CHAP Fall/Winter 2002 Newsletter

News

Babies

The stork has gone crazy. First, a summer trip to Halifax to deliver Kathy's little girl Sarah. Then, it had to carry the 9 lb 7 oz James to Toronto in Laura's Home on August 29, and finally dropped Tim to the VanHeeswijk's house on Oct 28. Now, it deserves a little rest! Especially knowing that it will have to fly over the Ottawa River around December 25 for a special Christmas gift to the Giguere's place. I warned it to be careful! Santa Claus will also be flying at the same time.

Congratulations to the Moms and Dads.

CHAP New Members

Andrea Murphy joined CHAP as a result of Kathy's maternity leave. Andrea's e-mail has been added to the listserve. You can also contact her at andrea.murphy@dal.ca. Welcome to CHAP.

Project Updates

Publications/Research

a) HIV Drug Interactions website paper:

The paper circulated for comments and was finalized last month. It has been submitted for publication in BMJ. In addition, it has been condensed and also submitted to AIDS in the concise communication section. I would like to congratulate all the members who participate in this project. It is the perfect example of common efforts in the realization of a specific and ambitious project. I also want to personally thank Alice, Debbie, Christine, Lizanne, Laura and Nancy for their hard work putting together all the pieces of the puzzle. CHAP was created to pool together the resources throughout the entire Country for the realization of the primary objectives of the network. I think we fulfilled it wonderfully.
Furthermore, we have been able to have the cooperation of Dr Woodend for her precious statistical assistance. On behalf of CHAP, I expressed our recognition and offered her a 150$ gift certificate in appreciation of the provided service.
I will keep you posted on the results of the journal submissions.

b) Position paper on TDM:

There were discussions at the last Annual Meeting regarding the development of a position paper on TDM. It was then decided that Rolf would chair that project with the input of Alice and Nancy to evaluate the necessity and the priority of going ahead with that project.
Over the last several months, numerous papers were published about the role of TDM in HIV disease. I proposed to bring back this topic at next year meeting to reassess the direction/future of that project.

Conferences:

Summary of past conferences:

Past Conferences

September 22-25, 2002
4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV
San Diego, CA

September 27-30, 2002
42nd Interscience Conference on Antimicrobial Agents and Chemotherapy
San Diego, CA

October 24-27, 2002
40th Annual Meeting of the Infectious Diseases Society of America
Chicago, Illinois

Upcoming conferences:

February 10-14, 2003
10th Conference on Retroviruses and Opportunistic Infections
Hynes Convention Center, Boston, MA
www.retroconference.org

Thursday March 27 - Saturday March 29, 2003
4th International Workshop on Clinical Pharmacology of HIV Therapy
CANNES, South of France
Early Registration (including payment) on or before 1 January 2003
Abstract Submission Deadline 1 February 2003

April 10-13, 2003

12th Annual Canadian Conference on HIV/AIDS Research
World Trade and Convention Center, Halifax, Nova Scotia
http://www.conventionalwisdom.ca/cahr.html

Deadlines:

Abstract submission: January 8, 2003
Early registration: February 10, 2003

July 13-17, 2003
The 2nd IAS Conference on HIV Pathogenesis and Treatment
Paris, France
Abstract deadline March 15, 2003

Drug Updates:

Efavirenz (Sustiva) 600mg tablets

Efavirenz 600 mg tablets received its NOC on. July 4th. Monograph revised to recommend taking on an empty stomach; DIN: 02246044, 02246045. It is available since Nov 1,2002. See attached Dear Pharmacist letter

Dear Pharmacist,
We are pleased to inform you that as of November 1, 2002, SUSTIVA (efavirenz), a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of HIV-1 infection, is now available in a new one-tablet, once-daily, 600 mg formulation. The existing formulations of SUSTIVA (50 mg, 100 mg and 200 mg) will still be available.*
The 600 mg one tablet formulation provides a new alternative to the current 200 mg capsules. Reducing the SUSTIVA dosage from three capsules to a single tablet may help to lessen the total number of pills that HIV patients need to take each day.
SUSTIVA tablets are administered in a once-daily dose: one 600 mg tablet orally, in combination with nucleoside reverse transcriptase inhibitors (NRTIs) and/or a protease inhibitor (PI). The bottle of 30, 600 mg tablets contains a 30-day supply.
SUSTIVA should be taken on an empty stomach, preferably at bedtime.
In Study 006, SUSTIVA, when used in combination with zidovudine and lamivudine, was shown to reduce viral load and increase CD4 + cell count in treatment-naïve patients. Furthermore, the durability of response continued through three years.†1
SUSTIVA is generally well tolerated.2

SUSTIVA 600 mg tablet
SUSTIVA should be stored at room temperature, 25°C (77°F), with excursions permitted to 15°-30°C (59°-86°F). Please see your wholesaler for product availability.
We hope that you will find the new SUSTIVA 600 mg tablet a valuable addition to the antiretroviral medications you currently dispense in the treatment of HIV-1. If you have any questions about the new 600 mg formulation please see your Bristol-Myers Squibb representative or call the medical information department at Bristol-Myers Squibb at 1-800-267-1088 ext. 4302. Full prescribing information for SUSTIVA is available upon request.
SUSTIVA is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. This indication is based on two clinical trials of approximately one year duration that demonstrated prolonged time-to-treatment failure.2
The type and frequency of adverse experiences in children have been generally similar to that of adult patients with the exception of a higher incidence of rash which was reported in 40% (23/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 7% (4/57) of pediatric patients compared to 0.9% of adults.2
In controlled trials the frequency of specific serious psychiatric symptoms among patients who received SUSTIVA or control regimens, respectively were: severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), non-fatal suicide attempts (0.4%, 0%), aggressive behaviour (0.4%, 0.3%), paranoid reactions (0.4%, 0.3%) and manic reactions (0.1%, 0%). Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse experiences with the frequency of each of the above events ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation.2
SUSTIVA has not been studied in pediatric patients below three years of age or who weigh less than 13 kg.2 SUSTIVA must be given in combination with other antiretroviral medications.2

Sincerely,
Josée Therien Paula Patrick
Marketing Manager, Virology Product Manager, Virology
Product number: B051035 Colour: Gold
UPC: 623131002158 Tablet dimension: 0.75" x 0.375"
D.I.N.: 02246045 19.1 mm x 9.5 mm
Strength: 600 mg Ink: Royal purple
Form: Coated, modified Tablet markings: Side 1: SUSTIVA
Capsular shaped tablet Side 2: SUSTIVA
Score: None Availability: Bottles of 30
Tablet weight: 1200 mg Cases of 48 bottles
REFERENCES: 1. Tashima KT, Staszewski S, Morales-Ramirez JO, et al. Continued viral suppression in patients treated with efavirenz

Ziagen

On July 19, abacavir was given a new indication for pediatric use; 8 mg/kg bid. Available in oral solution (20mg/ml) and tablets (300mg).

Clinical Pearls:

Tenofovir: CNS side effect

Marie

Hello
Has anyone read anything about CNS side effect of tenofovir? I thought I had read something but can't seem to find it. (Irritability, depression etc....)
Thanks

Pierre

Bonjour Marie,
At ICAAC, poster 1929, it was presented the final analysis of the 902 study. In table 3, there is a mention of depression in 8 patients (n=158). That table is included in my tenofovir presentation (re:CD of the CAHR meeting). I thought it may be attributed to other meds in the regimen (eg: EFV)Interestingly, it is not part of the US monograph... probably because of the low incidence.
A la prochaine...
.
Nancy

Hi Marie,
I had actually reported to Gilead a severe case of somnolence. The cie. then sent out a memo to everyone across Canada describing the case. The patient complained of somnolence for a period of two to three weeks. He stated that he slept more than 20 hours / day. Hard to believe, but apparently was true. We had started him on a new regimen (ABC or d4T / TNF / NLF, if I remember correctly). 24 to 48 hours after TNF was begun, the somnolence accompanied by a loss of taste developed. He had already been on the other ARVs and had never experienced these symptoms in the past. The somnolence resolved after a few weeks. That's all I've seen in terms of CNS toxicity.

I'll see you soon Marie. I should be starting at the Chest on August 26.
I'm curious...were these HIV +ve patients on therapy and suppressed at the time of the testing??

