

CHAP NEWSLETTER

WINTER 2006 (Sept 2005- Jan 2006)



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Many thanks to all those who contributed in the compilation of this newsletter!!!! Hope you are all having a great winter. We hope to put out one more newsletter before CAHR in May 2005, so keep up the good work.

Of note, the CHAP meeting is booked for the whole day from 08:00-17:00h on May 24, 2006 at the Hilton Hotel in Quebec City. This year we have two sponsors, BMS and Gilead. The agenda will be following as soon as we firm up the speakers. Hope to see you there.

Michelle & Debbie

I. RESEARCH PROJECT UPDATES

- **Project: Nelfinavir PK Study**
Principal Investigator: Nancy Sheehan

Sept 2005: There have been some delays with this project, mainly because of contract negotiations between U of Montreal research institute and Pfizer. As of August, the contract was still outstanding, but was necessary in order to predict how much overhead to budget. Once this is complete all sites will be receiving kits to resubmit to ethics (hopefully at the latest mid October).

Jan 2006: The Pfizer - University of Montréal contract has finally been completed and final version of the new protocol, consent forms, CRFs have been sent to all the sites participating in the "The effects of aging on the pharmacokinetics of nelfinavir and M8 in HIV-1-infected individuals" study. The sites are presently in the process of resubmitting the study to their ethics review board (either as an amendment or for some sites as a completely new study). I am hoping to organize a teleconference in March with the pharmacist at each site plus the research nurses to go over details (completion of CRFs, labeling and shipping of samples, etc). So I anticipate that the first patients will be recruited some time in March. We are still looking for 24 patients spread out in various age groups.

The sites that are presently participating are:

- Halifax (Kathryn Slayter)
- Ottawa Hospital (Lizanne Béique and Charles La Porte)
- BC Centre for Excellence (Linda Akagi and Elizabeth Phillips)
- Montréal Chest Institute (Nancy Sheehan)
- Regina (Linda Sulz)

- **Project: Drug Interaction: inhaled corticosteroid & ritonavir-containing regimen**
Principal Investigator: Lizanne Béique (lbeique@ottawahospital.on.ca)

Sept 2005: No site has yet joined in this project. Responses were received from Linda Akagi who mentioned that Elizabeth Phillips was planning on conducting a similar study, Jeff Kapler who mentioned his site would not have the appropriate patient population, and Marie Courchesne who said that her site will consider participating and that this will be discussed in their research meeting this September. The Ottawa site has started collecting data on a few patients. Given the nature of the interaction, the ethics committee of the Ottawa Hospital considers investigating this potential drug interaction with the measurement of cortisol levels +/- ACTH test as standard-of-care and does not require ethics approval. Ethics approval will, however, be required for the 'retrospective chart review' and publication of data. A big thank you to Pierre Giguere (Ottawa Hospital site) who is now also actively working on this project.

Next steps: Continue identifying more patients at the Ottawa site as well as in other sites to increase the amount of data. Aiming at publishing the results early Winter 2006.

Anyone interested in participating, please send an e-mail to:

lbeique@ottawahospital.on.ca

Jan 2006: Approximately 8 patients have been identified at the Ottawa Hospital site. The project will be revisited at the next CHAP meeting to increase the participation of other sites.

- **Project: NRTI Research Project**

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

Sept 2005: Two sites have expressed interested in participating in this study (Alice and Calgary). Christine is currently writing up the proposal and should have it ready in the next couple of weeks.

Jan 2006: The Northern Alberta Program has ethics approval to conduct two studies. Sites interested in participating can contact Christine Hughes.

- 1) Outcomes with tenofovir and didanosine backbones
- 2) Outcomes with abacavir/didanosine or tenofovir/abacavir backbones

- **Project: Clinical experience in the usage of Kaletra in pregnancy**

Contact: Jinell MahMing (Jinell.MahMing@CalgaryHealthRegion.ca)

Jan 2005: To date only two sites have expressed interest in this study (Northern Alberta Clinic in Edmonton, and Oak Tree Clinic in Vancouver). It is not certain whether the study will go ahead as the sample size may be too small, but there are plans to at least start a proposal and study design in the event that it is decided to pursue this project in the future.

Feb 2006: Unfortunately I have nothing to report. I think I will present my Kaletra in pregnancy idea again in the future (a few years from now), to see if more interest could be generated. Jinell

II. RECENT PUBLICATIONS

Strategies to prevent mother-to-child transmission of HIV.

Current Opinion in Infectious Diseases. 19(1):33-38, February 2006.

McIntyre, J.

Immune reconstitution inflammatory syndrome in HIV.

Current Opinion in Infectious Diseases. 19(1):20-25, February 2006.

Lipman, M, Breen, R.

Management of hepatitis C/HIV coinfection.

Current Opinion in Infectious Diseases. 19(1):8-13, February 2006.

Rockstroh, JK.

Tenofovir-Associated Acute and Chronic Kidney Disease: A Case of Multiple Drug Interactions.

Clinical Infectious Diseases 2006;42:283-290.

Zimmermann AE, Pizzoferrato T, Bedford J, et al.

Assessment of Drug-Drug Interactions Between Tenofovir Disoproxil Fumarate and the Nonnucleoside Reverse Transcriptase Inhibitors Nevirapine and Efavirenz in HIV-Infected Patients.

JAIDS Journal of Acquired Immune Deficiency Syndromes. 41(1):37-43, January 1, 2006.

Droste, JA, Kearney B, Hekster Y, et al.

Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy.

AIDS. 20(1):59-66, January 2, 2006.

Suy A, Martinez E, Coll O, et al.

Bone Disease and HIV Infection

Clinical Infectious Diseases 2006;42:108-114.

Amorosa V, Tebas P.

Determinants of HIV drug resistance mutations in plasma virus after treatment interruption.

AIDS. 19(18):2174-2175, December 2, 2005.

Chilton D, Dervisevic S, Pillay D, et al.

Protease inhibitor-based HAART, HDL, and CHD-risk in HIV-infected patients.

Atherosclerosis 2006;184:72-77.

Asztalos BF, Schaefer EJ, Horvath KV, et al.

Withdrawal of Pneumocystis jirovecii prophylaxis in HIV-infected children under highly active antiretroviral therapy.

