NATAP'S NATIONAL AIDS TREATMENT ADVOCACY PROJECT

POSITIVE + INFORMATION

Edited and Published by
Jules Levin
Executive Director/Founder
NATAP

580 BROADWAY, SUITE 1010, NEW YORK, NY, 10012 **1-888-26-NATAP** (212) 219-0106 fax (212) 219-8473 info@natap.org **http://www.natap.org**

IN THIS ISSUE:

Tipranavir

Tipranavir: new protease inhibitor is effective in large studies for patients with extensive resistance to currently available protease inhibitors

An Expanded Access Program started November 30, 2004 <https://www.tpv-eap.com>, which will provide access to tipranavir now through your doctor for patients who need it. You can also call 1-888-524-8675 for more information about the EAP. It's recommended to take tipranavir along with at least one additional new drug, to which a patient is fully sensitive. Fuzeon, a new entry inhibitor drug, is an option to consider and is being made available by Roche for individuals who are unable to access it. You can find out more by speaking to your doctor.

- 630 patients with extensive treatment-experience resistance to protease inhibitors were randomized to tipranavir or another boosted PI regimen in RESIST 1 Study

- Patients were highly treatment experienced: median of 12 prior antiretroviral HIV medications: 6 NRTIs, 2 NNRTIs, 4 protease inhibitors; patients had an average of 15 baseline protease mutations

- 41.5% of patients taking tipranavir vs 22.3% taking other PI regimens had at least 1 log reduction in viral load ($p<0.0001$) (Intent-To-Treat: non-completer=failure analysis, most stringent).

- 34.7% of patients taking tipranavir vs 16.5% taking other PI regimens had <400 copies/ml (ITT: non-completer=failure analysis)

continued on the next page...

New HIV Drug Class: 'Entry Inhibitors' Which Block HIV from Entering CD4 Cell

Perhaps the greatest hope in the foreseeable future of HIV treatment is the development of entry inhibitors. There are 4 promising orally administered entry inhibitors being studied in patients.

This report explains how entry inhibitors work. Below are extensive reports reviewing the current status of 5 new entry inhibitor drugs in active development: UK-427,857 CCR5 inhibitor (Pfizer), BMS' attachment inhibitor program, SCH-D CCR5 inhibitor (Schering-Plough), GW873140 CCR5 inhibitor (GlaxoSmithKline), and TNX-355 (Tanox) attachment inhibitor administered by infusion every week or two. These drugs are orally administered, except for the Tanox drug, which is administered by infusions at least one week apart perhaps two.

The three steps required for HIV to enter cells: attachment, binding to a co-receptor (CCR5, CXCR4), fusion of HIV into cell (CD4 cell). The currently available classes of drugs work to prevent the process of HIV reproducing itself and infecting new cells after HIV enters the CD4 cell: nucleosides (AZT, d4T, abacavir, tenofovir, 3TC, FTC, ddI) and non-nucleosides (efavirenz, nevirapine, delavirdine), and protease inhibitors (Reyataz, Kaletra, Crixivan, Saquinavir, Fosamprenavir, Viracept).

continued on the page 3...

• If also taking Fuzeon, 47% taking TPV/r vs 21.9% taking other PI regimens had <400 cp/ml

• 25.1% of patients taking tipranavir vs 10% of patients taking other PI regimens had <50 copies/ml. If also taking Fuzeon: 32.8% taking TPV/r vs 14.3% taking other PI regimens had <50 c/ml

• Viral load reduction at week 24: -0.88 for patients taking TPV/r vs -0.28 for patients taking other PI regimens. About 36% of patients in the study were taking Fuzeon.

• TPV/r treatment response was improved with use of other active ARV drugs in the optimized background regimen.

24 week results were reported just weeks ago for the first time from the 2 large phase III trials of tipranavir, the new ritonavir-boosted protease inhibitor developed for patients with resistance to currently available protease inhibitors. The RESIST-1 & 2 Studies examined the performance of tipranavir in over 1400 highly treatment-experienced patients in the USA and internationally. These studies found tipranavir is effective for many patients with extensive resistance to currently available protease inhibitors.

Study participants had on average 12 prior antiretroviral HIV medications (6 nukes, 2 NNRTIs, and 4 protease inhibitors), and had an average of 15 protease inhibitor drug mutations prior to entering the study. The two RESIST studies had similar results so I'll report here the results from RESIST-1 which was conducted in the USA.

Although patients in this study had extensive resistance to available protease inhibitors ranging from 12-fold to 77-fold, the average viral load reduction was -1.5 log copies/ml at week 4, a potent response. Unfortunately, by week 24 the viral load on average increased for some patients. At week 24, the average viral load reduction was -.88 log copies/ml. However, --a very important point-- patients who also took Fuzeon, the new entry inhibitor, along with tipranavir had a better response: 35% of all patients receiving tipranavir in this study achieved <400 copies/ml HIV viral load at week 24, but for patients who also took Fuzeon 47% had <400 copies/ml HIV viral load. *This demonstrates a very important point*: when starting a new regimen, it is crucial to achieving success to start simultaneously at least 2 new drugs to which the patient is fully sensitive. This will provide the best opportunity to achieve a good viral load response and for the response to be durable.

Tipranavir is expected to receive FDA approval around March/April 2005. If a person needs immediate access to tipranavir, the Expanded Access Program has started and a patient can gain access to it through their doctor. As well, Roche is making Fuzeon available to take along with tipranavir in this study if a patient needs availability. This way a patient can start with two new drugs and this should help in achieving the best viral load reductions that hopefully can also be durable.

We have long awaited results from large-scale efficacy studies of tipranavir. RESIST 1 and RESIST 2 are the large phase III studies conducted by Boerhinger Ingleheim examining the antiviral activity and safety of tipranavir. The 24-week results of RESIST-1, which is the US based study, was reported at ICAAC (October 04), and RESIST-2 results were reported at the European HIV Conference in Glasgow November 2004. Tipranavir is dosed at 500 mg twice daily along with 200 mg of ritonavir also twice daily to boost tipranavir levels.

RESIST study participants were randomized to receive tipranavir (500/200) or other boosted PI regimens, and all participants also received 2 nukes which could be selected by using resistance testing. The baseline characteristics were comparable for study participants who received tipranavir or the other PI regimen: 90% men; 75% white, 21% black; 8% had hepatitis; average CD4 count was 120; average viral load was 66,000 copies/ml; and on average each patient already had 15 protease inhibitor drug mutations. Patients had a phenotype resistance test (Virco assay) before starting the study and were in general sensitive to tipranavir, but highly resistant to other protease inhibitors: on average study participants had 77-fold resistance to Kaletra (LPV/r), 39-fold resistance to indinavir, 27-fold resistance to saquinavir, and 12-fold resistance to amprenavir.

36% of the study participants in RESIST-1 also were taking Fuzeon, but some patients had been on Fuzeon for a period of time before starting the study. Other patients started Fuzeon for the first time when they started tipranavir in this study; these patients were more likely to see a better viral response because the patients who had previously started Fuzeon may have already developed resistance to Fuzeon.

Results

Viral Load Response

The study protocol defined a treatment response as 1 log or more viral load reduction from baseline to week 24. You can see in the table below that patients who received tipranavir (TPV/r) did much better than patients who received other protease inhibitors: they had a better reduction in viral load, and were more likely to achieve an undetectable viral load. Patients who also took Fuzeon along with tipranavir had better success in achieving undetectable viral load (47% had <400 copies/ml and 33% had <50 copies/ml).

