

CHAP NEWSLETTER

SPRING 2006 (Feb to May 2006)



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Thanks to Christine, Jinell and Linda for all of their hard work this year on the newsletter. It made my job the easiest of all. To keep the newsletter alive we hope to have new volunteers coordinating various sections again. Keep this in mind if you might be interested.

See you soon!

Michelle & Debbie

I. RESEARCH PROJECT UPDATES

- **Project: Nelfinavir PK Study**

Principal Investigator: Nancy Sheehan

May 2006: The effects of aging on the pharmacokinetics of nelfinavir and M8 will start in certain sites in less than one month. Five sites are participating (Linda Agaki (Vancouver), Linda Sulz (Regina), Lizanne Béique and Charles La Porte (Ottawa), Kathy Slater (Halifax) and Nancy Sheehan (Montréal)). Vancouver and Montréal have both received approval from the ethics board and we are awaiting University of Montréal ethics approval (Line Labbé) so that sites can start recruiting. A cross Canada teleconference study launch meeting was held this week to go over the details of the study. Some research nurses, research coordinators and MDs joined us for the teleconference. We are in regular contact with all the sites to finalize certain details (ie: contracts, labels, etc). I would like to take this opportunity to thank all the study co-investigators for their continued motivation for this study. It has taken much longer than anticipated to start going but things should go more smoothly from now on. Thanks and see you in Québec city. Nancy Sheehan and Line Labbé

- **Project: Drug Interaction: inhaled corticosteroid & ritonavir-containing regimen**

Principal Investigator: Lizanne Béique (lbeique@ottawahospital.on.ca)

May 2006: No change for the inhaled corticosteroid project since last update. Will discuss this project at CHAP.

- **Project: NRTI Research Project**

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

May 2006:

- 1) Outcomes with tenofovir and didanosine backbones
 - This study has been completed at the Northern Alberta Program. We are hoping to present results at CAHR next year.
- 2) Outcomes with abacavir/didanosine or tenofovir/abacavir backbones
 - We have a research student who will be working on this project over the summer.

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

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

May 2006: No updates.

II. RECENT PUBLICATIONS

MANFREDI R, Calza L, Chiodo F.
Long-term statin use does not act on the temporal trend of CD4 cell count in patients on virologically effective HAART.
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Confronting chronic hepatitis B virus infection in HIV: new diagnostic tools and more weapons.
AIDS. 2006;20:451-3.

LLOYD-SMITH E, Brodtkin E, Wood E, Kerr T, et al.
Impact of HAART and injection drug use on life expectancy of two HIV-positive cohorts in British Columbia.
AIDS. 2006;20:445-450.

BARRY PM, Zetola N, Keruly JC, Moore RD, et al.
Invasive pneumococcal disease in a cohort of HIV-infected adults: incidence and risk factors, 1990-2003.
AIDS. 2006;20:437-44.

NAVAS-NACHER EL, Read JS, Leighty RM, Tuomala RE, et al.
Mode of delivery and postpartum HIV-1 disease progression: The Women and Infants Transmission Study.
AIDS. 2006;20:429-436.

LACOMBE K, Massari V, Girard PM, Serfaty L, et al.
Major role of hepatitis B genotypes in liver fibrosis during coinfection with HIV.
AIDS. 2006;20:419-427.

LEVY Y, Durier C, Lascaux AS, Meiffredy V, et al.
Sustained control of viremia following therapeutic immunization in chronically HIV-1-infected individuals.
AIDS. 2006;20:405-413.

THOMPSON M, Dejesus E, Richmond G, Wheeler D, et al.
Pharmacokinetics, pharmacodynamics and safety of once-daily versus twice-daily dosing with enfuvirtide in HIV-infected subjects.
AIDS. 2006;20:397-404.

MOORE DM, Hogg RS, Chan K, Tyndall M, et al.
Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response.
AIDS. 2006;20:371-7.

BRAITSTEIN P, Justice A, Bangsberg DR, Yip B, et al.
Hepatitis C coinfection is independently associated with decreased adherence to antiretroviral therapy in a population-based HIV cohort.
AIDS. 2006;20:323-331.