AIDS. 19(18):2103-2108, December 2, 2005.

Urschel S, Ramos J, Mellado M, et al.

Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV.

N Engl J Med 2006 Jan 19 ;354(3) :251-60.

Gallant JE, DeJesus E, Arribas JR, et al.

A direct comparison of drug susceptibility to HIV type 1 from antiretroviral experienced subjects as assessed by the antivirogram and PhenoSense assays and by seven resistance algorithms.

AIDS Res Hum Retroviruses. 2005;21:933-9.

Ross L, Boulme R, Fisher R, Hernandez J, et al.

Bone quality in perinatally HIV-infected children: role of age, sex, growth, HIV infection, and antiretroviral therapy.

AIDS Res Hum Retroviruses. 2005;21:927-32.

Rosso R, Vignolo M, Parodi A, Di Biagio A, et al.

Relationship between osteopenia, free testosterone, and vitamin D metabolite levels in HIV-infected patients with and without highly active antiretroviral therapy.

AIDS Res Hum Retroviruses. 2005;21:915-21.

Ramayo E, Gonzalez-Moreno MP, Macias J, Cruz-Ruiz M, et al.

The potential for interactions between antimalarial and antiretroviral drugs.

AIDS. 2005;19:995-1005.

Khoo S, Back D, Winstanley P.

Nevirapine plasma exposure affects both durability of viral suppression and selection of nevirapine primary resistance mutations in a clinical setting.

Antimicrob Agents Chemother 2005;49:3966-9.

Gonzalez de Requena D, Bonora S, Garazzino S, Sciandra M, et al.

Coinfection with HIV and Hepatitis C Virus and Immune Restoration During HAART.

Clin Infect Dis 2006;42:298-9.

Manfredi R.

HIV-Associated Lipoatrophy: What Are the Kinder, Gentler Agents?

Clin Infect Dis 2006;42:281-2.

Dube MP.

Body Fat and Other Metabolic Effects of Atazanavir and Efavirenz, Each Administered in Combination with Zidovudine plus Lamivudine, in Antiretroviral-Naive HIV-Infected Patients.

Clin Infect Dis 2006;42:273-80.

Jemsek JG, Arathoon E, Arlotti M, Perez C, et al.

Do Type and Duration of Antiretroviral Therapy Attenuate Liver Fibrosis in HIV-Hepatitis C Virus-Coinfected Patients?

Clin Infect Dis 2006;42:262-70.

Verma S, Wang CH, Govindarajan S, Kanel G, et al.

The role of zidovudine in development of lipoatrophy.

AIDS Read 2005;15:591-4.

Moyle GJ.

Interaction Between Atazanavir and Fosamprenavir in the Treatment of HIV-Infected Patients.

J Acquir Immune Defic Syndr 2006;41:124-5.

Khanlou H, Bhatti L, Farthing C.

Clinical validation of atazanavir/ritonavir genotypic resistance score in protease inhibitor-experienced patients.

AIDS 2006;20:35-40.

Vora S, Marcelin AG, Gunthard HF, Flandre P, et al.

Emtricitabine, a New Antiretroviral Agent with Activity against HIV and Hepatitis B Virus.

Clin Infect Dis 2006;42:126-31.

Saag MS.

Preventing HIV infection.

BMJ 2005;331:1285-6.

Jones R, Gazzard B, Halima Y.

Steady-State Pharmacokinetics and Tolerability of Indinavir-Lopinavir/R Combination Therapy in Antiretroviral-Experienced Patients.

Therapeutic Drug Monitoring. 27(6):779-781, December 2005.

Antonioni T, Tseng AL, van Heeswijk R P G, Walker S E, et al.

Pharmacogenetics of long-term responses to antiretroviral regimens containing Efavirenz and/or Nelfinavir: an Adult Aids Clinical Trials Group Study.

J Infect Dis. 2005 Dec 1;192(11):1931-42.

Hass DW, Smeaton LM, Shafer RW, et al.

Impact of Efavirenz on Neuropsychological Performance and Symptoms in HIV-Infected Individuals.

Ann Intern Med 2005 November 15;143(10):714-21.

Clifford DB, Evans S, Yang Y, et al.

Abacavir and Lamivudine Fixed-Dose Combination Tablet Once Daily Compared With Abacavir and Lamivudine Twice Daily in HIV-Infected Patients Over 48 Weeks (ESS30008, SEAL).

JAIDS Journal of Acquired Immune Deficiency Syndromes. 40(4):422-427, December 1, 2005.

Sosa N, Hill-Zabala C, DeJesus E, et al.

Safety of Enfuvirtide in Combination With an Optimized Background of Antiretrovirals in Treatment-Experienced HIV-1-Infected Adults Over 48 Weeks.

JAIDS Journal of Acquired Immune Deficiency Syndromes. 40(4):413-421, December 1, 2005.

Trottier B, Walmsley S, Reynes J, et al.

Prediction of Neuropsychiatric Adverse Events Associated with Long-Term Efavirenz Therapy, Using Plasma Drug Level Monitoring.

Clin Infect Dis 2005;41:1648-1653.

Gutierrez F, Navarro A, Padilla S, et al.

Dose-dependent influence of didanosine on immune recovery in HIV-infected patients treated with tenofovir.

AIDS. 19(17):1987-1994, November 18, 2005.

Karrer U, Ledergerber B, Furrer H, et al.

New paradigms in the management of HIV and hepatitis C virus coinfection.

Current Opinion in Infectious Diseases. 18(6):550-560, December 2005.

Soriano V, Martin-Carbonero, L, Maida I, et al.

Host determinants of antiretroviral drug activity.

Current Opinion in Infectious Diseases. 18(6):543-549, December 2005.

Boffito M, Winston A, Owen A

Stability of transmitted drug-resistant HIV-1 species.

Current Opinion in Infectious Diseases. 18(6):537-542, December 2005.

Cane, Patricia A

Does Exposure to Antiretroviral Therapy Affect Growth in the First 18 Months of Life in Uninfected Children Born to HIV-Infected Women?

JAIDS Journal of Acquired Immune Deficiency Syndromes. 40(3):364-370, November 1, 2005.

