



Canadian HIV/AIDS Pharmacists Network
*Association Canadienne des Pharmaciens
en VIH/SIDA*

CHAP NEWSLETTER

Winter 2007 (October to January 2007)

2006/07 CHAIR

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(Edmonton, Alberta)

SECRETARY

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(Ottawa, Ontario)

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Nancy Sheehan, B.Pharm.,
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NEWFOUNDLAND

Debbie Kelly, Pharm.D.

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Newsletter sections:

Newsletter Editor: Secretary

Research Update: Secretary

Thank-you to the following members for volunteering to assist with the newsletter:

Publications: Lizanne Beique

Conferences: Pierre Giguere

CHAP E-mails Marie Courchesne

I. WELCOME NEW MEMBERS

II. RESEARCH PROJECT UPDATES

Contact: Christine Hughes, BScPharm,PharmD (chughes@pharmacy.ualberta.ca)

Fall 2006:

- 1) Outcomes with abacavir/didanosine or tenofovir/abacavir backbones
Both the abacavir/tenofovir and ddI/abacavir nuc backbone studies have been completed. They have been submitted to CAHR
- 2) A review of the effectiveness and safety of ARVs in our pregnant women (between 1997-2006). This has been submitted to CAHR

III. RESEARCH PROJECT UPDATES –nonCHAP Initiatives

IV. ADDITION PUBLICATIONS

1. Foisy, Michelle
Infants rescued from grip of AIDS: Intensive treatment at birth has brilliant results
keeping babies of infected mothers virus-free
The Edmonton Journal
Fri 01 Dec 2006
Page: A1 / Front
Section: News
Byline: Jodie Sinnema
Dateline: EDMONTON
Source: The Edmonton Journal

V. AWARDS

1. CSHP Award 2006/07

Dalyce Zuk, Christine Hughes, Michelle Foisy

Hoffmann-La Roche Specialties in Pharmacy Practice Award for project entitled:

"The Safety and Effectiveness of Antiretrovirals in Pregnancy."

Professional Practice Conference, Toronto, Ontario January 2007

2. CSHP Fellow

Natalie Dayneka, B.Sc.Pharm.D., FCSHP

Fellow Canadian Society of Hospital Pharmacists

Professional Practice Conference, Toronto, Ontario January 2007

VI. CHAP E-MAIL CORRESPONDENCE (Marie Courchesne)

CHAP ATTENDANCE

- Hi Michelle, My current plans are to attend the meeting. If you were able to get Rodger MacArthur in, I'd be very interested in the resistance workshop....either Tuesday or Thursday would be fine with me...I don't mind skipping the symposiums on Thursday. Linda
- Hi Michelle, I plan on attending CAHR. I think a workshop by Rodger is always a good thing so would be willing to opt out of the Thursday symposiums. I agree Tuesday makes for a long week as us westerners would have to leave Monday:-) Christine
- Lucky for us that CAHR is in Toronto, I hadn't realized how close it was to the PK meeting. I would also prefer Thursday for the resistance workshop. Alice
- [Robinson, Linda] I too will be trying to attend the Pharm conference in Budapest this year so will not be able to attend both.
- Hi Michelle, I will try to go to the PK workshop this year. This will likely mean that I may be unable to go to CAHR. Having said this, I may be able to go to CHAP as long as the meeting is no longer than 1 day. I am not too interested to prolong my stay for a resistance workshop. Thanks pg
- Hi Michelle, I hope to attend the CHAP meeting and would prefer the resistance workshop on the Thursday. Thanks for all the planning ahead, including obtaining the sponsorship! Deborah
- Hi Michelle, We have a new pharmacist in our clinic, Gloria Tsang, so I anticipate that she will be going to the 2007 CAHR. Susan, Oak Tree Clinic, Children's & Women's Health Centre of B.C
- Thanks for organizing early - I will not be attending CAHR or CHAP either (mat leave). If Pierre or Charles do not attend, then the spot could be given to a general member (if I remember correctly, we had concluded that there would be 2 spots for The Ottawa Hospital for next year). Thanks- Lizanne
- Either options work for me. I would like to fly in Tuesday morning and have the Resistance workshop start at 1200h Tuesday (As I'm close, even a hthe group dinner Wednesday night and the Resistance workshop end early Thursday so people not staying for the conference can fly back early Thursday. Natalie

INTERESTING PUBLICATIONS

- McPherson R, Frohlich J, Fodor G, Genest G. Canadian Cardiovascular Society positions statement – Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular

disease. Can J Cardiol 2006; 22(11): 913-927.

