



CHAP Newsletter

Fall 2005



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Many thanks to all those who contributed in the compilation of this newsletter. Thanks to all CHAP participants for submitting and responding to e-mail questions. This type of information sharing makes the group such a valuable resource.

I. RESEARCH PROJECT UPDATES (SEPT. 2005)

Project: Nelfinavir PK Study
Principal Investigator: Nancy Sheehan

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).

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

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

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

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.

Project: Clinical experience in the usage of Kaletra in pregnancy
Contact: Jinell MahMing (Jinell.MahMing@CalgaryHealthRegion.ca)

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.

II. RECENT PUBLICATIONS

1. Manosuthi W, Sungkanuparph S, Thakkinstian A, et al. Efavirenz levels and 24-week efficacy in HIV-infected patients with tuberculosis receiving highly active antiretroviral therapy and rifampicin. *AIDS* 2005; 19(14):1481-1486.
2. Brennan-Benson P, Lyus R, Harrison T, et al. Efavirenz levels and 24-week efficacy in HIV-infected patients with tuberculosis receiving highly active antiretroviral therapy and rifampicin. *AIDS* 2005; 19:1541-1543.
3. Faggian F, Lattuada E, Lanzafame M, et al. Recreational substance use and tolerance of efavirenz in HIV-1 infected patients. *AIDS Care* 2005; 17:908-910.
4. Fairley CK, Permana A, Read TRH. Long-term utility of measuring adherence by self-report compared with pharmacy record in a routine clinic setting. *HIV Medicine* 2005; 6: 366.
5. Rendón AL, Núñez M, Jiménez-Nácher I, et al. Clinical benefit of interventions driven by therapeutic drug monitoring. *HIV Medicine* 2005; 6:360.
6. Back DJ, Burger DM, Flexner CW et al. The Pharmacology of Antiretroviral Nucleoside and Nucleotide Reverse Transcriptase Inhibitors: Implications for Once-Daily Dosing. *J Acquir Immune Defic Syndr* 2005;39 Suppl 1:S1-S23.
7. van Wijk JPH, de Koning EJP, Castro Cabezas M, et al. Comparison of Rosiglitazone and Metformin for Treating HIV Lipodystrophy. *Ann Intern Med* 2005;143:337-46.
8. Bani-Sadr F, Carrat F, Pol S, et al. Risk Factors for Symptomatic Mitochondrial Toxicity in HIV/Hepatitis C Virus-Coinfected Patients During Interferon Plus Ribavirin-Based Therapy. *JAIDS* 2005; 40(1):47-52.
9. Napravnik S, Edwards D, Stewart P, et al. HIV-1 Drug Resistance Evolution Among Patients on Potent Combination Antiretroviral Therapy With Detectable Viremia. *JAIDS* 2005; 40(1):34-40.
10. Morris A, Dobles AR, Cu-Uvin S, et al. Protease Inhibitor Use in 233 Pregnancies. *JAIDS* 2005; 40(1):30-33.
11. Stebbing J, Waters L, Mandalia S, et al. Hepatitis C Virus Infection in HIV Type 1 Infected Individuals Does Not Accelerate a Decrease in the CD4⁺ Cell Count but Does Increase the Likelihood of AIDS-Defining Events. *Clinical Infectious Diseases* 2005;41:906-911.

12. Negredo E, Bonjoch A, Paredes R, et al. Compromised Immunologic Recovery in Treatment-Experienced Patients with HIV Infection Receiving Both Tenofovir Disoproxil Fumarate and Didanosine in the TORO Studies. *Clinical Infectious Diseases* 2005;41:901-905.
13. Ray JE, Marriott D, Bloch MT, et al. Therapeutic drug monitoring of atazanavir: surveillance of pharmacotherapy in the clinic *British Journal of Clinical Pharmacology* 2005; 60: 291.
14. Chinnadurai R, Munch J, Kirchhoff F. Effect of naturally-occurring gp41 HR1 variations on susceptibility of HIV-1 to fusion inhibitors. *AIDS* 2005; 19(13):1401-1405.
15. de Echaguen A, Arnedo M, Xercavins M, et al. Genotypic and phenotypic resistance patterns at virological failure in a simplification trial with nevirapine, efavirenz or abacavir. *AIDS* 2005;19(13):1385-1391.
16. Brown T, Li X, Cole S, et al. Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the Multicenter AIDS Cohort Study. *AIDS* 2005;19(13):1375-1383.
17. Servin-Abad L, Molina E, Baracco G, et al. Liver enzymes elevation after HAART in HIV-HCV co-infection. *Journal of Viral Hepatitis* 2005; 12:429.
18. Storer TW, Woodhouse LJ, Sattler F, et al. A Randomized, Placebo-Controlled Trial of Nandrolone Decanoate in Human Immunodeficiency Virus-Infected Men with Mild to Moderate Weight Loss with Recombinant Human Growth Hormone as Active Reference Treatment. *The Journal of Clinical Endocrinology & Metabolism* 2005; 90:4474-4482.
19. Winston I, Bloch M, Carr A, et al. Atazanavir trough plasma concentration monitoring in a cohort of HIV-1-positive individuals receiving highly active antiretroviral therapy. *Journal of Antimicrobial Chemotherapy* 2005; 56(2):380-387.
20. Antoniou T, Raboud JM, Chirhin S, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Medicine* 2005; 6:284.
21. Imhof A, Ledergerber B, Günthard HF, et al. Risk Factors for and Outcome of Hyperlactatemia in HIV-Infected Persons: Is There a Need for Routine Lactate Monitoring? *Clinical Infectious Diseases* 2005;41:721-728.
22. Farmer Miller M, Haley C, James Koziel M, et al. Impact of Hepatitis C Virus on Immune Restoration in HIV-Infected Patients Who Start Highly Active Antiretroviral Therapy: A Meta-analysis. *Clinical Infectious Diseases* 2005;41:713-720.