European Collaborative Study

Once-Daily Regimen of Saquinavir, Ritonavir, Didanosine, and Lamivudine in HIV-Infected Patients With Standard Tuberculosis Therapy (TBQD Study).

JAIDS Journal of Acquired Immune Deficiency Syndromes. 40(3):317-323, November 1, 2005.

Ribera E, Azuaje C, Lopez R, et al.

Structured Treatment Interruptions in Primary HIV-1 Infection: The ANRS 100 PRIMSTOP Trial.

JAIDS Journal of Acquired Immune Deficiency Syndromes. 40(3):307-316, November 1, 2005.

Hoен B, Fournier I, Lacabaratz, C, et al.

Lopinavir/Ritonavir as Single-Drug Therapy for Maintenance of HIV-1 Viral Suppression: 48-Week Results of a Randomized, Controlled, Open-Label, Proof-of-Concept Pilot Clinical Trial (OK Study).

JAIDS Journal of Acquired Immune Deficiency Syndromes. 40(3):280-287,

November 1, 2005.

Arribas J, Pulido F, Delgado R, et al.

The Impact of Anemia on Energy and Physical Functioning in Individuals with AIDS.

Arch Intern Med 2005;165:2229-2236.

Semba RD, Martin BK, Kempen JH, et al.

Management of Newly Diagnosed HIV Infection.

N Engl J Med 2005;353(16):1702-10.

Hammer SM.

Randomised Study of the Safety and Efficacy of Fish Oil (Omega-3 Fatty Acid) Supplementation with Dietary and Exercise Counseling for the Treatment of Antiretroviral Therapy-Associated Hypertriglyceridemia.

Clin Infect Dis 2005;41:1498-1504.

Wohl DA, Tien HC, Busby M, et al.

Nontuberculous Mycobacterial Immune Reconstitution Syndrome in HIV-Infected Patients: Spectrum of Disease and Long-Term Follow-up.

Clin Infect Dis 2005;41:1483-97.

Phillips P, Bonner S, Gataric N, et al.

A Randomized Study of the Use of Fluconazole in Continuous versus Episodic Therapy in Patients with Advanced HIV Infection and a History of Oropharyngeal Candidiasis: AIDS Clinical Trials Group Study 323/Mycoses Study Group Study 40.

Clin Infect Dis 2005;41:1473-80.

Goldman M, Cloud GA, Wade KD, et al.

Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides.

AIDS. 19(16):1807-1818, November 4, 2005.

Dube MP, Parker RA, Tebas P, et al.

Timing of maternal and neonatal dosing of nevirapine and the risk of mother-to-child transmission of HIV-1: HIVNET 024*.

AIDS. 19(16):1857-1864, November 4, 2005.

Chi BH, Wang L, Read J, et al.

Evaluation of the Drug Interaction between Rifabutin and Efavirenz in Patients with HIV Infection and Tuberculosis.

Clin Infect Dis 2005;41:1343-49.

Wiener M, Benator D, Peloquin CA, et al.

The Relationship between Nucleoside Analogue Treatment Duration, Insulin Resistance, and Fasting Arterialized Lactate Level in Patients with HIV Infection.

Clin Infect Dis 2005;41:1335-40.

Lo JC, Kazemi MR, Hsue PY, et al.

Intermittent Episodes of Detectable HIV Viremia in Patients Receiving Nonnucleoside Reverse-Transcriptase Inhibitor-Based or Protease Inhibitor-Based Highly Active Antiretroviral Therapy Regimens Are Equivalent in Incidence and Prognosis.

Clin Infect Dis 2005;41:1326-32.

Sungkanupraph S, Overton ET, Seyfried W, et al.

The influence of hepatitis C virus-human immunodeficiency virus co-infection on the appearance of liver enzyme elevation in people on high activity antiretroviral treatment.

European Journal of Internal Medicine 2005;16:405-407.

Olalla J, Rubio R, Costa JR, et al.

Liver Injury and Changes in Hepatitis C Virus (HCV) RNA Load Associated with Protease Inhibitor-Based Antiretroviral Therapy for Treatment-Naïve HCV-HIV-Coinfected Patients:Lopinavir-Ritonavir versus Nelfinavir.

Clin Infect Dis 2005;41:1186-95.

Sherman KE, Shire NJ, Cernohous P, et al.

III. CHAP CORRESPONDENCE

CHAP Correspondence Sept 2005-Jan 2006

TOPICS Discussed

- 1. Herbals and Vitamins**
- 2. Emtriva**
- 3. CMV Gastritis and CMV Pneumonitis**
- 4. ATV/RTV and Clarithromycin drug interaction**
- 5. Case studies on Drug interactions/CSHP PPC**
- 6. IV Septra for PCP with hemodialysis**
- 7. Tenofovir dosing in renal insufficiency**
- 8. Antiretroviral resistance assays**
- 9. Protocols**
- 10. Boosted ATV, when used with TNF and EFV**
- 11. Garlic Interaction**
- 12. Birth Control and Nevirapine**
- 13. Kaletra Liquid and Taste**
- 14. Neonates and PEP**
- 15. Double Boosted PIs**
- 16. Nutrition**
- 17. Fuzeon Biojector**
- 18. Pharmacotherapy Dec 2005**
- 19. Regimen Suggestions**

RE: Herbals and vitamins (from Michelle Foisy)

This is a recurring question.

I am wondering which herbals you are not recommending in pts with HIV on ARVs. Based on reading and the Natural Products database the following list is what I have come up with. I am not sure that I find the CATIE book all that useful- a few good points.

Avoid with PIs and NNRTIs:

Vitamin C (> 1g/d)- avoid with all PI and NNRTIs to play it safe (14% decrease IDV AUC)

Garlic- 50% decrease SQV AUC; low doses did not affect RTV AUC

St. John's Wort- 57% decrease IDV AUC

Echinacea- may increase HIV viral production; may inhibit 3A4 (but this is not a bad thing in my opinion)

Ginkgo- may induce or inhibit 3A4

Caution:

Black cohosh- may inhibit 3A4- increase toxicity of ARVs

Ginseng- may inhibit 3A4

Any others or comments?

What are you recommending about vitamin A and other vitamins in pregnant and nonpregnant patients? See below. Also see forwarded papers. I have not reviewed all the literature out there and thought some keener out there may have addressed this issue already.