- POTENT INHIBITION OF THE CYTOCHROME P-450 3A-MEDIATED HUMAN LIVER MICROSOMAL METABOLISM OF A NOVEL HIV PROTEASE INHIBITOR BY RITONAVIR: A POSITIVE DRUG-DRUG INTERACTION. GONDI N. KUMAR, JENNIFER DYKSTRA, ELLEN M. ROBERTS, VENKATA K. JAYANTI, DEAN HICKMAN, JOHN UCHIC, YE YAO, BRUCE SURBER, SAMUEL THOMAS, AND G. RICHARD GRANNEMAN. This paper is available online at <http://www.dmd.org>
- **ABSTRACT:** ABT-378 is a potent in vitro inhibitor of the HIV protease and is currently being developed for coadministration with another HIV protease inhibitor, ritonavir, as an oral therapeutic treatment for HIV infection. In the present study, the effect of ritonavir, a potent inhibitor of cytochrome P-450 (CYP) 3A, on the in vitro metabolism of ABT-378 was examined. Furthermore, the effect of ABT-378-ritonavir combinations on several CYP-dependent monooxygenase activities in human liver microsomes was also examined. ABT-378 was found to undergo NADPH- and CYP3A4/5-dependent metabolism to three major metabolites, M-1 (4-oxo) and M-3/M-4 (4-hydroxy epimers), as well as several minor oxidative metabolites in human liver microsomes. The mean apparent K_m and V_{max} values for the metabolism of ABT-378 by human liver microsomes were 6.8 \pm 3.6 mM and 9.4 \pm 5.5 nmol of ABT-378 metabolized/mg protein/min, respectively. Ritonavir inhibited human liver microsomal metabolism of ABT-378 potently (K_i 5 0.013 mM). The combination of ABT-378 and ritonavir was much weaker in inhibiting CYP-mediated biotransformations than ritonavir alone, and the inhibitory effect appears to be primarily due to the ritonavir component of the combination. The ABT-378-ritonavir combinations (at 3:1 and 29:1 ratios) inhibited CYP3A (IC_{50} 5 1.1 and 4.6 mM), albeit less potently than ritonavir (IC_{50} 5 0.14 mM). Metabolic reactions mediated by CYP1A2, CYP2A6, and CYP2E1 were not affected by the ABT-378-ritonavir combinations. The inhibitory effects of ABT-378-ritonavir combinations on CYP2B6 (IC_{50} 5 >30 mM), CYP2C9 (IC_{50} 5 13.7 and 23.0 mM), CYP2C19 (IC_{50} 5 28.7 and 38.0 mM), and CYP2D6 (IC_{50} 5 13.5 and 29.0 mM) were marginal and are not likely to produce clinically significant drug-drug interactions.
- Lopinavir/Ritonavir Induces the Hepatic Activity of Cytochrome P450 Enzymes CYP2C9, CYP2C19, and CYP1A2 But Inhibits the Hepatic and Intestinal Activity of CYP3A as Measured by a Phenotyping Drug Cocktail in Healthy Volunteers. Rosa F. Yeh, PharmD,* Vincent E. Gaver, PharmD,* Kristine B. Patterson, MD, Naser L. Rezk, MS,* Faustina Baxter-Meheux, BS,* Michael J. Blake, MD, PhD, Joseph J. Eron, Jr, MD, Cheri E. Klein, PhD,§ John C. Rublein, PharmD,§ and Angela D.M. Kashuba, PharmD* (J Acquir Immune Defic Syndr 2006;42:52Y60)
- LAMIVUDINE-ZIDOVUDINE AND MATERNAL HIV-1 TRANSMISSION ©2001 American Medical Association. All rights reserved. (Reprinted) JAMA, April 25, 2001—Vol 285, No. 16 2093
- Downloaded from www.jama.com at National Institute of Health, on October 17, 2006
- Editorial Manager(tm) for Journal of Acquired Immune Deficiency Syndromes
- Manuscript Draft
- Manuscript Number: V8980R1
- Title: Safety And Pharmacokinetics Of Nelfinavir Co-administered with Zidovudine and Lamivudine In Infants During The First 6 Weeks Of Life
- Article Type: Revised Original Article
- Keywords: nelfinavir, HIV, pharmacokinetics, neonate
- Corresponding Author: Mark Mirochnick, MD
- Corresponding Author's Institution: Boston University
- The long term consequence of antiretroviral therapy: a review Mark Boyd and Peter Reiss Journal of HIV Therapy vol 2 No 2 2006

- Acid Suppressive Therapy and the Effects on Protease Inhibitors. Patricia Pecora Fulco, Urvi B Vora, and Gonzalo ML Bearman. *Ann Pharmacother* 2006;40:1974-1983. DOI 10.1345/aph.1H022 <http://www.theannals.com/cgi/content/abstract/40/11/1974?etoc>
- American Thoracic Society. **Am J Respir Crit Care Med Vol 161. pp S221–S247, 2000. Internet address: www.atsjournals.org Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection.** THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JULY 1999. THIS IS A JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) AND THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC). THIS STATEMENT WAS ENDORSED BY THE COUNCIL OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA (IDSA), SEPTEMBER 1999, AND THE SECTIONS OF THIS STATEMENT AS IT RELATES TO INFANTS AND CHILDREN WERE ENDORSED BY THE AMERICAN ACADEMY OF PEDIATRICS (AAP), AUGUST 1999.