23. Torti C, Maggiolo F, Patroni A, et al. Exploratory analysis for the evaluation of lopinavir/ritonavir-versus efavirenz-based HAART regimens in antiretroviral-naive HIV-positive patients: results from the Italian MASTER Cohort. *Journal of Antimicrobial Chemotherapy* 2005 56(1):190-195.
24. Winston A, Boffito M. The management of HIV-1 protease inhibitor pharmacokinetic interactions. *Journal of Antimicrobial Chemotherapy* 2005;56:1-5.
25. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS* 2005;19(11):1183-1188.
26. Gerber J, Rosenkranz S, Fichtenbaum CJ, et al. Effect of Efavirenz on the Pharmacokinetics of Simvastatin, Atorvastatin, and Pravastatin: Results of AIDS Clinical Trials Group 5108 Study. *JAIDS* 2005; 39(3):307-312.
27. Allavena C, Ferre V, Brunet-Francois C, et al. Efficacy and Tolerability of a Nucleoside Reverse Transcriptase Inhibitor-Sparing Combination of Lopinavir/Ritonavir and Efavirenz in HIV-1-Infected Patients. *JAIDS* 2005; 39(3):300-306.
28. Maggiolo F, Ripamonti D, Suter F. Switch strategies in patients on effective HAART. *Journal of Antimicrobial Chemotherapy* 2005;55(6):821-823.
29. Goedken AM. Once-Daily Abacavir in Place of Twice-Daily Administration. *Ann Pharmacother* 2005;39:1302-08.
30. Mirochnick M, Stek A, Acevedo M, et al. Safety and Pharmacokinetics of Nelfinavir Coadministered With Zidovudine and Lamivudine in Infants During the First 6 Weeks of Life. *JAIDS* 2005; 39(2):189-194.
31. Mobius U, Lubach-Ruitman M, Castro-Frenzel B, et al. Switching to Atazanavir Improves Metabolic Disorders in Antiretroviral-Experienced Patients With Severe Hyperlipidemia. *JAIDS* 2005; 39(2):174-180.
32. Fisac C, Fumero E, Crespo M, et al. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine. *AIDS* 2005;19(9):917-925.
33. Brown TT, Cole SR, Xiuhong L, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the Multicenter AIDS Cohort Study. *Arch Intern Med.* 2005;165:1179-1184.

III. CHAP CORRESPONDENCE

Tenofovir Combinations:

I was chatting with Christine about tenofovir combos and was curious to see what you are doing out there. It is becoming increasingly difficult to create new potent regimens both for naive pts (especially if you want once daily regimens) and experienced (who may have a long hx of thymidine analogue exposure and 3TC resistance).

I am especially curious about these ones:

abacavir/ tenofovir

abacavir/ ddI

ddI/ abacavir

ddI/ tenofovir- we are avoiding this now

1) Which nucleoside backbones are you definitely avoiding, vs use only if no other option? (for both naive and experienced pts)

2) Are there some nucleoside backbones you would use only with a potent PI like Kaletra (vs the NNRTIs)?

3) Are any of you adding in AZT or d4T to protect against getting the K65 mutation? What about 3TC to sensitize AZT and tenofovir?

4) Have you seen any recent articles that fully examine these issues? I have come up with tidbits here and there (especially on medscape), but not a good review.

Thanks for any input.

Michelle

From Tony: I have used ABC/TDF either with ATZ/r or Kaletra in some experienced patients with minimal degrees of NRTI and PI resistance (usually a 2nd line regimen). Sometimes I include a thymidine analog to protect against the K65R, but not universally. Interestingly, I just had a patient develop the 65R mutation and he had d4T on board with the TDF.

I use ABC/3TC a lot in naive patients for once daily dosing, prob. more than Combivir now.

For more heavily experienced patients who've burned through several regimens with pan-drug resistance, I don't mind if the 65R mutation ends up emerging, so I'll try using ABC/TDF/3TC with whatever other pills match the patients eyes, or clothes or shoes (just because you'll feel like crap, you don't have to clash with your meds). Since I'm going for immunologic restoration in these patients, I'll try to bring out the mutations that are the most crippling.

Definitely avoiding ddi/TDF for now, but I haven't changed those who are stable on it for now. Generally avoiding ddi/ABC, unless can't get TDF for those with pan-resistance, in which case I might try ddi/ABC to try to select for the 65R mutation.

From Linda Robinson

In Windsor if we want once daily in naive we start with ABC/3TC, mostly because we can't get our hands on TFV readily for ODB patients, otherwise we would probably go with this as well. In a similar vein, if Videx EC was readily available without jumping through Sec 8 hoops, ddi/3TC could be a starting place as well. What will be interesting to see in the future is whether most people start these once day nukes with NNRTI's or once daily PI, as emergence of K65R resulting from a first failed regimen may hypersensitize the virus to EFV. Also of interest is the latest 're-look' at triple nukes, namely TFV/3TC/AZT. From a resistance point of view, with the delay in development of K65R due to the thymidine, plus the 184 V hypersensitizing the virus to TFV as well as reportedly delaying the emergence of TAM's, this combination makes a lot of sense to me. Joel Gallant summarizes a couple of abstracts from CROI on the CCO website with respect to this combination. We seldom combine ddi/ABC and TFV/ABC unless we want K65R (as Tony eluded to). We are not starting anyone on ddi/TFV and haven't for a long time, but those that are on the combination and doing fine we are just carefully watching CD4 and trying to switch if it would still mean a viable cocktail and patient is willing. We do add AZT (not d4T) if we want to delay emergence of K65R as I thought I read something describing the possible mechanism as being related to the 'azido' group from a steric point of view. Also, we have had very good luck in nuke-experienced patients with nuke sparing regimens, namely Kaletra with either EFV or NVP. Recently we actually switched one of these patients from Kaletra/NVP to ATV/NVP, empirically I know, but he desired once daily and we desired nicer lipids, hence he has maintained viral suppression and continued immune reconstitution for 6 months now. Thanks for the great question! It's always nice on a Friday to make sense of and review what we're doing everyday!!!