AIDS Res Ther. 2005 May 6;2(1):4. Related Articles, Links

Vitamin supplementation for prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of randomized trial including more than 2800 women.

Mills EJ, Wu P, Seely D, Guyatt GH.

RE: Emtriva

Has anyone been able to access this for a patient?? One of our docs wants to use emtricitabine for a pt that has no other nuke options (ie resistant to many nukes including 3TC but not this agent-which seems strange??)

Kathy Slater

As far as I know, the M184V and K65R mutations are the main ones that confer resistance (and cross resistance) to emtricitabine and 3TC. Do you know the mutations that this patient had that would confer resistance to 3TC, but not emtricitabine?

Lizanne

p.s. I have never looked into getting emtricitabine...

Hi Lizanne-Michelle asked the same question, I can't recall but I will check when I go back up to clinic-to me doesn't make sense!!!!

K

RE: CMV Gastritis and CMV Pneumonitis

Have any of you had patients treated with valganciclovir for CMV gastritis, and CMV pneumonitis? (both conditions are in two separate patients) if so, what was the dose, and duration of treatment? Was the patient put on maintenance therapy afterwards? and if so, for how long? any info you can share with me, would be most helpful and appreciated. (Jinell)

Have used valganciclovir for CMV GI disease (colitis, esoph ulcers, esophagitis) and presumed CMV pneumonitis (no tissue bx but pulmonary infiltrates with CMV antigen in pulmonary secretions). Used 3 weeks induction treatment doses (ie. 900mg BID) in both cases with success...have left one patient with pretty severe CMV colitis (and presumed CMV cholangiopathy, ALP 800-1000) on maintenance therapy (900mg daily) after induction for one month...so far he's ok.
(Deborah Y)

Have you taken a look at the Canadian consensus guidelines for the management of CMV in HIV/AIDS? They are published in the Can J Infect Dis Med Microbiol 2004;15(6):327-335.

I can tell you that we have treated pts with CMV GI disease for 3 weeks with induction dosing of valganciclovir. We do not put pts routinely on maintenance therapy afterwards.
(Linda A)

For CMV colitis 3-4 weeks of valGCV at induction doses is something we have used a couple times, although it is not covered readily under Alberta Blue Cross (Social Services) for this indication. Ophthalmic CMV should be ruled out again at the end of induction. You may also opt to keep the pt on maintenance for a period of time (no fixed rule) if symptoms persist after induction or if starting HAART at the same time (possible CMV immune reconstitution syndrome if off GCV).
(Michelle)

Hmmm... funny you should mention this. Just yesterday we started a patient on valganciclovir 900 mg bid x 21 days for documented CMV esophagitis (significant ulceration), with suspected lower GI involvement also. Interestingly, this is for a patient with CD4 200!

Anyway, our plan is to treat for 3 wks at full dose, then repeat endoscopy to determine whether any additional therapy is needed. We felt comfortable using oral therapy since he doesn't have any significant reason to suspect poor absorption. We haven't really discussed the issue of maintenance therapy (which is controversial for GI CMV, from my understanding), particularly since the pt's CD4 count is already higher than we would expect for CMV. (Also of interest, he developed PCP in the spring when his CD4 was >250).

This guy also has documented HSV from the esophageal biopsy too. For now, we've continued his Famvir for this... what do you all think about that?

The OI treatment guidelines make very spare mention of CMV esophagitis, colitis or pneumonitis. They basically say treat for 21-28 days or until sx's resolve, preferably with IV therapy if GI symptoms are significant to suspect poor absorption. They also comment that some clinicians would reserve therapy unless disease is mod-severe, or not responsive to treatment for other pathogens (for pneumonitis).

I'll keep you posted on how our patient turns out, and would appreciate hearing updates on yours also.
(Debbie K)

Thank you everyone for all of your clinical input.

I did a medline search which generated very little information for treatment of invasive CMV in HIV infected patients. Our one pxt with the gastritis received IV GCV X 21 days, then stepped down to maintenance ValGCV (VL=4 million, CD4=0), but has been on HAART X 1 month and is now VL=25,000 CD4=8. Like Michelle mentioned, we will wait for the CD4 to go up to 40-50 before stopping (this pxt has multiple complications, and seems very ill).

Our other pxt with the pneumonitis is just discharged out of hosp, and got ValGCV 900mg BID, and I am still waiting for the discharge summary to all details and lab. In Alberta, ValGCV is only covered if pxt has the retinitis. So I will have to see if I can get it covered for these patients (Michelle, have you had success?).

Thanks again! (Jinell)

The same goes for Ontario that valGCV is only covered for CMV retinitis. I have written letters in the past for limited duration ie. to complete a 3 week course and had no problem. No experience with requesting for a longer duration in the case of maintenance for CMV colitis (we got lucky and there was suspicion of CMV retinitis as well.) (Deborah Y)

My only comment would be that GCV usually has good HSV coverage if I am not mistaken- may not need Fam on board as well (duplication of therapy)- look inot this further. Our patient with CMV coliits also had higher than expected CD4 counts (150)- not on therapy. Goes to show you they don't always follow the rules.
(Michelle)

Ganciclovir and acyclovir have comparable anti-HSV activity. You should be able to D/C the famciclovir. (Tony)

RE: ATV/RTV and Clarithromycin drug interaction

Do any of you have any info on boosted ATV/RTV and clarithromycin dosage adjustment?

All the reading I have done says to decrease clarithromycin 500mg BID by 50% as the AUC of Clarithro increases to 94% with unboosted ATV. And that ATV's AUC increases by 28%. Interestingly, the AUC and CMAX of the 14-OH Clarithro metabolite is decreased by 70%, and 72%, but Cmin increases by 124%. I have left two messages with the medical line at BMS yesterday, but no response. Any extra info or clinical experience would be greatly appreciated.

Thanks, Jinell

From the literature standpoint, I am not aware of any newer interaction report than the one you talked about (in unboosted).

From a clinical standpoint, I believe that this interaction is not any worse than the one with any other boostep PI. The only difference may be one of safety for ATV as there may be a risk for additional heart conductivity toxicity. Quite frankly, in clinic, I don't do anything about this interaction.

What are others doing ? (Pierre g)

Most of the time in BC when we have MAC patients who is prescribed atazanavir, we are switching their clarithromycin to azithromycin.