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AIDS. 2006;20:N1-2.
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Longitudinal study on mitochondrial effects of Didanosine-tenofovir combination.
AIDS Res Hum Retroviruses. 2006;22:33-9.
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Seroreversion in subjects receiving antiretroviral therapy during acute/early HIV infection.
Clin Infect Dis. 2006;42:700-8.
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Impact of a medically supervised safer injection facility on community drug use patterns: a before and after study.
BMJ. 2006;332:220-2.
- GUIARD-SCHMID JB, Poirier JM, Bonnard P, Meynard JL, et al.
Lack of Interaction Between Atazanavir and Proton Pump Inhibitors in HIV-Infected Patients Treated With Ritonavir-Boosted Atazanavir.
J Acquir Immune Defic Syndr. 2006;41:393-394.
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Correlates of Self-Reported Nonadherence to Antiretroviral Therapy in HIV-Infected Patients: The Swiss HIV Cohort Study.
J Acquir Immune Defic Syndr. 2006;41:385-392.
- SMOAK ND, Scott-Sheldon LA, Johnson BT, Carey MP, et al.
Sexual Risk Reduction Interventions Do Not Inadvertently Increase the Overall Frequency of Sexual Behavior: A Meta-analysis of 174 Studies With 116,735 Participants.
J Acquir Immune Defic Syndr. 2006;41:374-384.
- GEORGE C, Alary M, Otis J, Demers E, et al.
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Minimizing Resistance Consequences After Virologic Failure on Initial Combination Therapy: A Systematic Overview.
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J Acquir Immune Defic Syndr. 2006;41:315-322.
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Oxandrolone in the Treatment of HIV-Associated Weight Loss in Men: A Randomized, Double-Blind, Placebo-Controlled Study.
J Acquir Immune Defic Syndr. 2006;41:304-314.
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Selection and persistence of non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 in patients starting and stopping non-nucleoside therapy.
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Patients experiencing early virologic failure on a protease inhibitor- or nonnucleoside reverse transcriptase inhibitor-based initial regimen containing a thymidine analogue and Lamivudine can be successfully treated with a quadruple-nucleoside regimen.
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Maintenance of successful ritonavir-boosted indinavir and efavirenz therapy in an HIV-infected patient with tuberculosis.
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AIDS. 2006;20:1061-1063.

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Clin Infect Dis. 2006;42:1481-7.

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III. CHAP CORRESPONDENCE

CHAP Correspondance February 2006-May 2006

TOPICS DISCUSSED:

- 1. ARV interaction with Magic Mushrooms**
- 2. Drug Interactions: Birth Control Options; Food and Herbals in HIV**
- 3. SALVAGE THERAPY**
- 4. IV FORMULATIONS of ARVs**
- 5. ATV 600mg**
- 6. NELFINAVIR IN NEONATES**
- 7. PCP Prophylaxis**
- 8. TENOFOVIR ACCESS FOR PEP**
- 9. Stevens Johnson syndrome with AZT**
- 10. Phosphate measured and Tenofovir**
- 11. Teeth Cracking**

RE: ARV interaction with Magic Mushrooms

My pharmacy student and I cannot find a drug interaction between magic mushrooms and Kaletra, abacavir, lamivudine, tenofovir and enfuvirtide. Does anyone have any information on a possible drug interaction. Thank-you Natalie

RE: Drug Interactions: Birth Control Options; Food and Herbals in HIV

Have any of you put together any of the following:

1) Birth Control Options in HIV

- considers drug interaction etc....

- I am also curious to know what your sites are doing about this.... We have a flurry of pregnancies!

2) Foods and Herbals in HIV (drug interactions)

- short hand-out on this (vs the long CATIE booklet on herbals)

- grapefruit juice, garlic, St. John's Wort, Echinecea, etc...

Just thought I would check first before going ahead a making them up.

Michelle

RE: SALVAGE THERAPY

We have a 46yo male (<50kg) who our new ID doc wants to try combo of NFV 1250 q12h, DLV 400 q8h and CBV q12h.

