

## News

dayneka@cheo.on.ca 07/06/06 8:39 am

Important Safety Information Regarding Intracranial Hemorrhage in Patients Receiving Aptivus (tipranavir) Capsules - For Health Professionals - Boehringer Ingelheim (Canada) Ltd.htm>> Is anyone calling their individual patients on this medication to inform them of this ADR or is anyone modifying therapy? Thanks Natalie

**Subject:** Re: Intracranial Hemorrhage i& Tipranavir

I only have three pts on this so I simply went and checked history and other concomitant meds and all are fine Kathy

### **FDA Approves New HIV Treatment for Patients Who Do Not Respond to Existing Drugs**

**June 23 2006**

The Food and Drug Administration (FDA) today approved Prezista (darunavir), a new drug for adults whose infection with the human immunodeficiency virus (HIV) has not responded to treatment with other antiretroviral drugs. Prezista, a new HIV protease inhibitor, is approved to be co-administered with a low-dose of ritonavir and other active anti-HIV agents. Ritonavir, a protease inhibitor approved in 1996, slows the breakdown of Prezista in the body thereby increasing the concentration of Prezista in the patient's system.

The Food and Drug Administration (FDA) today (July 12, 2006) approved Atripla Tablets, a new fixed-dose combination of three widely used antiretroviral drugs, to be taken in a single tablet once a day, alone or in combination with other antiretroviral products for the treatment of HIV-1 infection in adults. Atripla is the first fixed dose combination available in the United States to combine two different classes of antiviral drugs in a single pill. This "one-pill-once-a-day" product to treat HIV/AIDS combines the active ingredients of Sustiva (efavirenz) a Nonnucleoside Reverse Transcriptase Inhibitor (NNRTI), with Emtriva (emtricitabine) and Viread (tenofovir disoproxil fumarate), two Nucleoside Reverse Transcriptase Inhibitors (NRTIs).

Just heard a rumour that TMC114 got it's NOC in Canada...there is supposed to be a press release tomorrow....EAP to stay in place until agreements are reached with each province (\$27.84/day without ritonavir)

Linda.

## Internet links

New iteration of HIV guidelines 06-06-2006 by Michelle

<http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=7&ClassID=1>

## Interesting Publications

Pharmacokinetics Drug Interactions between Opioid Agonist Therapy and Antiretroviral Medications: Implications and Management for clinical Practice

Bruce et al J Acquired Immune Defic Syndr 2006, 41:563-572

## ABC HLA testing

June 20, 2006 12:07 PM

To: chap\_acpv@yahoogroups.com

Hi Michelle,

We will be doing HLA genotyping in Ottawa. We are in the process of getting organized with our lab. I do not look after \$\$\$ or contracts (Dr Angel does). I would recommend you to contact Glaxo for more info. The person to talk to is Francis Vaillant (514 956-3142)

pg

--In BC, we will be offering HLA testing, but under a study setting. Compared to

other sites, we will be operational probably later because we are looking at a broader range of genetic markers ie not just B\*5701.

The main 'point person' for BC is Richard Harrigan. Richard would have all the info on proposals, budgets etc. you can email him at [prharrigan@cfenet.ubc.ca](mailto:prharrigan@cfenet.ubc.ca)

Linda.

## Cases discussion

### Case # !

Hi everyone,

I would LOVE to get some input on a patient we seen today. He is a 50 year old male who has been infected since 1991 and exposed to previous mono/dual NRTI treatment. He failed a nelfinavir-based regimen several years ago (2002) and resistance testing at that time was as follows:

RT: M41L, L74V, A98S, M184V, T215Y

Resistance basically to all NRTIs (low level to intermediate resistance to tenofovir depending on algorithm)

PI: D30N, L63P (resistance to nelfinavir)

He was started on efavirenz, Kaletra, tenofovir in 2002 and suppressed. We have monitored his Creatinine/PO4 which was at baseline ~76 and 0.62 respectively (PO4 low to begin with). His Cr has remained quite stable and has increased since Sept with the last two values being 114 and 116 respectively. His estimated GFR is now 59, phosphorus still 0.62, and two urinalyses have been abnormal with 1+protein, 3+

glucose (blood glucose normal). Our ID physician has spoken to a nephrologist who recommended looking at urine protein electrophoresis but basically recommended d/c tenofovir. In the meantime, we had switched his Kaletra to boosted atazanavir (400/100 mg daily) in April as the patient is on a ton of other meds, has chronic diarrhea requiring up to 6 Imodium per day (now resolved), and is at high risk of CHD with lipids not controlled. I had requested an atazanavir trough level from BC which came back at 2.58 ng/mL.

Just wondering what you would do? Double boosted PI? Which one(s)? Would you keep efavirenz? We do not really have access to TDM so would make following levels more difficult...I would probably add 3TC back into the next regimen regardless...

Thanks!

Christine

Hi Christine,

Based on resistance, I would consider:

1. 3TC/EFV/LPVr/ATV
2. 3TC/EFV/LPVr/SQV

if intolerant to LPVr:

3. 3TC/EFV/ATV/TMC114/RIT

deborah

Hi Deborah,

Thanks - those combinations came to mind as well. Would you use 4 caps bid of Kaletra with 400 atazanavir (or add any extra ritonavir)? His atazanavir level is a bit on the lower side right now. For the LPVr/SQV would you add extra ritonavir? Would anyone consider atazanavir/saquinavir? We still don't have TMC 114 as there are some issues with the patient consent..

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This case is complicated and you will get probably several different opinions. Here is mine. First, I would like to know what was the backbone therapy when he failed NLV. I trust genotyping assay but it tends to miss minority species... Second, I assume that the patient has been on previous AZT and AZT-ddI dual NRTI combination, which would explain the presence of TAMs.

About the renal dysfunction, some argue that even if TDF is associated with nephrotoxicity, that you should rule out any other possible causes (Again, I assume the patient is not diabetic). Considering the limited options, I would propose to do a biopsy. If clinically, you feel somewhat unwell with this situation and want to make a switch, I would rely on drug history and the genotyping.