Marie

Thanks Nancy!
Looking forward to seeing you. Great that it is sooner than we expected!. Heard you bought a condo?
Bye

Atazanavir

Christine

Hi everyone,
Just wanted to get your opinion regarding salvage regimens with atazanavir. I am in the process of trying to put together salvage regimens for a few patients who have major resistance to all of the available lasses of ARVs. We will be starting them on tenofovir + atazanavir + T-20 plus whatever else I can come up with. I would like to use two PIs (i.e. atazanavir + another PI) however many of the PIs have not been studied with atazanavir and cannot be used for the expanded access program. What is everyone else doing? The only real study I can find is comparing atazanavir + SQV 1200 mg once daily vs RTV/SQV twice daily. I also found another non-CTN trial on the BC website enrolling patients (Atazanavir in combination with other protease inhibitors as salvage regimen). In this study they are comparing 300 mg atazanavir + 100 mg ritonavir + tenofovir + NRTI vs 400 mg atazanavir + 1200 mg SQV + 300 mg tenofovir + NRTI vs lopinavir + tenofovir + NRTI.
Saquinavir would not be my first choice but there does not seem to be a lot of information out there...

Alice

Hi Christine,
According to the investigator's brochure, it seems that ritonavir and lopinavir/r are contraindicated with atazanavir, which is obviously a limiting step in designing regimens. It is interesting to note that efavirenz significantly decreases atazanavir concentrations, but that you can get around this by adding 100 mg RTV. So I wonder if they would allow it in this situation or other such instances.

Christine

Hi Alice,
Yes I seen that LPV and RTV are contraindicated. And indinavir is not recommended (both increase unconj bilirubin and they have not been studied together). The investigator's brochure also states that atazanavir "has the potential" to increase NFV and AMP but the significance is unknown. I guess we just have to wait until more studies are available...

Mich

I had the same question going through my mind.... We have a couple we are hoping to use atazanavir in as salvage, and when I read the protocol, I realized it would be somewhat limiting. Are you going to use SQV then???

As Al mentioned, I wonder if they would make some exceptions to use RTV if the patient is also on EFV.

Christine
I am going to add saquinavir 1200 mg qd. All of the patients I am looking at are resistant to NNRTIs.

PI combos

Debbie

Hi folks:
Does anyone have any experience using another PI in a Kaletra containing regimen, when the Kaletra is dosed 4 caps bid?

Our patient rashes with all the NNRTI (we've tried various techniques to get his through the rash, but he just doesn't seem to tolerate this class well at all). He is on the 4 caps of Kaletra because he is receiving carbamazepine for seizure prophylaxis following a bout of toxo last year (he's had a few very bad seizures prior to the CBZ -- none since starting CBZ).

I've seen the dosing for SQV, NFV, and IDV with Kaletra 3 caps bid, but not for 4 caps. Any advice would be much appreciated!!

Have a great long weekend!

Rolf

Hi Debbie,
I don't think there is any (PK) data on PI + 4 caps of Kaletra. However, I don't expect an important difference between 3 or 4 caps of Kaletra on a co-administered PI. A recent study found a minor effect of RTV on NFV (AUC NFV + 20-30%, and AUC M8 +80%), but no difference between 100 or 200 mg of RTV (Kurowski et al. CPT 2002;72:123-132). The effect of RTV on SQV has been shown to be maximal at 100 mg, so no effect to be expected here. For IDV, there may be a small effect of the higher RTV dose: IDV Cmin is expected to be (a little bit) higher with 4 caps, but little effect on Cmax.

I would suggest to add IDV 600 mg bid, or SQV 800 mg bid.
Enjoy the weekend,

Debbie

Thanks Rolf!

Question on antidepressants and Echinacea

Anita

A patient on Combivir, abacavir and efavirenz, zopiclone and venlafaxine is enquiring about the use of Echinacea. Natural Medicines would suggest potential concern with 3A4 substrates. I am certain that many of you have practical experience in dealing with this commonly used herbal in combination with antiretrovirals. I am curious to know how it may have been dealt with. Thanks for any input...

Michelle

HI Anita,
Based on what Natural Medicine says, ie. that echinacea may have CYP450 3A4 inhibitory effects, I would not be too concerned about the interactions with current meds. It may boost EFV levels, but if patient is tolerating EFV already and through the initial CNS S/E, it shouldn't be a problem. Venlafaxine is a 2D6 substrate, so there should be no interaction. Zopiclone is heavily metabolized, but I am not sure of the pathway. As such zopiclone levels may increase a bit. The patient could just monitor for hangover.

As far as use in HIV, I know many patients took it when I worked in Toronto for immunostimulant effects, but I have seen no firm studies in HIV. I tried to discourage continuous use, but supported intermittent use for colds if the patient wanted.

Alice

I know that some people in the community feel that echinacea is "bad" for people with HIV, one theory being that the immunostimulant effect may in fact increase risk of HIV replication with long term use. I don't think this has ever been proven.

The only other comment I would add to Michelle's is that while agents may initially demonstrate inhibitory effects in vitro, sometimes in vivo chronic exposure can result in enzyme induction. Hard to predict without studies in humans. Again, if echinacea is just being used intermittently for colds (it's hard to avoid it these days in the drugstore), it's probably not a big problem.

Marie

Hi Anita
I just wanted to report the case of a patient who used echinacea for its immunostimulant effect. He was started on a new antiretroviral therapy and developed a rash within 7 days. It was first thought that the antiretrovirals were responsible.

When I inquired a bit more about his medications, he had started echinacea at the same time. Patient was atopic for ragweed and grass. I suggested to stop first echinacea and symptoms resolved within 4 days.

I normally suggest to patient who have had previous allergic reactions to meds to avoid it specially if they are known atopic.

Anita

Thanks Alice & Michelle!

Mailing HIV meds

Michelle

Hi guys,
I have a patient who is moving to the UK for a year as a student. He would like to continue getting his meds covered here in Alta and have them sent out. He is taking 3 mos with him and then wanted some sent later as he does not wish to take a whole year supply with him.
If you have had a similar situation, perhaps you can share some info on these questions:

1) Air travel and immigration in UK-
Concerned about carrying labeled HIV meds and confidentiality issues or even denial into the UK. Apparently the meds should be labeled and in a sealed container with accompanying prescription.

2) ARV shipping to another country.
Apparently we are allowed to ship via Canada post. He is concerned about disclosure as the meds have to be properly labeled with copies of prescription. I also called UPS courier and they do not allow shipments from pharmacies/hospitals and also do not allow the meds is they are meds available in the UK.

3) Finally I am looking into the UK's policy on HIV admissions into the country.

Any thoughts on this would be appreciated

Debbie

Hi Michelle:
I have not had experience with this specific circumstance (ie. patient going oversees for extended period of time, mailing meds), however one of our patients regularly travels to Europe (usually Spain) for a couple of months at a time, and has not encountered problems taking meds with him (labeled, in original containers).
Interestingly, there was an article in the \"En Route\" magazine on Air Canada last month dealing specifically with entry-restrictions for people with HIV/AIDS traveling to other countries. They recommended consulting the Canadian Dept of Foreign Affairs website for entry restrictions on each country. I checked the website specifically for the UK restrictions (http://www.voyage.gc.ca/destinations/menu_e.htm), but the information does not say anything about denying access to people with HIV. There are phone numbers on the website for the British High Commission in Canada, where you can call to ask specific questions. I think this would be the safest thing to do.

Your patient may also want to check out the type of insurance he has. I don\'t know if he would qualify for travel insurance or not... something to check out. Another website I found (http://www.britainincanada.org/FAQs/trvlfaqs.htm) stated that the UK does not have a reciprocal health care agreement with Canada, but that students may be covered under the NHS. It would certainly be easier if he could find a way to obtain the meds over there. One of the concerns I would have about mailing meds is the likelihood of temperature fluctuations (especially in winter) and time it takes to send through the post.
Not sure if this is useful or not... These questions are always so difficult to find answers to. Good luck!

Jeff

Hi Michelle,
We recently had a T-20 patient go to the UK for a 5-week visit (you can imagine all of the paraphenilia he had with him), he wasn't searched (as a tourist) and nobody gave him or his baggage a second glance. We provided him (as we do all patients who request one) with a travel letter indicating that he was taking these medications for a chronic medical condition, with Clinic contact info should there be questions (our letterhead does not specify that we're an HIV/AIDS treatment centre).

We also have one client who spent 6/12 in Tobago (managing a villa, the lucky bastard!). Rather than ship the meds ourselves, he had a relative pick up a three month supply of meds from us and he couriered it (I'm not sure which company he used). We made a policy of not taking the responsibility of shipping meds outside of Canada, and I don't think BC CfE will even ship out of province.

I don't suppose your patient is at a point he might safely take a treatment interruption, with prophylactic meds prn? Can he get labwork done in the U.K. and send you the results?