Correspondence

- Hello everyone, I thought I would update you on the patient I had requested help with earlier in the year. This was the gentleman we and the patient wanted to stop stavudine on (due to metabolic syndrome) who did not want a PI. He wanted to remain on his efavirenz with a backbone of tenofovir, lamivudine (fitness) and abacavir. After explaining my and the CHAP expertise concerns and suggestions to the physician and patient, he was prescribed the regimen above :(. Prior to the switch his ultrasensitive was <50. Two months after the switch his viral load was <400. One month after this it was 813 (June) and 536 (August). We are waiting for a viral load done in October. This patient is very adherent and had not missed any doses. I thought the group might find this interesting. Jennifer

Kaletra capsules

- Hi everyone, Can you please let me know whether or not your province has added Kaletra film coated tablets onto formulary? If not, can you provide a guesstimate of how long you think the approval process will take? I'm trying to 'guess' how long capsules will still be available in Canada. (We are still using them in some of our pediatric patients.) Thanks, Linda.
- Officially not yet in AB, but the rubber stamp should land withing the next month. Jeff Kapler, Pharmacist
- Yes added. Kathy Slayter
- Fyi. . here's the "plan' re: the new Kaletra formulation for Sask (from the pharmacologist on our gov't review committee) FYI -- DQAC = Drug Quality Assessment Committee, a prov'l committee of our SFC, the prov'l Formulary committee Hi Linda: We received a submission for the tablet formulation September the 12th. The product will go to the DQAC at its next meeting (November 8, 2006) and on to the SFC on December 7, 2006. If it is approved it would be eligible for coverage April , 2007. Abbott has indicated that the capsule formulation will be phased out once the conversion to the tablets is completed (expected within 1-2 years). I hope this answers your questions. Best regards Lorne Davis, Pharmacologist, Drug Plan & Extended Benefits Branch Saskatchewan Health. Linda A. Sulz (BSP, PharmD)

Do any of you have any literature, ongoing studies, or experience in dosing nelfinavir in preemies???

- We have 30 wk old twins and generally use triple tx for prophylaxis. HIV status unknown at this time. For the Montreal group- what are they doing about the NFV dosing at St. Justine in their perinatal protocol? Do you have a contact person there that I could speak to? Michelle Foisy, Pharm.D.
- We have not had to address this issue. As you know, a literature search does not help. The evidence in pediatric literature (and October 2006 Adult guidelines) stress nelfinavir as a second line so I wonder if we see any premie work, it will be with Kaletra. If you do replies, please forward them to me as I am very interested. Are you planning on 30-40 mg/kg/dose po bid (newborn dose)?

Natalie

- Here is some F/U info from the ACTG 353 author about NFV dosing. They only go as low as 1500g babies and the dose is 100mg BID (~67mg/kg BID). Still under study. M
- hi, sorry for the delay but I was out for 1 week. we don't do dosing for nelfinavir for prem and we use 40 mg /kg /dose bid but our younger prem was 34 to 35 wk old. Marie-France Goyer, pharmacienne, H^ôpital Ste-Justine
- more info from the PACTG 353 protocol.....

From: Mirochnick, Mark [mailto:Mark.Mirochnick@bmc.org]

Sent: Wednesday, October 18, 2006 8:54 AM

To: Mofenson, Lynne (NIH/NICHD) [E]; Foisy, Michelle

Cc: Mirochnick, Mark H

Subject: RE: Nelfinavir in neonates and premmies

Dr. Foisy,

Lynne answered your question before I had a chance to, and as usual, her reply was very complete. I can only add the following:

1. While our current study that Lynne described below allows enrollment down to 1500 gm, we have had only 1 infant enrolled below 2500 gm. So we do not have any useful pk data in low birth weight infants and I would have no idea how to dose nelfinavir in a 30 wk gestation newborn.
2. I have attached a copy of the manuscript from our previous study of nelfinavir pk in newborns (Mirochnick M, Stek A, Acevedo M, Keller M, Holland D, Capparelli E, Connor J, Huang S, Hughes M, Watts H, Mofenson L, Bryson Y. Safety and pharmacokinetics of nelfinavir co-administered with zidovudine and lamivudine in infants during the first 6 weeks of life. JAIDS 2005;39:189-194.). We found low NFV plasma concentrations in around 30% of infants receiving 40 mg/kg bid. Our current study is using a larger dose (weight band dosing to provide 50-75 mg/kg as described below) and, as Lynne described, we found increased variability with the higher doses but unfortunately still low plasma concentrations in 50% of the infants. I suspect the problem is absorption and I do not think that giving even larger doses is going to solve this problem.

If I can be of any more help, please let me know.

Regards,

Mark Mirochnick

From: Mofenson, Lynne (NIH/NICHD) [E] [mailto:mofensol@exchange.nih.gov]

Sent: Tuesday, October 17, 2006 12:50 PM

To: Foisy, Michelle

Cc: Mirochnick, Mark H

Subject: RE: Nelfinavir in neonates and premmies

Dr. Foisy: I am ccing Dr. Mirochnick, as he is much better placed to give you recommendations on nelfinavir dosing in preterm infants. We have data from term infants, but to my knowledge there are not data in preterm infants – but if anyone would know it would be Dr. Mirochnick, so I will let him answer this for you.