(ITT analysis)

	TPV/r	**Other PIs**
% with Treatment Response (1 log viral load reduction)	41%	22%
Median viral load reduction		
Week 4	-1.5 log	0.5 log
Week 24	-0.88	-0.28
Proportion with Undetectable Viral Load		
<400 copies/ml	35%	16%
TPV+Fuzeon	47%	22%
<50 copies/ml	25%	10%
TPV+Fuzeon	33%	14%
Median CD4 Increase	+36	+6

Side Effects
Patients taking TPV/r were more likely to experience grade 3-4 laboratory abnormalities in lipids (cholesterol, triglycerides) and in liver enzyme function tests (ALT/AST). 4% of patients taking TPV/r experienced grade 3-4 elevations in cholesterol; 21% of patients taking TPV/r experienced grade 3-4 elevations in triglycerides. 6.9% of patients taking TPV/r experienced grade 3-4 elevations in ALT. 19/22 TPV/r patients with grade 3-4 ALT/AST were asymptomatic and continued treatment. 64/66 patients with grade 3-4 triglycerides continued treatment.

New HIV Drug Class: 'Entry Inhibitors' Which Block HIV from Entering CD4 Cell cont'd.

Since Entry Inhibitor drugs target the virus before it enters cells, this is a potentially attractive proposition because it's possible that the toxicities, particularly lipodystrophy, associated with currently available drugs may be less likely to be associated with entry inhibitors.

We are entering a new era of HIV treatment not unlike in 1995 when protease inhibitors were launched. In 1995, protease inhibitors were a new class of HIV drugs that were pivotol in launching a new and better approach to treatment of HIV. Two years ago Fuzeon was the first 'entry inhibitor', a fusion inhibitor, to become available for treatment. Fuzeon is administered by subcutaneous self-injection, like insulin for diabetes, but four orally administrated new entry inhibitors, CCR5 & attachment inhibitors, are now in studies in HIV+ individuals at various stages of clinical development.

The furthest along in development is Pfizer's UK-427,857, which is entering large Phase III studies at the end of 2004. Schering Plough's SCH-D is close behind as phase III studies are expected to start soon. Hopefully this new class of HIV drugs will be proven safe & effective. If so, a new era of therapy for HIV will be born. Around the corner is the GlaxoSmithKline CCR5 inhibitor GW 873140 and Bristol-Myers Squibb's attachment inhibitor.

If these drugs are safe and effective, we will still have to elucidate through studies & clinical use how to use each of these new drugs. Some key questions are:

(1) how will we use entry inhibitors within the context of currently available classes of drugs (NRTIs, NNRTIs, PIs)
(2) can we combine entry inhibitors
(3) can we compose a regimen entirely of entry inhibitors
(4) will safety & tolerability issues emerge
(5) can we combine Fuzeon with other entry inhibitors in patients with advanced HIV

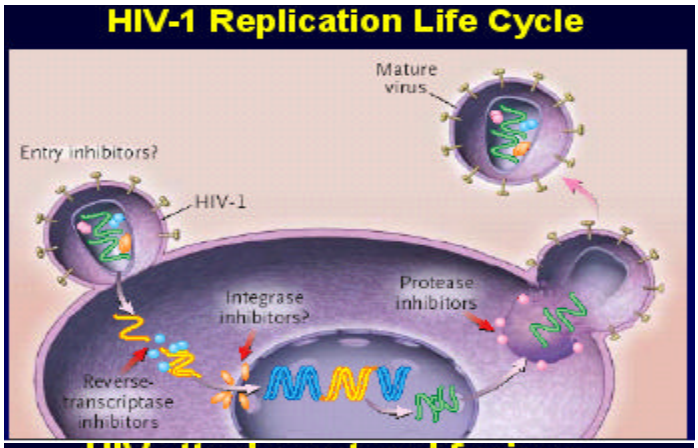
Introduction to how Entry Inhibitors Work
Entry inhibitors block the virus' ability to enter & infect a cell. Essentially there are two steps to 'Entry' of HIV into the CD4 cell. HIV attaches to the CD4 cell & then fuses with it. After fusing with the cell, HIV can dump its genetic material into the CD4 cell, the material it needs to reproduce itself in the CD4 cell. There are two steps to attachment: attaching to the CD4 receptor and then to a co-receptor, either CCR5 or CXCR4. Currently available HIV drugs (nukes, non-nukes, protease inhibitors), other than Fuzeon, prevent HIV from reproducing once HIV is in the cell.

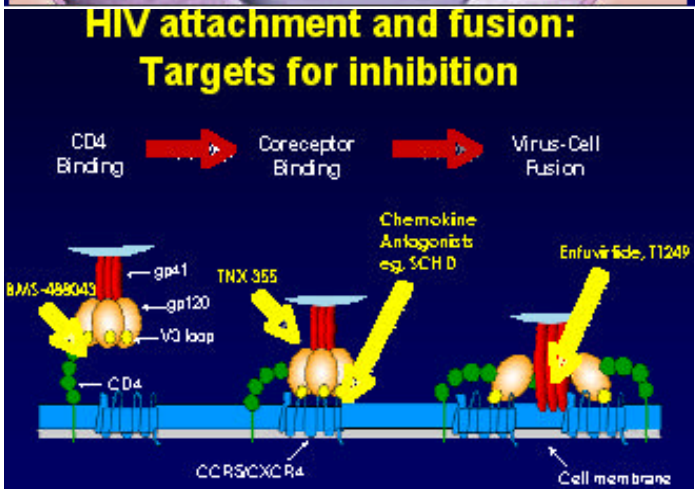
How Entry Inhibitors Work: (1) Attachment, (2) Co-Receptor Binding, (3) Fusion

The events of virus entry into cells occur in several steps: the first step in the HIV-cell interaction that leads to virus entry is "attachment" and binding to a co-receptor, followed by "fusion" which is necessary for entry into the cell: The virus' gp120 surface molecule fits into the CD4 receptor on the cell surface like a key in a lock and the virus becomes attached, but it is left hanging loosely from the cell surface by this gp120-CD4 connection.

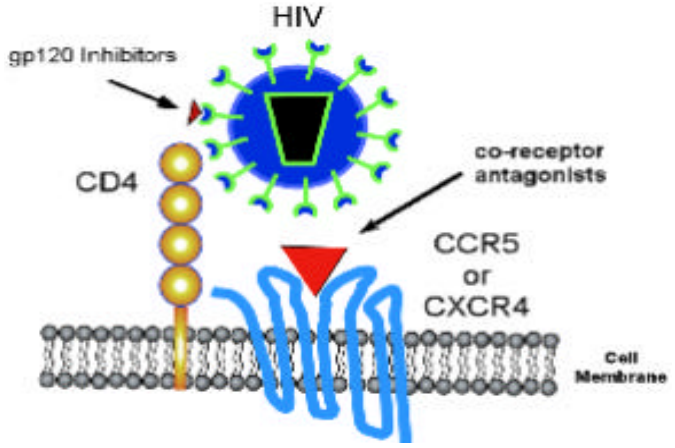
Once it is attached, gp120 is bound to another receptor (either one of the "co-receptors" for gp120, called CCR5 or CXCR4). Thus doubly bound, the gp120 molecule flips around to expose HIV's previously hidden "harpoon" molecule, gp41.

Once the free end of gp41 spears the cell membrane, solidifying HIV's attachment, gp41 doubles itself up into a tight coiled-coil structure. This brings the two ends of gp41 (one holding HIV, and one holding the cell membrane) very close together. The cell membrane and virus envelope come into contact and fuse. Fusion results in the virus' contents getting dumped into the interior of the cell. Virus 1, Cell 0.