(Linda)

RE: Case studies on Drug interactions/CSHP PPC

I will be doing a session at CSHP's PPC this Feb on managing HIV drug interactions. In order to try to spice up this pretty dry topic, I'd like to take a case-based approach. If anyone has any interesting cases they can share that you don't mind me using (I'll acknowledge your contribution at the talk), I'd love to get them! I'm planning to focus more on interactions between antiretrovirals and non-HIV meds since most of the audience will not have an expertise in HIV.

Thanks in advance!!

(Debbie K)

I have a great case-very unfortunate though!!! I had a gentleman on Combvir/Sustiva (ARV naive prior to this) and was PPD postive so we

started him on INH. He consistently had high viral loads and his T-cells were not budging so we had many many adherence chats with him as his baseline genotype indicated that he was sensitive to all agents. Finally the gloves were off and we accused him of totally "snacking" on his pills. Turns out after physical review of his other medications that his community pharmacist had filled the isoniazid with rifampin!!!!!!!!!!!!!! ("didn't really see the big deal-isn't it a TB drug too??") Good grief, anyhow the other big issue is that our pts usually get their antiretrovirals from our outpatient hospital pharmacy but even though I give them a copy of their calendar to share with their community pharmacist this doesn't always happen. It wouldn't have mattered in this case though as the pharmacist filled the Rx as isoniazid (in computer) but put rifampin in the bottle!!!!

So really 2 issues here!!!

You can just make up the numbers Deb for Tcells and Viral load etc
(Kathy S)

Eek!! I guess you lost the NNRTI's for that patient after that...

Very unfortunate. Thanks for the case, Kathy. (Deb K)

Yes we did !!!!!!!!!!! Very unfortunate (K S)

We have a teenager who drank vodka at lunch with some of her classmates (Now suspended, of course). She was the only one who passed out. I was wondering if her exaggerated response was from a drug interaction with the abacavir she is taking. Having alot of "adolescent issues" (to put it mildly) in our clinic recently, I now have profound respect for health care providers that work in Adolescence focused clinics!!!!

(Natalie D)

There was also an interesting case report published earlier this year about a potential drug interaction between EFV-Phenytoin. For some reason, I cannot access the online journal right now, but let me know if you

would like me to try again later and e-mail you the article:

Robertson SM et al. A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. CID 2005; 41: e15-8.

There are also of course the infamous St John's Wort- and garlic- drug interactions...

(Lizanne)

I like the valproic acid/AZT interaction as well. I know Tony et al had written a case report on this. We have also seen it in a couple patients...

(Christine)

RE: IV Septra for PCP with hemodialysis

We have a 16 year patient (45 Kg) who requires IV Septra for PCP. He requires hemodialysis for his end stage renal disease creatinine 550 (71-133) and BU 20 (3-7). Using the dose of 5 mg/kg/dose IV q 6h (20 mg/kg/day divided q6h) with normal renal function, I would give 5 mg/kg/dose IV q24h (to be administered after dialysis). (The method of extending the interval as the creatinine clearance diminishes). The other

option would be to give 10 mg/kg/dose IV q48h after dialysis Monday, Wednesday and Friday. He has cardiac complications so I want to avoid large doses (requiring large infusion volumes). Micromedex uses 15-20 mg/kg/day for normal renal function and 15-20 mg/kg/dose for hemodialysis. This dosing regimen is not repeated in other pediatric references (Pediatric Dosage Handbook, Harriet Lane, Stanford (adult), so I have no confidence with this. Dec 2004 MMWR Opportunistic Inf

The adult Opportunistic Infections Treatment guidelines (Dec 2004) have these guidelines for renal impairment which I interpret as 7 - mg/kg/dose IV after dialysis Monday, Wednesday & Friday. This would fall in line with my 5 mg/kg/day(given after dialysis) or 10 mg/kg/dose IV q48 (given after dialysis)
(Natalie D)

RE: Tenofovir dosing in renal insufficiency

It would be very beneficial for me to use tenofovir in a salvage regimen for one of my patients whose CrCl is 48ml/min. I found a review article on Tenofovir dosing in renal insufficiency by Deeks and they gave a table of suggested dosing reductions based on renal function. The product monograph, however still states that we shouldn't use it in pts. with CrCl<60. I just wondered what everyone's opinion is on this and what you are doing in your clinics.(Michelle and Alice, maybe this is addressed in your new handbook, but I haven't got my copy yet! My rep is coming next week but I'll thank you both in the meantime for your hardwork on updating such a great reference!)

(Linda Robinson)

You can adjust the dose. I've attached the most recent product info with suggested dosage modifications. (Tony)

I've always wondered about the clinical significance of alcohol/abacavir interaction. Anyone else seen any suspected cases? (Deb K)

RE: Antiretroviral resistance assays

I am in the process of creating a CE module on " Understanding and Interpreting Anitretroviral Resistance" to be presented at CANAC in April. Are there any centres in Canada that are using a resistance assay other than the vircoTYPE HIV-1 report? I've heard that Quebec may be using something different. How about other provinces? I'd like to make sure I make reference to all commonly used assay reports in this Canadian module so all attendees and users can get some practical information from the module.

Thank you so much!
(Linda Robinson)

We use Trugene here in Edmonton. (Christine)

Here in BC we use the vircoTYPE HIV 1 report run by the virology lab at the Centre for Excellence in HIV/AIDS at St. Paul's Hospital. (Dom)

A useful directory for finding websites

<http://www.virology.net/garryfavwebaids.html>

Michelle

RE: Protocols

Just thought I would share these with others.... Feel free to adapt to your centres if you wish.

If your programs have developed protocols, pre-printed orders,,,etc.... it would be great to share.

Please find attached the final HIV treatment guidelines. We have incorporated all feed-back as much as possible.

Of note, these do not serve as 'pre-printed orders' and we are unable to write prescriptions that say 'as per protocol'. They are merely guidelines in assisting to arrange therapy and prescribe treatment for more complex drugs.

Thanks for you input- much appreciated. If there are other types of guidelines you would like the have developed, please let us know.

