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### I ANTI-HIV AGENTS

#### A. Highlights from the 3<sup>rd</sup> International Workshop on Clinical Pharmacology of HIV Therapy

The 3<sup>rd</sup> International Workshop on Clinical Pharmacology of HIV Therapy was held 11-13 April 2002, in Washington, DC. At this meeting, researchers from Europe and North America gathered to mostly present and exchange information about how some anti-HIV drugs, when taken together, can affect levels of one another in the blood. This effect is something that occurs when certain anti-HIV drugs — protease inhibitors and non-nukes (non-nucleoside reverse transcriptase inhibitors, or NNRTIs) — are taken.

In the mid-to-late 1990s, when protease inhibitors (PIs) were first released in North America, researchers found that when one PI called ritonavir (Norvir) was taken with another PI, saquinavir (Invirase), ritonavir boosted saquinavir levels in the blood much higher than when saquinavir was taken without ritonavir. Researchers also found that not only did ritonavir boost saquinavir levels, it also prolonged the time that saquinavir levels remained high. This discovery resulted in people with HIV/AIDS (PHAs) being able to take their saquinavir boosted with ritonavir only twice daily rather than three times a day. Similarly, PHAs who take other ritonavir-boosted regimens are usually only required to take their PIs twice daily. Ritonavir is now used to boost other PIs, including the following:

- amprenavir (Agenerase)
- indinavir (Crixivan)
- lopinavir (in Kaletra)

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A new PI called atazanavir (BMS-232632, Zrivada, or simply “Taz”), which is still in clinical trials, is also being tested both by itself and as a booster for saquinavir.

### **The downside of boosting with PIs**

While boosted-PI regimens can be beneficial and convenient for some PHAs, they also have their problems. Some PHAs may find it difficult to tolerate large doses of ritonavir. This drug, and likely other PIs, may increase levels of cholesterol and triglycerides in the blood of some users, increasing the risk of developing heart disease. As PI levels in the blood increase because of boosting, other side effects may appear or pre-existing side effects may grow worse. To reduce some of these difficulties, researchers are testing other drugs which also have the potential to be used as PI boosters, including the non-nuke delavirdine (Rescriptor) and the anti-ulcer drug Tagamet (cimetidine).

This issue of *Treatment Update* is devoted entirely to a report from the 3<sup>rd</sup> *International Workshop on Clinical Pharmacology of HIV Therapy*.

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### **B. Fine-tuning saquinavir**

Some HIV treatment regimens can be complex — PHAs may have to take their medications several times daily, with food and water restrictions. As well, some treatments need to be taken on a strict schedule. Such complexities may make it difficult for PHAs to take their medicines exactly as prescribed and directed — an issue called “adherence.” Not adhering to one’s drug regimen will lead to the growth of HIV that is drug resistant. Having drug-resistant virus reduces treatment options and possibly increases the risk of developing AIDS-related complications.

In the hope of improving adherence, researchers are trying to create once-daily dosing regimens. In order to do this with protease inhibitors (PIs), large doses of these drugs need to be taken with another PI, usually ritonavir (Norvir). This is because ritonavir boosts the level of the other PI in the blood for prolonged periods of time. Ritonavir is often used to boost the following PIs:

- agenerase (Amprenavir)
- indinavir (Crixivan)
- saquinavir (Invirase, Fortovase)

### **Two types of saquinavir**

Two formulations of saquinavir are currently available:

- Invirase — the original hard-gel version
- Fortovase — the newer soft-gel form

After Invirase was released (it was the first protease inhibitor on the market), researchers found that levels of saquinavir in the blood were relatively low. To improve absorption, the manufacturer, Hoffmann-La Roche, created a new formulation of saquinavir called Fortovase. Although Fortovase could be taken as a single PI in combination therapy, it was often taken twice daily, either in combination with ritonavir or without this boost.

### **Boosting saquinavir**

At first, saquinavir and ritonavir were often prescribed in a combination of 400 mg of each drug taken twice a day. Because the large amount of ritonavir in this combination was not always well tolerated, doctors conducted experiments — increasing the dose of saquinavir to 1,000 mg twice daily while reducing the dose of ritonavir to 100 mg or 200 mg twice daily. To compare the effects of these dose regimens (400/400 vs. 1,000/100), researchers across the U.S. conducted a study. The results of this small study suggest that both regimens are equally effective (see the next story for details about this study).