CCR5 Inhibitors: Schering (SCH-D), Pfizer (UK-427,857), GSK (GW873140)



Arole for extracellular agents: attachment and entry inhibitors
In the quest for agents that might have improved activity compared with older drugs, investigators have wondered if equally potent drugs targeting the parts of the virus life cycle that occur outside the cell might be better than drugs targeting events that take place inside infected cells. Why? The toxicities and side effects of PIs, NRTIs, and NNRTIs may not occur when using drugs that target HIV before it infects a cell. Perhaps lipoatrophy might be prevented or be less severe. Our limited time of use with Fuzeon suggest this may be possible. Here is a second reason why entry inhibitors might be better. Anti-HIV drugs that must be inside the cell to be active can be efficiently neutralized by some cells, using primitive, innate self-defense mechanisms such as "efflux pumps" which sense toxins and eject them outside of the cell. Many experts believe that this kind of "cellular resistance" could be an important reason for the viral persistence and evolution in patients on seemingly potent combination therapies. "Extracellular ART" would completely circumvent this problem. More immediately, any drug working on a separate part of the virus' life cycle would have little potential for "cross-resistance" with NRTI, NNRTI or PIs.

Current Therapy
The current range of approved HIV medications includes drugs that inhibit various steps in the virus' life cycle. Most classes of these drugs act inside HIV infected cells: many agents interfere in one way or another with reverse transcriptase (RT)-a viral enzyme which the virus uses to replicate itself within the cell. ("Nucleoside or nucleotide" and "non-nucleoside" RT inhibitors--NRTI and NNRTIs--are chemically very distinct and can work together with powerful synergy against this one target.) Other existing drugs interfere with the activity of HIV protease-which the virus uses to package itself for export out of an infected cell, to begin new rounds of destruction. The third major drug target that has been successfully exploited is HIV gp41-a molecule on the virus' surface that has to change its shape in a specific way in order for the virus to "fuse" with the cell it is attacking and empty its payload inside. At the Bangkok Intl AIDS Conference in July 2004, researchers reported 96 weeks followup of Fuzeon phase III studies showing the drug to be durably potent for the 2 years. The 96-week data is reported in this newsletter.

New Entry Inhibitor Drugs Moving Quickly in Human Studies

There are several entry inhibitors moving along in clinical development-- in studies in HIV+ individuals. **Pfizer's CCR5 antagonist 'inhibitor' UK-427,857** is entering phase III studies now & has shown antiviral effectiveness by significantly reducing HIV viral load in studies so far conducted. In a 10-day monotherapy study UK-427,857 was administered to patients at doses up to 300 mg bid & appeared safe & tolerable and reduced viral load by 1.3-1.6 log (see UK-427,857 report below).

Bristol-Myers Squibb has a program with a stable of 'attachment' inhibitor candidates. It's possible that CCR5 and attachment inhibitors can be used together in combination therapy, and there is potential for a regimen composed entirely of entry inhibitors. BMS is developing an attachment inhibitor, which will be a novel, oral small-molecule **attachment inhibitor** of HIV-1 that blocks viral entry by preventing the binding of the viral envelope protein gp120 to cellular CD4 receptors. Attachment is the earliest step in the entry of the virus into the host cell; it is the attachment of gp120 on the virus coat to the CD4 receptor on the cell surface. At the 2004 Retrovirus Conference, BMS researchers presented data on one of the candidates '043'. In an 8-day phase II monotherapy study of daily dosing of 800-1800 mg every 12 hours, HIV viral load was significantly reduced by 1-2 logs and the drug appeared safe & tolerable. BMS is refining this drug candidate for 'swift' development. Last year they showed data on BMS-378806 a fore-runner for the new molecule, BMS-488043, they presented at this past CROI conference. Both of these are small molecules, which have activity against viruses using all co-receptors, and in in vitro and animal studies appear non-toxic with no cross-resistance to currently available agents. The EC50 for the new compound is 36.5 compared to 61.5 for BMS-378806 and it has a superior half-life. The latest study, AI430-003 was a proof of concept trial involving subjects not receiving antiretroviral therapy and with a CD4 count >250 and a viral load between 5 and 500,000 copies/mL. Subjects were randomised 4:1 to receive active drug or placebo and two cohorts of 15 subjects were given 800mg or 1800mg twice daily with a high fat meal. There were 2 women in the lower dose cohort and 1 in the 3600mg cohort. Baseline median viral load was 4.77 and 4.65 log10 copies/mL and median CD4 count 413 and 372 respectively. Viral load decline at day 8 was 0.72 and 0.96 log10 copies/mL for the two dosage groups and maximal median decline was 1.01 and 1.23 log10 copies/mL. CD4 cell rises were seen of 106 cells (range -214 to +272) for the 1600mg arm and 48 cells (range -177 to +191) for the 3600mg arm. The percentage rates at the two dose levels was for >1-log decline, 58% versus 67%, and for >1.5-log decrease, 24% compared to 42%. No serious adverse events or discontinuations occurred and apart form mild fatigue in 4 subjects and headache in two no side effects were reported. The optimization of exposure-response relationship is ongoing for this drug and it appears a very promising new agent.

Schering-Plough is developing its' 2nd generation **CCR5**

inhibitor, SCH-D. At CROI 2004, results were reported from a 14-day monotherapy study in which patients received 10, 25 & 50 mg twice daily, and HIV viral load reductions were 1 to 1.6 log, and the drug appeared safe & tolerable. To date two hundred and seventy five individuals have received this agent and no significant toxicity has been seen. There appears to be a good correlation between in vitro activity and in vivo efficacy, which will allow correlation of potency to be evaluated. It would appear also that this drug is extremely difficult to select resistant viruses for which bodes well for the durability of efficacy, however this will only be clear when prolonged dosing has been undertaken. This drug is in further development, phase II studies are ongoing (see report below on this attachment inhibitor development program).

GlaxoSmithKline is also developing a new orally administered drug from this new class of HIV antivirals, which demonstrated a 1.5 log reduction in viral load at the first presentation of this data at the recent ICAAC (October 2004). **GW873140** is a novel CCR5 receptor antagonist that binds specifically to human CCR5 and has demonstrated potent in vitro anti-HIV activity. At the 2004 Retrovirus Conference GSK researchers reported results from an early study looking at single & multiple doses to investigate safety, tolerability & drug levels (pharmacokinetics) in healthy volunteers. The study investigators said the drug was safe & tolerable. Based on drug levels 'PK' in the study researchers said they would investigate once or twice daily dosing. GSK is developing this drug & results from initial studies in patients are reported below. Subsequent phase IIb studies are planned including a look at nuke-sparing therapy.

Steve Piscitelli from GlaxoSmithKline presented exciting data on GW873140 at CROI. This drug has an IC50 of 1-5nM, and a unique binding profile to the CCR5 receptor, which suggests that the binding sites or effect of binding of GW873140 on CCR5 are different from those of previously published CCR5 inhibitors. The data also might help to construct the optimal combination regimens of CCR5 inhibitors. A double blind randomized placebo controlled study was conducted in 70 fasted uninfected subjects (57 men and 13 women). Subjects received single doses of 50, 200, 400, 800 or 1200mg fasted or 400mg with a standard breakfast in cohorts of 10 subjects (8 treated and 2 placebos). Thereafter a multiple dose phase was conducted with a 7 day dosing of 200, 400, 600 and 800mg twice daily. Adverse events were reportedly generally mild & self-limiting; primarly GI in nature: mild to moderate side effects included abdominal cramping, nausea, loose stools, and diarrhea. No changes occurred in ECG measures, specifically not QT prolongation, which has been a potential side effect (in other drug development programs) and no serious or grade 3 or 4 adverse events were seen. The AUC increased from 130 to 479 ng/ml from the 200 to 800mg dose level and food increased the AUC by 1.7-fold and the Cmax by 2.2-fold. In the single dose arms there was 66-84% occupancy of the receptor at 24hrs post dose whereas in the multiple dose arms occupancy at 2 and 12 hours post dose was 93-99%. The prolonged CCR5 occupancy suggests a long half-life for GW873140 binding to the receptor, suggesting QD or BID dosing. This agent unfortunately appears to have minimal CNS penetration but looks set to advance through the development process at a rapid pace with a favourable safety profile and viral load decline data. As with the other CCR5 inhibitors under evaluation, the question of whether the drug can be given once daily needs clarification in further clinical trials.