Christine

Hi Michelle,
I have one patient that goes to England every year for 6 months. He and his partner have a place there and spend the winter. He has never had a problem with immigration and takes his medications with him labeled, however I don't believe we write a letter for him. We give him 6 months of his antiretrovirals to take with him as he has been stable for several years. Unfortunately I don't have experience mailing medications outside of Canada....

Andrea

Hi, Michelle.
I had a patient last week that was going to Australia and being a new member to the clinic team, I had no idea what we would have to do. We provided the patient with a letter signed by the doctor with our clinic address on it (not indicating that it is an HIV clinic) indicating the medications were his regular regimen and for a chronic illness. He had enough supply for the time he would be away. I'm sorry I don't have any suggestions for the shipping ... it's too bad he isn't interested in taking the full year's supply.

Michelle

Thanks to all for your replies.
I will let you know what the outcome is for this pt.

Ritonavir-Indinavir

Michelle

HI guys,
Just wondering if any of you have used the IDV 400/ RTV 100 BID dosing at all? I am aware of the Peytavin data 2001, showing increased Cmin and decreased Cmax vs IDV 800mg q8h.... any clinical experience?

Pierre

Hi Michelle,
We were not really impressed with those data in our clinic. We know that 100/800 or 200/600 kinetics are superior to 800mg q8h regimen. I have to admit that we almost exclusively use boosted PI here because of improved PK profile and efficacy. Going back to the same PK profile of a single PI (here indinavir) is not attractive. We have not used 100/400 regimen yet. If we suspect toxicity, I think we would do TDM and bring down the dose in a stepwise fashion (probably 100/600 first) until good tolerance achieved. We have not been facing this situation because very few patients are on indinavir. Those who were intolerant were rather switched. Starting patient on 100/400 bid has not been studied. So, until we learn more, we wait.

Rolf

I agree with Pierre. I think the 400/100 mg bid should only be considered after trying 600/100, based on symptoms of IDV-related toxicity, and guided by plasma IDV concentrations. Median PK parameters (Cmin, Cmax) seem OK, but there is large variability. Some viral load data on this regimen were presented at the 1st IAS conference, showing that 47 patients with <200 copies at baseline, who were then switched to 400/100 remained undetectable after a median of 24 weeks (Katlama/Peytavin et al. www.aids2001ias.org).
Regards,

Resistance Cards & Nonoxinol-9

Michelle

Hi guys,
In case you have not come across these sites:
1) Resistance cards- updated June 2002 Free of charge if you order < 10 cards.
www.iasusa.org <http://www.iasusa.org>
send request to : resistance@iasusa.org <mailto:resistance@iasusa.org>

2) Another website....
Has some interesting clinical cases- good for review or for teaching students.
<http://www.ucsf.edu/hivcntr/resources/resistancecases/index.html>

Andrea

Thanks, Michelle.
I have a question for you all. I feel a bit embarrassed about not finding this out earlier but when I was reading MMWR (May 2002) (link = http://www.cdc.gov/mmwr/PDF/rr/rr5106.pdf>) there is a section about nonoxynol-9 increasing the risk of HIV transmission. See page 5 of the report on the right hand side of the page. I have to pull the JAMA 2002 article offline to get the full scoop as it references this article. I was just wondering (if there is a true risk) what you all are telling patients and are you putting bulletins up, giving out a pamphlet, etc.? Our clinical nurse specialist also received similar info in a bulletin. We are going to have a more formal discussion about it with all the clinic staff this coming week.

Michelle

HI Andrea,
I am not sure if we have ever had this discussion here in Edmonton. Perhaps we should bring it up to the team, HIV Edmonton, etc..... What do you think Christine?

Christine

Hi Andrea,
I remember when that data came out which was surprising as prior to that it was recommended. I must say I do not do the counseling regarding safe sex practices etc. That is usually handled by our nurse specialist (and maybe doctor as well). I could ask to see what he is recommending to patients...

jeff

I was always a bit skeptical about the warning.... is the problem more that people who use nonoxynol-9 happen to also be more likely to be engaging in higher-risk activities without barriers (and more often).

Harm reduction counselling is most often done by RN's and social workers at our clinic, but sometimes because of rapport I do get questions - we've always stood behind condoms (not specifically with or without the N-9 lubricant), never recommended just using N-9 gels.

Christine

Here is a link to the report which describes the study. There are flaws in the study and general applicability, but even so I don't think we can really recommend it to prevent HIV transmission (and it could possibly increase the risk)....

http://www.cdc.gov/HIV/pubs/mmwr/mmwr11aug00.htm

Atazanavir & PPIs/H2-antagonists

Hi everyone,

I wanted to get your opinion on the "contraindications" listed in the atazanavir expanded access protocol, specifically H2receptor antagonists and proton pumps inhibitors. I presume this is because of the interaction with ddI tablets (I have not seen anything specifically with acid suppressors).

Has anyone encountered this? These agents are quite commonly used and I am surprised they have listed them as "contraindications" versus caution.

Christine

Michelle

HI guys,
Just wanted to know if you are completely avoiding the IDV-PPI intx? Do you have some patients on the combo? What about if they are on IDV/RTV- I am not sure if this would make much of a difference in IDV levels if the PPI intx is an absorption intx.... any thoughts?
I recently saw a woman who is on a bunch of meds. She has been on IDV x 2 yrs (TID, not q8h) with d4T and ddI and also on PHT 100mg TID x 2 yrs and lansoprazole 30mg/d since at least June 1998. She has an undetectable VL and has done well despite the potential intxs.... She weighs about 60kg.
I am trying to get her off the PHT as there is no clear indication. I am not sure how hard I should push to D/C the PPI. I guess I want to prevent resistance, even if she does not have it currently.

I was looking to see if any studies were actually done on the PPIs and IDV and found this one reference, which suggests that it is an individual intx, and not necessarily seen in everyone.
OMEPRAZOLE
1. Summary: Data from nine patients receiving omeprazole 20 mg to 40 mg daily and indinavir 800 mg three times daily suggest a pharmacokinetic interaction between these two agents. Four of the nine patients had an indinavir plasma concentration below the 95% confidence interval (CI), four patients had a concentration within the 95% CI, and one patient had an indinavir concentration above the 95% CI. One of the patients who had an indinavir plasma concentration that was 96% of the reference value before omeprazole had a decrease to 38% of the reference value after he started combination therapy with omeprazole. There is a probability that these differences solely represent interindividual variability in the pharmacokinetics of indinavir. However, indinavir requires an acidic environment for good dissolution prior to absorption in the gastrointestinal tract. The elevation in gastric pH caused by omeprazole may inhibit the solubility of indinavir. The relevance of this potential pharmacokinetic interaction can only be determined once the relationship between plasma indinavir concentrations and antiretroviral activity is established (Burger et al, 1998).

2. Adverse Effect: decreased indinavir plasma concentrations
3. Severity: minor
4. Onset: rapid
5. Documentation: poor
6. Probable Mechanism: decreased indinavir solubility and absorption from the gastrointestinal tract due to an increased pH from omeprazole

Burger DM, Hugen PWH, Kroon FP et al: Pharmacokinetic interaction between the proton pump inhibitor omeprazole and the HIV protease inhibitor indinavir. AIDS 1998; 12:2080-2082.

Lizanne

Hi Michelle:
I have not come across such a situation, but I agree with you that failure to the regimen may still occur even if it has not yet taken place. If she needs the PPI, I would consider adding RTV on board to simplify her dosing schedule (BID) (especially given that she is also on ddI!), and minimize the risk of DI between IDV and the PPI.

Alice

Hi Michelle,
I asked Merck this question when IDV first came out. At the time, they had no info on the combination. Part of their written response to me includes the following paragraph:
"Omeprazole, lansoprazole, and pantoprazole are all proton pump inhibitors, a class of drugs known to cause profound and long lasting inhibition of gastric acid secretion. The manufacturers of omeprazole and lansoprazole note that it is theoretically possible that these drugs may interfere with absorption of drugs for which gastric pH is an important determinant of bioavailability. Solutions of indinavir sulfate in water or weakly buffered aqueous solutions are acidic and as such, indinavir should readily dissolve in and be absorbed from the stomach, even under conditions of relative hypochlorhydria induced by proton pump inhibitors. Alkaline buffering agents would be more of a concern with simultaneous administration; thus as stated above, indinavir and didanosine (which is alkaline buffered) should be administered at least one hour apart on an empty stomach."
There may be more info now, but I haven't had any problems in patients taking indinavir plus a PPI, although I sometimes recommend that they take their IDV with some OJ or Coke if they are really worried about absorption.
I agree that the phenytoin is probably a bigger concern.