PMH - 8 years ago had PCP and in ICU, but survived and did well & was compliant for quite awhile (VL <40 for 2 years, then he started to be

non-compliant and ended up moving away. He has previously been on AZT, 3TC, SQV (single PI), then IDV, d4T exposure.

Recent genotyping done as VL = 3700 (hasn't been undetectable for a couple years I think) and on NVP & CBV x 2 years and recently moved back to our clinic. Shows resistance to ABC, 3TC, NVP, STV and decreased response to AZT, ddi, Tenofovir and S to all PIs and d4t.

One question is the genotyping shows NO PI resistance and i wondered if this was b/c at the time of the test he had not been on a PI for a few years. .

can the virus revert back to a "wild" type?

also am concerned re: lack of info on using nfv with dlv. . see that some references say nfv increases 50-70%. . should we half the dose in anticipation of this (especially cuz he's so small)? And Dlv my decrease by about 50%, so should it be increased (i think in Canada we only have 100mg tabs, so lots of pills!)

worst case scenario might be complete R to all NNRTIs (is that reasonable to think DLV can still be effective when others are R?) and get a R to Nelfinavir which may still allow a change to other PIs . if i can believe the current genotyping.

Comments? Suggestions? Much appreciated. Linda Sulz

do you have a viral sample to genotype when the patient was failing SQV or IDV? the lab usually keeps old samples for many years and this may offer you information on possible archived PI mutations. (Deborah Y)

We never use delavirdine and basically if he is resistant to the other NNRTIs, I would consider him resistant to this as well. I like Deborah's idea re: trying to get a genotype from an old sample. Alternatively (or probably in either case), I would try to use a boosted PI (i.e. Kaletra) in a situation like this - I really like Combivir + tenofovir + Kaletra (not sure if you have access to tenofovir). This takes advantage of the 3TC mutation and may improve AZT and tenofovir activity...What is STV? (I thought it was stavudine but then you said he is sensitive to d4t).. (Christine)

oops STV is Sustiva (EFV. .i guess i should say)

thanks guys! I am feelin' kinda anxious about this . . .i'm still trying to figure out our new doc's "nuances" and her experience in the area and it's a bit challenging as she is wanting to do things much differently than we have been used to. . for instance she will more rapidly initiate ARV therapy b/c she thinks simply waiting for a VL >100,000 is too high even with a CD4 count well over 350. She says they are symptomatic if they seem to have a lot of complaints of "skin infections" (i.e ?eczema, psoriasis) or vaginal candidiasis. Not sure how to go about addressing this, but am somewhat concerned we are starting people much too early. .especially those with CD4 well over 400 and really no HIV symptoms per se.

/Linda

RE: IV FORMULATIONS

I am working offsite and have just received a question about one of our patients in the ICU who has an ileus and is not absorbing his feeds. We need to switch all his meds to IV, but I have not been able to find anything for IV formulations of 3TC and Kaletra. Does any such beast exist for these two? His other med is AZT, which of course is not a problem.

If anyone has a list of IV formulations, or where I can find this info, I'd be interested in receiving it. (I apologize if this info is in the Handbook of HIV therapy... I don't have it with me at this site!!)

Appreciate any help you can offer!

Deb

PS. Also, if no IV available, and absorption is questionable, would you advise d/c'ing the ARV's until GI tract is functioning again, or chance continuing to administer via NG with questionable absorption? Perhaps a stupid question, as I think we should d/c, but have very little critical care experience... Thx!

Deborah Kelly

If absorption is questionable, we will hold ARVs (this is a common case we've experienced in the ICU....not usually a big issue in the long run) Deborah Y

RE: ATV 600mg

There is clinical info on ATV 600 vs. ATV 400 mg and NFV (AIDS 2003; 17:2603-2614.), but I was wondering if anyone has PK info (AUC, Cmin and Cmax) of ATV 600 mg relative to ATV 400mg and ATV300/r100mg?

Lizanne

RE: PCP Prophylaxis

An interesting and complex patient...

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History significant for toxo in 2001 – treated with pyrimeth and sulfadiazine but experienced sulfa-induced renal failure (this is likely what contributed to his current bout of renal impairment also as they had him on Septra in ICU). Following this, until CD4 increased, we used pentamidine inh for prophylaxis of PCP.