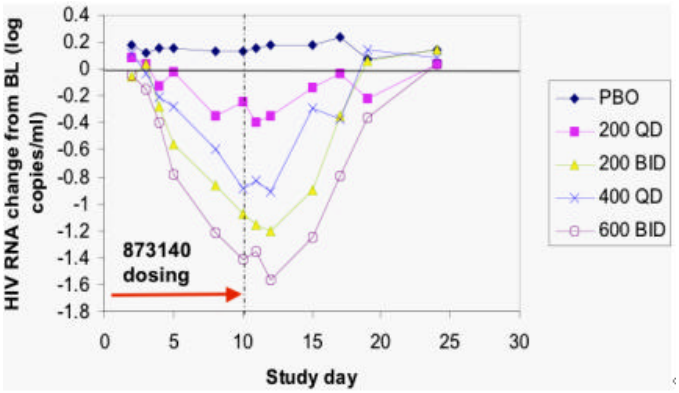
At the ICCAC conference (October 2004), results were reported from the first study in HIV+ individuals-- **'873140, A Novel CCR5 Antagonist: Antiviral Activity and Safety During Short-Term Monotherapy in HIV-Infected Adults'.** This was a 10-day monotherapy study in HIV+ treatment-naive and experienced HIV-infected individuals. The study was a randomized, placebo-controlled trial with 40 patients (8 active/2 placebo per dose cohort), and 4 treatment arms.

Doses were administered for 10 days with a moderate fat (30%) meal: 200mg once daily, 200 mg twice daily, 400 mg once daily, and 600 mg twice daily. Serial sampling was performed for HIV RNA, PK, receptor occupancy, and safety on treatment and for 14 days post-dosing.

Both treatment naïve and experienced patients were enrolled. Experienced patients had no ARV treatment for the preceding 12 weeks and could have failed up to 2 previous HAART regimens. Plasma HIV RNA was >5000 c/ml and stable over the previous 30-90 days. CD4 nadir was >200 cells. The Virologic Phenosense HIV Entry assay was used to try to identify whether patients had R5 or X4 virus upon study entry. This assay has a limit of 10%, ie if a patient has less than 10% of their viruses as X4 the assay won't pick it up. In this study, subjects had to have only R5-tropic virus at entry.

Baseline Characteristics of Study Patients. Average age 34-49 yrs. 4 females. 19 patients were treatment-naïve. 8 patients were HCV+ and no significant changes were observed in HCV viral load during 873140 therapy. Average CD4 count was 297-404. HIV RNA viral load was 4.2-4.7 log copies/ml (about 50,000 copies/ml). There were 20 whites, 16 african-americans, and 4 latinos in the study.

Median HIV RNA Viral Load Changes from Baseline
Median viral load change from baseline at nadir:
Placebo: -0.09 log (n=9)
200 qd: -0.51 log (n=7)
200 mg bid: -1.20 log (n=8)
400 mg qd: -1.02 log (n=8)
600 mg bid: -1.49 log (n=8)



% Subjects with 1 log drop at Nadir

placebo:	0%
200 qd:	16.7% (1/7)
200 bid:	75% (6/8)
400 qd:	62% (5/8)
600 bid:	100% (8/8)

Viral Tropism Monitoring

CCR5 and CXCR4 serve as the co-receptors for HIV infection and binding of the virus to one of these co-receptors is required for viral entry. As the study reported below finds for most patients, the virus population in early HIV infection uses CCR5 receptors and is classified as 'R5-tropic'HIV. Over time, however, virus that is capable of using the CXCR4 co-receptor can emerge; such virus is classified as pure "X4-tropic" or "R5/X4-tropic" (dual/mixed).

Tropism and IC50 was evaluated in this study at screening & days 1, 5, 10, and 24. Investigators reported minimal variation was observed in fold change in IC50 versus control virus during the study suggesting that in vitro resistance to this CCR5 inhibitor did not develop during this short-term study. One subject in the study at the 200 mg qd dose had R5-tropic virus on day 1 and day 5, dual/mixed-tropic virus on day 10, and R5-tropic virus on day 24. Investigators report that preliminary analysis demonstrated dual tropic virus was pre-existing on day 1, but below assay detection limit.

Circulating Lymphocyte CCR5 Occupancy

Median R5 receptor occupancy on day 10 was >97% across all doses. Substantial and prolonged receptor occupancy was observed for several days post-dosing. Higher doses tended to result in longer duration of occupancy after discontinuation of dosing, but there was no correlation after 10 days of dosing between occupancy and antiviral activity.

Safety and Tropism

There was 1 withdrawal (unrelated to drug); no serious adverse events; no grade 4 clinical AEs; no clinically significant abnormalities on EKG; most common AE: loose stools, diarrhea, abdominal pain, nausea, flatulence, which generally resolved on drug within 3 days. Other adverse events included headache, dizziness, fatigue. Several patients on placebo & drug reported CNS side effects. The authors said GW73140 was well tolerated with minor, self-limiting GI events as the most common AE.

Development for this drug appears on the fast-track. Phase IIb clinical trials including NRTI-sparing therapy are being planned.

One of the important questions facing the development of CCR5 inhibitor drugs is will R5 inhibitors be effective and have antiviral activity for individuals with CXCR4 virus, that is HIV that uses the CXCR4 receptor to connect to cells. Another important question is will R5 inhibitors be safe for patients with advanced HIV. There has been some controversy and concern that patients with advanced HIV (low CD4 count) could see their virus switch from R5 to X4, and this might accelerate HIV progression. This concern is speculative as data so far suggests this would not occur. But that's why studies are conducted. Phase II and III studies being conducted for all the CCR5 inhibitor drugs are expected to provide answers to these questions. See further discussion about this below in the article by Lisa Dunkle on **Schering-D : CCR5** in the section called Intriguing Questions. Because of these controversies two studies on the subject were presented at the ICAAC meeting.

Recent study finds that most HIV+ individuals appear to have CCR5 virus, few have CXCR4. HIV that uses the CCR5 doorway (called R5-tropic virus) is the type typically transmitted to a newly infected person. As HIV disease gets worse, the virus may change to the CXCR4 receptor (and become X4-tropic). But that doesn't always happen. Plenty of people get to the final stages of AIDS with only R5 virus; perhaps most people with low CD4s may have R5 virus. In vitro study has found X4 or dual tropic virus non-responsive to R5 inhibitor drug, but clinical studies have yet to answer this question. Rating virus in 325 treatment-naive people and 117 with treatment experience, GSK's Jim Demarest found in his study which he reported at ICAAC that R5-tropic virus predominated in both groups. R5-tropic HIV turned up in 88% of treatment-naive people, 67% of treatment-experienced people, and 82% overall. He found mixed R5/X4 virus in 12% of the naive, 28% of the experienced, and 16% overall. Purely X4-tropic virus cropped up in none of the naive, 5% of the experienced, and 2% overall. These data reflect the HAART era. Before HAART about 50% of patients with AIDS had X4 virus. This is speculative, but X4 virus might be akin to an opportunistic infection, reversible by HAART.