#### REFERENCE

1. O’Brien WA, Acosta E, Felizarta F, et al. Switch of saquinavir 400 mg/Ritonavir 400 mg to saquinavir 1,000 mg/Ritonavir 100 mg during BID four drug antiretroviral therapy. *3rd International Workshop on Clinical Pharmacology of HIV Therapy*, 11-13 April 2002, Washington DC. Abstract 2.1.
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### **C. Saquinavir with low-dose ritonavir twice daily**

Researchers at several sites in the U.S. recruited 21 HIV positive subjects for this study which compared the effect of two different boosted protease inhibitor (PI) regimens:

- saquinavir (Fortovase) 400 mg with ritonavir (Norvir) 400 mg, both twice daily
- saquinavir 1,000 mg with ritonavir 100 mg, both twice daily

The PI combinations were taken with two or

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more other anti-HIV drugs.

The profile of subjects was as follows:

- 3 females, 18 males
- average age – about 40 years
- average CD4+ count – between 400 and 700 cells
- average viral load – fewer than 400 copies

Before entering the study, all subjects were taking a combination of saquinavir and ritonavir (saq/rit) at a dose of 400/400 mg twice daily in combination with two or more anti-HIV drugs. Subjects were randomly assigned to receive one of the two previously mentioned PI dose combinations and were monitored for six months.

### Results

Three subjects left the study for the following reasons:

- painfully swollen pancreas gland, or pancreatitis (2 males)
- very high levels of cholesterol and triglycerides (1 female)

One subject, who was taking the 400/400-mg regimen had his viral load rise above the 1,000 copy mark during the study.

By the sixth month of the study, more subjects (9) on the 1,000/100 regimen had suppressed their viral load compared to subjects on the 400/400 regimen (6).

Over time, there were trends to lower triglyceride and cholesterol levels in subjects given 1,000/100. CD4+ counts were also higher in that group. As well, the 1,000/100 combination was better tolerated than the combination that included a higher dose of ritonavir.

### REFERENCE

1. O'Brien WA, Acosta E, Felizarta F, et al. Switch of saquinavir 400 mg/Ritonavir 400 mg to saquinavir 1,000 mg/Ritonavir 100 mg during BID four drug antiretroviral therapy. *3rd International Workshop on Clinical Pharmacology of HIV Therapy*, 11-13 April 2002, Washington DC. Abstract 2.1.

### D. Invirase vs. Fortovase: unexpected results?

Two formulations of saquinavir are currently manufactured — Invirase, the original hard-gel form, and Fortovase, the newer soft-gel form. A

capsule of each product contains 200 mg of saquinavir. Results from a very small study suggest that saquinavir (either Invirase or Fortovase) 1,000 mg, in combination with ritonavir 100 mg, both taken twice daily, leads to roughly equivalent levels of saquinavir in the blood. So researchers in Berlin decided to conduct a larger study.

### Study details

Twenty-four healthy, HIV negative subjects were divided into two groups and given one of the following combinations taken twice daily for one week:

- Invirase 1,000 mg and ritonavir 100 mg
- Fortovase 1,000 mg and ritonavir 100 mg

At the end of that time, subjects were switched to the combination they had not yet received.

### Results

- In analysing blood samples, technicians found that subjects who received Invirase had significantly higher levels (about 35% to 40%) of saquinavir in their blood than those who received Fortovase.
- The combination of Invirase/ritonavir was better tolerated than Fortovase/ritonavir, with fewer reports of diarrhea and bloating.

The research team suggests that PHAs who are receiving Fortovase/ritonavir and who have diarrhea, bloating and other gastrointestinal (GI) side effects may benefit from a switch to Invirase/ritonavir.

### Why was Invirase better tolerated?

Fortovase contains an ingredient called capmul which is supposed to help dissolve and disperse saquinavir rapidly once it is in the digestive tract. Some researchers suspect that it is the presence of capmul which makes Fortovase users more prone to GI side effects. This is not the first time that researchers have noted that high doses of Invirase/ritonavir are better tolerated than Fortovase/ritonavir. We wonder if some doctors may begin switching their patients who are experiencing GI toxicity on Fortovase to Invirase.

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1. Kurowski M, Sternfeld T, Hill A, et al. Comparative pharmacokinetics and short-term safety of Fortovase/ritonavir and Invirase/ritonavir 1000 mg/100 mg BID. *3rd International Workshop on Clinical Pharmacology of HIV Therapy*, 11-13 April 2002, Washington DC. Abstract 7.17.

2. Montaner JSG, Saag M, Baryliski C, et al. FOCUS study: saquinavir QD regimen versus efavirenz QD regimen: 24-week analysis in HIV-infected patients. *41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)*, 16-19 December 2001, Chicago. Abstract I-669.

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## E. Saquinavir once daily

A team of Australian, Dutch and Thai researchers has been testing a combination of the soft-gel formulation of saquinavir (Fortovase) 1,600 mg in combination with ritonavir 100 mg, both protease inhibitors (PIs) taken once daily. Taken in this way, ritonavir greatly increases saquinavir levels in the blood and prolongs the time that saquinavir remains in circulation. According to their results, after six months of observing 69 HIV positive subjects who were taking this combination of PIs together with two nukes (nucleoside reverse transcriptase inhibitors, or NRTIs), this regimen was able to suppress levels of HIV to fewer than 50 copies in the blood of 93% of subjects. In the remaining subjects, viral load remained below the 300 copy mark. This boosted regimen of saquinavir was associated with a significant increase in CD4+ cells.