1) IV pentamidine (including the IV Drug Manual Monograph)

2) IV ganciclovir (including the IV Drug Manual Monograph)

3) aerosolized pentamidine

4) Septra desensitization (including the Pharmacy Dept Guidelines for dosing the drug)

Michelle

Thanks, Michelle for sharing the protocols. It is always so nice to not have to re-invent the wheel or to at least have a starting place. As I've been working on a resistance project, I've come across some interesting web pages and will forward them to the group as we go, just in case someone finds them useful. The link below is very interesting as a resistance consultation panel reviews and gives opinions on cases. Kind of interesting and fun to work through. I also have recently revamped PEP protocols if anyone would like them. The ER risk assessment page is capable of electronic transmission but samples of the pharmacy protocol and the Rx form need to be faxed. If anyone is interested, please contact me with your fax number and I'll send all components along.

My email is lrobin@wrh.on.ca. We've also recently re-written hospital P&P for HIV+moms and babies and it is going to P&T next month for final approval. I can share those as well if anyone is interested.

Thanks,
(Linda Robinson)

P.S. Does anyone have a good article or reference that gives an amount of time after an immunization such as the influenza vaccine that one can expect a transient rise in

the viral load? I found one reference with kids that said 6 to 8 weeks. I found many for adults that discuss the transient rise but not in any time frame. Does something exist? or is this an empirical judgement. Just thought it might be worth asking in case anyone else has had to look this up.

http://www.ucsf.edu/hivcntr/Clinical_Resources/R_Cases.html

Hi Linda:

I'd be interested in the mom-baby protocols that you're putting through P&T. Here's a link to ours that are posted on our website.

<http://www.bcwomens.ca/Services/HealthServices/OakTreeClinic/ClinicalGuidelines.htm>

(Dom)

RE: Boosted ATV, when used with TNF and EFV

Just wondering if anyone could share some wisdom on a boosted atazanvir dose when used in combination with tenofovir and efavirenz as part of a multidrug regimen in a heavily treated patient. Individually we would use the 300/100 boosted but would this be adequate when all three are combined? I have seen references for a 400/100 boosted dose with efavirenz. We do not do any TDM for antiretrovirals, so I am a little concerned about what this higher dose would do to the tenofovir.

Thanks

Jennifer

We routinely give 400/100 when combined with tfv and efv, especially in experienced pts when you are aiming for 'boosted' atv.

(Linda R)

We do the same here as Linda in Windsor. We have been using ATV/r + EFV quite a lot here (in NRTI-intolerant patients as well as experienced patients) +/- TDF. We tend to have a low threshold to increase the dose of ATV to 400.

I did not experience any serious problem with that approach except for one patient. This patient was put on ATV/r 400/100 + NVP and unfortunately developed a Steven's Johnson syndrome after 4 weeks of Tx. We then switched from NVP to EFV after the reaction was resolved and the patient developed jaundice while on the same ATV dosing regime. It looks like EFV did not induce as much ATV metabolism than NVP... We dropped ATV dose to 300mg and jaundice resolved... Does anyone have any similar cases ? (Pierre)

I would also suggest to go with ATV400/r100 mg od, but monitor for renal toxicity of tenofovir. When given with ATV400/r100, TDF levels increase by about 65%. This may be different in the presence of EFV (no info as far as I know), but the levels may still be higher than normal.

I think if your goal is to go with levels of boosted ATV, it would be preferable to go with ATV 400/r100. If ATV400/r100 + TDF + EFV are given together, the ATV levels will likely be between those of ATV400 mg od and ATV300/r100, my guess would be closer

to ATV300/r100. With EFV, you will get levels similar to those of ATV300/r100, and the levels may be further decreased slightly by TDF.

If you were to go with ATV 300/r100 + TDF + EFV, the ATV levels will be decreased by about 25% (vs. ATV300/r100 without TDF) because of TDF and on top of that, you would have the decrease in ATV levels caused by EFV. My guess is that the levels then would still be between those of ATV 400 and ATV300/r100, although probably closer (likely above) to those of ATV 400.

This is obviously very theoretical and some of the data are based on healthy volunteers, not HIV+ pts. (Lizanne)

I had one patient on atazanavir (usual boosted) + efavirenz + tenofovir - we sent levels to BC as he was slightly viremic. He is a very big guy and the levels came back low (both atazanavir and ritonavir was not really detected) - BC recommended titrating the dose to 400/200 - he is doing well however we have not repeated the levels. I think BC is using a fair bit of 400/100 and even 200 but maybe Linda can comment..

(Christine)

Yes. We are using 400/100 and 400/200....but, this is usually based on levels. (Linda A.)

In Calgary, we are continuing with ATV 300/RTV 100mg with Tenofovir and Efavirenz. We do not have access to TDM, however, our pxts on this regimen have remained virologically suppressed. (Jinell)

RE: Garlic Interaction

Hello All - I have been asked by the dietician working with the HIV patient population at our hospital to provide information related to garlic interaction with antiretrovirals. What advice do you provide to patients on antiretrovirals, related to garlic ingestion (supplements or food source) specifically? Thanks!

Anita Richard

CATIE has a little information sheet on this for patients in the herbal book they have....
http://www.catie.ca/herb_e.nsf

A few cooked cloves should not cause major interactions.

I would avoid garlic supps in patients who are PI monotherapy or NNRTIs.

It is likely ok with boosted PIs, but I am unaware of any data to support this. As such I would avoid supps in patients on PIs or NNRTIs to play it safe.

(Michelle)

Our practice is similar to what Michelle suggests. We counsel on avoiding garlic supplements with both NNRTI and PI regimens (boosted and unboosted), but using garlic in cooking is acceptable (used in moderation up to 2 cloves per day).

(Jinell)

If I recall correctly, the data on the interaction b/w SQV and garlic involved supplements providing the equivalent of 8g of garlic daily; 8g amounts to two big fat cloves of fresh garlic. (Jeff)

RE: Birth Control and Nevirapine

My apologies if this has been asked before. Just curious what everyone is recommending for patients who are taking ARVs (e.g. nevirapine) and who want to use birth

control. I know the standard recommendation is to use another form of birth control however I don't find this is readily accepted by many of our patients.

Anyone using

Depo-Provera? I can't find any specific information with nevirapine although there is some data to support lower levels with rifampin...