Considering previous exposure to AZT (Assumed), I doubt that there is any activity left for AZT/d4T.

ddI activity will be decreased due to 74V mutation (I guess he had been on it too)

3TC is only a good choice to preserve the 184V and I would also tend to introduce it into the new regime.

Finally, you don't have many options left. I would throw in ABC (ie Kivexa) as backbone (understanding that the sensitivity is reduced) and keep ATV/r 400/100 + EFV. I would even consider to put in back on Kaletra, despite the lack of lipid control, if drug interaction is an issue.

Good luck

Pg

Just to add, he was on AZT mono and then AZT/ddI. I am not 100% sure of his NRTI backbone while on nelfinavir but I know he was on 3TC and possibly d4t (don't have his chart with me now). His genotype back in 2002 makes sense to me based on his previous history.

He is not diabetic - we checked his blood glucose again. The nephrologist and our ID physician felt quite strongly that this is a pretty specific tubular issue - the protein electrophoresis is to rule out other causes. Her suggestion is to stop tenofovir. I must say I would rather d/c

tenofovir then have to have a kidney biopsy. My debate is whether to try Trizivir or Kivexa + efavirenz + boosted atazanavir or look at some other dual-PI based combination..

Others opinions are welcome!

Christine

Hi Deborah,

Thanks - those combinations came to mind as well. Would you use 4 caps bid of Kaletra with 400 atazanavir (or add any extra ritonavir)? His atazanavir level is a bit on the lower side right now. For the LPVr/SQV would you add extra ritonavir? Would anyone consider atazanavir/saquinavir? We still don't have TMC 114 as there are some issues with the patient consent..

Christine

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Hi Christine,

Very interesting and challenging case.... On paper the way to go is EFV with a double boosted PI +/- 3TC.

I agree with the doses Deborah mentioned. EFV 600/d, LPV 4caps BID with ATV 300-400mg/d with no extra RTV. We might be able to do TDM on the meds once we sort out our policy with BC. Hey Ottawa.... Can you do some TDM for us???

The question is will he tolerate this??? I find the GI toxicity is so high with the double boosted PI's- what kind of success are others having?

How high are the lipids and what meds is he on for this? IS he HCV? Are his LFTS ok?

Has the diarrhea improved off Kaletra and now improved on ATV/r?

You could Kaletra liquid if he is willing just to see if it may decrease the diarrhea. Can you get him a supply of Maltrex Kaletra Tabs somehow? Also try other diarrhea measures like Lomotil, codeine, etc...

Is he a motivated patient willing to put up with side-effects and compliance issues?

It would be good to keep following the renal function and U/A to see if the side-effect reverses once TDF is discontinued.

A riskier (but better tolerated) approach would be 3TC plus EFV/Kaletra OR EFV/ATV 400/r100- give a little extra ATV here... (going along with the fact that Kaletra or ATV monox might be enough in a suppressed patient).

Mich

Case # 2

Hi All,

I am familiar with the published data on PI monox with Kaletra or ATV/r.

I am wondering if any of you have actually tried it on any of your patients who really want a very simple regimen and have resistance to NNRTI and NRTIs?

What has your success rate been? Did you use the step-down approach (i.e. achieve VL < 50 with triple ARVs and step-down to just Kaletra), or did you implement monox despite high viral loads.

I have a patient who does not want T-20 and is resistant to NRTIs/NNRTI's. He did not tolerate a double boosted PI regimen (Kaletra caps + ATV) and gave up after only 1-2 weeks on this due to major GI toxicity. We don't have access to other investigational classes of meds here.

The question will be whether to risk trying PI monotherapy in him (+ 3TC- has the 184V mutation), or to wait until we have more new classes available to construct a more sound regimen. He runs high lipids, smokes, CD4 is 110 (10%), VL > 100,000. He is not a terribly motivated patient and suffers from depression.

Any opinions? (I would like experience from the other Edmonton folks too!!!)

Hi Michelle,

We have few patients on PI monotherapy as part of Clinical Trials. These patients were naive to treatment and are taking Kaletra. I think the evidence is not strong enough to recommend it widely. In patients were prior resistance, I would be even more cautious and likely not use this option.

pg

Hi Michelle,

I also have never seen PI monotherapy in practice. Coming from BC, we used several meds in salvage regimens although I didn't often see the genotypes of these patients so I do not know the resistance, but I assume there was a lot. Linda, any new comments from BC?

Cara Hills-Nieminen, BSc (Pharm)

Northern Alberta HIV Program

Office: 780.407.8372

Fax: 780.407.7827

Pager: 780.445.3677

Email: [carahills@cha.ab.ca](mailto:carahills@cha.ab.ca)

Hi Mich,

I have never used PI monotherapy and I would be a bit hesitant. I have read some commentaries that it is possible we may see more HIV CNS problems with nuc sparing regimens. There is also some literature suggesting it is beneficial in keeping nucs on board, even if there is resistance, in salvage regimens. So, depending on his nuc mutations and history of patient tolerance, I might consider adding Kivexa, tenofovir/3TC or even Combivir/tenofovir..Also, I have had the odd patient who has suppressed on regimens that based on genotype should not have worked so one never knows.....

Christine

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Case # 3

From: Jinell MahMing <Jinell.mahming@CalgaryHealthRegion.ca>

Reply-To: [chap\\_acpv@yahoogroups.com](mailto:chap_acpv@yahoogroups.com)

To: CHAP network <[chap\\_acpv@yahoogroups.com](mailto:chap_acpv@yahoogroups.com)>

Subject: [chap\_acpv] K65R

Date: Wed, 26 Jul 2006 11:26:28 -0600

>Hello Everyone,

>

>I am not an expert on resistance, so I hope the rest of you are!