### What about Invirase?

The hard-gel form of saquinavir, sold under the brand name Invirase, appears to cause fewer side effects — diarrhea, nausea, bloating — than the soft-gel formulation, sold under the brand name Fortovase. Invirase may also have other advantages, including the following:

- its smaller capsule size
- it does not need refrigeration
- it is easier to manufacture
- it is less costly

To find out if once-daily saquinavir levels are any different when taken as Invirase or Fortovase, both formulations were tested in HIV positive Thai subjects.

### Study details

Researchers randomly assigned 13 subjects (6 female, 7 male), who were already receiving Fortovase/ritonavir (1,600 mg/100 mg) once daily along with two nukes, to the following:

- Invirase/ritonavir and two nukes for one week. In the following week, Invirase was replaced with Fortovase.

Before entering the study, subjects had at least 351 CD4+ cells and their viral load was below the 50 copy mark.

## Results

Overall, subjects who received Invirase had slightly higher levels of saquinavir in their blood than when they received Fortovase. Two subjects who received Invirase and four who received Fortovase developed less-than-adequate levels of saquinavir in their blood toward the end of a 24-hour period. There was no difference in ritonavir levels when subjects were taking either Invirase or Fortovase.

### Why might Invirase be better?

The researchers suspect that higher levels of saquinavir that occur when Invirase is taken happen because the absorption of Invirase (hard-gel capsules) is slower, increasing the time that Invirase can be boosted by ritonavir.

The researchers also noted that saquinavir levels seen in this study were similar to those seen in other studies where saquinavir/ritonavir was taken in a dose of 1,000 mg/100 mg twice daily.

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1. Cardillo PG, van Heeswijk RP, Hassink EA, et al. Simplifying protease inhibitor therapy with once-daily dosing of saquinavir soft-gelatin capsules/ritonavir (1600/100 mg): HIVNAT001.3 study. *Journal of Acquired Immune Deficiency Syndromes* 2002; 29(5):464-470.
  2. Cardillo P, Monhaphol T, Mahanontharit A, van Heeswijk RP, et al. Pharmacokinetics (PK) of once-daily saquinavir-hard gel caps and saquinavir-soft gel caps boosted with ritonavir in HIV-1+ Thai patients: HIV NAT001.4 substudy. *3rd International Workshop on Clinical Pharmacology of HIV Therapy*, 11-13 April 2002, Washington DC. Abstract 1.2.
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## F. Teaching adherence to substance users

Taking medications every day exactly as directed — called adherence — is difficult for some people, particularly those who have chaotic lives and substance abuse problems. To ensure that such people take their treatment, researchers developed Directly Observed Therapy (DOT) programs where medication-taking is observed and confirmed by health care workers. This has been particularly useful in helping to control tuberculosis.

Now researchers in Miami are testing DOT in selected PHAs. What's different about the Miami study is that in some cases researchers were able to successfully educate PHAs about the importance of adherence. Moreover, preliminary results from

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this study suggest that the HIV DOT program may not have to be used life-long.

### Study details

Researchers at the University of Miami recruited 22 subjects with HIV/AIDS who had never previously used anti-HIV therapy. These subjects were considered by the research team to be at high risk for non-adherence because of the following:

- They were injection drug users.
- In some cases, they developed AIDS without knowing they were HIV positive.
- They had a history of using emergency room visits for obtaining regular medical care.
- They had a history of missing medical appointments.

All subjects received a combination of the protease inhibitors amprenavir (Agenerase) 1,200 mg boosted with ritonavir (Norvir) 200 mg taken once daily. They also received 3TC (lamivudine, Epivir) and ddI (Videx) in standard doses, both taken once daily. DOT was supervised by case managers. Subjects were monitored for six months.

### Results

Researchers were “impressed” that only 5 of 22 subjects did not complete the six-month study. In the remaining subjects, amprenavir levels in the blood were, on average, about five times greater than levels found in other studies where amprenavir was used without ritonavir.

In subjects for whom data was available, 14 of 16 subjects had achieved a viral load of fewer than 400 copies after six months. At the start of the study, CD4+ cell counts averaged about 24 cells for the group. By the sixth month of the study, the average count had climbed to 157 CD4+ cells. No serious side effects were noted in the study.

Study researchers suggest that by educating subjects, adherence improved over time in most. Whether or not this improvement in medication-taking is sustained remains to be seen. Nonetheless, educational programs such as the one explored in this study are perhaps one of several steps needed in helping to bring anti-HIV therapy to low-income injection drug users.