A multivariate analysis involving treatment-experienced people picked out three factors that raised the odds of having X4 virus:

- PI experience: odds ratio (OR) 4.167, P = 0.0085
- Each additional year of age: OR 1.055, P = 0.039
- Non-Caucasian race: OR 5.13, P = 0.0015.

A couple of points. We don't know the clinical significance of having X4 or R5 virus, and we don't know if having X4 is cause or effect. In other words, we don't know if having X4 predicts advancing disease or if having X4 is simply a reflection of having advanced disease. So, detecting X4 does not necessarily mean that a patient will advance in disease status, but it could mean they developed X4 as a result of advancing HIV. I hope & expect that clinical studies by GSK, Schering, and Pfizer will answer these important questions. Finally, multivariate analysis among treatment-naives in the GSK study found CD4/CD8 ratio associated with X4 tropism: 0.1 decrease in ratio increases odds ratio of detectable X4 tropism by 1.76 (OR), p<0.0001).

The PI and racial variables may be misleading, Demarest warned. PI experience could simply be a marker of more overall antiretroviral experience, and the racial finding may reflect poorer access to health care among nonwhites, and thus a higher risk of advanced HIV disease, when X4 virus emerges.

A second study was also reported at ICAAC by London's Chelsea and Westminster Hospital. Graeme Moyle traced

coreceptor tropism in 563 people, 161 with and 402 without treatment experience. Compared with people carrying R5 virus, those with mixed R5/X4 virus or just X4 tended to have a higher viral load (66,228 versus 35,800 copies/mL, P < 0.001), lower CD4 count (231 versus 307 cells/µL, P = 0.007), and lower CD4% (15.4% versus 18.7%, P = 0.001). This analysis found 60% of patients with <50 CD4s had R5 virus, 58% with <100 CD4s had R5 virus, and 85% of patients with 100 to >300 CD4s had R5 tropic virus. Moyle's multivariate model confirmed the highest risk of X4 tropism in people in:

- The highest viral load quartiles
- The lowest CD4 quintiles
- The lowest natural killer (NK) cell quintiles

But, reflecting Demarest's results, Moyle's study showed that R5- and X4-tropic virus can be found among people in all CD4 and viral load strata. So when coreceptor antagonists do find their way to pharmacy shelves, clinicians may have to test for tropism before prescribing these drugs. Unless studies find that R5 drug inhibitors are safe and have antiviral activity for individuals with X4 virus.

UK-427,857, a New CCR5 (entry) Inhibitor: Viral Load, Safety QTc Interval, Tolerability, Food Effect in 10 Day Monotherapy Study, Orally Administered

- first CCR5 (entry) inhibitor to enter large Phase III studies, expected to begin soon
- 10-day monotherapy study shows –1.3 to –1.6 log viral load reductions
- Genetic evidence indicates blocking of the CCR5 receptor on cells should have a profound effect on viral replication and HIV disease progression in patients who carry R5 HIV variants.

Safety question regarding possible tropism switch. In vitro studies find dual & X4 tropic virus may not respond to a CCR5 inhibitor. But patients with a low percentage of dual or X4 virus may respond to R5 inhibitors or HAART containing R5 inhibitors. Still, there may be numerous factors involved in response to R5 inhibitor therapy by a dual or X4 tropic patient, which hopefully phase III studies will evaluate. Before reporting the results of the antiviral activity and safety observed in the 10-day monotherapy study of UK-427,857, here is the report presented at ICAAC (October 2004) regarding two patients in the study who were found to have R5/X4 dual tropic HIV after 10 days of monotherapy with UK-427,857. One of the theoretical safety concerns of using a CCR5 inhibitor drug is that patients might switch from R5 to X4-tropic virus which has been associated with accelerated progression of HIV. That is, HIV switches where it binds on the cell, from the R5 co-receptor to the X4 co-receptor. So far there has been no data from studies in patients indicating this can occur nor that it is a real safety concern, but a concern was raised when it was discovered that these two patients had dual tropic virus after 10 days of treatment, because pre-study testing found only R5 virus. Other than these 2 patients, virus has remained CCR5 tropic at all timepoints analysed for remaining patients followed (61/63) in the 10-day monotherapy study. Here is the report from Pfizer presented at ICAAC on the two patients.

Clinical Response (so far there is no indication that the presence of dual tropism found in these 2 patients has had any negative impact, but follow-up continues): the 2 patients (A & B) who were both taking 100mg qd had viral load decreases of 0.71log10 and 1.26log10 copies/ml respectively. Both patients were treatment -naïve. Further follow-up of patient B was done to evaluate the evolution of his virus over time. At the last time point (1 year after study start) he remained clinically well and on no anti-retroviral treatment. His viral load is not significantly different from values obtained prior to dosing, but his CD4 count has declined by approximately 40% from his lowest value pretreatment. As he has stopped HIV therapy a CD4 decline could naturally occur and may not have any significance related to his tropism change. Patients A and B showed the emergence of CXCR4-using virus at day 11. Circulating virus from Patient A reverted to R5 by day 40. A clonal analysis of his baseline sample revealed the presence of X4 clones, which represented about 2% of the total clonal population. Patient B, however, has remained dual tropic. Based on gp160 sequencing and phylogenetic analysis, the R5X4 variants which emerged post-treatment in Patient B were genetically distinct from the original R5 population. Therefore, it is extremely unlikely that X4 virus emerged from the R5 population during the 10-day dosing period since they are genetically quite distinct, but rather, that X4 virus was either present in the circulation at extremely low levels or was archived and entered the circulation following CD4 redistribution from the central to the peripheral compartment. The relevance of these monotherapy study findings for the use of UK-427,857 as part of a HAART regimen requires elucidation in larger phase 3 trials: in other words, when UK-427,857 is used as part of a HAART regimen, changes in tropism may not have any clinical negative significance, but of course this needs to be examined and confirmed in the phase III studies. Stay tuned for more.

In clinical study of Schering's CCR5 inhibitor (SCH-D), two patients had dual & X4 tropism and still had HIV viral load reductions. One subject who was of mixed CCR5 and X4-virus showed a 0.5 log10 copies/mL drop in viral load with no change in susceptibility over the treatment phase. Another individual with >1.5 log10 copies/mL showed a transient detection of X4 virus following cessation of the drug.

Antiviral activity and safety results from 10-day monotherapy study. UK-427,857 is being developed by Pfizer and is the first CCR5 inhibitor to enter phase III studies. Three large international Phase III studies are expected to begin by the end of 2004. UK-427,857 is a selective CCR5 antagonist with potent anti-HIV activity in vitro (in the test tube). To date, studies in healthy volunteers have demonstrated that the drug is safe and well tolerated with plasma concentrations in excess of the antiviral IC90 obtained at doses of 100 mg BID (twice daily). At the Intl XV AIDS Conference in Bangkok (July 2004), researchers (Fatkenheuer et al) reported short-term monotherapy study results in HIV patients to evaluate the effect of this drug on viral load, and the relationship between viral load reduction

and pharmacokinetics/pharmacodynamics parameters, the effect of food, and to explore the effect of various doses on viral load reduction. As well the study examined safety and tolerability. Here is the author's report.

Brief Summary: UK-427,857 at doses up to 300 mg (bid) was safe and well tolerated in this study. HIV viral load was reduced by 1.3 to 1.6 log after 10 days of this monotherapy study, with the same doses that will be used in Phase III studies. Doses of ≥100 mg BID and 300 QD (once daily) resulted in viral load reductions of >1 log when given as short-term monotherapy. Dosing with food did not have a significant effect on the antiviral efficacy. Comparison of the 150 mg bid fed and fasted data suggests this despite the fact that food reduces the Cmax and AUC by about 60% and 50%, respectively. For Phase III studies, 300 mg once daily and twice daily doses (or their equivalent exposures based on the need to dose adjust depending on coadministered antiretroviral agents) are being examined.