>

>We have been avoiding the ABC, 3TC, Tenofovir backbones due to increased

>selection of K65R. However, it there a lower rate of this mutation

>surfacing when AZT is added to the mix (Trizivir + Tenofovir)?  
>  
>Do you clinically use these NRTIs all together?  
>  
>I have so far read that if you have:  
>1. K65R, that AZT resistance is reduced  
>2. If you have TAMs the phenotypic effect of K65R is antagonized, and  
>resistance to tenofovir and ABC are reduced.  
>  
>What about patients who do not have these mutations yet? Are we even  
>concerned?  
>  
>thanks,  
>  
>Jinell

Hi Jinell,

I wouldn't classify myself as a resistance expert either, but here goes:

- 1) You are right that Trizivir with TFV would not lead to the development of K65R, nor would CBV/TFV for that matter, because in the event of failure, the most likely resistance to develop will be M184V, of course, and TAMs. It is rare if never that you will see TAMs and the K65R emerge together under this drug pressure.
- 2) The effect of TAMs on TFV and ABC is not to be discounted, however, especially the TAM pathway 1, 215Y, 41L, 210W vs. TAM 2, 67, 70,219. Any 3 of these with M184V = abacavir resistance, and can have an effect on TFV as well.
- 3) The problem with using ABC/TFV/3TC is that the resistance to develop will most likely occur in the following order, M184V...K65R, with maybe the 74 mutation in between. What one could possibly sequence after this would be limited to thymidine based with 3TC or FTC and tenofovir.
- 4) The premise for the above is that M184V is thought to delay the emergence of TAMs, confer increased susceptibility to Tenofovir, (not abacavir) and the K65R is assumed to confer increase susceptibility to TFV.
- 5) As far as using the 3 agents in question together in a naive patient, with no resistance, (keep in mind primary resistance if infected recently) as a backbone with a strong PI or non-nuke is not out of the question, considering their once daily beauty, but why use the third agent at all? Either TFV or ABC with 3TC or FTC will make a nice backbone and allow for intensification and use of thymidine in the next regimen if needed in this group of patients. ( I personally think that using TFV/CBV after Kivexa makes more sense, however than using Trizivir after Truvada.

Just my thoughts,

I'd love for others to comment or question,

Linda

patients switching from tipranavir to other PIs

Tseng, Alice Dr wrote:

> Hi everyone,  
>  
> Recently, I have received a number of queries from physicians who are  
> interested in switching patients from tipranavir to other PIs, but worried  
> about obtaining adequate drug levels. The main concern has been that since

> tipranavir is such a potent enzyme inducer, even after stopping the drug the  
> induction effects could last for around 2 weeks and possibly decrease levels  
> of the new PI that will to be started. Quite often the physicians do not  
> wish to interrupt HAART in order to bypass the lag time for the inducing  
> effects.  
>  
> Boehringer-Ingelheim does not have any recommendations on how to switch or  
> dose-adjust in this situation, and there are no data currently available.  
>  
> Charles and I thought it might be interesting to measure serial plasma  
> levels in patients undergoing such switches. For instance, in someone  
> switching from tipranavir/ritonavir to lopinavir/ritonavir, the suggested  
> dosing schedule might be:  
> days 1-14: d/c tipranavir, continue with ritonavir 200 mg BID, start  
> lopinavir 400/100 mg BID  
> thereafter: d/c extra ritonavir capsules, continue with regular dose  
> lopinavir 400/100 mg BID,  
> with trough concentrations measured at various timepoints before, during and  
> after the switch-over period. We could look at levels in people making  
> switches to other PIs too.  
>  
> This information would be used for informational purposes only (samples  
> would be analyzed in batches, rather than done in "real time"), but we think  
> the accumulated data could be very helpful for understanding more about  
> tipranavir kinetics and eventually coming up with dose-switching algorithms.  
>  
> Has anyone else encountered this situation in clinical practice? Especially  
> in light of the recent data on intracranial hemorrhage with tipranavir,  
> hepatotoxicity issues, and expanded access of darunavir, there may be a  
> number of patients who may be interested in switching from tipranavir to  
> other agents, so this may be a timely issue to look at.  
>  
> If you have any tipranavir patients that you are considering switching to  
> another PI and who might be interested in having drug levels done, please  
> let us know the approximate numbers.

>  
> Thanks,  
> Alice & Charles  
>07/11/2006

Very good idea. I have no patients at my site. We have relatively new patients and few deep salvages. I have often wondered the same thing about switching patients from EFV or NVP to a PI. Any thoughts?

- if switching to Kaletra, use Kaletra 4 caps BID x 2 weeks, then back down to 3 caps BID  
- if switching to ATV, simply use boosted ATV 300/100mg

etc...

Michelle  
Hi Michelle,

What you wrote is what I've been doing in these situations, also waiting 2 weeks before decreasing the dose of the PI to a standard dose.

Lizanne 07/11/2006

Hi Alice,

We have 2-3 patients we are planning to switch that I can think of (1 hemophiliac, 2 on anticoagulation)...likely to darunavir. What would be involved with respect to having drug levels done, need ethics approval?

Deborah

Hi,

We are running into this issue often with patients switching off tipranavir and onto TMC-114. As the TMC-114 expanded access specifies that a 2 week washout period is needed between tipranavir and TMC-114 we have been putting patients on another PI (mostly lopinavir at standard doses) temporarily. We haven't done TDM on these patients yet. The results would come in after the switch and therefore would have less clinical relevance to that specific patient.

I think it would be great to have this data. However, knowing our ethics committee, collecting samples from a group of patients to measure them in batch without it having relevance to clinical care of each specific patient would definitely be considered research and would need to be under the umbrella of a research protocol.

Nancy

...that, and knowing our ethics committee they will ask for pharmacogenotyping!

It looks like there is some variation between centres on ethics requirements, as I have had other people contact me already wanting to send samples.