Christine

Hi Michelle,
I remember we had this as a discussion item a few years back. I checked in our old newsletters and found it in the April/May 99 issue.

Nikola was querying this interaction between IDV and omeprazole. Alice had responded (Alice I hope you don't mind me quoting you) that she had checked with Merck on this one a year previously and they felt it was likely OK to administer as indinavir itself is acidic. Merck thought it would only be a problem if there was a sudden chance in GI pH at the same time (as with antacids and ddI). This was supported by the data showing no interaction between IDV and cimetidine. Alice was suggesting at that time to have patients take IDV with orange juice/cola if they are on acid-suppressing drugs. I would presume that when used with ritonavir it would be less of an issue.

I think it is really hard to avoid the combinations as a lot of people have GERD or other indications for PPIs. The suggestion re: OJ and cola is a good one.

Just an update re: Atazanavir + PPIs

Here is a response from BMS. Will keep you posted when I hear back.

Hello Kim,
You have forwarded this to the right person. I do handle these questions now.
There was an interaction study done with Videx (buffered formulation) and it showed that the total amount of drug in the blood (AUC- area under the curve) was reduced by 90%. This lead to the conclusion that ATV needs an acid environment for full absorption. Because the H2 Blockers and Proton Pump inhibitors change the stomach PH for prolong periods, spacing the dosing would not really help with the interaction.
I am going to call the US and find out if they have any suggestions or recommendations or even more information on this. I will keep you posted. In the meantime please pass this message on to Christine.
Let me know if you have any other questions,
Mitra

HIV pharmacy funding

Michelle and Christine

HI guys,
Christine and I have recently had a meeting to try to accrue more provincial funding for our HIV positions. We currently only have 0.25 FTE coming from the province for our two positions. In an effort to strengthen our submission to the province, we were hoping to include benchmarking data from other Canadian institutions. We would really appreciate any info you can give us on the following:

1. Type of practice (i.e. clinical pharmacist in the clinic, dispensing pharmacist directly linked with drug distribution or a combination)
2. # patients in site and region you serve
3. # patients you as a pharmacist serve at the site
4. # FTE HIV pharmacist time (clinical vs dispensing)
5. average amount of time spent per patient
6. How your position is funded?
7. Location

Thanks for any info.

Anita

I would be interested in your findings since we have 0 FTE in Manitoba.

Andrea

Jinell, Jeff, and Kathy

Hello.
I will try and pick Kathy's brain about some of these issues as my current situation at the clinic doesn't represent the norm.

Hello,
How is the weather where you are??? In Calgary, we have been buried by snow! In fact this made me

two hours late for work this morning (usually only a 30min drive). Anyways, I hope the rest of Canada has not been hit by winter....

As for our Southern Alberta Clinic, we are centrally located in Calgary. We are a downtown medical clinic which encompasses an area for medical visits, for our patients; and an area that facilitates research (clinical trials, and in-house studies).

Scroll downwards...

1. Type of practice (i.e. clinical pharmacist in the clinic, dispensing pharmacist directly linked with drug distribution or a combination)

We have a combination of pharmacist practice. The pharmacist is a jack-of-all-trades here. We participate in physician clinics, multidisciplinary rounds, conduct inservices/teaching to both community and professional groups, we participate in clinical drug trials, we answer drug information questions, submit hospital/provincial formulary reviews/protocols for ARV use, we are consulted on the annual drug budget, and we even visit our pxt in hospitals to consult with caregivers about their medication profiles. We have a dispensary in our clinic limited to ARVs only (including clinical trial medications). All ARVs are provincially covered 100%, and the patient must obtain them from the clinic in order for them to be free of charge.

2. # patients in site and region you serve

We currently have about 700 patients in which 65% of them are on ARVs. In general, we serve HIV positive patients South of Red Deer, AB.

3. # patients you as a pharmacist serve at the site

The pharmacist routinely sees every patient that is on ARV therapy as we provide each patient with ARVs on a monthly basis (and they get regular counselling/monitoring), in addition, we often will see patients that are getting psychiatric care, and neurological care at our clinic regardless of whether they are taking ARVs or not, as we are consultants to these treatments as well.

For patients not on ARVs but on prophylaxis or treatment for OIs, we see them as well.

4. # FTE HIV pharmacist time (clinical vs dispensing)

We currently have 1.5 FTE shared between 3 pharmacists.

5. Average amount of time spent per patient

10 minutes

6. How your position is funded?

Calgary Health Region

7. Location

Calgary, AB
Happy thanksgiving everyone!

Michelle

Thanks!
Do you know if all of the pharmacy funding (1.5FTE) comes out of the PWS budget?

Michelle

HI Anita,
I am aware of the lack of funding for HIV pharmacy in Manitoba, however I am still interested in knowing what pharmacy services (if any) you have for HIV patients? If you have any data on the questions below, I will include it in the table I am assembling.

Marie

Hello
Originally we had 0.6 fte pharmacist funded by the government. I do not see the budget anymore so I am not sure if this has changed or not. We had roughly 750 patients at the time.
Thank you

Pierre

Hi Guys,
Sorry if I have been hiding over the last few weeks or months... it has been extremely difficult to maintain my duties with the group in part because of the workload here.

To the questions:

1. Type of practice (i.e. clinical pharmacist in the clinic, dispensing pharmacist directly linked with drug distribution or a combination)

The job title at TOH is clinical Pharmacy specialist. It was previously clinical pharmacist but it has changed approx 2 years ago. In the past, we use to be involved in everything:

- Drug distribution through the HIV Ontario drug distribution program (ODDP)
- Drug distribution of meds from EAP, SAP or free drug supply from drug companies.
- Clinical management of drug therapy of the patients attending the outpatient clinic
- Drug counselling of all new or changed HIV Tx.
- Pharm. Care of HIV inpatients
- Request for Section 8 (ou medicament exception)
- Education to clinic staff, and med. students/residents, TOH pharmacists, PLHA.
- Management of HAART side effects.

Now, with the new position, I was able to bring the following changes:

- I stopped making myself the HIV drug distribution; distribution is made by the hospital main pharmacy and I am responsible for its coordination.
- I added a research component
- I increased the education involvement.

2. # patients in site and region you serve
   Approx 900

3. # patients you as a pharmacist serve at the site
   The same

4. # FTE HIV pharmacist time (clinical vs dispensing)
   It was increased from 0.6 FTE to 1 FTE.

5. average amount of time spent per patient
   Very hard to estimate considering the variety of service offered. I would estimate it around 20 minutes.

6. How your position is funded?

The clinic was allowed money from the Ministry of Health for Pharmacy services. It was split as 0.6FTE for Pharmacist and 0.4FTE for Tech. This has changed 2 years ago. Apparently, it is now money given to TOH as part of their annual budget. So now, I am funded 100% by the Hospital.

7. Location

Ottawa. The clinic covers the area from Cornwall to Pembroke and also covers Outaouais.

Michelle

Merci Pierre,
Is it fair to say thought that your position is still funded via MOH, or is it out of the general hospital fund? Also, are you able to see all 900 patients? Are you the only HIV pharmacist out of the General site or are there others as well in a 'non-specialist' capacity?

Pierre

I am under the impression I am paid by the Hospital. The reason is that when we decided to increase to 1 FTE, MOH was not consulted. But I understand that the 0.6 FTE was from MOH back in 1994.

Do I see all the patients? Well, I do not work on a consultation basis. Of course I can not see all the patients that have an appointment at the clinic. We see approx 20-25 patients over a 3-hour period of time. However, I know virtually everybody as I use to revise the cases retrospectively or I will eventually catch them up at a later visit. Maybe 5% of them escape from my review.

For instance, looking at my last statistics on the number of follow-ups, I range around 140-200 per month. Those stats though are not very accurate as they seem to underestimate (reporting problems). I probably see around 200-220 patients a month.

I cannot see more patients as I am supposed to allow 70% of my time for clinical work. The rest should be dedicated to research and education.

I am the only HIV pharmacist at the clinic. I do have a back up when I am away/sick/at school, but the back-up only deals with urgent problems and give me the follow-up when I return. It does not reduce my workload.

Jinell

Hi Michelle,

Actually, none of our funding comes from PWS. Our positions are created and funded by the Calgary Health Region. So we are all considered hospital pharmacists (same pay, same benefits...) who are working in an outpatient clinic environment.
Hope this helps,

Andrea
Hi - sorry I have been so slow getting to this and I haven't had time to e-mail or ring Kathy so I'll give you some of what I know. My preamble is that I started covering Kathy's maternity leave near the end of August so take that into consideration.
1. I am covering Kathy's maternity leave in a 50% capacity which allows me to cover the HIV clinic (3 half days a week - tues and thurs 9am - 12:30pm, Wednesday 1-4pm and Monday is our rounds from 12-2pm) and I do ID odds and ends through consult/pages. I don't have any distribution responsibilities nor did Kathy. KAthy's position is more than 50% - I am half time because my job at the school of nursing is 50%.