The poster at Bangkok reported results from two studies (A4001007 and A4001015), which were randomized, double-blind, placebo-controlled studies in asymptomatic HIV-infected patients. Patients were therapy-naïve, or off therapy for at least 8 weeks prior to study start. Patient's CD4 counts were >250 and viral load >5000 copies/ml. Patients had CCR5 tropic virus only. The Virologic Pheno Sense entry assay was used to screen for the patient's tropism: either CCR5 or CXR4 (or dual/mixed tropic): screening with this assay was conducted on days 1, 11 and 40.

80 patients with CD4 count >250 and plasma viral load >5000 received UK-427,857or placebo for 10 days and were followed up until day 40. In order to evaluate qd versus bid dosing regimens, doses of 25, 100, and 300 mg qd and 50, 100, 150, and 300 mg bid were evaluated. Additionally, a dose of 150 mg bid following a high-fat meal was evaluated in order to assess the effect of food on antiviral efficacy. Patients were pre-screened for the presence of CCR5-tropic virus only. Viral load, UK-427,857 plasma concentration, and CCR5 receptor saturation were evaluated regularly throughout the study. Clinical safety evaluations, including ECGs and laboratory safety tests were performed.

Results
There was no significant difference between the antiviral effects of 150mg bid and 300 mg qd with decreases of 1.45 log and 1.35 log, respectively. In addition, the antiviral effect of 150mg bid of UK-427,857 appeared to be independent of food intake, with reductions of 1.34 log and 1.45 log for the fed and fasted groups, respectively. For the patients taking 150 mg doses or greater, after dosing stopped on day 10 viral load reductions were sustained for up to 5 days without an increase in viral load at which point viral loads started to increase back to baseline.

CCR5 Receptor Saturation with UK-427,857
Using an experimental assay CCR5 saturation was evaluated predose and 4 hours postdose on day 1, predose on days 5 and 10, and on days 11, 13, 15, 19, and 40. Mean CCR5 receptor saturation in patients receiving all doses of UK-427,857 was equal to or in excess of 85% on days 5 and 10 predose, except for subjects receiving 25 mg qd whose mean receptor saturation fell <80% by day 10 predose (steady state). Saturation remained above 60% for 5 or more days after drug was stopped at day 10 for the higher dose regimens. This may be related to the delay in viral load rebound after dosing was stopped on day 10. Saturation slowly declined from 60% to 40% from day 20 to day 40.

Viral Tropism
61/63 patients with CCR5 tropic virus at baseline and who received UK-427,857 for 10 days remained CCR5 tropic throughout the study.

Viral tropism changes were seen in 2 patients receiving 100mg qd who responded well, with viral load declines of 0.71 and 1.26, respectively.

One patient had a transient emergence of dual tropic virus at day 11, but reverted to being CCR5 tropic at day 40.

Dual tropic virus was detected at day 11 in the second patient, and has been detectable at all timepoints since.

Detailed clonal analysis of the virus at different timepoints, and followup of this patient is ongoing.

The patient remains clinically well, with viral load not significantly different from previous values, but with an approximate 40% reduction in CD4 count (while off HAART) from the lowest values pretreatment more than one year earlier.

QTc Interval in Healthy Subjects
In a separate poster Davis et al presented in a poster results from a study designed to estimate the effect of single doses of UK-427,857 on the QTc interval in healthy subjects. Single doses of UK-427,857 (100, 300, and 900mg) and moxifloxacin 400 mg were given in a randomized, placebo-controlled, 5-period crossover study. Thirty male and 31 female subjects were assigned to treatment. The QT:RR relationship was evaluated from 12-lead ECGs recorded pre-dose and on a run-in day in period 3.

Results
The authors concluded that single UK-427,857 doses up to and including 900 mg have no clinically significant effect on the QTc interval in healthy subjects. Mean plasma concentrations-time profiles were similar in male & female subjects. UK-427,857 was rapidly absorbed with Tmax occurring in 1.0 to 4.0 hours. The mean difference in QtcI from placebo for all primary endpoints was <4 ms for UK-427,857 (100, 300, and 900mg). The upper limit of the 90% confidence interval was below 7 ms for all primary endpoints. There were no UK-427,857 treated subjects showing maximum QTcI values >450 ms (males) and 470 ms (females), or maximum increases from baseline in QtcI >60 ms. Moxifloxacin caused a mean increase in QTcI of 12-14 ms for all 3 primary endpoints. No serious adverse events were reported. The most commonly reported AE was dizziness, following UK-427,857 900mg. Other reported adverse events included headache, postural hypotension, nausea, and cystitis.

Safety & Tolerability
UK-427,857 was safe and well tolerated in HIV+ patients, with an AE profile similar to that seen in volunteers. All adverse events, except for 1 episode of diarrhea, were graded as being mild or moderate. Two patients discontinued treatment, 1 receiving 25 mg qd withdrew his consent on day 3, and another receiving 100 mg qd discontinued on day 3 due to a nontreatment-related adverse event. There were no clinically significant lab abnormalities or effects on QTc interval observed during dosing with UK-427,857. Adverse events, and the types and number of events, were not dose related. The events reported were asthenia, dizziness, gingivitis, headache, and nausea.

Tanox is a small company that is developing **TNX-355**, an anti-CD4 domain 2 monoclonal antibody. **TNX-355 is an attachment inhibitor that targets host CD4 cell receptors**. It has showed potent anti-HIV-1 activity in vitro and in a phase 1a single-dose study in HAART-experienced subjects. Unfortunately this drug is administered by IV infusion which makes this drug less attractive but it may provide a useful treatment option. Since the plasma half-life is 63 hours and could be found still attached to circulating CD4 cells up to 27 days after a single dose, the drug could be a useful treatment option. The company hopes to explore the potential for once monthly administration, but don't count on it. Because the drug is a monoclonal antibody no toxicities and minimal side effects are expected. The manufacturing process and ultimate cost of the drug is an unknown.

At CROI 2004 researchers said "Clearly, this drug is aimed for patients willing to receive intravenous administration once weekly or perhaps every two weeks and most likely for patients with extensive HIV drug resistance. Administration can be conducted in doctor's office or at infusion centers or by home attendants. If the drug completes development & is FDA approved it could be administered in the home by a visiting nurse weekly or every other week".

Phase II study results were reported where patients received varying doses once or twice weekly for 9 weeks. Virtually all patients 21/22 had at least 0.5 log reduction in viral load. Many of patients had at least 1.0 log reduction. The study consisted of 21 treatment-experienced patients. There were several adverse events reported in this study report at Retrovirus, but company officials say they were not related to the study drug: serious adverse events (3) were recurrence of known depression (2) in same person with history of depression; suicidal ideation after 4th dose, 2nd episode after dose 8; new-onset grand mal seizure after vaso-vagal reaction during phlebotomy; transient acute renal failure with known renal insufficiency requiring dialysis: developed 38 days after final dose in subject with renal insufficiency with proteinuria and chronic hyponatremia; renal function returned to baseline after hydration and discontinuation of NSAID; there was 1 injection site reaction: infusion is into subcutaneous tissue. Again, company officials say these adverse events were not drug related.