HI everyone,

I was following the email trail re: the prolonged induction effect of TPV to take into account when switching to TMC, aware of the 2week suggested washout. My issue with a patient that I need to do this with is that he is finally suppressed after 5 years since being on TPV/r/ENF/TFV/3TC for the last year. He is, however, a vasculopath, diabetic, on anticoags, and his TG's are through the roof! He has multi-class resistance, including 47 fold resistance to Kaletra. I am still considering bridging him with 4 caps of Kaletra bid + extra ritonavir. However, would anyone consider the following:

- just continuing 200mg rrv bid for 2 weeks

- starting the TMC114 ( at least after EAP) right away and maintaining the extra 100mg rtv bid x 2 weeks.

I have brought this subject up to the folks at Tibotec, to hopefully provide me us with some sort of suggestion since their initial market target is going to be the TPV switches.

Does anyone have any other suggestions? I guess my issue in this patient is why Kaletra if there is just as much, if not more resistance to it in this patient , than to any other PI. Help!

Linda R

Home office email: [rxlinda@hotmail.com](mailto:rxlinda@hotmail.com)

Here is some information re: the tipranavir to TMC114 switches from Tibotec I received in an email if anyone is interested.

Linda R

-----Original Message-----

**From:** Tai, Frankie [JOI Sales] [mailto:ftai@JOICA.JNJ.com]

**Sent:** Wednesday, July 26, 2006 5:27 PM

**To:** 'Robinson, Linda'

**Subject:** FW: TPV/r Induction - Washout

**Importance:** High

Hello Linda,

I hope that all is well... sorry that this took a few days to sort out.

All I was able to get was the following (see email from Farah Hussein-Bhabha). Farah works in our clinical affairs dept. overseeing the TMC 114 EAP.

Not sure if this helps.

Thanks

Frankie

**Frankie Tai, HBSc, CCPE**

Medical Liaison, Virology

**Tibotec**

19 Greenbelt Drive,

Toronto, Ontario, M3C 1L9

Tel: 1.800.387.8781, ext. 3614

[ftai@joica.jnj.com](mailto:ftai@joica.jnj.com)

Hi everyone,

To follow-up on our initial inquiry, attached is a protocol for the tipranavir PK sampling study that Charles, Nancy and myself, along with our HIV resident, Nimish Patel, are proposing. The intent is to assess PI levels in patients switching from tipranavir to another PI, by using lopinavir/ritonavir (and extra ritonavir) for the first 2 weeks immediately following tipranavir discontinuation.

If you have patients switching from tipranavir to another PI in the near future, and would be interested in participating, please let us know. The attached protocol may be modified as needed for local REB submissions.

Thanks,

Alice, Charles, Nancy, Nimish

We will draft something for those centres that require ethics approval.

Alice 07/12/2006

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patient , than to any other PI. Help!

Linda R.

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Thanks,

Alice, Charles, Nancy, Nimish

**Switching from Boosted Tipranavir (TPV/r) to other Protease  
Inhibitors (PI's): A Pharmacokinetic Analysis to Ascertain if a 14-  
day Switch-over Regimen Allows Adequate Lopinavir Trough  
Concentrations and Genotypic Inhibitory Quotients Following TPV/r  
Discontinuation**

**Research Ethics Board PROTOCOL**

**Principle Investigators:**

Charles la Porte, Pharm.D., Ph.D.  
The Ottawa Hospital, General campus  
Clinical Investigation Unit, Mailbox 223  
501 Smyth Road  
Ottawa, ON K1H 8L6

Alice Tseng, PharmD  
University Health Network – Toronto General Hospital  
585 University Ave., 13<sup>th</sup> Fl. Immunodeficiency Clinic  
Toronto, ON M5G 2N2

**Co-Investigators:**

Nancy Sheehan, B.Pharm, M.Sc  
Montreal Chest Institute  
3650 St. Urbain  
Montreal QC

Nimish Patel, PharmD  
University Health Network – Toronto General Hospital  
585 University Ave., 13<sup>th</sup> Fl. Immunodeficiency Clinic  
Toronto, ON M5G 2N2

## **RATIONALE**

The pharmacokinetics of tipranavir (TPV) / ritonavir (r) are starting to become of greater interest, especially with respect to the strong induction properties of the p-glycoprotein efflux pump and cytochrome P450 3A4 isoenzyme. Reduced lopinavir, saquinavir, and amprenavir levels have been seen with co-administration of TPV/r<sup>1</sup>. In 16 HIV positive patients who received 27 doses of amprenavir/ritonavir 600/100mg twice daily concomitantly with 28 doses of TPV/r 500/200mg twice daily a reduction in pharmacokinetic (PK) parameters of amprenavir/ritonavir was seen: 39% decrease in peak concentration ( $C_{max}$ ), 44% decrease in area under the curve (AUC), and 55% decrease in trough concentration ( $C_{min}$ ). A similar reduction in PK parameters of lopinavir/ritonavir was seen with 21 HIV positive patients who received 27 doses of lopinavir/ritonavir 400/100mg twice daily with 28 doses of TPV/r 500/200mg twice daily. Lopinavir/ritonavir  $C_{max}$  was reduced by 47%, AUC reduced by 55% and  $C_{min}$  reduced by 70% when coadministered with TPV/r. In 20 HIV positive patients receiving 27 doses of saquinavir/ritonavir 600/100mg twice daily with 28 doses of TPV/r 500/200mg twice daily saquinavir/lopinavir  $C_{max}$  was reduced by 70%, AUC reduced by 76%, and  $C_{min}$  reduced by 82%<sup>1</sup>.

Higher doses of lopinavir/ritonavir have been studied in patients concomitantly taking TPV/r. In patients taking either lopinavir/ritonavir 400/300mg or 533/233mg twice daily with TPV/r and no other protease inhibitors or non-nucleoside reverse transcriptase inhibitors, target trough concentrations were similar and above the 4mcg/ml target trough for treatment experienced patients on days 1 and 14 with no statistically significant differences noted. The median day 1 trough concentrations for the 400/300mg and 533/233mg twice daily groups were 4.17mcg/ml and 4.77mcg/ml. The median day 14 trough concentrations for the 400/300mg and 533/233mg groups were 7.05mcg/ml and 5.20mcg/ml<sup>2</sup>. Similarly, lopinavir trough concentrations of HIV patients before therapeutic drug monitoring taking lopinavir/ritonavir 533/233mg twice daily with TPV/r 500/200mg twice daily was 4257ng/ml. After therapeutic drug monitoring trough concentrations of lopinavir were 6151ng/ml<sup>3</sup>.