I'm not sure who was collecting the information on costs related to institutional ethics review, but at our site (St. Paul's Hospital) the cost is \$1500 for an industry-sponsored study (no charge if it's not industry sponsored.)

Linda.

Responses:

Can you check with your site what they consider as industry-sponsored.

Though we are receiving money from Pfizer for the nelfinavir in elderly study they it is considered as an unrestricted grant. It is investigator-driven and in the contract with the PI they are including that they are keeping no rights. They cannot review data before

publication. I would ask all the sites that are participating in this study (Linda Agaki, Linda Sulz, Lizanne Beique, Kathryn Slaytor, Christine Hughes) to confirm their cost for ethics review as well as overhead keeping in mind it is an investigator-driven study and not a pharm study. (Nancy)

Hi Vivienne,

Dr. A. McLeod suggested that I contact you regarding my question. I am wanting to know what the Ethics committee considers as an 'industry-sponsored' trial (i.e. would be charged \$1500 for processing.) We are participating in a study that has received an unrestricted grant from a drug company (Pfizer) ie there is not any contract with Pfizer for the study. This is a multi-site, investigator-driven study that involves other HIV outpatient clinics in Canada. As per the email discussion below, Pfizer has no rights to any of the data generated and cannot review the data before publication.

One of the sites participating (Dalhousie University) has reported that their Ethics committee would consider this study to not be industry "contract" research and would therefore not be subject to their usual fee for such studies. Can you tell me if this would be the same case here?

Any help at all on this topic would be much appreciated.

Thanks,

Linda Akagi

This review should not be subject to the \$1500 REB fee if there is no agreement or contract between the investigator and Pfizer. However, we have found in the past that some 'unrestricted educational grants' do in fact, involve contracts, therefore, it is best if you submit a signed letter from Pfizer outlining the terms of the unrestricted grant, so that it is clear for the REB.(Vivienne)

Perhaps it's just my mind going blank on me (not an infrequent occurrence!), but I was hoping to find out the latest on access to trimetrexate. Is it available via SAP? has anyone tried to obtain it recently?

**Thanks,
Alice**

Responses:

I believe it is SAP, from the US. I haven't needed to obtain it (ever), but it is SAP status. (Deborah Kelly)

I haven't had to use it but as Deborah indicated it is available through

SAP from MEDIMUNE ONCOLOGY INC. (Christine)

From: Dr. Deborah Kelly

How is tenofovir being handled by the various provincial payers? The Common Drug Review by CCOHTA has recommended that tenofovir NOT be covered, and as a result, it is not being listed in NL (at least for now). At the CHAP meeting a few wks ago, I was under the impression that it was covered pretty much everywhere else. Is this the case?

Responses:

Tenofovir has been covered in BC, since the end of the EAP. We have had several discussions with BC Ministry of Health staff to provide support for our decision to list tenofovir, in light of the CCOHTA recommendation. The BC Ministry of Health is aware that most of our treatment experienced patients have switched to tenofovir as a result of intolerance/toxicities to other NRTIs (mainly stavudine) and that this is one of the exceptions listed by CCOHTA. (Linda Akagi)

Ditto in AB..... Our understanding is that with the centralized model of HIV care here (including drug prescribing and distribution), Alberta Health & Wellness takes the CDR into account but allows us clinical leverage to balance the decision on funding approval. Funding for antiretrovirals comes from a special pool of money (Province-Wide Services High Cost Drugs budget) which also covers certain drugs for transplant, CF, etc., rather than from a general drug budget (Jeff)

Yes, we are similar to BC, in that Tenofovir is covered by Alberta Health and Wellness (a provincially governed committee for high cost drugs), after the EAP ended. Medical directors of both the Southern and Northern Alberta Clinics have outlined that Tenofovir be used for certain pts under the following criteria:

- usage in salvage regimens (sensitivity demonstrated from genotype/virtual phenotype)
- demonstrate (mitochondrial) toxicity from the other NRTI agents
- in once-daily regimens, if adherence is problematic

Tenofovir is not to be used as a first line regimen.

Therefore, regardless of the CCOHTA recommendation, we were granted coverage, as long as Tenofovir is prescribed under the outlined criteria (above). (Jinell)

Ontario:

Hi all. In Ontario, private coverage picks up Tenofovir and has done so pretty much since the EAP finished. The Ontario Drug Benefit, however requires Section 8 approval before they will cover Tenofovir. For those who do not know, this requires a letter of petition specifying certain criteria for a review board to decide if they will grant approval for a 6 to 12 month time period. originally there were many hoops to jump through for TFV including sending extensive information, genotypes, VL and CD4 history and complete ARV history along with the letter of intent as to why the doc wanted to use it. It was really only getting approval in cases that were failures, no other nuke options, and genotypic proof of sensitivity to TFV. Recently, however they have lightened up the criteria a bit. One still, however has to prove that TFV is required

because there are no other viable nuke options, be it for toxicity, tolerance, adherence or other, that are less costly alternatives. In the cases of failure, genotypic proof of TFV sensitivity is still required. (Linda Robinson)

Hi Jeff,

I am wondering then, what is going to happen with fos-APV coverage in AB? I thought the PWS was waiting for the CDR to come out first. Are you guys using it yet? (Michelle)

The submission to PWS for fosamprenavir was as a cost-neutral addition, no extra money needed in the budget for it as it is the same cost as NFV even taking the RTV boost into account. We chose to switch to it without waiting for PWS approval on that basis. It looks like the CEDAC recommendation was sent out last week, so either way, the CDR decision will be public soon. (Jeff)

This is really the first drug in NS that we have ever had to fill paperwork out for (we have been so lucky up until now) We essentially have an abbreviated version of Ontario's Guidelines (attached) that we need to adhere to (Kathryn Slayter)

Hi Alice,

Hope you are enjoying this summer weather that has finally arrived!