We are doing a perinatal prevention study I discuss below that includes nelfinavir to HIV-exposed infants and are giving weight-based dosing to provide a minimum of 50 mg/kg BID (giving 200 mg BID if >3000 grams, 150 mg BID is 2000-3000 grams, and 100 mg BID if 1500-2000 grams – we don't allow enrollment of infants <1500 grams). We have done a PK substudy that showed at 4-6 days of age that only 50% (7 of 14) infants receiving this dose met the target nelfinavir AUC₀₋₁₂ of 15 ug*hr/mL (or AUC₀₋₂₄ 30 ug*hr/mL), although the trough level at 12 hours was above 100 ng/mL in all infants (more than 10 times the IC50). There was extensive variability among infants and we have opted not to increase the dose in our clinical trials. However, as I noted, we did not enroll preterm infants with weights <1500 grams.

As an aside, I personally think that giving three drugs to the infant if the mother has HIV RNA over 1,000 is overkill. We have no data yet to demonstrate that additional drugs provide additional efficacy compared to 6 weeks of AZT alone, and there is potential toxicity. There are some data that suggest that the combination of AZT/3TC may be more likely to result in anemia and neutropenia than AZT alone (see Mandelbrot L et al. JAMA 2001, attached PDF). I personally would reserve use of multiple drugs for a very special circumstance, such as potentially if the mother was on triple drugs for several months and had an HIV RNA >100,000 at delivery making resistance highly suspect. That said, in the absence of better data, I think the best one can do is to do what one feels is optimal (and others would probably agree with you about multiple drugs, I am giving you my own opinion) but ensuring that the mother understands that there are not data to say that additional drugs provide additional protection, although theoretically it might.

We are currently doing a study in US, Brazil, Argentina and South Africa to address this question in infants whose mothers have not received any antenatal antiretroviral therapy, where we compare 6 weeks of AZT with 6 weeks of AZT plus either 2 weeks of 3TC/nelfinavir or 6 weeks of AZT plus 3 doses of NVP in first week of life (birth, 48 hours, 96 hours). Hopefully, this study will address the question of multiple drugs at least in the setting whether no maternal therapy has been received.

Lynne

Lynne M. Mofenson, M.D.

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Second new email: Lynne.Mofenson@nih.hhs.gov

From: Foisy, Michelle [mailto:MFoisy@cha.ab.ca]

Sent: Tuesday, October 17, 2006 11:30 AM

To: Mofenson, Lynne (NIH/NICHD) [E]

Subject: Nelfinavir in neonates and preemies

Greetings from Canada,

I have been in touch with yourself and Dr. Mirochnick in the past and am seeking advice on the latest dosing for nelfinavir in neonates.

We have a fairly aggressive perinatal HIV protocol and use triple drug therapy (AZT/3TC/nelfinavir) in neonates whose mother's have VL > 1000 at the time of delivery. Based on previous evidence, we have

selected a mid-way dose of nelfinavir 50mg/kg BID in the newborn. However, we just had twins born at 30 weeks gestation each weighing about 1500gm. We withheld the nelfinavir as we were not sure what dosing to use in preemies. I was unable to find any literature and was hoping you might have some insights based on your research.

I am also curious to know which dose of NFV you are now using in term babies?
Thanks for any information you may be able to provide.

Michelle

Congratulations to Natalie whose practice is highlighted in the 1st Pharmacy Practice Spotlight in the CSHP journal.

- Thanks for mentioning our group Natalie and for providing this much needed service and support to these young victims & their families. /Linda

Also, congratulations to Charles for his recent publication "Updated guideline to perform therapeutic drug monitoring for antiretroviral agents", Rev Antiviral Ther 2006;3:3-14. Alice

Hi guys, I have a few good questions for you regarding ritonavir drug interactions.....

1) I noted in the Kaletra product monograph in the Drug Interaction section it states that RTV only inhibits CYP3A4 at Kaletra doses (low dose RTV) and does not impact the other cytochromes... (2D6, 2C9, 2C19, 2E1, 2B6 or 1A2, etc.....)

Your thoughts? Do we need to worry about intxs with the other cytochromes (other than 3A4) in our Kaletra or other boosted PIs? I was always concerned about potential intxs with the other isoenzymes, but now am not sure if I should be.

2) I am also wondering about RTV's induction properties. Are they dose dependent as well? I have not researched this one and thought I would ask first. From the info I have RTV induces GT and CYP 1A2 (and possibly 2C9 and 2C19)? Is there a dual inhibition/induction effect on 1A2, 2C9, 2C19?

Any comments?

3) Voriconazole and RTV interaction

Voriconazole is a 2C19, 2C9, 3A4 substrate. I was surprised to see the magnitude of this interaction and the fact it was an induction intx.

The voriconazole (VFEND) monograph states that it is contraindicated with RTV at RTV doses of 400mg BID due to a > 80% decrease in voriconazole AUC. In this situation I assume it is because RTV is inducing 2C19 and 2C9 at the higher doses. The lower RTV dose of 100mg BID decreased voricon AUC by 39%.

Bottom-line, if a pt is on Kaletra or a boosted PI with RTV doses of 100-200mg/day, do we need to be concerned about this intx with voriconazole? Would you dose adjust voricon?