There are several virologic or pharmacologic markers of response. However, the genotypic inhibitory quotient (GIQ) has been shown to be a better predictor of virologic response when compared to other virologic or pharmacological variables were used. Also a strong, positive correlation between GIQ and viral load reductions has been demonstrated. The GIQ is defined as the quotient between the  $C_{min}$  and the number of protease mutations related to resistance to the ARV. Targeted  $C_{min}$  for lopinavir in protease inhibitor-experienced patients is 4mg/L<sup>4</sup>. Targeted GIQ are 2.1 for heavily protease inhibitor-experienced patients<sup>5</sup>.

What remains unclear is the duration of induction properties once TPV/r has been discontinued. Concerns about resistance exist with suboptimal protease inhibitor (PI) concentrations when patients are changed from TPV/r to an alternate PI. This interaction is of greater interest for highly treatment experienced individuals with multi-PI resistance HIV-1, as these patients are most likely using TPV/r. The objective will be to ascertain knowledge of TPV/r's induction effect on other PI's, after TPV/r has been discontinued by examining Cmin and genotypic inhibitory quotients of lopinavir.

**Primary Objective:** To determine if the proposed 14 day switch-over lopinavir / ritonavir regimen allows adequate lopinavir minimal concentrations and genotypic inhibitory quotients for three weeks after discontinuing tipranavir / ritonavir.

**Secondary:**

- i) To determine if additional ritonavir (RTV) is effective for achieving adequate lopinavir concentrations during the two-week switchover period.
- ii) Target GIQs achieved during 2 week switch-over period

## **STUDY DESIGN**

**Design/Methodology:** Prospective pharmacokinetic analysis using serial blood concentrations.

Patients included in this analysis will have been taking TPV/r 500/200mg twice daily at the time of enrolment for at least 14 days and are being switched to another PI for either toxicity or efficacy reasons. Subjects will be requested to use lopinavir/ritonavir plus additional ritonavir for two weeks following discontinuation of tipranavir. After two weeks, subjects may continue with either regular dose lopinavir/ritonavir or switch to a different PI-based regimen of their physician's choice. The lopinavir/ritonavir dose during the two-week period was selected based on preliminary data suggesting that adequate lopinavir dosages may be achieved in the presence of tipranavir when higher lopinavir and/or ritonavir dosages are used<sup>2,3</sup>.

Upon discontinuation of TPV/r, patients will receive lopinavir/ritonavir (LPV/r) 400/100mg + 200mg ritonavir (RTV) twice daily for 7 days. Subsequently, patients will receive LPV/r 400/100mg + 100mg RTV twice daily for 7 days. After the 14 days of receipt of LPV/r, the patient will receive either LPV/r 400/100mg or be switched to another PI. Morning trough concentrations will be measured on Days 1, 3, 7, 14, and 21. Adherence will be measured using the Simplified Medication Adherence Questionnaire (SMAQ) in Appendix D. A copy of the patient's latest genotype will be submitted to perform GIQ calculations. The GIQ will be calculated by dividing the C<sub>min</sub> by the number of protease mutations related to resistance of lopinavir.

### **Blood sample collection and preparation procedures**

Seven to eight-mL venous blood samples will be collected in heparinised tubes just before ingestion of the next dosage (12 hours after the previous dose). Plasma will be isolated by centrifugation (900 G for 10 min) on the same day and will be stored at -20 to -70C until analysis. Batched analysis will be performed therefore these results will not be used for PI dose adjustments during the study.

### **Bioanalysis**

Concentrations of tipranavir, lopinavir and ritonavir in plasma will be measured by a sensitive and selective high-performance liquid chromatographic method coupled to tandem-mass spectrometry (LC-MS/MS), at The Ottawa Hospital. Sample pre-treatment consists of liquid-liquid extraction of 250  $\mu$ L of plasma with Methyl-tert-butyl-ether after addition of Ammoniumhydroxide and Internal Standard (6,7-dimethyl-2,3-di-(2-pyridyl)quinoxaline). The lower limit of quantitation for the protease inhibitors is 25 ng/mL. This bioanalytical method has been validated as part of the International Quality Control Program for Therapeutic Drug Monitoring in HIV Infection.

**Criteria for Withdrawal:** Participation in the analysis is completely voluntary. Patients may withdraw at any time without penalty. Patients will be terminated from the study if they violate the study protocol, take any non nucleoside reverse transcriptase inhibitor (NNRTIs)

or known drug inducers, fail to attend clinic visits for blood samples, refuse to provide blood samples, fail to adhere to medication, and other situations whereby patient safety is jeopardized or validity of the study results is compromised.

## **SUBJECTS**

Patients included in this analysis will be HIV-1 positive treatment-experienced individuals taking TPV/r for at least 14 days. There will be no control group in this pharmacokinetic analysis. All patients must sign informed consent to participate in this analysis. All patients must discontinue the use of all natural health products 2 weeks prior to day 1 of the study.

Exclusion criteria for this analysis will be those patients taking concomitant NNRTIs and other enzyme inducers of CYP3A4. Receipt of strong CYP3A4 inhibitors, which may result in significant interactions with study medications, will be excluded per investigator analysis.

**Sample size justification:** To examine the pharmacokinetic variability among patients, 6 – 10 patients will be required to carry out this analysis.

## **STUDY INTERVENTIONS**

### **Usual Standard of Care:**

Therapeutic drug monitoring is not the standard of care in HIV medicine. It is typically done as an adjunct in complicated cases or special populations. TPV/r is a relatively new agent to the Canadian market and switching to another PI from TPV/r with dose adjustments is done as per clinical judgment.