We have a pregnant woman at the clinic who is going to restart her medications in the next week or two. Due to allergies, intolerance and resistance, her choice of nucleosides is limited. We are considering using tenofovir as one of the meds in her regimen. There is limited information about it's use in pregnancy as you know and we were wondering if, in your clinic population, you had used tenofovir at all. Your clinic is much larger than ours and we were hoping that you might have some experience with tenofovir in this situation that you might be able to share with us.

Thanks for your help.

Heather

Hi everyone,

I'm forwarding a question from Heather Jarman, a pharmacist from London, about tenofovir use in pregnancy. Does anyone have any experience with using tenofovir in pregnancy that they can share?

Thanks,
Alice

Responses:

We've treated two pregnant women so far on tenofovir. The first one delivered about a year ago with no complications. The second woman was started on it about 3 weeks ago due to profound anemia caused by zidovudine. She reported a significant increase in her energy level, decreased nausea, and her hemoglobin as increased about 20 points since the switch. (Dom)

What sources/references are you using for information on natural products/herbals/homeopathy in HIV? I really like the Natural Products Database in general, but find it's often not helpful for HIV-related issues. (Deb. Kelly)

Has anyone seen a case of a woman on tipranavir/ritonavir getting pregnant? If so how about the baby's health? Any thoughts on risks for the baby. Company suggests to stop medication but patient is resistant to everything? Ethically what would you consider re: absence of info for tipranavir
Thanks Marie Courchesne

We've not used this combo in our pregnant women.
(Dom)

Look out for the 'Dear Doctor' letter that is being released by BMS and Gilead. It's in regards to the coadministration of tenofovir, didanosine EC with nevirapine or efavirenz. Besides the info on the high rates of virological failure and emergence of resistance, there are dosing guidelines for the combination of tenofovir and didanosine EC in patients under 60kg.

Linda Akagi.

Are any centres supplementing zinc po for patients who are zinc deficient to potentially enhance antiretroviral agent activity? I can find no potential drug interactions with ZDV, 3TC or Kaletra. Does anyone see a problem? (I would predict a potential problem with the old ddI formulation but that is all). I can find 2 articles on the topic which are sort of related:
1) Therapeutic application of zinc in HIV vs opportunistic infections. J of Nutrition 2000;130(5S):1424s-1431s.
2) Zinc serum level in HIV in relation to immune status. Biological Trace Element Research 2000;73(2):139-49.

Thanks for your help, Natalie

We are not routinely using zinc. I remember our dietician in Toronto used it quite a bit back in the 90's. (Michelle)

We are in the process of reviewing the aerosolized pentamidine protocol- we rarely use it, but it is a source of confusion for the odd patient that requires it. Do any of

you have written protocols for aerosolized pentamidine that you can circulate? This includes administration of Ventolin, etc.... If so, can you e-mail or fax over?

Thanks Michelle

Some patients come to the clinic to receive pentamidine; others who are capable of doing it at home in a ventilated room can sometimes borrow a neb pump from us while they need pentamidine. Instructions are on our website:

<http://www.crhahealth.ab.ca/clin/sac/aeropent.htm> (Jeff)

We have only a couple of patients on nebulized pentamidine. One guy has found having some chewing gum afterwards helpful to get rid of the bad taste. Our pharmacy supplies the drug, SWI, and syringe and needle. (dom)

Can some of you share the highest elevations in bilirubin that you've Seen so far with Atazanavir? We have a patient whose total bilirubin has Just come back as 87.5 (previous total, 50 and direct 12.9) The direct was Not done at this time. He has no symptoms and his LFT's are all normal. I Am just curious as to whether any of you have seen it go this high and Still not have a yellow patient!

Thanks, Linda Robinson

I just saw someone recently who had a total bilirubin of 121 (no direct done, previous TBil was around 19) after 11 days of boosted atazanavir. However, he was very yellow (sclera, skin)....and not very happy. His comment was that every time he looked in the mirror, he scared himself. All of his liver transaminases were normal. We did a 'stat' atazanavir level, but it didn't contribute any real useful information. In the end, we switched him to efavirenz. (Linda A).

I've had a couple of people go into the 90's with no jaundice (Tony)

I saw one yesterday that was about 86 and no jaundice (and have had Others in that range). I have only stopped one patient due to jaundice However can't remember off-hand how high the bili was... (Christine)

I was curious to see if you advise patients against eating cheese and other tyramine-containing food when they take isoniazid. The info sheets we use do not mention this, but Micromedex mentions palpitations, flushing, chills, nausea, vomiting, hypertension, tachycardia (due to inhibition of monoamine oxidase).

Lizanne

Lizanne , dans mon feuillet , j'ai mis les recommandations nutritionnelles avec l'INH voir le site. Je dois t'avouer que contre je n'en parlais jamais avec les patients jusqu'au jour où nous avons eu un cas de crise hypertensive. Ce patient ne mangeait rien d'autre que des Hotdog et de la pizza. Bonne journée (Rachel Therrien)

Est-ce qu'il serait possible que vous m'envoyiez un copie de votre feuillet. Merci (Natalie)

Le feuillet est sur le site www.guidetherapeutiquevih.com (Rachel)

47yo male on this combo since July/03. Last 2-4weeks, complains of racing heart and feeling fatigued. Went to ER and found he had heart rate of just under 200 with many pvc's. Then he said he gets brady (50 bpm). His usual HR is around 60. He asked whether it could be due to his HIV meds. I didn't think so, but wanted to see if any of you have had this experience. He is an ER nurse and reads a lot. ..

Anyway, I only know of cardiovascular risk as it relates to metabolic changes, , haven't heard of rate changes or as a cause of arrhythmias. He is scheduled for a 24h Holter next week, but is feeling so crappy that he may have to be off work.

PS. . he DID say he was taking Sudafed for nasal congestion recently which I indicated is the most likely cause. .He stopped this once he realized this fact, but still feels like his heart races and then slows down dramatically.