Suggested options for PCP prophylaxis now?

- Sulfa not feasible due to renal failure (likely sulfa-induced)
- Pentamidine inh not easy from a practical standpoint while an inpatient
- Dapsone??? – (risk of further renal failure – is this even a concern?) Also, risk of hemolytic anemia (even if not G6PD deficient I read... is this true?)
- Atovaquone???

Any thoughts/advice appreciated. Thanks! Debbie Kelly

RE: NELFINAVIR IN NEONATES

I am wondering which dose of nelfinavir you are using in newborns? [P.S. If you are not using NFV in this group, which dose would you recommend?]

As I have mentioned previously, peds ID uses NFV as part of triple therapy prophylaxis in newborns whose mom's have high VL and have not received ARVs in pregnancy... The debate is whether to use 40, 45 or 50 mg/kg BID

We currently use 50mg/kg BID in our pediatric patients.

Any input would be useful as we are finalizing our revised protocols.

Thanks Michelle

I use the PACTG 353 dose of 40 mg/kg/dose PO BID which is the dose cited (with high interpatient variability) in the current HIV Ped Guidelines, Nov 3, 2005. I use 50 -55 mg/kg/dose po BID over 6 weeks of age eventhough the Guidelines recommend this dose over 2 years of age. My target for > 6 weeks of age is 55 mg/kg/dose because of the results from Carstensen Floren L et al. Pediatrics 2003;112(3):3220-e227 where they reported that for > 8 mos of age 55 mg/kg/dose BID provided comparable exposure to 30 mg/kg/dose po TID. I am interested in other opinions. (Natalie)

At the CMIS (centre maternel et infantile de l'hôpital Ste-Justine) we decide to use the dose of 40 mg/kg/dose bid for 6 weeks (prophylaxis in newborns) with a change in dose every two weeks when we see the patient at the clinic (at 2 and 4 weeks). (Marie-France Goyer)

Our protocol here in BC is not to start ARVs in neonates/infants until they are confirmed HIV+ (ie 2 positive PCRs are reported). It's been about 4 yr since our last positive infant was identified. We follow the NIH doses as outlined below. How many infants are you both following on triple drugs per year? Are they high risk, HIV exposed infants or confirmed HIV positive? (Dom)

We too only start newborns on zidovudine when mom has a viral load < 50. Depending on the risk, we may add 2 dose nevirapine (mom/baby or baby x2), lamivudine or lamivudine/nelfinavir. We have only had one patient in the last 12 months receive ZDV/3TC/NFV and 2 patients (twins) receive ZDV/3TC. We may have 2-3 patients a year who require the NVP 2 dose protocol. (Natalie)

In Calgary, we do the NVP dose to mom/baby, and AZT to baby X 6 weeks for prophylaxis, if the mom has never been on ARVs and has a detectable viral load. We also do not do triple tx until we know for sure the baby is positive. (Jinell)

In Windsor we only use the NVP with AZT a) if the mom has not reached <50 or presents not on ARV's. b) in the babies of these moms with detectable viral load and in the those, even if the mom is undetectable if we question her ability to adhere to the dosing schedule with AZT. We also do not start triple therapy unless baby is confirmed HIV+ on 2 PCR's. (Linda R)

Our protocol for moms with VL > 50 is presently evolving. We are constantly being challenged by the adult ID drs to treat babies exposed to HIV the same way we treat adolescents/adults exposed to HIV through sexual assault (triple therapy). Why are these 2 types

of exposure treated differently? As I believe Canada has not had an HIV exposed baby on zidovudine become positive in the last 4 years (is this true?), what we are presently doing (ZDV alone except for Montreal) must be working. (Whereas HIV is obviously being

transmitted through sexual intercourse). However, we are reconsidering how aggressive to be when mom presents untreated or with an increasing viral load.