## **ETHICAL ISSUES**

### **Recruitment and Consent:**

Clinic physicians wishing to switch their patients off of TPV/r to an alternate PI will identify patients who are eligible for this analysis. Clinic physicians will refer their patients to the Primary Investigator or Co-Investigator to verbally discuss the analysis for consent to be obtained. An informed patient consent form will be given to the patient (Appendix A) to be signed. Only patients capable of offering consent will be included in the analysis. Once consent has been obtained, clinic physicians or an agent on their behalf will fill out a patient history form (Appendix B) and a Pharmacokinetic Test Request form (Appendix C). These forms will be submitted to the Primary Investigator.

### **Enrolment in Multiple Studies:**

Many HIV patients are enrolled in multiple studies. Concurrent enrolment in other studies will not affect safety/welfare of patients for this analysis, as the other studies provide the standard of care for HIV+ patients.

## **RISK/BENEFIT ESTIMATES**

**Benefits:**

The benefit to participation in this analysis will be to provide clinicians with a clearer understanding of TPV/r pharmacokinetics and its inductive properties on other PI's.

These data may eventually be used to develop dosing algorithms or recommendations to achieve optimal drug concentrations when changing from tipranavir to other PI-based regimens.

**Potential Harms:**

Seven to eight millilitres of blood will be collected for each trough concentration evaluation. The risk associated with the 40ml of blood taken spread out over 21 days is negligible. At the body site where the blood is taken local reactions or pain might occur which usually disappear shortly after the sample has been taken.

**PAYMENTS:**

Subjects will not be reimbursed for their participation in this analysis.

**PUBLICATION/DISSEMINATION OF RESULTS:**

The results of this analysis will be compiled in abstract format and presented as a poster at a national/international meeting. Afterwards, a manuscript will be authored and will be submitted to journals for publication.

**COLLECTION AND USE OF PERSONAL HEALTH INFORMATION:**

All samples collected will be sent for analysis. Information recorded from laboratory reports will be recorded as de-identified patient information in the database. Only the primary investigator will have a list linking the de-identified data with the identities of the patients. This information will be kept on the primary investigator's password protected computer.

**FUNDING AND CONTRACTS**

**Budget:**

Anticipated Costs:

Blood samples 5 samples per patient x 10 patients = 50 samples	
\$50/sample x 50 samples =	\$2500
Cost for presentation at a conference and publication	<u>\$2500 +</u>
<b>Total (CAD):</b>	<b>\$5000</b>

Sources of Funds:

Abbott (MFG of Kaletra) to be approached for funding

**Liability:**

The subject will be covered by the University Health Network (UHN) insurance policy for damages not covered by the provincial health plan as a direct result of study participation.

## **PARTICIPANT INFORMATION AND CONSENT FORM**

### **Switching from Boosted Tipranavir (TPV/r) to other Protease Inhibitors (PI's): A Pharmacokinetic Analysis to Ascertain the Duration of the Inductive Properties of TPV/r Following Drug Discontinuation**

**Sponsor:** **Abbott Laboratories**

**Principal Investigators:** **Alice Tseng, PharmD**

**Study Site:** **University Health Network – TGH  
585 University Ave., Immunodeficiency Clinic  
Toronto, ON M5G 2N2**

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#### **Introduction**

You are being asked to participate in a research study to investigate the blood concentration effects of changing from tipranavir/ritonavir (Aptivus™) to another drug in the same class of anti-HIV drugs known as protease inhibitors. This consent form gives information about the research study. You will be asked to read this consent form and discuss anything that you do not understand with the study staff. Once you understand the study and if you decide to participate, you will be asked to sign this form and you will be given a copy for your records. You are free to choose not to participate or to withdraw from the study at any time, without affecting the care you receive at this institution, either now or in the future.

#### **Purpose of the study**

A growing number of prescribers are switching their patients from tipranavir/ritonavir (TPV/r) to other protease inhibitors (PI's) for a number of reasons: drug interactions, side effects, lack of response, etc. Unlike other PI's, TPV/r has the ability to increase the metabolism (otherwise known as breakdown) of itself and several other drugs, including other anti-HIV drugs. This can result in lower blood concentrations of anti-HIV drugs, possibly leading to an increased risk of drug resistance. What is currently unknown is how long these properties of TPV/r persist after the drug has been discontinued and how this effects blood concentrations of the new PI's.

You are currently receiving an anti-HIV drug named TPV/r. Your prescriber wishes to change you to another drug in the PI class of medications. This study will investigate the effects on blood levels of the new PI after discontinuing TPV/r for two weeks.

A total of 6 – 10 subjects across Canada will be enrolled in the study, which will consist of 6 clinic visits. If you decide to participate, five (5) blood samples will be taken, for a total amount of approximately 35 – 40 ml (approximately 3 tablespoons).

#### **Study procedures**

##### **Screening visit (Visit 1)**

If you decide to participate in this study, you will be asked to come for a screening visit. During this visit, you will be examined by a physician. You will be asked to provide information about your medical and medication history. Your doctor will fill out a referral form to determine if you are eligible in the study.

### **Medication**

If you are eligible for participation in the study and if you are taking two 250 mg capsules of Aptivus (tipranavir) with two 100mg capsules of Norvir (ritonavir) twice daily, you will be asked to replace these capsules with three 133.3/33.3mg Kaletra (lopinavir/ritonavir) capsules plus two 100mg Norvir (ritonavir) capsules twice daily for 7 days. On day 8, you will take three 133.3/33.3mg Kaletra (lopinavir/ritonavir) capsules plus 1 (ONE) 100mg Norvir (ritonavir) capsule twice daily for 7 days. On day 15, your doctor will decide to either keep you on Kaletra (lopinavir/ritonavir) or to put you on a different PI. Kaletra and ritonavir should be taken with food, either a full meal or a snack.

If you are currently using any natural health products (herbal medicines), you will be asked to stop using these products 2 weeks prior to the second study visit.

### **Study Day 1 (Visit 2)**

You will be asked to come to the clinic early in the morning for a seven to eight-millilitre blood sample, 12 hours after your first dose of study medication the evening before. A small plastic needle (intravenous catheter) will be placed in a vein in one of your arms to draw blood. You may take your morning dose of Kaletra and ritonavir after your blood sample has been obtained.