?? Comments. Thanks (Linda A. Sulz (BSP, PharmD))

Just wondering if anyone has any new tips for masking the Ritonavir liquid taste. We have a patient that has tried chewing gum, drinking after, sucking on candies after it. Any other ideas? We were wondering if anyone has had a compounding pharmacy try to make something out of it to mask the flavour (ie sucker, gummy bears, etc). I thought that the company probably wouldn't recommend this but if anyone has any ideas please email me back. Thanks a lot, Cara Hills

As far as the trial tasting done with patients when Norvir was used as an ARV, it was premixed chocolate milk that ended up being chosen by patient to mask the taste. Salty stuff like chips had also been used.....(Marie Courchesne)

I have developed a pamphlet on masking the bad taste of ritonavir. Send me your fax number and I will send you a copy. It has many suggestions. (Natalie)

Have any of you had pts say that the Med Reminder beepers go off frequently (i.e. every 20 minutes)? Just wondering if they tend to be defective or am I missing the boat on programming them? (Michelle)

Actually one of our fellows was telling me that a patient of theirs complained of this...I haven't heard any others complain thus far.. (Christine)

I have had some patients complain of the same thing. As it turns out, if the user fails to acknowledge the reminder when it sounds... " the light will continue to blink indefinitely and the alarm will sound the alert for 30 seconds every 10 mins and q 15mins after the first hour..." this may explain what is happening... the instruction sheet goes into how to stop it (Nelson DaSilva)

Well, we have our FIRST HIV +ve child - a 5y old from Sudan.)<:

I've reviewed the latest Ped guidelines from Mar/05, but would like to get an idea of your usual 1st choices.

Her CD4 =261=15%. She's small for her age - 98cm and 15.9kg. If you dose by m2 what formula do you use? ?Haycock. . .

Additionally, I'm not sure of the usual issues which I can expect to arise in this age group. So if you have an insight there as well, it would be greatly appreciated.

Thank you. Linda A. Sulz

I recall this question coming up previously. I have a new pt with psych S/E form EFV (has been on EFV x 1 mos). We are switching to nevirapine. Given that his enzymes should be already induced, would you still do the 2 week escalation with nevirapine or just go to full doses? I started him on the escalation since we can't do TDM, but just wondering what your clinics are doing?

Also, when discontinuing an NNRTI, what are your clinic policies about stopping the NNRTI vs the timing of the nukes? (Michelle)

There was a small study that looked at your question, "Dose escalation or immediate full dose when switching from efavirenz to nevirapine-based highly active antiretroviral therapy in HIV-1 infected individuals" (AIDS 2004;18 (3): 572-574)....and found you could just switch. no "policy"...if I get the chance to intervene ie. pt. did not yet stop, I usually will suggest stopping 1 week before the nukes (Deborah)

I skip the 2 week induction when switching from EFV to NVP and go right to full dose.

For D/C'ing NNRTIs, I keep the nukes around for an extra week (I haven't had too many cases of this though). (Tony)

Hi Michelle.... now I remember why I save almost every CHAP email (and my account is HUGE!). Responses from Rolf and Nancy are pasted below, from Nov 2002 (although I don't have the article Rolf cited). (Jeff)

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

Best regards,
Rolf

> -----Original Message-----

> From: Nancy Sheehan [SMTP:nancy.sheehan@muhc.mcgill.ca]

> Sent: Wednesday, November 20, 2002 6:16 PM

> To: chap_acpv@yahoogroups.com

- > Subject: Re: RE: [chap_acpv] Sustiva & patients with history of
- > depression
- >
- >
- > Interesting question Jeff,
- >
- > I initially believed we began with NVP 200 QD for 2 weeks and then
- > increased the dose of nevirapine to BID simply to decrease the risk of
- > developing a rash. I was at first scared for the development of NVP
- > resistance and NNRTI cross-resistance during the first 2 weeks. However, I
- > was informed that one of the primary reasons is that nevirapine
- > auto-induces its own metabolism (notion that I hadn't read), and therefore
- > during the first two weeks possibly 200 mg QD is sufficient for adequate
- > ARV activity. In which case, continuing EFV wouldn't be necessary. I
- > have
- > always been a bit perplexed with this notion.
- >
- > What do you guys think? Nancy Sheehan

There was an interesting paper looking at the persistence of detectable NVP levels in women receiving single-dose intrapartum NVP; the authors found detectable NVP levels at up to 20 days post-dose, and hence suggested that in these cases, 1 month of additional ARV therapy may be considered to prevent the emergence of resistance.

However, the authors note that since the women in the study only received single-dose NVP, their levels could persist for longer periods vs. those patients who have been on chronic NVP due to auto-induction.

Another study published last year suggested that 5 days of additional ARV therapy may be appropriate for people discontinuing NVP. This falls into line with the 1 week ARV cover period that most people seem to be using. Copies of both papers are attached. (Alice)

Turns out I have / had an intensive pk study up and going called the Switch study (EFV to NVP)...intensive pk study to find out what actually happens during the first 14 days of concomitant use (3A4 inhibition or induction of EFV on NVP) to determine which NVP dose to start with.

It's gone through ethics more than a year ago. Problem is no one wants to switch to NVP...they prefer the low grade long term CNS toxicity of EFV to the potential hepatotoxicity of NVP. We have never been able to recruit any patients for our study and are reconsidering the whole thing.
(Nancy Sheehan)

Has anyone had any cases of photosensitivity with EFV? It's listed as a possible adverse effect in the monograph, though I've never had anyone experience it before (to my knowledge). One of our patients on EFV wishes to go to the solarium...

Thanks, Deb Kelly

I don't have this at my fingertips at home, but I recall there was at least 1 case report published the literature on this. Remember, I'm still using the excuse of pregnancy brain, so don't quote me on this.

(Michelle)

We had a patient who developed skin rash after going to a tanning salon. When told to stop rash disappeared

(Marie Courchesne)

Attachments sent by Alice:

Efavirenz-induced photoallergic dermatitis in HIV_AIDS01.htm

EFV photosensitivity in Japanese patient_Intern Med04.pdf

skin eruption 8 days after single EFV dose_Jpn JID01.htm

Nancy,

Nous devons aussi parler de ce projet.