Christine

Cohn et al presented an abstract at CROI 2005 (Abs 82). 13 HIV+ women were taking NVP + Depo-provera. As per the levels of progesterone that were measured q2weeks, they concluded that there no ovulation occurred over 12 weeks. They found a statistically significant increase in exposure to NVP, but unlikely clinically significant (AUC 10.48 vs. 11.14ngXh/mL). I think they were planning on measuring plasma concentrations of depo-provera. Perhaps they presented the results at a subsequent conference, but I am not sure. Based on this, it would seem ok to give the two drugs together. (Lizanne)

We do have a few women on Depo, but generally not widely accepted due to side effects (bloating, weight gain, spotting, mood changes). There's also a recent concern of decreased bone density secondary to progesterone. We have a few women on OCs with at least 30 mcg of estrogen while on ARVs. We've recently explored the option of the NuvaRing (vaginal ring with estrogen and progesterone), the patch and most recently even the Mirena IUD (have not recommended the IUD to any patients yet).

Unfortunately, the data on these newer delivery systems is very limited in the HIV/ARV patient. Of course, we also recommend a barrier method in addition.

I'd be interested to hear what others are doing? (dom)

We are also avoiding Depo-Provera due to the concerns about reduced BMD and fractures. We don't have any experience with the newer forms of BC yet... seems when we explain the concerns about DI for oral contraceptives and osteoporosis for Depo-Provera, the couple of ladies we've had have been more convinced to use condoms (I think one may also have gotten a diaphragm too, but I can't remember for certain). (Deb K)

RE: KALETRA LIQUID and TASTE

I am wondering if Kaletra oral liquid can be mixed with Ensure or Choc. Milk (like liquid ritonavir)? What is the stability? I have not seen any info on this.

Any other tips for increased palatability?

We have an adult patient on it in the hospital.

Michelle

I don't know about the stability of Kaletra and other liquids, but I can't imagine that it's a problem if it's consumed right away. I saw this post on 'The Body' this summer, which I've copied below. (I don't know about the Marinol suggestion.) We are giving our patients Reese's peanut butter cups when they are 'sampling' Kaletra liquid for the first

time in the clinic. The problem seems to be the aftertaste...very bitter. A patient told one of our pharmacists (Junine Toy) that Altoids peppermints (in the red tin) worked wonders for him. (Linda A).

Aug 22, 2005

i take the liquid form of kaleta the taste of is so bad that I'm considering changing to something else but i have few options left and i don't tolerate the the pill form at all it really messes with my stomach is there anything i can do about the taste any suggestions would be helpful thanks very much

Response from Dr. Henry

The last time I taste sampled that liquid it tasted like cherry flavored diesel fuel. There is a new pill formulation of Kaletra under development so that might help some. Patients tell me that drinking the Kaletra after taking a drink of dense chocolate milk, chocolate syrup, or after eating a peanut butter sandwich helps sometimes. Marinol sometimes seems to help some patients.KH

Here is my patient pamphlet with all the suggestions. I do not have any stability data for mixing and NOT taking immediately. PS When you print the PowerPoint pamphlet, print doublesided and it will align. (Natalie D)

RE: Neonates and PEP

Do you have anymore peds teaching sheets that you can share?

Also, do you have anything specifically on neonatal drug administration (i.e AZT syrup; we are also giving 3TC and nelfinavir tablets to neonates as PEP if their mom has a

VL that is detectable at birth (i.e. > 1000).

Michelle

I have been having some interesting e-mail discussions with Dom and Natalie about ARV prophylaxis in the neonate. Thanks for your input!

Our peds ID group here is prescribing triple therapy (i.e. AZT/3TC/NFV) rather than just AZT for neonates born to moms with higher viral loads (or unknown VL with Hx of non-compliance). This is an extrapolation of adult PEP (where we would use 3 drugs).

I wanted to get your input on what other centres are doing in the neonate? Triple Tx is potentially toxic and difficult to administer in this population.

If you know of any studies, (ongoing, abstracts,,,, etc) please feel free to let us know. Also, who would the peds contact be in Toronto/Montreal? We would like to know what the larger centres are doing.

Thanks

Michelle

Here in Hôpital Ste-Justine in Montréal we are using the triple tx (AZT, 3TC ,NFV) since 1998 . Because of the dose we are given (40 mg/kg/dose) for the nelfinavir, we crush the tablets and make capsules to open for the mother and to mix with peach or pear sauce (easier to give than given with milk or using the powder form of 50 mg/g). And we see the mother and baby every 2 weeks for adjusting the dose with the weight .

An article has been published on june 2005 regarding the " safety and pharmacokinetics of nelfinavir coadministered with AZT and 3TC in infants during the first 6 weeks of life " : J. Acquir Immune Defic Syndr Vol 39 ,Number 2 , June 1 2005 and in this article the author make the conclusion that further investigations of larger doses for nelfinavir ,such as 75 mg/kg twice a day should be undertaken because 1/3 of the infants receiving 40 mg/kg/dose failed to meet the pharmacokinetic target .

In our population over 300 patients since 1998 , 1 patient has been infected . We will wait for the results of larger doses before changing the dose (Marie-France Goyer)

RE: Double boosted PIs

Thought I would take a poll on your favorite double boosted PI combos.

I have a guy who is NRTI and NNRTI resistant and does not wish to use T-20. He has very high lipids (TGs- 35).

- Do you feel a double boosted would be adequate to suppress? (I have really never had to use the PI class alone for therapy)

- Which double boosted regimens are you having good success/ low side-effects with? Of course his lipids are a big concern- I am not sure that including atazanavir in his combo would really help, since it will be boosted, thus losing some of its lipid sparing effects.

Thanks

Michelle

I've done SQV/LPVr, LPVr/ATV, ATV/SQV/r with success as they are all synergistic...although I've not used it, LPVr/IDV also has success (recent pilot study in AIDS 2006; 20:129-131)
(Deborah M. Yoong)

Have you used them alone with no other meds? (Michelle)I have a lot of guys on just dual PI with no nukes or non-nukes. I

most frequently use Kaletra/Invirase, and this has been consistently successful for the guys on it. I have one guy on just Kaletra/IDV, and he's been suppressed for > 2 years. I also have used ATZ/Invirase, usually with ritonavir, but in a couple of guys without, usually to good effect. I've had two guys with blips on this one though, both were getting it with extra ritonavir. Interestingly, the three who are not on extra ritonavir (ie just ATZ/Invirase) are suppressed.