### **Study Day 3 (Visit 3)**

You will be asked to come to the clinic early in the morning for a seven to eight-millilitre blood sample, 12 hours after your dose of study medication the evening before. A small plastic needle (intravenous catheter) will be placed in a vein in one of your arms to draw blood. You may take your morning dose of Kaletra and ritonavir after your blood sample has been obtained.

### **Study Day 7 (Visit 4)**

You will be asked to come to the clinic early in the morning for a seven to eight-millilitre blood sample, 12 hours after your dose of study medication the evening before. A small plastic needle (intravenous catheter) will be placed in a vein in one of your arms to draw blood. You may take your morning dose of Kaletra and ritonavir after your blood sample has been obtained.

### **Study Day 14 (Visit 5)**

You will be asked to come to the clinic early in the morning for a seven to eight-millilitre blood sample, 12 hours after your dose of study medication the evening before. A small plastic needle (intravenous catheter) will be placed in a vein in one of your arms to draw blood. You may take your morning dose of Kaletra and ritonavir or of your new PI after your blood sample has been obtained.

### **Study Day 21 (Visit 6)**

You will be asked to come to the clinic early in the morning for a seven to eight-millilitre blood sample, 12 hours after your dose of study medication the evening before. A small plastic needle (intravenous

catheter) will be placed in a vein in one of your arms to draw blood. You may take your morning protease inhibitor dose after your blood sample has been obtained.

### **Use of Blood Samples**

Blood samples will be used to measure the blood concentrations of tipranavir, lopinavir and ritonavir. The blood samples will be kept at Toronto General Hospital and shipped to the Ottawa Hospital for analysis. Blood collected for this study will be destroyed once the results are analysed and published. The blood samples will not be used for future studies, including any future genetic studies.

### **Benefits**

Participation in this study will not be of particular benefit to you. However, the results of this study may give valuable information on the effects on blood concentrations of changing from TPV/r to other PI's. People living with HIV/AIDS may benefit in the future from the knowledge obtained in this study. If you wish, the results of this study can be communicated to you when the results are known.

### **Risks and discomforts**

You may experience some discomfort, pain or bruising on insertion of a needle for the intravenous catheter that will be used for the collection of the blood samples. In rare cases infection may occur.

### **Participation and withdrawal**

Your participation in this study is voluntary. You may withdraw from this study at any time without it affecting the care you receive now or in the future at the Immunodeficiency Clinic at the Toronto General Hospital. The study doctor may choose to withdraw you from the study if you experience a serious reaction to any of the drugs you receive or if you fail to keep appointments. It is important to follow study directions.

### **Research-related injury**

If you are injured as a result of your participation in this study, medical care will be provided to you. Financial compensation for such things as lost wages, disability, or discomfort due to an injury is not routinely available. You do not give up any legal rights by signing this form.

### **Reimbursement**

There will be no financial incentives for your participation in this study.

### **Confidentiality**

All information about participants collected throughout the study will be confidential. If you agree to participate in this study, information that does not identify you by name may be used for medical and scientific purposes including teaching and/or publication. You will be referred to only by a code number and not by name. No records bearing your name will leave the clinic. The ethics committee, which has approved the study at this institution, as well as regulatory authorities, will have access to your medical records, for the purpose only of ascertaining that this study has been performed properly, for a period of five (5) years. A copy of this consent form will be placed in your medical chart so that health care providers at this institution will know that you are participating in a study and what it consists of.

## **QUESTIONS AND CONTACT PERSONS**

## Questions about the study

For answers to questions relating to this research study, or for information about study procedures you may contact: **Alice Tseng at 416-340-4800, ext 8763.**

## Rights as a research participant

If you have questions about your rights as a research participant and wish to discuss this with someone not associated with the study, you may contact the **Research Ethics Board at 416-946-4438.**

### *Research-related Injury*

In case of a research-related injury, you should call **Alice Tseng at 416-340-4800, ext 8763** during work hours and after hours or in an emergency, you should go to the emergency department and ask for the physician-on-call for the Infectious Disease Department.

**If you believe that you have been injured as a result of participating in this study, you may contact Alice Tseng at 416-340-4800, ext 8763.**

# CONSENT FORM

## University Health Network Toronto General Hospital – Immunodeficiency Clinic

I am being asked to come to the Immunodeficiency Clinic, Toronto General Hospital for blood sampling. The maximum volume of blood taken will not exceed 40mL (equivalent to 8 teaspoons) and the maximal study period will be 21 days. If I agree, I shall come in for \_\_\_\_\_ hour on the dates of *(5 sampling dates)*, to have \_\_\_\_\_ blood samples taken. The amount of blood that will be taken for each sample is 7-8 mL (equivalent to 1.5 teaspoon). The samples will be analyzed for research purposes only. Any information with my name on it will be kept confidential. No records bearing my name will leave the University Health Network.

My participation is voluntary. If I choose not to undergo this study, or change my mind, it will not affect my care at the University Health Network. If I have any questions or concerns I will contact **Alice Tseng at 416-340-4800, ext 8763.**

I agree to participate.