For moms with viral load > 50, we are thinking about augmenting zidovudine (ZDV) therapy (this proposal is a summation of evidence, not evidence based itself):

Mom's viral load < 50

1) zidovudine to mom (IV) and baby (PO X 6 weeks)

Mom's viral load > 50

1) add 2 dose Nevirapine (NVP) therapy (mom + baby or baby x 2) if mom's viral load is decreasing on appropriate therapy

2) 2 dose NVP + [lamivudine (3TC) x 6 weeks] if mom's viral load is increasing on appropriate therapy

3) ZDV + [3TC + nelfinavir (NFV) x 6 weeks] when mom has a high viral load and presents untreated

4) add 2 dose NVP depending on the type of incidence during birth (e.g., baby receives superficial, small scalpel cut during delivery)

Can this be challenged? Absolutely. Will it be the same in 6 months? Unsure (Natalie)

Thanks for your replies.

Once our protocol is done we will be posting it on a website with external access. We had ~20 babies in 2005 and several of them had the triple therapy given as prophylaxis. No new positives that I know of yet. (Michelle)

Thanks for all the info you provided on NFV dosing in neonates.....

We are going to include a few other agents in our protocol (just in case mom has AZT resistance or NFV/PI resistance).

The baby would still always get po AZT, but peds ID may order other agents for the baby as well. I was further examining the peds doses for the following and need an opinion on dosing for newborns:

1. ddI - the guidelines say 100mg/m²/dose po BID for ages 2 wks to 8 months (50mg/m²/dose BID may be more appropriate for 2 weeks- 4 mos)

- should we therefore go with the 50mg/m²/dose BID x 6 weeks in the neonates?

2. Any experience or new data in newborns for Kaletra use? The data I have says there is no experience in peds < 6 mos.

3. Nevirapine 5mg/kg/dose once daily (or 120mg/m²/dose) x 14 days, then 5mg/kg/dose BID x 14 days, then 200mg/m²/dose po BID x 14 days.

- do you prefer dosing by m² or by mg/kg?

Michelle

. I would be surprised if ddI (& d4T) would be ordered in a neonate or ARV naive patient - these drugs are quickly falling out of favour because of their metabolic ADR potential. I can only see if being used in an HIV+ baby - 50 mg/m²/dose po bid (< 90 days old)

2. no experience with Kaletra in the newborn yet

3. The doses per weight or BSA work out to be the same so I (4-5 mg/kg/dose) so I would use either for nevirapine. (Natalie)

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Any thoughts/advice appreciated. Thanks!

Debbie

Did you consider IV pentamidine 4mg/kg IV once monthly?

Here is the blurb from MMDX.... While it has been reported to cause nephrotoxicity, it would be less likely with just one dose monthly. (Michelle)

Thanks for your reply. The team ended up going with atovaquone for him. They were reluctant to try pentamidine due to the fear of worsening nephrotoxicity, particularly since he's still hemo-dependent, and now appears to be experiencing an anemia of chronic renal failure. While nephrotoxicity may occur with atovaquone (as can worsening anemia), the team felt more comfortable with this approach for now. Hopefully his counts will come back up soon and we'll be able to d/c it altogether.

I appreciate the info and will keep it handy in the event we need to switch the atovaquone.

Thanks Debbie

RE: TENOFOVIR ACCESS FOR PEP

Can you please let me know if a person in your province was accidentally exposed to blood/infectious body fluids and HIV transmission was a concern, would it be a problem for that person to access tenofovir (as part of their post-exposure prophylaxis, PEP)?....or does it depend entirely on their private prescription coverage?

I guess that I'm also wondering what nuke background most centres are using for PEP in Canada.

Thanks, Linda A.

Due to access issues, our starter pack contains Combivir (plus Kaletra if expanded PEP required). Tenofovir is not easily accessible in Ontario if they have provincial coverage. We are also able to access Combivir and Kaletra through each company's compassionate program for individuals without any coverage. However, if there was private coverage, we would have no problem suggesting 3TC+TDF as the backbone. (Deborah Y)

In AB, if the exposure is community based and the Medical Officer of Health was involved, the cost of all PEP (any ARV) will be covered by Community Health budget. If it was work-related, the employer or WCB get billed (again, any ARV).
(Jeff)

We still do not have coverage in Saskatchewan so have no patients on it at all. For HIV PEP we use Combivir + Nelfinavir in our pre-packed kits.
(Linda S)