Schering D "690" CCR5 Inhibitor: A New Class of Antiretrovirals

Written for NATAP by Lisa M. Dunkle, M.D.
Senior Director, HIV Global Clinical Research
Schering-Plough Research Institute

Introduction
In the mid-1990s investigators identified co-receptors on the host cell surface that worked in tandem with CD4 to facilitate the binding and entry of HIV into human cells. The predominant co-receptors were the chemokine receptors CCR5 and CXCR4. It was quickly determined that CCR5 is the receptor associated with macrophage-tropic HIV and CXCR4 is associated with T-lymphocyte-tropic and syncytium-inducing virus. Because M-tropic viral strains predominate in the early stages of HIV infection, inhibition of this facilitated entry provided a potentially novel target for antiviral activity. The value of this approach was supported by the observation that healthy individuals harboring a mutation in their CCR5 gene (the Δ32 deletion) appeared to be relatively resistant to HIV infection in spite of documented repeated exposures. Several groups of researchers began the search for small molecule CCR5 inhibitors that might become a new class of antiretroviral agents. The concept of how such a molecule might function to prevent HIV entry into the host cell is shown below.

Binding, first to CD4 and then to the co-receptor, results sequentially in a change in conformation of the viral envelope protein such that the virus is ultimately fused to the host cell membrane and then incorporated into the host cell. Blocking either step would presumably prevent entry of the virus and subsequent infection of the cell. Another attractive feature of this mechanism of antiviral action is that the molecule does all its work outside the host cell. It is speculated (and hoped) that this will lead to antiviral drugs that are less likely to interfere with human cell activities and are, therefore, less likely to be associated with the long-term toxicities seen with other classes of drugs, such as metabolic abnormalities, lipid disorders, neuropathy, etc.

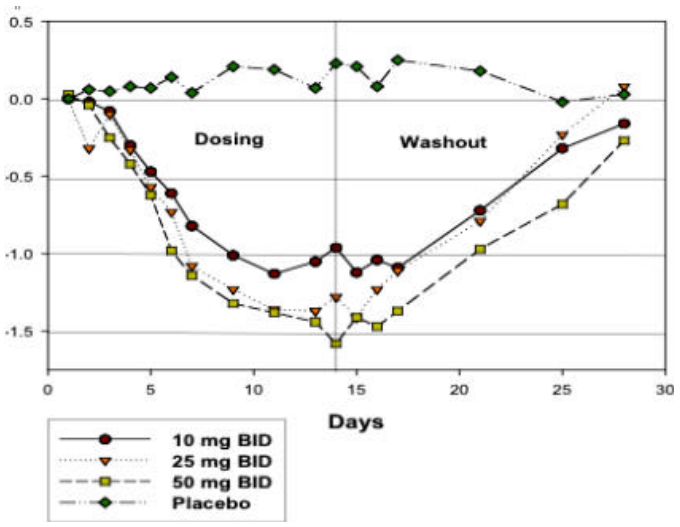
Schering Series of CCR5 Inhibitors
The Schering-Plough Research Institute Discovery labs were among the groups that began the search for such a molecule. Within relatively short order, a new series of compounds, all small molecules, were identified that exhibited potent anti-HIV activity in the test tube; the most promising candidates began to undergo further testing to evaluate whether they should be advanced toward clinical development. The first compound that passed muster to enter human trials, SCH-C, progressed through the early studies to a preliminary trial in HIV-infected individuals. It soon became apparent that SCH-C caused mild prolongation of the QTc interval that would require more extensive characterization. Thus, SCH-C was deprioritized in favor of accelerating SCH-D, the next compound in the series, which had come along very quickly. This compound was even more potent against HIV in the test tube and lacked the effect on heart muscle and electrical impulses. Toxicology studies supported the safety of this compound for testing in humans and SCH-417690 was born.

The first tests of safety and pharmcokinetics, performed in HIV-seronegative volunteers confirmed that SCH-417690 ("690") was well tolerated and demonstrated pharmacokinetic properties desirable for a drug to be administered on a chronic basis.

Early Clinical Data

In the first study conducted in HIV-infected individuals, -690 was administered alone to volunteers who were not receiving other antiretroviral agents. Most had relatively high CD4 counts and were otherwise healthy. All had detectable HIV RNA. The drug was administered to small groups of volunteers sequentially at doses of 10, 25 or 50 mg twice daily for 14 days. Subjects (several of whom in each group received a matching placebo) had HIV RNA measurements daily for a week, then every other day for an additional three weeks (two weeks after completion of dosing). CD4 counts were checked frequently, plasma drug levels were measured at several time points and safety of the subjects was monitored closely.

The results of this trial, presented at the 11th CROI, February, 2004, were very encouraging. SCH-417690 was well tolerated by the subjects, with no adverse events or laboratory abnormalities more common in recipients of active drug that in placebo recipients. Further, plasma concentrations indicated that the drug was handled in HIV-infected individuals the same way it was handled in seronegative volunteers. Finally, the effect on plasma HIV RNA levels was dramatic, indicating a mean viral suppression of as much as 1.62 log10 over the 14 days of dosing. There was no statistically significant difference among the three dose levels in terms of viral suppression and, as expected, there was little change in HIV RNA levels in individuals who received placebo.



A significant number of studies were conducted to evaluate its pharmacokinetic behavior in combination with other drugs that will likely be part of combination regimens. The only drug interactions observed were that exposure to 690 was boosted by ritonavir and reduced in the presence of efavirenz. Plans for dosing in combination regimens take these effects into account. To date two hundred and seventy five individuals have received this agent and no significant toxicity has been seen.

Clinical Development

The Phase 2 studies of -690 are currently ongoing in North America and Europe. One study, being conducted by the AIDS Clinical Trials Group (see www.ClinicalTrials.gov), is enrolling individuals who have detectable plasma viremia but are clinically stable on a ritonavir-containing HAART regimen. They must have failed one previous HAART regimen. Patients are screened to assure that they have no detectable CXCR4-tropic virus and that their HIV RNA is above 5000 copies/mL. Standard laboratory tests (blood counts, liver and kidney function tests, etc) are monitored for safety before and frequently during the study. The 120 subjects to be enrolled are randomized to receive one of three doses of -690 or placebo in addition to their ongoing HAART regimen for two weeks, after which the remainder of their HAART regimen is optimized based on the sensitivity pattern of their individual HIV strain(s). Any commercially available antiretroviral agent (except efavirenz) can be used as part of the optimized regimen. Patients will then continue their follow-up and regular evaluations of safety, viral loads, CD4 counts and viral sensitivity and tropism for the remainder of the year of the study. Schering-Plough will offer continued -690 for all study participants who wish to stay on the drug after the conclusion of the study.

The second Phase 2 trial, being conducted in Europe and Canada, is enrolling treatment naïve individuals for whom the initiation of therapy is judged appropriate. The 80 subjects to be enrolled in this trial should have CD4 counts above 150 and HIV RNA levels above 5000. They, too, are screened to assure that their infection does not include the CXCR4-tropic virus, that they have no serious latent infections (including HCV) and that their standard laboratory values indicate that participation in this trial is safe. They are randomized to receive one of three doses of -690 or placebo for two weeks after which triple combination HAART therapy is begun with the addition of Combivir to all groups and the replacement of placebo with efavirenz in the fourth group. The triple combination regimens are continued with regular monitoring of the same parameters as in the other trial for the remainder of the year of the trial. These patients, too, will be offered the opportunity to continue -690 after the trial.

It is anticipated that Phase 3 trials will begin in 2005. During Phase 3 there will be other additional clinical questions addressed in supplementary trials, including safety and activity in pediatric patients and utility in patients with very advanced disease. Interaction studies with other drugs of interest will be undertaken as needed and an Expanded Access Program will be initiated when it is judged safe to expand usage into a large, less controlled and potentially less carefully monitored population.