(Tony)

In individuals with total NRTI and NNRTI resistance....the docs aren't comfortable without any nuke on board (even if they are all resistant),

so often it may be just a 3TC thrown in or 3TC+TDF to try to elicit M184V +/- K65R (although most of them have many TAMS so I don't imagine that is helping) (Deborah Y)

RE: Nutrition

We don't have a dedicated dietician for the program. I am wondering if any of your programs have developed the following:

- 1) Nutrition for inner city patients on a tight budget- the CATIE pamphlet is way too detailed**
- 2) Nutrition for HIV patients with lipid disorders**
- 3) Nutrition for HIV diabetic patients**

Michelle

We are very fortunate to have a dedicated HIV dietitian! She's developed a nice tear off sheet that can be given to patients for management of lipid disorders (It should be close to printing soon with a lipid management project we did with BMS)...I will try to send a PDF copy. I will ask her about the others.
(Deborah Y)

RE: Fuzeon Biojector

We have only one patient who is using the Fuzeon biojector, who is complaining of "seeing liquid run down his skin" after he removes the applied pressure from the gun. We have reviewed his technique and he assures us that he is applying pressure with the gun for the suggested 10 seconds and then holding pressure on the site for 1 minute afterwards. My question is, has anyone else had a patient complain of this? My understanding is that there would not be any medication left to "run down the skin" if dispersed properly on injection. However, I only have the one patient and nobody to compare him too. If anyone could share more experience I'd really appreciate it.

**Thanks,
Linda Robinson
Windsor**

The only thing I can think is if he had accidentally left the vial adapter on when he did the injection.....I did that once myself when I was learning the technique (he said sheepishly) (Jeff)

I've not heard of such a problem. Perhaps have pt administer one of the doses under observation & you may find out if he's really using proper technique. It should lie completely level on the skin.

The few of my pt who started on it have switched back to standard method. (Tom)

I agree with Jeff's comment... (Linda Akagi)

RE: Asthma Wan

Hello All - Is anyone familiar with a Chinese medicine called Asthma Wan (which I have been asked to assess potential for interaction with a patient's antiretrovirals)? Nothing in Natural Medicines.

Thanks!

Anita Richard

RE: pharmacotherapy Dec 2005

I believe congratulations are in order for a couple of our CHAP colleagues. Congrats Nancy and Christine on your publications!

Michelle

Chronic Hepatitis C Virus Management: 2000-2005 Update (January)

Christine A Hughes and Stephen D Shafran

Ann Pharmacother published 20 December 2005, 10.1345/aph.1G263

<http://www.theannals.com/cgi/content/abstract/aph.1G263v1?etoc>

Possible Interaction Between Lopinavir/Ritonavir and Valproic Acid Exacerbates Bipolar Disorder (January)

Nancy L Sheehan, Marie-Josée Brouillette, Marie-Soleil Delisle, and James Allan

Ann Pharmacother published 20 December 2005, 10.1345/aph.1G418

<http://www.theannals.com/cgi/content/abstract/aph.1G418v1?etoc>

RE: Regimen suggestions

Happy new year everyone! We have an interesting heavily treated client currently on a regimen of stavudine, abacavir, lamivudine and efavirenz since 1999 (he transferred to us on this regimen from BC, I think). This regimen had been chosen for him based on resistance testing. He does tell us zidovudine had been d/c'd due to resistance. He has many metabolic issues, diabetes (now starting insulin), lipid issues and is very concerned with lipodystrophy. He would like to change (and we agree) his regimen to eliminate stavudine. He is not very receptive to the idea of PIs because of his lipodystrophy, which is a very big concern for him. Cd4 is 455 and viral load is <50 currently. He had wanted to switch the stavudine to tenofovir but we are uneasy with those 3 NRTIs together. We would appreciate any thoughts anyone might have on options for this fellow.

Thanks

Jennifer

Challenging case! If you do not have it already, I would track down his ARV history and resistance test(s) from BC. The NRTI backbones can definitely be a challenge. There is limited data on the possibly "fragile" NRTI backbones such as tenofovir and abacavir when used with a PI or NNRTI. We are planning to look back at our experience as often you are forced into using them together. I would presume in this case he has previous 3TC resistance and it is just on board for viral fitness? I am definitely more leary using the tenofovir/abacavir

combination with an NNRTI (easier to develop resistance). I have used it with a PI (definitely Kaletra and more recently with boosted atazanavir). I don't think we really know about lipodystrophy with atazanavir but certainly much less risk of lipid elevation/diabetes. Again depending on what his NRTI/PI mutations are, I might consider changing efavirenz to boosted atazanavir in this case... (Christine)

As per Christine's comment, if you are lacking any history, I can try and dig some up for you. Linda Akagi
(my direct number is 604-806-9096)

I support Christine's point of view. Depending of your patient's PI experience, I would likely consider switching to ATV (boosted or not). Your patient seems like he has some sort of metabolic syndrome (diabetes, ? lipid elevation, Lipoatrophy). Definitely, I would argue to stop d4T. Adding TDF would not be a must for me if you can make sure to offer a good third agent into the regimen. BMS is doing a study (REAL study) on the potential reversal of lipodystrophy in patients on PI by switching to ATV. The only evidence so far is the case serie of 3 patients with reversed buffalo humps published in AIDS a few years ago. Again, we need to know more on drug history +/- genotyping.
(Pierre)

Thank you everyone for the advice. In answer to Christine's question, yes we do believe the lamivudine is only there for viral fitness. Just dropping the stavudine left us with only two active agents which we were a little uneasy with. We are digging in his file to see if we were sent a copy of his previous resistance testing. His history is as follows: 1990 azt mono; 1992 ddI mono; 1993 azt+ddI; 1993 azt+ddC; 1994 azt+3TC; 1996 azt+3TC+indinavir; 1999 d4T+ddI+abacavir+3TC+efavirenz+hydroxyurea (based on genotyping); 1999 ddI d/c'd GI intolerance; 2003 hydroxyurea d/c'd. Thanks again for your help.
Jennifer