\_\_\_\_\_  
Patient's Name

\_\_\_\_\_  
Patient's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Investigator/Delegate's Name

\_\_\_\_\_  
Investigator/Delegate's  
Signature

\_\_\_\_\_  
Date

Contact persons:

**Alice Tseng, PharmD**

**Tel 416-340-4800, ext8763**

Referring Physician:		Tel:			
<b>Patient Information</b>					
Patient Last Name:		Patient First Name:			
DOB (dd/mm/yyyy):		Sex:			
Weight (lbs/kg):					
Date of last viral load (d/m/y):		Viral load:			
Date of last CD4 (d/m/y):		CD4:			
Genotyping/virtual phenotyping available? (please circle) a) Yes b) No		Date of genotyping/virtual phenotyping:			
<b>If genotype/virtual phenotype available – PLEASE FAX to 416-340-4890</b>					
<b>Antiretroviral History</b>					
Duration of time on TPV/r (months):					
Reason for TPV/r discontinuation (circle all that apply): a) Toxicity b) Viral breakthrough c) Adherence d) Other (please specify): _____					
Past antiretroviral history (excluding current Rx) – please circle one: a) Naïve b) 1 – 3 regimens c) >3 regimens					
Medications (circle all that patient is concurrently taking and indicate dose adjacent to the drug):					
NRTIs a) Zidovudine b) Didanosine c) Stavudine d) Abacavir e) Lamivudine f) Emtricitabine g) Tenofovir h) Zalcitabine		NNRTIs a) Efavirenz b) Nevirapine c) Delavirdine			
		Fusion Inhibitors a) Enfuvirtide			
		Study Agents (please list):			
PI's a) Amprenavir b) Atazanvir c) Fosamprenavir d) Indinavir e) Lopinavir f) Nelfinavir g) Saquinavir h) Ritonavir i) Tipranavir j) TMC114 (darunavir)					
<b>Other concomitant therapy</b>					
Drug	Dosing	Start Date	Drug	Dosing	Start Date
<b>Comorbidities</b>					
Hepatitis C (please circle): a) Yes b) No			Hepatitis B (please circle): a) Yes b) No		

**Pharmacokinetic Test Request**

*“I understand and acknowledge that the reported plasma concentrations are for research purposes only. Consequently, The Ottawa Hospital and The Ottawa Health Research Institute will not be held liable in any manner whatsoever if the reported plasma concentrations are used for treatment of a patient or in patient care management since the role of Therapeutic Drug Monitoring of antiretroviral drugs has not been established in clinical practice in Ontario.”*

Patient ID		
Patient Identifier:		MRN:
DOB:		PHN:
Physician Information		
Physician Number:		Name:
Physician Signature:		
Medication Information		
Drug:	Last dose taken (date/time):	Quantity taken
Kaletra (LPV/r)		# capsules
Ritonavir mg		# capsules
Tipranavir/r		# capsules
Sample		
Date of Sample:		Time of Sample:
Reason for TDM: Drug-Drug Interaction		
<p>Procedure to obtain sample:  About 8ml of blood should be collected for drug level analysis using heparinized tubes (green top). Plasma should be isolated the same day by centrifugation at room temperature (10 minutes at 900 G), and stored at -20C (or lower) until shipment. ONLY PLASMA should be shipped for analysis, in a TIGHTLY CLOSED PLASTIC tube, safely packed and shipped at ambient temperature according to the regulations for the shipment of infectious material. Samples should be sent to:</p> <p>The Ottawa Hospital, General Campus  Laboratory N1, mailbox 221  Attn: Jeremy Zhang  501 Smyth Road  Ottawa, ON K1H 8L6</p> <p>Dr. Charles la Porte should be notified via email when the sample has been shipped <a href="mailto:claporte@ohri.ca">claporte@ohri.ca</a>. The email should include the patient identification number and the date when the sample was obtained.</p> <p>Sample Processing:</p> <ul style="list-style-type: none"> <li>• Enter the Date and Time of Collection and the Collector ID in the shaded portion below</li> <li>• Label each tube with Patient Identification, DOB, and Sample Collection Date and Time as they appear on the requisition</li> <li>• Mix tube immediately after collection by inverting 10 times. Hold sample and requisition in the Ottawa Hospital Laboratory N1 storage container in the refrigerator for pick-up by the Ottawa Hospital Laboratory N1 staff.</li> </ul> <p>Collection Date:  Collection Time: _____  Collector ID: _____</p>		

**Simplified Medication Adherence Questionnaire (SMAQ)**

Do you ever forget to take your medicine?

- a) Yes
- b) No

Are you careless at times about taking your medicine?

- a) Yes
- b) No

Sometimes if you feel worse, do you stop taking your medicines?

- a) Yes
- b) No

Thinking about the last week. How often have you not taken your medicine?

- a) Never
- b) 1-2 times
- c) 3-5 times
- d) 6-10 times
- e) >10 times

Did you not take any of your medicine over the past weekend?

- a) Yes
- b) No

Over the past 3 months, how many days have you not taken your medicine at all?

- a)  $\leq 2$  days
- b)  $> 2$  days

References:

- 1) Aptivus [Package Insert]. Ridgefield CT: Boehringer Ingelheim Pharmaceuticals Inc.; 2006
- 2) Peytavin G, Marcelin A, Rouault A, Bonmarchand M, Aït-Mohand H, Cassard B, Schneider L, Costagliola D, Calvez V, Katlama C. Therapeutic Drug Monitoring of Boosted Tipranavir with and without Combination to Lopinavir or Fosamprenavir. Abstract. 13<sup>th</sup> Conference on Retroviruses and Opportunistic Infections. 2006.
- 3) Harris M, Ramirez S, Joy R, Phillips E, Harris F, Sabo JP, Kraft M, Montaner J. Effect of lopinavir (LPV) and ritonavir (RTV) dose adjustments on the pharmacokinetic (PK) interaction between LPV/RTV and tipranavir (TPV). Poster Presentation. 13<sup>th</sup> Conference on Retroviruses and Opportunistic Infections. 2006.
- 4) Back D. et al. Optimising TDM in HIV Clinical Care A Practical Guide To Performing Therapeutic Drug Monitoring (TDM) For Antiretroviral Agents. v.1. 2003. [www.hivpharmacology.com](http://www.hivpharmacology.com). Date accessed: August 9, 2006.
- 5) Marcelin AG. Et al. Virological and Pharmacological Parameters Predicting the Response to Lopinavir-Ritonavir in Heavily Protease Inhibitor-Experienced Patients. AAC 2005, 49(5) 1720-6.

Just heard a rumour that TMC114 got it's NOC in Canada...there is supposed to be a press release tomorrow....EAP to stay in place until agreements are reached with each province (\$27.84/day without ritonavir)

Linda.