2. I think the number of patients is over 300 - I went to an Atlantic Canada HIV group meeting and can get the exact number when I find the materials from the meeting. We serve NS (including Cape Breton) and also have people that come over from PEI)

3. the number of patients I see varies but it seems as though on average, 8-13 people could be booked for clinic appointments/clinic day - of those 8-13 people I could see anywhere from 1 to 5 or 6/day (it all depends on the needs) . I usually review all of the charts quickly before/during clinic to target those that need some DRP attention and I see all the people that get started on a new/changed regimen to go over it with them. When I am not having direct patient care, I usually am kept busy with the non-HIV drug related questions (more general medicine issues, etc.), lking at blood work, etc. I have been spending a lot of time lately trying to arrange for people to get their drugs covered (valganciclovir for example!). It seems as though as time is passing, I am getting to know more of the names and issues so I think I have been seeing quite a few people.

4. this one is a tough one. Kathy (and for the time being - me) is the only "clinical" pharmacist for the clinic. We have an outpatient dispensary in the hospital where the patients get their meds that is staffed by several pharmacists but I think they serve other programs so I'm not sure how to break that down with respect to specifics of the HIV patient population.

5. average amount of time per patient - I think I am too new at this to really say but I think on average I spend at least 20 minutes with patients to the extreme of over an hour with one or 2 people.

6. I am paid through the pharmacy department and my position is clinical coordinator with them and ID.

7. Location = halifax.

Thanks,

Rachel

First sorry again for my terrible English

1. Type of practice (i.e. clinical pharmacist in the clinic, dispensing pharmacist directly linked with drug distribution or a combination)

We see outside patients, ambulatory patients, and inside patient (around 15 beds), we do multidisciplinary rounds every week. We participate in clinical drug trials as distribution but also co or principal investigator. We do teaching for community, professionals and students. We are also involved in different government committees. We order emergency drug….

2. # patients in site and region you serve
We currently have about 1500 in total for the 3 sites. We have a lot of IDU patients.

3. # patients you as a pharmacist serve at the site
We see every inside (30 beds sometime more or less) and ambulatory patient (4 or more per week) and around 20 outside patients (with patients on protocol) per week. Excluding follow-up by phone.

4. # FTE HIV pharmacist time (clinical vs dispensing)
We currently have 9 days share with 3 pharmacists on 3 site paid by the government. The pharmacy ad 2 days in one site and we have 2 days more paid by an other subvention. All pharmacists do at least one-day distribution per week.

5. average amount of time spent per patient
First visit (with new therapy) : 30 or more if it is with the family or with an other professional of my team (nurse , dietician or social worker).

If it is difficult for the patient I will see him 2 times (2 x 20 minutes)
Follow-up : 10-15 minutes
Phone call : 5-10 minutes

6. How your position is funded?
Goverment

7. Location
Montréal, Québec

Linda

Hi Michelle,
Sorry for the late response. I am just returning from several weeks of vacation. See my responses below.

1. Type of practice (i.e. clinical pharmacist in the clinic, dispensing pharmacist directly linked with drug distribution or a combination)

We have both situations, however most of the funded positions are a combination of clinical duties with dispensing. My position is the exception...ie I am pretty much administrative.

2. # patients in site and region you serve approximately 2700 patients in the province. We have 5 offsite pharmacies that are compensated on a per prescription basis. Level of service provided varies from pure dispensing to mostly clinical(ie BC Childrens)
3. # patients you as a pharmacist serve at the site
   approximately 700-800 at St. Pauls
4. # FTE HIV pharmacist time (clinical vs dispensing)
   At St. Paul's the Centre funds myself (administrative) plus 4 FTE (full time) and approx 2 FTE (part time - shared by 4 employees)...these are all clinical + dispensing positions..plus they pay for 1 FTE dispensing pharmacist and for our HIV pharmacy resident position. The Centre also provides funding for tech support...approx. 6 FTE.
5. average amount of time spent per patient
   15 minutes -refills
   30 minutes - new prescriptions
   45 minutes - new or complicated patients
6. How your position is funded?
   global budget from provincial pharmacare, administered by the CFE
7. Location
   Vancouver, B.C.

Efavirenz suspension

Michelle

HI,
I am wondering if you have any leads or contacts on how to obtain efavirenz susp via expanded access. I called BMS head office and they were unaware.

Dom

Hi Michelle:

We have used Sustiva liquid (30 mg/ml-180 ml bottle) for one of our pediatric patients about a year and half ago. At the time we obtained the supply via the expanded access program through Applied Clinical Concepts Inc 4204 Technology Drive Suite, Durham, NC 27704 Phone 919-668-8880 Fax 919-471-2633. It was under the Dupont Pharmaceutical Protocol DMP 266-913. The liquid is an oily, bland tasting liquid. Our patient (8 yrs old) was not keen on the taste and was motivated to learn to swallow the Sustiva capsules shortly after starting the liquid.
I hope this helps.

Dom

Hi Michelle:
A bit more information re: Sustiva liquid. According to our research nurse she's been in recently in contact with Shelly Guilmette at Sleac Parexcel International - Sustiva Oral Liquid Expanded Access Program at 1-877-373-7097 (Massachusetts).
Good luck.

Andrea

Hi, Michelle.
I just called our technician who looks after all of the special access and open label meds (e.g. dapsone, tenofovir) and she didn't know anything about it - I haven't seen it used. Sorry.

Nancy

HI everyone,
Less than a year ago, when I was doing a rotation at the Children's Hospital of Eastern Ontario in Ottawa we were using the following phone number to obtain the Sustiva liquid formulation: 1-877-372-7097. It was also for a Dupont clinical trial but I had the impression that the phone number was in Canada. With children, we sometimes recommended to open the capsules and add it to food or liquid. It has a peppery taste which is perhaps difficult to mask. Grape jelly might do the trick. We didn't recommend applesauce as it causes a burning sensation in the mouth. Certain children did try the capsule formulation. For example, the 50 mg caps. were easier to swallow.
I hope this information can help a bit.

Valganciclovir and LSD-like reaction with 3TC?

Andrea

Hi, everyone.
I need help with your clinical expertise. We have several people on valganciclovir (CMV retinitis) and I am having a few problems with provincial formulary coverage (!!) and dose adjustments in patients with cytopenias.
My questions:
1. Is valganciclovir covered by your province? (our province hasn't received the submission package form the company yet and there is no supply from them!).

2. How are you dose adusting with neutropenia, thrombocytopenia, etc?
I know with ganciclovir it is recommended to stop with ANC <500 and plts < 25000. I have spoken with someone in renal and KP transplant in BC and they are decreasing the dose to 450 mg/day when the WBC is < 3.5. I have 2 patients with decreased WBC and one has decreased platelets. They are both getting GCSF and the thoughts of those involved in the care of this patient are going towards increasing GCSF when I am wondering if we shouldn't just back off on valgan? I am doing more searching into this to look to see if there is efficacy for CMV retinitis prophylaxis at lower doses...

3. I also have a question unrelated to valgan - have you seen "LSD type reactions" with 3TC? we had a patient on 3TC, nevirapine and d4t in the past - he had an LSD type reaction (as he described it) but it was hallucinations, etc., after about 6 days of therapy. The thought was that it was nevirapine. After several years with no meds as he didn't really meet criteria, he had decrease in T cells, etc. and it was more appropriate to have a trial of meds - he was just recenlty tried on Trizivir and called me in a panic on a friday night because he had the same LSD type reactions after only 3 doses! I have been doing monograph and literature searches and have also asked for any Health Canada reports from our adverse reaction reporting person. Have any of you ever seen this with 3TC? The patient also smokes marijuana, which complicates things, and I think he should have psychiatry involved in his care as he is anxious as his baseline mood.

Any help/thoughts you have would be appreciated!! Thank you.

Anita

Andrea - Manitoba has just approved via EDS (Exceptional Drug Status) its first patient (that I am aware of) for treatment with valganciclovir. This is a patient who has been on long term (years) IV ganciclovir through the Home IV Program. I have no information on dosing adjustment to share with you. I understand this patient has been on normal doses of IV ganciclovir.

Pierre

Hi guys,
1) Valcyte is not yet covered in Ontario, although I have not tried Section 8 yet (anyone else tried?). For the 2 patients left on it, I get compassionate release from Roche.