### REFERENCE

1. Garg V, Brill M, Rodriquez A, et al. Clinical Pharmacology of amprenavir in highly challenged naïve patients following a once daily HAART regimen under directly observed therapy (DOT). *3rd International Workshop on Clinical Pharmacology of HIV Therapy*, 11-13 April 2002, Washington DC. Poster 2.5.

## G. Could cimetidine be used as a booster?

The protease inhibitor (PI) ritonavir (Norvir) is commonly used in dual-PI combinations as a booster because ritonavir significantly raises the level of other PIs and prolongs the time they remain at high levels in the blood. This has led to the creation of twice- or even once-daily PI-based regimens. However, ritonavir is not always well tolerated. And, according to Italian researchers, there is also the theoretical risk that by exposing HIV to two simultaneous PIs, the virus may more easily develop resistance to PIs, limiting future treatment options.

A possible alternative to the boosting effect of ritonavir is the use of the anti-ulcer drug cimetidine (Tagamet). This drug was tested as a potential immune booster in PHAs in the late 1980s and early 1990s. Unfortunately, trials with cimetidine produced little evidence that this drug delayed the appearance of AIDS.

Now researchers in Italy and the UK are testing cimetidine again, this time as a possible booster for the PI saquinavir (Fortovase). The rationale for this stems from the fact that cimetidine impairs the activity of certain liver enzymes that help break down saquinavir. By reducing the effectiveness of these enzymes, cimetidine could prolong the time that saquinavir remains in the blood.

### Study details

Researchers in Turino, Italy, recruited 12 healthy, HIV negative subjects (4 females, 8 males) for a four-week study. For the first 13 days, subjects received saquinavir 1,200 mg three times daily. After this, the dose was reduced to 1,200 mg twice daily, and cimetidine was added at a dose of 400 mg twice daily.

### Results

On average, when cimetidine was used, the amount of saquinavir that entered the blood increased by 120%. Moreover, levels of saquinavir remained higher for longer when it was taken with cimetidine than when it was taken without.

The next step is to conduct studies of cimetidine and saquinavir in HIV positive people to confirm these findings and to study the long-term results and side effects.

#### REFERENCE

1. Boffito M, Trentini L, Raiteri R, et al. Pharmacoenhancement of saquinavir by cimetidine: an alternative booster to ritonavir? *3rd International Workshop on Clinical Pharmacology of HIV Therapy*, 11-13 April 2002, Washington DC. Abstract 2.8.

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### H. Delavirdine in rescue regimens

There are currently three licensed non-nukes (non-nucleoside reverse transcriptase inhibitors, or NNRTIs) available:

- delavirdine (Rescriptor)
- efavirenz (Sustiva)
- nevirapine (Viramune)

The most commonly used drugs in this class are efavirenz and nevirapine. However, delavirdine is increasingly being considered for study as a booster for protease inhibitors (PIs) because it can block the activity of liver enzymes that break down PIs.

Researchers in British Columbia, Canada, studied the effect of switching subjects who used efavirenz or nevirapine to delavirdine or simply adding delavirdine to a pre-existing regimen that included PIs. The main purpose of this study was to assess delavirdine's impact on levels of PIs in the blood.

#### Study details

Researchers reported results on 15 male subjects whose previous treatment regimens were failing. All subjects received Kaletra (lopinavir/ritonavir) twice daily with or without the following PI:

- amprenavir (Agenerase) 750 mg twice daily
- saquinavir (Fortovase) 800 mg twice daily

All subjects also received various nukes and delavirdine 600 mg twice daily. Technicians performed an extensive analysis of blood.

#### Results

A total of six subjects left the study due to side effects from delavirdine — mostly nausea and diarrhea. In general, switching from efavirenz or nevirapine to delavirdine resulted in higher levels of lopinavir, ritonavir, amprenavir and saquinavir. In subjects who had not recently used another non-nuke, adding delavirdine to their regimens did not consistently raise PI levels.

This type of study, although designed to assess changes in drug levels in the blood, illustrates the complex treatment regimens that some PHAs must take in order to suppress their viral load and maintain or increase their CD4+ cell counts. Further study of such regimens is needed to find out about their toxicities and long-term benefits.

#### REFERENCE

1. Harris M, Alexander C, Ting L, et al. Delavirdine effects on exposure to ritonavir-boosted protease inhibitors. *3rd International Workshop on Clinical Pharmacology of HIV Therapy*, 11-13 April 2002, Washington DC. Poster 7.15.

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**Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.**

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**Writer** Sean Hosein  
**Research assistant** Tim Rogers  
**Editor** RonniLyn Pustil

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**by mail**  
505-555 Richmond Street West  
Box 1104  
Toronto, Ontario  
M5V 3B1  
Canada