Line

Salut Line,

T'es stressante avec les différents projets aujourd'hui....tu devrais pas être sur une plage en string comme les femmes du Brésil...amuses toi un peu, penses pas juste au travail

Nancy

We have a patient with MAC who weighs 40 kg. As part of her regimen, we would like to give rifabutin, but dosed at 5 mg/kg, i.e., 200 mg/d because she has elevated LFTs. From what I can see, rifabutin is available as 150 mg caps, but not liquid.

I was wondering how you proceed for pediatrics or low-weight patients.

thanks, Lizanne

Has anyone heard this? I was just reviewing some updated med charts from HIV InSite, and one of them indicated that the adult formulation of APV has been d/c in the U.S., and other charts no longer include APV in the PI sections. Is this true for Canada also? Deb.K

I understand they will keep it around until everyone is able to access fosamprenavir ie. on all the provincial benefit programs. (Deborah Y)

I heard back from the company today and they indicated they are not aware of any plans to d/c it in Canada. In fact, they weren't even aware it was d/c in the U.S.... makes me wonder if as you mentioned, there are plans to take it off the market once fosamprenavir is established. Interesting...(Debbie K)

I had talked to a Glaxo rep at CAHR who indicated that it would be removed once fosamprenavir was funded by all of the provinces, but that they would be keeping the amprenavir oral solution (at least for now...).(Christine)

For antiretroviral-experienced adolescents & adults, is everyone ONLY using ATV with ritonavir 100mg po once daily? The pediatric guidelines only list one option for antiretroviral-experienced patients - ATV 300mg po OD + RTV 100mg PO OD.

Thanks Natalie D.

For patients who have never failed PI-based therapies in the past and provided HIV is still sensitive to NRTIs, I would feel comfortable using unboosted ATV if the viral load was not too high. (Lizanne)

We are going to a once daily regimen to support adherence as opposed to failure to present regimen so I would like to stay away from RTV. Thanks for the help. (Natalie)

Hi everyone.... I have a lady who has been off ART since 1999 and not seen here since 2002. Her CD4 in may was 128 and viral load 140,000. She's admitted and now post treatment for PCP, on treatment for MAC and thrush. Her liver is cirrhotic from alcohol. She's allergic to sulfa, and while on dapsone for PCP tx her platelets were dropping; switched to IV pentamidine which led to pancreatitis (I see lipase was elevated, now within normal limits, don't know if she was symptomatic). The doc in hospital is leaning away from PIs for reasons of tolerability and interactions, considering efavirenz + 3TC + tenofovir. In that case, we'll bump her rifabutin dose up to 450 mg qd, but I'm not quite sure what to do with the atovaquone, as levels may be decreased by 34% by rifabutin according to the manufacturer info - which also states that combination is not recommended at all. For ongoing prophylaxis (if she survives), would the group consider:

- 1. presumptively increasing atovaquone dose (she's getting 1500 mg daily, her weight is ~60 kg some of which could be ascites)**
- 2. switch to pentamidine via neb and monitor for recurrence of pancreatitis (this would be more simple and MUCH cheaper, unless the pancreatitis reoccurs and prolongs her hospitalization)**
- 3. any other thoughts??**

Jeff

I'm a bit surprised that the monograph says to avoid rifabutin and atovaquone; the authors of the study you mentioned concluded that no dosage adjustment was needed when the two are combined. Even though pancreatitis with inhaled pentamidine is virtually non-existent, I'd be inclined to continue as is with the atovaquone (i.e. no dose adjustment) (Tony)

Christine and I were reviewing our drug monitoring protocols and had a few questions about what other centres are doing?

1) Bone monitoring- at CAHR the talk by Andrew Carr suggested doing BMD monitoring via DXA q1-2 years in the following: hypogonadism, wasting or low BMI, heavy smokers, ETOH use, sedentary lifestyle, long-term TDF use

- are your centres doing something similar?

2) TDF and MDRD (Modification of Diet in Renal Disease) GFR: For routine monitoring of TDF renal toxicity, we are doing SeCr and PO₄, and using a cut-off of < 60 ml/min/1.73m² (Stage 3- moderate decrease in GFR) as a prompt to do further renal tests in patients on tenofovir.

- just wondering what others are doing?

Michelle

We do not have access to TDF yet, so I don't have any input for your second question. Re: BMD measurements, we don't have a specific protocol that we are following for all patients. We have recommended BMD for a couple of our ladies who have multiple risk factors, including peri-menopause, as well as one other fellow who is hemophiliac and very small. I do consider it for patients on PI who have other significant risk factors for BMD loss/osteoporosis, and try to counsel on non-pharmacologic prevention like weight-bearing exercise, smoking cessation and diet, for those that seem to be higher risk.

(Deb K)

We are not routinely referring our patients for DXA. However, if someone has other risk factors for osteoporosis (as per your list), they may be referred, but we don't have a routine referral process and it kind of depends on the physician seeing the patient.

As far as renal monitoring with tenofovir, we refer patients for further investigation when their SCr approaches 1.5x their baseline level (ie pre-TNF). This is what the nephrologists here have suggested as a cut-off, however I know that patients have been referred before their SCr reaches this level, as well. The other thing that we do (but not routinely) is a basic urinalysis (and it's cheap to do!) ie glucose, protein....sometimes allows you to catch renal problems, before you see a rise in the Scr. nb. We measure PO₄ as well, but find that it's not as useful. (Linda A).

In Ottawa, we don't do any BMD monitoring... and do not do any specific renal monitoring other than the serum creatinine. My feeling is that If DXA is warranted, we would likely send a consult to our medicine guys. (Pierre)

Although it's not routine, we are starting to offer BMD on many of our patients as a baseline of general care. If all is normal then a repeat in 3-5 years recommended. If there's osteopenia found, then a repeat in 2-3 years and if osteoporosis is found, then yearly monitoring. David Burdge is just finishing up a paper on Bone Health and HIV positive Women which will be submitted for publication in the next few months.