Here is the info from MDX:

1.BJ Ritonavir

1) Interaction Effect: decreased plasma concentrations of voriconazole with high-dose and, to a lesser

extent, low-dose ritonavir, and risk of decreased voriconazole efficacy

2) Summary: Concomitant high-dose ritonavir significantly reduced plasma voriconazole concentrations in healthy subjects. Therefore, coadministration of voriconazole with high-dose ritonavir is contraindicated. Concomitant low-dose ritonavir also reduced plasma voriconazole concentration, along with slightly decreased plasma ritonavir concentrations. Therefore, coadministration of voriconazole with low-dose ritonavir should be avoided unless it is determined that the potential benefit from this combination justifies the risk (Prod Info VFEND(R) injection, oral tablets, oral suspension, 2006).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant administration of voriconazole with high-dose ritonavir (400 mg every 12 hour) has resulted in significant reduction of plasma voriconazole concentrations and is therefore, contraindicated. Coadministration of voriconazole and low-dose ritonavir (100 mg every 12 hour) has also resulted in decreased plasma voriconazole and ritonavir concentrations and should therefore be avoided unless it is determined that the potential benefit justifies the risk.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of voriconazole by ritonavir

8) Literature Reports

a) Coadministration of high-dose ritonavir significantly decreased plasma voriconazole concentrations. Ritonavir (400 mg every 12 hours for 9 days) decreased the steady state maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) by an average of 66% and 82%, respectively, in healthy subjects. At the same dose of oral voriconazole, concomitant low-doses ritonavir (100 mg every 12 hours for 9 days) decreased the steady state C_{max} and AUC of voriconazole by an average of 24% and 39%, respectively. Additionally, steady state C_{max} and AUC of low-dose ritonavir were decreased by 24% and 14%, respectively. Voriconazole did not significantly affect steady state C_{max} and AUC of high-dose ritonavir (Prod Info VFEND(R), 2003h; Prod Info NORVIR(R), 2005).

Michelle

After taking a look at some of these articles I know for my sake, a nice summary of this complicated information would be very useful, first for myself, and then for our students. Does anyone have a student right now that this task could possibly be assigned to? ...and could we share it when finished?

- I have a student coming up but not for another month. Linda Robinson BSc.Phm
- It is interesting that in the cases Charles sent show and increase in voriconazole levels (and not decreased as the product monograph suggests). I am not sure what to make of it. Mich
- We have a student starting, but he already has another project to work on (antimalarial intx). If he is done this one early, we can assign the RTV intx one to him. Michelle

Just wondering if anyone is aware of any current pharmacy CE programs on HIV?

Christine Hughes, BscPharm, PharmD

Michelle and I wanted to get your input re: tenofovir and lopinavir.

- Is anyone doing dose adjustments due to the possible decreased lopinavir/ritonavir levels? Are you concerned re: once daily versus twice daily? For those of you who have access to TDM, do you routinely order levels (and require dose increases) on this combination? Thanks Christine

Just wondering if those of you working with peds have gotten access to darunavir for your patients.

- We have a ID peds fellow working with us that is running into some barriers of getting access. EAP restricts use to >18y, Health Canada won't approve because it's "off-label" use, company won't supply without health Canada, etc. anybody have success? thanks, Deborah
- Health Canada not approving due to Off-label is rubbish. 70-80% of all drugs we use in our pediatric tertiary care hospital are not approved for children. Please email me at dayneka@cheo.on.ca and I will give you a name and phone number of whom to speak to at SAP to get your drug approved. Natalie (PS we have not yet requested darunavir for a peds patient.)

Wondering if any of you have patients who have CRF and are HIV positive?

- Our ID clinic nurse would like a contact person and phone number to discuss some issue with them. Linda A. Sulz (BSP, PharmD)
- I don't have any at my site. I do have a contact number for a nephrologist who deals with HIV at Sunnybrook in Toronto. Would you like this? Michelle

Has anyone been using fosamprenavir in their peds patients?

- As you may know, Amprenavir caps are being discontinued at the end of December (this is the first I am hearing of it so not much notice!). We have a few pediatric patients that we are using the caps for as there is still no dosing approved for fosamprenavir in peds. Has anyone been using fosamprenavir in their peds patients? I hate to have to put the kids on the liquid amprenavir as most of them seem to prefer tabs/caps. Any info you have would be great! Thanks, Cara

citrate in HIV patients

- One of our drug information pharmacists had a caller inquiring about citrate in HIV patients, indicating that they had heard something about "citrate" (e.g., use as anticoagulant in dialysis catheters) being a problem in HIV patients. Our drug information pharmacist did a Medline search and found one report saying that HIV patients have low citrate levels. Are any of you aware of any problems regarding citrate and HIV patients? Any help would be greatly appreciated. I am including the drug information pharmacist's (Irene Worthington) email address, and it would be appreciated if she could be included in any replies to this question. Thank you so much for your help. Sandy
- Hi Sandy Off the top, I have never come across this as being a concern. Michelle

For anyone who has their genotype/phenotyping done in BC-wondering if darunavir is going to be included soon (haven't seen it yet) Kathy

- Hi Kathy, I just spoke with Richard Harrigan and it seems that there is a 'technical issue' at Virco that needs to be addressed, before BC will include darunavir on the virtual phenotype reports. When I asked for a possible timeline for the fix, Richard was not able to provide any information, since it's up to the Virco people. Linda.