2) Dosing adjustment with Valganciclovir should not be different that what is currently done for IV ganciclovir. I think the 2 approaches are valid and the decision should be based on the general clinical picture. For instance, somebody on HAART recovering his CD4 (let's say in 100s), I may decide to decrease the dose but if my suspicion for relapses is high, I would prefer G-CSF or switching to Foscarnet. My threshold for changing treatment based on CBC is high, especially if the patient was chronically thrombo/neutropenic before the initiation of valganciclovir.

3) 3TC and LSD-like reaction? I have never heard about that. And everyone here has been on 3TC at least one time in their HIV treatment experience .I would investigate with psychology/psychiatry any underlying psychiatric causes. Try placebo BID in an attempt to rule out the latter....

Good luck

Andrea

Thanks, Pierre
I spoke with someone from Roche again yesterday and it looks like there was some "confusion" from the person I spoke with the last several times -- we don't have the submission here in NS because it hasn't been sent out by their market access department as of yet and when I was originally told by the company that they would no longer give us drug, this was apparently also incorrect. They are now going to supply us with drug until the submission arrives in the province because if they didn't, patients would "fall through the cracks" ... now it looks like the only limitation will be what the province will decide to do with it in terms of approval (hopefully will cover it under exception status). Thanks for your thoughts on the dosing.

I agree that I think this patient has further issues with regard to his psychiatric/psychological situation and that these should be investigated...

Thanks again,

Jeff

Hi everyone...
Valcyte was added to Alberta Blue Cross Drug Benefits List a couple of months ago... we haven't had the need to use it yet, so I can't add anything about dosage adjustments, sorry!

Alfred

We have a patient who was just prescribed 900 mg/d of valganciclovir for maintenance. The patient would like to take it 450 mg bid.
Is there any therapeutic reason not to do this? I'm so distant from HIV now that I have no idea.

Pierre

Hi Alfred,
I never checked the literature on this but I did it for one of our patient to split the pill burden...I cannot foresee any problem doing this. Does anyone see a theoretical reason not to do so ?

Ribavirin and NRTI intxs

Michelle

Hi,
I am wondering if you have experience in using ribavirin with NRTIs? Hep C tx is becoming more of an issue in our patients. Are you avoiding AZT, d4T in light of the in vitro intx of inhibition of phosphorylation and increased mitochondrial toxicity, or just monitoring (i.e anemia with RBV and AZT)? What about the other nucleosides?
I would be interested in hearing your comments/guidelines you have in place.

Nancy

Hi Michelle,
I remember searching for information on this topic last year during my residency. Dr. Fletcher had a patient on ribavirin and wanted to know if it would interact with the NRTIs. I found at least 15 references on this very same question, and though theoretically it can interact, if I remember correctly, no in vivo clinical data supported the decision to discontinue the ribavirin. I believe we recommended the ribavirin be continued.

Andrea
Hi, Michelle.
I really don't have any experience with this one. I can check and see if there is anything that is laid out in our clinic.

Atazanavir interactions

Andrea

Have any of you been using atazanavir yet? I have been having quite a time finding info that is readily available. I have recently asked one of the research nurses for some info from the open-label package they were sent. One of the docs asked about boosted atazanavir but I only have found one abstract so far with saquinavir + atazanavir. I don't think there's much out there on PK data as of yet. The drug-drug interactions look like a source of restriction for its use.

Tom

Abstract H-1716 by Agarwala et al (BMS) at ICAAC2002 ATV 300mg + RTV 100mg QD in 30 healthy subjects. RTV PK not affected ATV - Cmax increased by 1.86, AUC increased by 3.4-fold. This regimen is in Phase III evaluation in HIV+ subjects

Christine

Hi Andrea,
As Tom indicated, there was an abstract at ICAAC with ritonavir boosting. However, I think the company is being pretty cautious about allowing boosting (possibly due to concerns re: PR interval prolongation that is dose dependent?). The drug interactions are a pain as many are not studied. If you have patient on PPIs or H2-antagonists it is a problem - we have a couple and the company is not allowing the use of these agents. Not many options for patients with severe GERD...

Michelle

Here are a few abstracts from 9th CROI 2002 on ATV intxs that I came across.
http://63.126.3.84/2002/Sessions/754.htm

443-W.
Evaluation of Steady-State Interaction between Atazanavir (ATV) and Efavirenz (EFV)
S. Preston*1, P. Piliero1, E. O'Mara2, V. Mummaneni2, D. Randall2, C. Morvillo1, M. Geraldes2, S. Agarwala2, and G. Drusano1
1Albany Med. Coll., NY and 2Bristol-Myers Squibb Pharmaceutical Res. Inst., Princeton, NJ

Background: ATV is a new protease inhibitor (PI) with excellent anti-HIV activity. ATV may be combined with EFV (a non-nucleoside reverse transcriptase inhibitor) as part of a HAART regimen. EFV can induce cytochrome P450 (CYP) 3A and may lessen ATV exposure. The objective was to assess the pharmacokinetic (PK) profile of ATV when co-administered with EFV.

Methods: 31 subjects received open-label drugs with a light meal as follows: 400-mg ATV qd for 6 days, followed by concomitant administration of 600-mg EFV qd for 14 more days. Serial blood samples were collected for PK profiles on days 6 and 20.

Results: Below are non-compartmental ATV PK parameters:

PK parameter	ATV (day 6)	ATV + EFV (day 20)
Cmax (ng/mL)a	3369 (38)	1375 (60)
AUC(TAU) (ng*h/mL)a	20659 (41)	5462 (60)
Tmax (h)b	2.00 (1.00, 4.00)	

2.50 (1.00, 5.00)

Half-life (h)c
7.0 (2.1)
5.1 (2.3)

aGeometric Mean (CV%); bMedian (Range); cArithmetic Mean (SD)

Concomitant administration of EFV and ATV resulted in ATV Cmax and AUC (TAU) values that were 41% and 26% of those following ATV alone. The ratios of the geometric mean (90% confidence interval, C.I.) for (ATV+EFV)/ATV were 0.408 (0.329, 0.506) and 0.264 (0.217,0.322) for Cmax and AUC (TAU), respectively. Mean EFV PK parameters were similar to literature values in HIV+ patients. No serious adverse events were noted.

Conclusion: To combine ATV with EFV, a regimen modified from a 400-mg standard ATV dose, to counter EFV's exposure-reducing effect, is needed.

445-W.
Pharmacokinetic (PK) Effect of Rifabutin (RIF) on Atazanavir (ATV) with and without Ritonavir (RTV) in Healthy Subjects

S. Agarwala*1, V. Mummaneni1, D. Randall1, M. Geraldes1, R. Stoltz2, and E. O'Mara1
1Bristol-Myers Squibb Pharmaceutical Res. Inst., Princeton, NJ and 2GFI, Inc., Evansville, IN

Background: ATV is a new protease inhibitor with excellent anti-HIV activity. RIF, an antimicrobial agent, is a cytochrome P450 (CYP) 3A inducer and may be used with ATV, a CYP3A substrate. The objective was to evaluate the PK effect of RIF on ATV with and without RTV.

Methods: Healthy subjects (n=30) received 400 mg ATV qd in an open-label, randomized study for 14 days. For the next 14 days, 10 subjects each received (A) 400 mg ATV+150 mg RIF qd; (B) 600 mg ATV+150 mg RIF qd; or (C) 400 mg ATV+150 mg RIF+100 mg RTV qd. All doses were administered with alight meal. Serial blood samples were collected for PK profiles on days 14 and 28.

Results: Geometric mean (CV%) and ratio of the geometric means (90% confidence intervals, C.I.) for the PK parameters of ATV are shown.

Parameter Group	Day 14	Day 28	Ratio (90% C.I.)	
Cmax (ng/mL)				
A	3551.27	4770.30	1.34	(1.14, 1.60)
B	3347.13	6833.05	2.04	(1.76, 2.37)
C	3903.10	7062.67	1.81	(1.51, 2.17)
AUC (TAU) (ng·h/mL)				
A	22107.25	25368.58	1.15	(0.98, 1.34)
B	21099.22	44088.77	2.91	(2.46, 3.45)
C	24851.84	72353.22		

ATV exposure at 400 mg did not change with RIF (Treatment A), but was 2- to 3-fold higher with Treatments B and C. The geometric mean (CV%) for the AUC of RIF for treatments A, B, and C were 7693.77 (20.34); (B) 6291.70 (19.66); and (C) 7386.71 (19.48), respectively, suggesting that the PK of RIF was comparable across treatments but 2.5 fold higher than literature values for a standard 300-mg dose. There were no SAEs reported.