We are following similar renal monitoring for TDF and would refer patients with abnormal values to a nephrologist. So far, we've had one patient who experienced renal toxicity secondary to TDF and the medication was discontinued with a return to normal renal function. (Dom)

Here is a herbal site that may be of interest. I can't comment on the quality of it though. <http://content.nhiondemand.com/dse/consumer/main.asp>

Michelle

Just curious what you use to treat MAC when patients are on efavirenz (i.e. azithro or clarithro)? The product monograph suggests avoiding clarithro as efavirenz reduces the levels, although other references suggest it is reasonable to monitor given that there is no clinical information (by the way I think this would be a great CHAP project!). Christine

I've almost always used clarithro unless the patient needed everything once daily, then I would use azithro, and I've never had a problem of failure. I guess the increased active metabolite of clari must make up for it. (Deborah Y)

Thanks - that has been my experience as well. I had to look up the level of activity of 14-hydroxyclearithromycin against MAC - on the AIDS info website it indicates it is 4-7 times less active than clarithro against MAC in vitro but the clinical significance of this is unknown. I was asked about a patient from an ID doctor who works in private practice re: drug coverage of MAC for a patient who does not have a plan. Clarithromycin is quite a bit cheaper but she had ruled this out due to the interaction...I am interested in other's thoughts as well. (Christine)

I've been lucky in the past with getting compassionate supplies from Pfizer; I think someone else is marketing Zithromax for them now, but free drug might still be available. (Jeff)

Hi everyone. I had a colleague in BC asking me if anyone on the CHAP email knows how medications are paid for in Nova Scotia. They have a BC patient moving to NS and he is currently on disability 2 so he is covered for all non-HIV meds by social services. Does anyone know about med coverage (HIV and non-HIV) in that province?

Thanks a lot! (Cara)

In Nova Scotia if someone does not have private insurance then antiretrovirals will be covered completely by the provincial AIDS program (9.00 professional fee per script) -regardless of their financial status if they still have private insurance it will be accessed first. So if this gentleman has no private insurance then his meds will be completely paid for, if he does have insurance but a sizable copay ie 20% then the provincial AIDS program will cover that for him.

Unfortunately if someone is on disability and does not have private insurance then non-HIV meds must be paid for out of pocket. However if someone is on family benefits/welfare/social assistance etc then folks will have all non-HIV meds paid for under social services. Hope that this makes sense (Kathy Slayter)

Hi Kathy,

Hope the weather in Halifax has been better than S.J. this summer :(Do you have any contacts with pharmacists who specialize in pediatrics HIV treatment? I tried Sick Kids in Toronto but they do not have anyone according to their DI people. We have an 11 year old we would like to

switch to a once a day regimen. I found kinetic info from a study that concluded once daily dosing of lamivudine and abacavir in pediatrics should be comparable to the recommended twice daily regimen and recommended safety and efficacy trials. I wanted to see if this dosing was being used routinely in pediatrics as all the references still suggest the twice daily regimens in kids.

Thanks Jennifer

I am hesitant to go to ONCE daily NrtI's in an 11 year old, while I'm not for an 15 year old. What Tanner stage is this youth in his maturation? I know that the intracellular half-lives of 12 to 18 hours should approach adequate coverage, but until I can utilize TDM to ensure that the other drugs (PI's) used with this combination are providing adequate coverage, I would wait. I had an adolescent express surprise when I explained that going to ONCE daily meant taking the medications at relatively the same time each day and that once daily did not mean you can take it any time in the 24 hour period. He was less interested in once daily. Dom, what was your answer?

(Natalie Dayneka)

We have jumped with both feet into the once-a-day regimens for our kids to optimize adherence, especially with the pre-teens who are turning out to be real challenges. We are using EFV or NVP or ATV/RTV with ABC/3TC or ABC/TDF or 3TC/TDF (and DDI/TDF in the recent past). So far we've had good success with virologic and CD4 parameters. I agree with your caution about timing of OD dosing that it needs to be around the same time each day. (Dom)

I am not up to date with the latest pediatrics HIV literature, but are there sufficient pharmacokinetic studies in pediatrics showing adequate levels with once-daily PIs to safely use them OD? Considering the great pk variability in children, especially amongst different age groups, I find this a bit risky if there is no literature to support this. The kids may have a good initial virologic and immunological response as their background meds will be contributing, but may fail earlier down the road compared to kids taking meds BID. Something to look out for. I know Manon van der Lee is in the process of completing (not published yet I believe) a pk study with OD Kaletra in pediatrics. The poster was presented at the last CROI (see below). Though the mean may have been similar to adult PK data with OD dosing, I have seen individual pk data from children of different age groups with lopinavir BID and the amount of variability with many children having suboptimal Cmin was impressive. Supporting that the pediatric population may be a potential indication for TDM. Anyhow, this is just food for thought. Dom, if this isn't already done, I may suggest that you contact Elizabeth Phillips at St. Paul's (UBC) to see if you can send her TDM samples for the PIs of children receiving them OD (Cmin). (Nancy Sheehan)

Sorry, I should have read the string of e-mails more closely. I thought PIs

other than TAZ/rtv were also being given OD in children with the NRTIs. It may however eventually become possible and perhaps we should consider starting some pk studies in children. Unfortunately, I am not aware of anyone in Canada measuring intracellular NRTI concentrations. (Nancy)

Thanks for your comments and the info on Kaletra PK. Yes, it would be good to do more PK studies in kids. We have sent 1 child to the PK lab at St. Paul's Hospital/CFE for ATV levels because he refused to take RTV (capsules/liquid). He also has refused Kaletra and has no NNRTI options left. His pre ATV levels were undetectable (despite good adherence per parents) as we suspected so it brings us back to adding back RTV. We have temporarily held his meds until the "psycho-social" challenge of engaging him into taking all his ARVs is accomplished.
(Dom)