Tenofovir is only covered in NL under special circumstances (demonstrated resistance test indicating sensitivity, with no other nuke options). Our PEP kits contain AZT and 3TC (plus Kaletra, if a third drug is indicated). PEP is generally covered under Worker's Compensation program for health care workers in NL. (Debbie K)

Thanks everyone.....it sounds like most sites are using Combivir for their nukes and either Kaletra or nelfinavir for the 3rd drug. We are going to be changing our A/E kits in BC. The new kits will include tenofovir, 3TC and nelfinavir. We are planning to switch the nelfinavir to Kaletra when the new Meltrex formulation is available. (Linda. A)

RE: Stevens Johnson syndrome with AZT

Has anyone seen a Stevens Johnson reaction with zidovudine, lamivudine and nelfinavir develop 7 days after initiation of therapy in a naive-HIV negative patient (exposed)? I am concerned about a patient here today. Natalie

RE: Travel to China

Hello all..... anyone have experience with a patient applying for visitor visa for China? Apparently there's a medical questionnaire, and apparently declaring that you're HIV+ve may result in visa being declined. I've asked the pt to anonymously contact the Chinese Embassy in Ottawa..... any experience or suggestions?

Jeff

RE: Phosphate measured and Tenofovir

Could you please let me know if you measure phosphate as standard of care for your patients on tenofovir, and if so, what cut-off you use before making an intervention?

At the Ottawa Hospital, phosphate is not measured as part of the standard of care - we're looking into perhaps changing this.

**Thanks,
Lizanne**

We are measuring phosphate as standard of care. Last year we had a PharmD student do a review of tenofovir and renal toxicity and hypophosphatemia was present in almost all of the case reports. I do not think we have a specific "cut-off", but if the patient has changes in creatinine and/or phosphate we would likely do further investigations including urinalysis if not already done.(Christine)

We also recommend a phosphate level as part of our standard of care.....though we don't have a specific 'cut-off' value. Our nephrologist has recommended the following for our patients on ARVs (ie not just for patients on tenofovir, as he has seen many HIV patients with renal complications due to a host of other pathologies.)

Pre-treatment: urinalysis with microscopic examination, calcium, phosphorus and creatinine. Follow-up (anywhere from monthly to Q3months): urinalysis with microscopic examination, calcium, phosphorus, magnesium, random sample urine for albumin/creatinine ratio, hemoglobin A1C and creatinine. (Linda.A)

We routinely measure on all folks receiving tenofovir-interestingly even prior to starting folks may have low phosphate level (Kathy Slayter)

We routinely measure serum phosphate as well. (Natalie)
Thanks everyone for your input! To add to the list of references, here are some IDSA guidelines on chronic kidney disease in HIV(although they are from last year and not helpful in answering the TDF-phosphate issue).(Lizanne)

RE: Teeth Cracking

Has anyone heard of cracked teeth as an adverse effect of PI's? The patient who posed this question is on Kaletra, d4T, and abacavir since early fall 2005. He has experienced several cracked teeth over the past couple of months, and one tooth has cracked completely off so he is awaiting follow up with a dental surgeon. I've tried searching for information on this with no luck. Any assistance appreciated, Thanks Deb

Never heard of, maybe a dentist can help if this is a known dental syndrome or something??(Charles)

Thanks, Charles. His regular dentist (who sees several of our patients) asked him to ask us if it could happen! But perhaps his dental surgeon may know something as well. Unfortunately (or fortunately, depending how you look at it) we don't have a lot of HIV+ patients here, so it's difficult for subspecialties outside of HIV to develop any sort of clinical expertise in their area for their patients. Perhaps in larger centers, the dentists would have more experience? Thanks for your help.(Deb)

We know there is osteopenia associated with ARVs May be associated with calcium loss? (Marie)

Never heard of this.....(Michelle)

Debbie, is he on other meds? (Tony)

Yes, gabapentin and metoclopramide. Also of note, since Oct 2005, he's had 4 courses of antibiotics (7-14 days each) to treat a stubborn staph infection (clox or cephalixin). (Deb)

As a way out there explanation, bruxism as a result of metoclopramide-Kaletra interaction (but that is reaching).(Tony)