Conclusion: ATV may be co-administered without modification at the standard dose of 400 mg with RIF. RIF dose modification may be necessary.

444-W.

Steady-State Pharmacokinetic Interaction Study of Atazanavir (ATV) with Efavirenz (EFV) and Ritonavir (RTV) in Healthy Subjects

E. O'Mara*1, S. Agarwala1, D. Randall1, M. Geraldes1, R. Stoltz2, and V. Mummaneni1
1Bristol-Myers Squibb Pharmaceutical Res. Inst., Princeton, NJ and 2GFI, Inc., Evansville, IN

Background: ATV is a new protease inhibitor (PI) with excellent anti-HIV activity and a cytochrome P450 (CYP) 3A substrate. EFV is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that induces cytochrome P450 (CYP) 3A. Addition of EFV to ATV (400-mg once-daily [qd]) reduced ATV exposure 74% vs ATV alone. RTV is a potent inhibitor of CYP 3A4 that, at 200-mg qd, increased ATV exposure 3-fold vs ATV alone. The objective was to assess the ability of RTV to offset EFV's inductive effect upon ATV.

Methods: 20 healthy subjects received open-label drugs co-administered with a light meal as follows: ATV alone for 14 days at 400-mg qd followed by addition of RTV at 100 and EFV at 600-mg qd for 14 more days. All had an ATV pharmacokinetic (PK) profile drawn on day 14. PK profiles for ATV, RTV, and EFV were drawn on day 28.

Results: Summary of ATV pharmacokinetic parameters:

Treatment (qd)	Cmax* (ng/mL)	Tmax (h)**	Cmin* (ng/mL)	AUC(TAU)* (ng·h/mL)	T-HALF*** (h)
ATV 400	2307.55 (53.09)	4.00 (1.50, 8.00)	149 (101)	18590.72 (48.42)	5.53 (2.13)
ATV 400 (with EFV 600 +RTV200)	5167.97(31.50)	2.50 (1.00, 5.00)	1149 (74)	63472.97 (38.17)	9.88 (3.40)

*Geometric Mean (CV%) ** Median (Range) reported. ***Arithmetic Mean (SD)

The ratios of geometric means (90% confidence intervals, C.I.) for Cmax and AUC (TAU) of ATV+EFV+RTV vs ATV are: 2.24 (1.86, 2.70) and 3.41 (2.96, 3.94), respectively. No serious laboratory or clinical adverse events were observed during review of preliminary safety data.

Conclusions: Addition of RTV at 200-mg qd to ATV+EFV overcame the inductive effect of EFV on ATV but increased ATV exposure by 3-fold vs ATV alone.

Advice on journal submission

Jinell

Hello everyone,
I have written a case report of a patient stabilized on atorvastatin, with ARVs (Kaletra, 3TC, and EFV). He developed rhabdomyolysis when he was given clarithromycin in hospital for a community acquired pneumonia, in addition to all his usual meds. I would like some advise on "which" journal would be most appropriate to submit. Our medical director prefers a medical journal over a pharmaceutical one. Any ideas?
Thanks,

Pierre

AIDS usually are reluctant to publish case-report. They prefer case-serie. You can try Journal of AIDS or CID.
Good luck

Mich
I agree, those are your best bets. If not, then Annals of Pharmacotherapy.

Pulmonary embolism

Andrea

Hi, everyone.

Out of interest, I'm curious to see if any of you have had patients with PEs. We have had 2 clinic patients develop PEs within one week of one another. The common drugs in both of the regimens were 3TC and abacavir. One of the patients was on Megace which could be the cause and I have yet to call the second patient to see if he was taking Megace (not in his chart) but the nurses didn't think he was. Neither of the patients is known to have malignancies. I think they are both being sent to hematology to see if there is some underlying reason they could be hypercoagulated. I am now looking forward to helping out with warfarin therapy in combination with ritonavir!
I also had a patient last week who started taking Kaletra and he also told us for the first time that he takes sildenafil sporadically - I fortunately had some guidance with the Toronto Hospital clinic online info and as 25 mg had given him a great response in the past I had suggested that even trying 12.5 mg could be another alternative.
Thanks for the help with atazanavir drug interactions! I was able to track down my own copy of the protocol in addition to the abstract data.
Hope you all have a great weekend.

Jinell

Andrea,

About a year ago I did a pub med search which revealed two papers that describe HIV/AIDS pxts have 10 x the risk of being in a hyper-coagulative state. No case reports found in relation to antiretroviral agents as the cause at that time. We have a about 5 patients (out of 700) that I can think of off hand that have had an episode (or more) of thrombosis.

Try:
1. Saif MW, and Greenberg B. HIV and Thrombosis:a review.AIDS Patient Care and STDs.2001;15(1):15-24
2. Saber AA, Aboolian A, Laraja RD, Baron H. HIV?AIDS and the risk of Deep vein thrombosis: A study of 45 patients with lower extremity involvement.
American Surgeon.2001;67(7):645-7

This may not be an answer to your question, but I hope the information may lead to it. If you need me to fax the papers, just send me your number.

Michelle

I have not researched this recently. I don't recall any cases of PEs, but we did have a number of cases of DVTs when I worked inpatient HIV in Toronto-our fellow at the time was thinking of writing a case series on this....Pis had been out for a year or 2. I don't think the cases were ever written up. Subsequently I do recall seeing some abstracts at conferences on this. If I tract them down, I will send them.
About the RTV-sildenfanil.... A patient in our clinic who took the combo and passed out a few years back.... not willing to try it again with a lower dose. I think the dose he received was 50mg (too high) and this was never picked up.....

Deborah

Andrea,
In addition to the articles mentioned by Jinell, when I did a brief search some time ago, I also found this article:
Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. AIDS 2000 Feb 18:14(3):321-4

Hope it’s of some use.

Andrea

Sustiva 600mg

Hi, Debbie.
I had just received the Dear Pharmacist letter last week or maybe the week before. I spoke with the rep today and she is sending (via e-mail either tomorrow or the next day) the updated product monograph as well as something else (can't remember). I can forward it all to you if you like. She said the monograph will be available in print form soon.
She confirmed for me that it is cost neutral but now I'm wondering if we can just interchange the 3X200 mg for the 600 mg without hassle for those that do not get their meds from us. I'll have to call pharmacare to see what the status is. It looks like our plan in the dispensary is to use up the rest of our 200 mg sustiva supply on those with refills and then switch to the single 600 mg and the new starts will get the 600 mg.

Debbie

Hi Andrea:
Our plan is to use up the supply of 200mg caps first also. I am not sure if BMS will take back any of the 200mg stock if placing a 600mg order -- didn't bother to check since we were almost ready to reorder anyway.
I think it is definitely worth checking with the provincial plans to give them the "heads up" on the new formulation. Really it should just be a technicality getting it covered, but for the first few patients there maybe a hassle if you don't pave the way for drug coverage first, has been my experience with these things!

ATV protocol changes

Michelle

Heads up on a recent letter (Nov 13 or 14th) stating changes to the ATV protocol which will be forthcoming (onset?)
- can use ATV 400mg/d with RTV 100mg/d
- can use ATV with EFV if RTV is also used to offset the intx
- any VL or CD4 is acceptable

Thought this would be useful info, as it was pretty restricted before. Until the new protocol is out, we are applying for exemptions to the above scenario via written letters, but I am not sure if they will approve requests prematurely.

Andrea

Hi, Michelle.
I was wondering when the protocol was coming out because it seemed to be vague in the company's notice about this.
I am wondering what everyone is doing about EKGs. I know it is not recommended unless the patient meets their specific cardiology symptoms or previous history criteria as outlined in the protocol and that the concern is with higher doses (800 mg) but I am uncertain as to what we should do if we are using a drug that could be an inhibitor but that has not been studied by the company and potentially causing increases in AUC. We were discussing this at rounds and decided it wouldn't be cost effective for most patients to have an EKG but I feel like there are some patients that would fall into an unclear area.
I am taking part in a conference call on Wednesday (with the company people as far as I can tell from the invitation from the research nurse) and some other questions that I have are concerning other drugs which can prolong QTc (e.g. TCAs) and PR interval. (I have to do some looking to see whether other ARV can cause QT problems.) I will also ask if they know when the protocol is coming out.

Anyone have any other questions they'd like me to ask?

Michelle
Here is the response from our research nurse.

I have no further info regarding when the revised protocol is coming. Although when I spoke with the CRO last week, it didn't sound like any time soon.
Regarding EKG,s, I am doing them on pts with a history of heart problems or on cardiac drugs. This is required by study.