**RE: HIV PEP in Kids ; Generally speaking, could we use the adult regime of Combivir i tab plus Nelfinavir 1250mg po bid if they are 13 or older? 12 or older?? Is the bid dosing sufficient or do we need to use nelfinavir q8h?
Thanks. Linda A. Sulz (BSP, PharmD)**

According to the guidelines, the zidovudine dose is the same as adults for those > or = 12 years. Lamivudine is dosed based on weight but I would think most 12/13 year olds weigh at least 37 kg. Nelfinavir can be dosed bid in peds - the dose is ~ 50 mg/kg/dose bid (or possible a bit higher) - you do not have to weigh that much to max out on the nelfinavir dose (25 kg)... (Christine)

We use BID dosing in all our children 2 years of age and older and would consider it for even younger (TID has such unacceptable complications - such as undesirable disclosure to school/caregivers, etc). I would only go to nelfinavir q8h after TDM (which we have yet to start to do). Based on the child's weight/height, I calculate the doses of each individual drug. Independent of the child's age, I max out at the usual adult dose. So when the dose reaches the Combivir strength, I will use this but ONLY if the child/adolescent can swallow that large size of a tablet! Linda - if you want to send me the child's age, weight & height, I would review the calculations for you
(dayneka@cheo.on.ca)

The question I have, if a young adolescent is overweight and reaches over 60 Kg, do other pharmacists use 40 mg stavudine? (Natalie)

We also use nelfinavir BID at our peds patients. In BC, the PEP programs uses 3TC/d4T/NFV for both adults and children. We've tried to make the dosing in kids as easy as possible for the first 5 day starter kit. We then fine tune the dosing once it was determined to continue for the full 28 day course. The BC guidelines are on the Centre for Excellence's website <http://cfenet.ubc.ca/guide/page/sectg/sectg.html>

Kids > 40 kg: 3TC 150 mg BID, d4T 40 mg BID, nelfinavir 1250 mg bid
Kids < 40 kg: 3TC 4mg/kg/dose BID, d4T 1 mg/kg/dose BID, nelfinavir 35 mg/kg/dose BID (there are some instructions for caregivers to mix up doses of these for kids who can't swallow tablets/capsules) The dose of NFV needs to be updated with the next revision of the PEP guidelines. We've not started any new kids on D4T lately, but I would tend to use the 40 mg dose for those above 60 kg. (Dom), Oak Tree Clinic

Thanks Dom/Natalie. .much appreciated. . Now something else has come up from this reference: Peter L. Havens, MD & Committee on Pediatric AIDS Postexposure prophylaxis in children and adolescents for nonoccupational exposure to human immunodeficiency virus. Pediatrics 2003; 111:1475-89. http://pediatrics.aappublications.org/cgi/reprint/111/6/1475?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=Havens+PL&andorexactfulltext=and&searchid=1125087564097_11181&stored_search=&FIRSTINDEX=0&sortspec=relevance volume=111&resourcetype=1&journalcode=pediatrics When you look at Table 10 (Page 1484) the dose for nelfinavir says 750-1250mg/dose 3 times/day or 1250mg po bid. (maximum 2000mg/dose!). In what situation if any, would we exceed the normal adult dose?? How would you choose a dose between 30-50mg/dose 3 times daily as this reference suggests? Or is that so you can round off to use the tabs??

Dom -do you mean the dose of nelfinavir is to be updated to the 55mg/kg/dose twice daily?
(Linda A. Sulz)

Yes, the recent recommendation for NFV dosing is 45-55 mg/kg/dose BID (max dose the usual adult dose). I don't know if any reason to exceed the usual adult dose. We're tending to use the higher range when calculating doses, but rounding to convenient tablet size (or half tabs). (Dom)

We also do not exceed the adult dose of 1,250 mg po bid. I had emailed the author at phavens@mcw.edu at the time the article came out but his comment was the doses were from the references but the reference for this chart is wrong - referrence 121 is a 2 pager about adults with NO dosing guidelines and the drugs mentioned are NVP, ZDV & IDV. It was not a rewarding experience so we agreed at my centre to regard the maximum dose of 2,000 mg for nelfinavir as an error. (Natalie)

RE: Dyslipidemia: Where do you place boosted atazanavir on the PI list likely to cause dyslipidemia. Is it placed just above atazanavir (at the bottom) or does it go up to RTV > LPV/RTV >ATV + RTV > NFV> ATV? Any evidence? Thanks Natalie

Study AI424-045 (ATZr vs. ATZ/SQV vs. LPVr) showed ATZr better than LPVr in TC, LDL, TC (Deborah)

Thanks for your reply. I have a study that shows ATV + RTV has less effect than LPV/RTV but I

do not have a comparison of nelfinavir (NFV) vs. ATV + RTV (although the studies show that ATV alone has less effect than NFV). (Natalie)

as of July 1st, I was aware of all studies involving ATV. If you are looking at direct comparison with ATV/r and nelfinavir, I am afraid that you will not be able to find such study. It was not planned to be done because NFV is not much used anymore as first-line therapy. The only piece of information you will be able to get is from retrospective review analysis, keeping in mind the many limitations of this kind of study. There was a EAP analysis done at last CROI that described the lipid effect of changing to ATV/r from a variety of ARVs. I unfortunately don't have the poster in my work computer. I would suggest that you send an e-mail to Mitra Montazeri (Medical Liaison; mitra.montazeri@bms.com) for more info on this.

Personally, I believe that even boosted-ATV is safer than NLV on the lipids. But this is not science.....(Pierre)

Pierre: Thank-you for the erudite response - that was exactly what I am looking for. BMS has not returned my call so I will try the email address. In pediatrics and our adolescents, we do not see the same extent of dyslipidemia that is seen in adults. Our adolescents were subjected to full dose ritonavir liquid and capsules so even boosted ritonavir has its downsides. (Natalie)