like us to think- that is the same or possibly not even as good as nevirapine (we rarely use delavirdine except in salvage therapy). This thinking is based on some preliminary results being discussed of some studies in progress that show results quite to the contrary of the data that Dupont is using to promote their product (sorry, I can't put my finger on the study/investigator's name at the moment). In fact, many have questioned the data and analysis of that study. On top of that, many patients and clinicians are concerned with the high incidence of CNS effects and not really wanting to expose patients to that. In addition, B.C. is NOT covering Sustiva due to the excessive pricing and so patients are not being started on the drug at all until this is resolved. Naive patients are generally being started on 2 NRTIs and either nevirapine or a PI (single or reduced dose combination PI). Of course, there are always exceptions!!!

Also PI containing regimen is usually used if the VL is significantly high (such as >100,000 or there abouts) whereas an NNRTI containing regimen is usually used in patients with VL in the 10,000-50,000 or so range. Again, this depends on the individual patient's circumstances and choices as well as the clinician's preferences

(Nikola)
Physicians at our clinic are currently using either Efavirenz or Protease Inhibitors as part of first line therapy. At this point deciding factors may include patient life-style, perception of side effects, other meds, etc. So it is quite individualized and both PIs and Efavirenz are considered. We are not using Nevirapine or Delavirdine however; these are also not covered by the Alberta government.

15. Post Exposure Prophylaxis
(Sandy) I wonder if I could get some feedback (a poll) of what each of your institutions are doing for post-exposure prophylaxis with respect to the protease inhibitor...are you using indinavir or nelfinavir? We are still using indinavir, but are in the process of re-evaluating. Thanks. I appreciate your feedback.

(Pierre)We still use IDV officially. However, we do not hesitate to substitute for Nelfinavir if needed (eg. side effects, conveniance in regards to dosing...)

(Alfred)We still use indinavir since the province covers the 1st week of prophylaxis. Otherwise the patient will have to pay for nelfinavir if that is what is decided. I haven't heard whether Manitoba Health is re-evaluating their guidelines. Revisions may be made regarding other issues though.

(Ann)In British Columbia, we decided to go with Nelfinavir for a number of reasons- 1) easier to take -TID with food vs Q8H on empty stomach; 2) risk of nephrolithiasis vs diarrhea - overall, nelfinavir seems to be better tolerated. We have used indinavir in the past in definite high risk exposures and both patients developed nephrolithiasis, one requiring hospitalization; 3) somewhat less drug interactions -seems to be, anyway. 4) formulation and dosing available for children - as our program includes community exposures. Hope that this helps. PS. we have also switched our basic drug regimen from AZT/3TC to D4T/3TC based on the high incidence (>70%) of side effects associated with AZT that was resulting in patients discontinuing medications or having to change to stavudine during the course of treatment. The change occurred this spring and the side effect incidence has dropped dramatically

(Nikola)We are still using Indinavir in combination with AZT and 3TC at this point.

(Linda)In Regina, we're still using Indinavir for PEP, however we're using more 2 drug regimens lately (AZT/3TC) Good to know what's happening across the country though.

In Print
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Pai VB & MC Nahata Annals of Pharmacotherapy March 1999;33Nelfinavir pp325

Pp 294 SR Smith, EL Boyd, DM Kirking Nonprescripion and Alternative Medicine Use by Individuals with HIV Disease

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Guidelines

The draft version of the 1999 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus is available on the ATIS website (http://www.hivatis.org).

The draft 1999 Guidelines represent an update of guidelines published in 1995 and in 1997. They include recommendations to prevent major opportunistic infections in the era of highly active antiretroviral therapy (HAART). Changes made to the guidelines from the 1997 version are bolded.

Bureau of Surveillance Pilot Project

Patient Reporting of Adverse Drug Reactions to HIV/AIDS Drug Therapies

The Bureau of Drug Surveillance is conducting a pilot project called **Enhanced Post Marketing Surveillance of HIV/AIDS Drugs Therapies**. Reasons for inititiating this project include:limited safety data for HIV/AIDS therapies, fast-tracked onto the market, limitations of spontaneous reporting systems (ie underreporting), and the HIV/AIDS community advocacy of patient reporting.

One enhancement to post marketing surveillance is the reporting by patients of suspected adverse drug reactions or side effects to their HIV/.AIDS drug therapies. A patient reporting form was developed for this test pilot. During the next three to four months, a patient self-reporting process and the form will be tested at two HIV/AIDS treatment facilities in Ottawa- the University of Ottawa Services clinic and the Ottawa Hospital Campus clinic. Patients will be asked to complete and return the form to their respective clinic.

As a pharmacist, you may be shown this form. Should a patient approach you for help in completing the form, you expertise in ADR reporting would be very valuable. We may be calling upon you to participate in the pilot at a later date.

Reports from Working Groups

(Sandy) Publications

I just received comments back from the reviewers for our paper. The major areas for revision include the following:
1. Including a pharmacodynamic interaction sections (maybe as part of the drug interactions / ADR section)...could the individuals involved in this section please help me out?
2. Provide more information on "how" to do things rather than inform pharmacists that they should do things like patient counselling.
3. Improve the special populations section to address the needs of patients such as hemophiliacs, drug users, and patients on methadone.....Would individuals involved in this section please help me out with this section?
4. One reviewer wants us to consider rewriting the paper to focus in defining the role, goals and guidelines of the HIV/AIDS Pharmacy Network Group and provide a detailed description on how we plan to help practicing pharmacists in the various areas described in the paper.

I will be trying to sort through the comments...any words of advice or direction or guidance would be appreciated.

(Yvonne Education)
Any progress Yvonne ??

(Alfred) Communications
Any progress Alfred ??

(Nikola) Research
Wastage study is coming to a close, please provide Christine with a summary from June, July, August as soon as possible so that we can perhaps have an abstract sent off for the Retrovirus 2000 Conference.

Final Thoughts
I hope that everyone continues to have a nice relaxing summer. I will be in touch about the Conference and meeting in January. Bye for now