Debbie

I think I am also tempted to do a baseline EKG for patients taking other drugs that can prolong QT since use of multiple medications with QT prolonging potential is associated with increased risk of torsades and other arrhythmias. Question is, should this also include all of our patients on Biaxin?? May be easier to just switch to Azithro since clarithro and erythro are both considered potentially QT prolonging agents, though not azithro.

In case anyone is looking for some references on the whole QT prolongation issue, there is a good website at http://www.qtdrugs.org/

As well, the TDP has a guidance document on assessment of the QT prolongation potential of non-antiarrhythmic drugs that can be found at:
http://www.hc-sc.gc.ca/hpb-gps/therapeut/zfiles/english/consult/draft_guidance/qt_prolong_gd_draft_e.pdf

Andrea

Hi, Debbie.
I don't have it with me right now but in the protocol they recommend a dosage adjustment for clarithro - here is a link from medscape where they show it as well (http://www.medscape.com/viewarticle/442247) (try this link).
Thanks for the websites. There was also an article in Drugs from way back talking about drugs and how they affect the EKG - I'll get that reference from my files and send it along too.
Thanks,

Sustiva & patients with history of depression

Linda

1) Do you avoid this agent in this case? (Currently he's not on antidepressants, but has a family hx of depresssion /- suicide and has been treated for depression in the past).

2) Have you seen evening of primrose used to prevent development peripheral neuropathies? What do you tell patients re: this?

Thanks for the assistance. Much appreciated.

Michelle

Many of our patients have a Hx of depression and are taking EFV (many on antidepressants as well). They require close monitoring in the first couple of mos to ensure they do not go downhill. I have had only 1 patient become suicidal and hospitalized - this patient had major depression/psych hx but still wanted to try it.... I do find that some patients who have anxiety disorders worsen, but then usually stabilize.

Jeff

Much the same experience here.... sometimes support is sufficient until the patient adjusts to the efavirenz, but it's clear that a few patients are better off on nevirapine if an NNRTI is the way to go. We also recall one patient institutionalized shortly after starting Sustiva; she became a new woman when we switched to Viramune, doing very nicely now. Anecdotally, it seems like the patients who are most agitated about meds in general are the ones who don't do as well efavirenz; too bad there isn't a litmus test to tell the difference up front!

Nancy

HI Linda,

Concerning your question on evening primrose oil, the use of this agent for prophylaxis or treatment of peripheral neuropathies in HIV is sometimes seen. After doing a complete lit search on the use of alternative therapies in HIV and a separate lit search on the treatment of PN in HIV, I haven't seen any studies that prove its efficacy in HIV. One small trial (n = 22) was done with evening primrose oil in diabetic patients with neuropathy. The dose used was 4 g QD x 6 months. It is said to have provided "significant" symptomatic improvement. Unfortunately, I wasn't able to put my hand on the reference or paper.

I don't think I would recommend it as prophylaxis, perhaps as therapy if all else fails and if the d drugs have been discontinued and the PN persists. It isn't without side effects: common side effects = nausea, headache and diarrhea. In patients already predisposed it can increase the risk of mania and seizures. Also, have to be cautious with anticoagulants as it increases bleeding time.

Hope this helps a bit,

Pierre

We are really reluctant here to prescribe EFV to patients with depression. We have done it in stabilized patients with relatively good success. Only a few (I remember 2 of them) had an exacerbation of their depression. In those situations, we usually stop EFV and switch to NVP (despite BMS suggestions to increase the dose of antidepressant...). I agree with Michelle that patients with anxiety disorders seem to be also at risk. We had one woman with post traumatic disorder (family killed in Africa) who became psychotic shortly after starting EFV.

I don't believe it is an absolute CI but it will need a closer monitoring.

Jeff

A related question, when you switch from efavirenz to nevirapine, do you overlap the two for a period until the nevirapine is at full dose? (We start the nevirapine at 200 mg qd for a couple of weeks, then increase to bid)? I haven't seen any clear recommendations....

Nancy

Interesting question Jeff,
I initially believed we began with NVP 200 QD for 2 weeks and then increased the dose of nevirapine to BID simply to decrease the risk of developing a rash. I was at first scared for the development of NVP resistance and NNRTI cross-resistance during the first 2 weeks. However, I was informed that one of the primary reasons is that nevirapine auto-induces its own metabolism (notion that I hadn't read), and

therefore during the first two weeks possibly 200 mg QD is sufficient for adequate ARV activity. In which case, continuing EFV wouldn't be necessary. I have always been a bit perplexed with this notion.

What do you guys think?
Thanks,

Rolf

This is a difficult question. It has been shown that when EFZ 600 mg qd and NVP 400 mg qd are co-administered, the EFZ AUC decreases by about 22% while the NVP PK was unaffected (Veldkamp et al, JID). This suggests no effect of EFZ on NVP PK, and therefore I would suggest to follow the standard dose-escalation scheme for NVP, without overlap of the NNRTIs.

Best regards

ATV- glucose ,LD

Michelle

HI ,
I am wondering if any of you have seen data on the effects of ATV on glucose and LDS (in particular increased abd. girth). I have a patient with high lipids, glucose and LDS and I am considering ATV as an option to address the lipidemia, but don't want to exacerbate the glucose and abd. weight gain.

Deborah

Michelle,
You may find useful links from this site with respect to BG and atazanavir:
www.natap.org/2002/lipoWorkshop/day2.htm

Hopes this helps some,

New References

New Treatment Guidelines:

British HIV Guidelines

Draft British HIV Association (BHIVA) / Medical Society for the Study of Venereal Diseases (MSSVD) guidelines on provision of adherence support to individuals receiving antiretroviral therapy (2002)

http://www.aidsmap.org/about/bhiva/bhiva_adherence.asp

Use of Antiretrovirals in Pregnant HIV-1 infected Women.

Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States - August 30, 2002

http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=66

Other Articles of interest

"Therapy Adherence and Highly Active Antiretroviral Therapy: Comparison of Three Sources of Information"

AIDS Patient Care and STDs (10.02) No. 10; Vol. 16: P. 487- 495::John Vincke, PhD; Ralph Bolton, PhD

Patient adherence, a critical component in the management of HIV, has become a behavioral problem since the advent of HAART. Failure to adhere to a therapeutic regimen can dilute beneficial effects of the drugs and cause the emergence of drug-resistant strains of HIV. A central limitation to studying adherence to HAART is that often researchers have to rely on self-reported measures of adherence, which tend to overestimate.

The current study combines information on adherence from several sources: patients' self reports, perception of adherence reported by the patients' designated most significant others, evaluation of adherence by the physicians in charge of treatment, and HIV-1 RNA levels.

Investigators gathered data from 86 participants in the French- and Flemish-speaking areas of Belgium. The study used variables based on the health belief model, a value-expectancy theory that views behavior as a function of the subjective value of an outcome and the subjective expectancy that a specific action will result in the outcome. To improve the explanatory power of the health belief model, the authors also measured adherence-specific social support, and satisfaction with the patient-provider relationship.

The researchers found that the best results for explaining adherence were those reported by the medical staff in charge of treatment. Perception of barriers to following the complicated treatment regimen was the most important predictor of adherence. The impact of received benefits was the second most important predictor. Doctors noted that patients who report high benefits from the regimen were more compliant. Female patients also showed to be more compliant than males. Adherence varied with the complexity of the treatments. More complex treatments resulted in lower adherence. Contrary to expectations, the authors found that a higher satisfaction with the doctor-patient relationship, as reported by medical staff, resulted in lower adherence.

Adherence reported by the participants had only one significant predictor, perceived self-efficacy. Respondents with high self-efficacy reported fewer missed doses of medication. None of the variables as seen by respondents' most significant other had a significant impact on adherence. The study found older participants to have higher viral load levels, and lower levels of viral particles in the blood of respondents reporting high levels of perceived benefits in following HAART therapy.

"We did find that the health belief model is able to explain a considerate amount of the variation in adherence as reported by the medical staff," the authors noted. "Benefits and barriers are related to adherence. We also found for HIV-1 RNA levels that perceived barriers were significant."

Since little is currently known about the long-term outcomes of HAART, the researchers suggested that adherence could become more stringent as treatment effects stabilize over time and benefits become more visible.

"While this study has limitations related to sample size, statistical power, and missing data, nonetheless, we strongly believe that relying on and combining different sources of information on therapy adherence will sharpen our insights into the complex process of adherence and produce more effective therapeutic outcomes," the researchers concluded.

Drug interactions between recreational drugs and antiretroviral agents

Congratulation to Tony Antoniou and Alice Tseng for this extensive review! In Ann Pharmacother 2002;36:1598-613.