This is my first pregnant HIV positive patient and of course it is not straight forward.

- She has had a significant TB exposure that suggests prophylaxis (if she was not pregnant). She has a viral load < 50 on zidovudine, lamivudine and nelfinavir. She is early in her first trimester. For those in the adult world where this is routine, would anyone hesitant to suggest the addition of isoniazid (plus pyridoxine 25mg/day)? Any words of advice? Natalie
- Here is a comment from one of our ID docs who sees lots of TB in Africa and here. Mich

From: shouston@ualberta.ca [mailto:shouston@ualberta.ca]

Sent: Saturday, January 13, 2007 12:13 AM

To: Foisy, Michelle

Subject: RE: [chap_acpv] TB, HIV & pregnancy

M

No hesitation whatsoever. There is immense experience with isoniazid in pregnancy in the setting of treatment with no evidence of concern—and routinely recommended. I was surprised to find it listed as “C”. Here is the relevant paragraph from the Am Thoracic Soc gdl.

I would feel strongly that HIV, being the most potent known risk factor for TB reactivation, “prophylaxis” should not be delayed till delivery because of the significant risk of developing active TB in that time period. I wouldn’t even necessarily wait till the end of the first trimester but I guess I would be prepared to negotiate on that point. Agree with vit. B6.

Pregnancy and lactation. Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease (133, 134). Although one study demonstrated a decrease in lymphocyte reactivity to tuberculin during pregnancy (135), other studies have not demonstrated an effect of pregnancy on cutaneous delayed hypersensitivity to tuberculin (136, 137). The current classification scheme for interpreting the Mantoux tuberculin skin test is likely valid in pregnancy, although it has not been verified in this group of women. There is no evidence that the tuberculin skin test has adverse effects on the pregnant mother or fetus (138).

Pregnant women should be targeted for tuberculin skin testing only if they have a specific risk factor for LTBI or for progression of LTBI to disease. Although the need for treatment of active TB during pregnancy is unquestioned, the treatment of LTBI in pregnant women is more controversial. Some experts prefer to delay treatment until after delivery because pregnancy itself does not increase the risk of progression to disease, and two studies suggest that women in pregnancy and the early postpartum period may be vulnerable to isoniazid hepatotoxicity (91, 92). However, because conditions that promote hematogenous spread of organisms to the placenta (e.g., recent infection and HIV infection) or progression of LTBI to disease can endanger both the mother and baby (139), many experts agree that pregnant women with these conditions and LTBI should be treated during pregnancy and have careful clinical and laboratory monitoring for hepatitis. The possible risk for isoniazid hepatotoxicity must be weighed against the risk for developing active TB and the consequences to both the mother and her child should active disease develop.

Extensive use of isoniazid during pregnancy has indicated that although it readily crosses the placental barrier, the drug is not teratogenic even when given during the first 4 mo of gestation (140). Regarding rifampin, one study revealed that 3% of 446 fetuses exposed *in utero* to rifampin had abnormalities (i.e., limb reductions, central nervous system abnormalities, and hypoprothrombinemia) compared with 2% for ethambutol and 1% for both isoniazid and controls (138). Hemorrhagic disease of the newborn has been described following the use of rifampin in the mother (141). However, extensive experience with the use of rifampin to treat TB in pregnant women suggests it is safe in most circumstances. Although pyrazinamide has been used to treat TB in pregnant women, no published data exist concerning the effects of the drug on the fetus. Thus, although pyrazinamide may be considered after the first trimester in women with HIV infection (142), it should otherwise be avoided.

The preferred regimen for treatment of LTBI in pregnant women is isoniazid, administered either daily or twice weekly. Although rifampin is probably safe, no efficacy data support its use. For women at high risk for progression of LTBI to disease, especially those who are infected with HIV or who have been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For these women, careful clinical and/or laboratory monitoring for hepatitis should be undertaken. Pregnant women taking isoniazid should receive pyridoxine supplementation.

Toxic effects of antituberculosis drugs delivered in breast milk have not been reported. One study concluded that a breastfeeding infant would develop serum levels of no more than 20% of the usual therapeutic levels of isoniazid for infants and < 11% of other antituberculosis drugs (143). Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, infants whose breastfeeding mothers are taking isoniazid should receive supplemental pyridoxine. The amount of isoniazid provided by breast milk is inadequate for treatment of the infant.

- Hi Nathalie. In the general population we normally delay prophylaxis treatment until after pregnancy

since the likelihood of developing TB is not 100% after exposure. You are talking about a significant exposure, what do you mean exactly? How was this evaluated? From reactivity test (Mantoux) or from history or X ray?. Then is it recent exposure? with a MDR TB patient or not. How about her CD4 count? A pneumologist specialized in TB should probably be consulted. I forgot to mention that there is a test now done as part of research to see if the patient is carrier of the gene that makes it more likely to develop TB. Marie Courchesne

Switch of 3TC- TBF to truvada

- patients do complain of side effects such as nausea and headache at the time of switch. For some patients it lasted about 6 weeks. It is really like any change of medications. So even though emtricitabine is similar to 3TC patients feel it is a new molecule and incur side effects. Marie Courchesne

VII. RECENT PUBLICATIONS (Lizanne Beique)

Topics:

Adherence
Adverse Events
Drug Interactions
Guidelines
Pediatrics
Treatment Outcomes/ Resistance
Other

ADHERENCE

Efficacy of Interventions in Improving Highly Active Antiretroviral Therapy Adherence and HIV-1 RNA Viral Load: A Meta-Analytic Review of Randomized Controlled Trials. JAIDS 43 Supplement 1:S23-S35, December 1, 2006. *Simoni, Jane M PhD **; *Pearson, Cynthia R PhD **; *Pantalone, David W MS **; *Marks, Gary PhD +*; *Crepaz, Nicole PhD +*

Sustained Benefit From a Long-Term Antiretroviral Adherence Intervention: Results of a Large Randomized Clinical Trial. JAIDS 43 Supplement 1:S41-S47, December 1, 2006. *Mannheimer, Sharon B MD **; *Morse, Edward PhD +*; *Matts, John P PhD ++*; *Andrews, Laurie RN, MPH [S]*; *Child, Carroll RN, MSc ||*; *Schmetter, Barry BS [P]*; *Friedland, Gerald H MD [S]*; *for the Terry Bein Community Programs for Clinical Research on AIDS*

Practical and Conceptual Challenges in Measuring Antiretroviral Adherence. JAIDS 43 Supplement 1:S79-S87, December 1, 2006.
Berg, Karina M MD, MS; *Arnsten, Julia H MD, MPH*

Validity of a Stage of Change Instrument in Assessing Medication Adherence in Indigent Patients with HIV Infection. Ann Pharmacother published 9 January 2007. R Chris Rathbun, Kevin C Farmer, Staci M Lockhart, and Johnny R Stephens

Adherence in antiretroviral therapy: a review of qualitative studies. AIDS. 21(3):271-281, January 30, 2007. *Vervoort, Sigrid CJM a*; *Borleffs, Jan CC a*; *Hoepelman, Andy IM a*; *Grypdonck, Mieke HF b*

**** The entire JAIDS issue of Dec 1 has various articles on adherence ****

ADVERSE EVENTS

Ezetimibe, a promising lipid-lowering agent for the treatment of dyslipidaemia in HIV-infected patients with poor response to statins. AIDS. 2006 Nov 14;20(17):2159-64. Eugenia Negrodo; José Moltó; Jordi Puig; Denise Cinquegrana; Anna Bonjoch; Núria Pérez-Álvarez; Raquel López-Blázquez; Asunción Blanco; Bonaventura Clotet; Celestino Rey-Joly

Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review.

AIDS. 2006 Nov 14;20(17):2165-74 Todd T Brown; Roula B Qaqish

Atazanavir Urolithiasis. NEJM November 16, 2006 Volume 355:2158-2159. Chang, Pablo.

Renal Function in Patients Receiving Tenofovir With Ritonavir/Lopinavir or Ritonavir/Atazanavir in the HIV Outpatient Study (HOPS) Cohort. JAIDS. 43(5):626-628, December 15, 2006. Buchacz, Kate PhD *; Young, Benjamin MD, PhD +; Baker, Rose K MS ++; Moorman, Anne BSN, MPH *; Chmiel, Joan S PhD [S]; Wood, Kathy C BSN ++; Brooks, John T MD *; the HIV Outpatient Study (HOPS) Investigators

Truvada intolerance. AIDS. 21(3):382-383, January 30, 2007. Vemuri, Sreevani a; Bratberg, Jeffrey b; Burke, Karen a; Skowron, Gail a

Randomized Controlled Trial of Zinc Supplementation for Persistent Diarrhea in Adults With HIV-1 Infection. JAIDS. 43(2):197-201, October 1, 2006. Carcamo, Cesar MD, PhD *+; Hooton, Thomas MD ++[S]; Weiss, Noel S MD, DrPH *; Gilman, Robert MD ||[P]; Wener, Mark H MD ++; Chavez, Victor MD #; Meneses, Rosario MD, PhD **; Echevarria, Juan MD ++; Vidal, Margot MD **; Holmes, King K MD, PhD *+[S]

DRUG INTERACTIONS

Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*, 2007, **81(2)**: 222-227. Cohn SE, Park JG, Watts DH, et al.

Pharmacokinetic interaction between TMC114/r and omeprazole or ranitidine in HIV-negative healthy volunteers. *Antimicrob Agents Chemother*, 2007. Sekar VJ, Lefebvre E, De Paepe E, et al.

Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects.

Clin Pharmacol Ther, 2007, **81(1)**: 69-75. Hogeland GW, Swindells S, McNabb JC, et al.

The in vitro drug interaction potential of dietary supplements containing multiple herbal components. *Drug Met Dis*, 2007, **35(2)**: 185-188. Foti RS, Wahlstrom JL, Wienkers LC.

Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr*, 2006, **43(3)**: 278-283. Kearney BP, Mathias A, Mittan A, et al.

Ritonavir-fluticasone interaction causing Cushing syndrome in HIV-infected children and adolescents. *Pediatr Infect Dis J*, 2006, **25(11)**: 1044-1048. Arrington-Sanders R, Hutton N, Siberry GK.

Possible drug-metabolism interactions of medicinal herbs with antiretroviral agents.

Drug Metab Rev, 2006, **38(3)**: 477-514. van den Bout-van den Beukel CJ, Koopmans PP, van der Ven AJ, De Smet PA, Burger DM.

Pharmacokinetic interactions between buprenorphine and antiretroviral medications. *Clin Infect Dis*, 2006, **43 (Suppl 4)**: S216-223. Bruce RD, McCance-Katz E, Kharasch ED, et al.

Interactions between buprenorphine and antiretrovirals. I. The non-nucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. *Clin Infect Dis*, 2006, **43 (Suppl 4)**: S224-234.

McCance-Katz EF, Moody DE, Morse GD, et al.

Interaction between fosamprenavir, with and without ritonavir, and nevirapine in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother*, 2006, **50(9)**: 3157-3159.

DeJesus E, Piliero PJ, Summers K, et al.

Pharmacokinetic drug interactions with non-nucleoside reverse transcriptase inhibitors. *Expert Opin Drug Metab Toxicol*, 2005, **1(3)**: 473-485. Ma Q, Okusanya OO, Smith PF, et al.

Drug interactions between psychoactive substances and antiretroviral therapy in individuals infected with human immunodeficiency and hepatitis viruses. *Subst Use Misuse*, 2006, **41(10-12)**: 1395-1463. Neuman MG, Monteiro M, Rehm J.

Acid Suppressive Therapy and the Effects on Protease Inhibitors (CE) Ann Pharmacother published 31 October 2006, Patricia Pecora Fulco, Urvi B Vora, and Gonzalo ML Bearman

Pharmacokinetics and Safety of Tenofovir Disoproxil Fumarate on Coadministration With Lopinavir/Ritonavir JAIDS 2006 Nov 1;43(3):278-83. Brian P Kearney, PharmD; Anita Mathias, PhD; Angelique Mittan, BA; John Sayre, RN; Ramin Ebrahimi, MS; Andrew K Cheng, MD, PhD

Nifedipine-lopinavir/ritonavir severe interaction: a case report. AIDS. 21(1):119-120, January 2, 2007. Baeza, Maria T a; Merino, Esperanza a; Boix, Vicente a; Climent, Eduardo b

GUIDELINES

Updated guidelines to perform therapeutic drug monitoring for antiretroviral agents. *Reviews in Antiviral Therapy*, 2006, 3: 3-14. la Porte CJL, Back DJ, Blaschke T, Boucher CAB, Fletcher CV, Flexner C, Gerber JG, Kashuba ADM, Schapiro J, Burger DM.

PEDIATRICS

Treatment interruption in children with HIV infection. *Current Opinion in HIV & AIDS*. 2(1):62-68, January 2007. *Green, Hannah; Gibb, Diana M*

TREATMENT OUTCOMES/ RESISTANCE

The level of persistent HIV viremia does not increase after successful simplification of maintenance therapy to lopinavir/ritonavir alone. *AIDS*. 20(18):2331-2335, November 28, 2006. *McKinnon, John E a; Arribas, Jose R b; Pulido, Federico c; Delgado, Rafael c; Mellors, John W a*

Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. *AIDS* 2006 Nov 14;20(17):2183-2191 The French Cryptococcosis Study Group

Virologic Response of Zidovudine, Lamivudine, and Tenofovir Disoproxil Fumarate Combination in Antiretroviral-Naive HIV-1-Infected Patients. *JAIDS* 43(5):530-534, December 15, 2006. *Rey, David MD; Krebs, Magali; Partisani, Marialuisa MD; Hess, Georgette MD; Cheneau, Christine MD; Priester, Michele MD; Bernard-Henry, Claudine MD; de Mautort, Erik MD; Lang, Jean-Marie MD*

Food and Drug Administration analysis of tipranavir clinical resistance in HIV-1-infected treatment-experienced patients. *AIDS*. 21(2):179-185, January 11, 2007. *Naeger, Lisa K; Struble, Kimberly A*

***** Entire issue of Current Opinion in HIV and AIDS Jan 2007 Vol 2, Issue 1 is on treatment interruption****

OTHER

Circumcision and HIV. *JAMA* 2007;297 254. Joan Stephenson

Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *J Pharm Pharmaceut Sci* (www. cspsCanada.org) 9 (3): 398-426, 2006. Beverley D Glass¹ and Alison Haywood²

VIII. CONFERENCE DATES (Pierre Giguere)

See attachment

CHAP Annual Meeting

Wednesday 8am to 5pm April 25, 2007
Westin Harbour Castle, Toronto, Ontario

Agenda items:

1) Renal Workshop:

Nephrologist Dr. Michelle Hladunewich from Sunnybrook

2) Conference Updates

3) Clinical Forum

4) Research Forum.

5) Resistance Workshop:

Dr. Rodger McArthur

3 hour resistance overview with cases on Thursday April 26, 2007 8-11 am