Intriguing Questions

As we embark on the development of this new class of compounds with a novel mechanism of action, there are some intriguing questions that will need to be addressed. ***The first is what effect will CCR5 blockade have on the function of the immune system?*** It is known that the mutation in the CCR5 gene that renders the receptor nonfunctional is relatively common. The good news for those individuals is that

they seem to be resistant to HIV infection. Some have, however, observed that infection with HCV leads to a higher level of HCV viremia than in individuals with fully functional CCR5 receptors. Whether this is an indicator that inhibiting the CCR5 receptor could lead to an adverse effect on HCV or other latent infections is a question that must be carefully researched and answered during the clinical trials.

The other issue that will need to be monitored is **whether suppression of CCR5-tropic viruses will, in the context of multi-drug HAART therapy, allow the emergence of CXCR4 virus.** During the monotherapy trials conducted early in the development of at least two CCR5 antagonists (-690 and Pfizer's UK 427,857), CXCR4 virus emerged in a small number of patients whose initial viral load was determined (after the fact) to have been mixed CCR5/CXCR4. Upon discontinuation of the CCR5 antagonists, the CXCR4 virus disappeared, leading to speculation that administration of CCR5 antagonists in combination with conventional antiretrovirals will prevent such emergence. This, too, is a question that can and must be addressed in the clinical trials.

As with any new drug, the **development of resistance to the CCR5 antagonists** (as opposed to switching to CXCR4-tropism) will be part of the evaluations performed during the clinical trials. Resistance to -690 in vitro has been very difficult to induce. Nevertheless, monitoring for this event will need to be incorporated into the further development of these compounds.

Conclusions

This is an exciting time in the evolution of treatment paradigms for HIV. We saw the strategies for treatment (and the successes) change dramatically with the introduction of the protease inhibitors in the mid-1990's. The development and introduction into clinical practice of this new class called entry inhibitors and the CCR5 receptor antagonists, in particular, may offer the first really new treatment options in over a decade. We at Schering-Plough are proud to be part of this new era and look forward to -690 being an important addition to the HIV treatment armamentarium.

Attachment Inhibitors – A Novel Class of Antiretrovirals in Clinical Development

Written for NATAP by Richard Colonno, PhD, Vice President Infectious Diseases Drug Discovery, Bristol-Myers Squibb

The process by which HIV can enter a human cell and begin an infectious cycle is a multi-step and complex process. Viral entry begins with an attachment step, involving the interaction of the outer viral envelope protein (gp120) with a primary cellular receptor called CD4. This leads to conformational changes within the viral envelope protein and exposure of a site that binds to a second cellular receptor, referred to as co-receptors and named CCR5 and CXCR4. After binding to both CD4 and a co-receptor, further conformational changes occur that allow the third and final steps of viral fusion of the virus and cell membranes to occur. Inhibition of any step in this entry process prevents entry of the virus and HIV replication.

A series of small-molecule compounds have been identified by Bristol-Myers Squibb that block the first step of viral entry. These HIV Attachment inhibitors (AIs) are selective for HIV-1 and display potent inhibition in vitro against macrophage-, T-, and dual-tropic HIV-1. They bind directly to the viral envelope protein and cause conformational alterations to occur which prevent interaction with the cellular CD4 receptor and downstream entry events. Most importantly, the AIs work against HIV strains that are currently resistant to existing classes of antiretrovirals, including NRTIs, NNRTIs and PIs. However, targeting the envelope gp120 protein of the virus has its own challenges, since this is a protein designed to readily alter its sequence to continually evade the immune system. As a result, there is a wide range of susceptibilities to AIs (similar to the fusion inhibitor Fuzeon) and high drug concentrations will likely be required to ensure coverage of the diverse collection of viruses in circulation and to provide an effective barrier to resistance emergence.

Clinical studies in healthy subjects have demonstrated promising oral bioavailability and a good safety profile for AIs. A prototype compound in this series, named BMS-488043, was evaluated in a placebo-controlled, 7 day study in HIV-1-infected adults. Two dose levels were tested, 800 and 1800 mg given twice a day. Results showed an average drop in viral load of about 1 log, with some subjects achieving viral load reductions of as much as 2 logs. This level of reduction is as good as any other class of antiretrovirals. There were no serious adverse events and no discontinuations from the study, and monotherapy with BMS-488043 was generally safe and well-tolerated.

This study in HIV-1 infected patients was a first and important step in proving that AIs can indeed inhibit HIV replication and that this class of inhibitors has the potential to be a powerful component of combination regimens. However, a relatively high dose of drug was utilized and pharmaceutical characteristics were sub-optimal for meeting patient needs. Additional advances will likely be needed before large-scale studies can begin. Bristol-Myers Squibb is very committed to this new class of inhibitors and is currently testing several compounds and formulation approaches to overcome these technical issues before proceeding into full development. Overall, this new class of AIs, along with other classes of viral entry inhibitors, may represent an exciting alternative for patients resistant to one or more of the current classes of antiretrovirals.

Fuzeon 96 Week Study Results: Reported at Bangkok

At the Bangkok IAC, researchers reported FUZEON 96 week study results, which showed Fuzeon's durability of viral load reductions and CD4 increases:

- at week 24, 37% of patients had undetectable HIV viral load (<400 copies/ml);
- at week 48, 34% had <400 c/ml;
- at week 96, 26% had <400 c/ml.

When to begin using Fuzeon?
First thing to keep in mind: it is important to use effective drugs along with Fuzeon, otherwise you might quickly develop resistance to Fuzeon. Fuzeon is potent, and it is particularly effective for patients with resistance to all other classes of drugs (protease inhibitors, NNRTIs, NRTIs)-- because it is a new class of drug. You can have resistance to current classes of HIV drugs but should be fully sensitive to Fuzeon. That is, you should not have any cross-resistance to Fuzeon since being a new class of HIV drug its mechanism of action is completely different.

But patients can be discouraged from wanting to use Fuzeon because it is self-injected, cumbersome to administer, and usually causes injection site reactions. But, some patients report that they have fewer injection site reactions if they learn how to properly inject. It is important to learn how to properly inject.

Researchers (Montaner et al) reported at Bangkok that typically those patients who initiated Fuzeon with less treatment experience and less advanced HIV disease had a better chance of achieving undetectable viral load (<400 copies/ml). Patients who started Fuzeon when their CD4 count was >100 and who were still sensitive to two or more ART drugs in addition to Fuzeon were more likely to achieve <400 copies/ml (46% vs 20%).

Four key factors were identified in the study that predicted an increased magnitude of viral load reduction and CD4 increase:
- starting Fuzeon when CD4 count was >100
- starting Fuzeon when when HIV viral load was <100,000 copies/ml
- prior treatment with 10 or less ART drugs
- using a regimen with 2 or more active drugs in addition to Fuzeon

Also using Kaletra along with Fuzeon was associated with a better response.

Overall, 67% of patients who started Fuzeon with all 4 factors achieved <400 copies/ml after 48 weeks of treatment with Fuzeon. 58% of patients with 3 of these 4 predictive factors had <400 copies/ml; 42% of patients with 2 of the predictive factors had <400 copies/ml; 20% of patients with 1 factor and 11% of patients with 0 factors had <400 copies/ml.

46% of patients who used two or more active ART drugs along with Fuzeon achieved <400 copies/ml compared to 15% who had no other active drug besides Fuzeon, and 32% who had 1 active drug in addition to Fuzeon.

Patients who started Fuzeon when their CD4 count was >100 were more likely to achieve <400 copies/ml compared to patients who started Fuzeon with <100 CD4s (47% vs 22).

If you waited to use Fuzeon until your viral Load was >100,000 copies/ml, you were less likely to achieve <400 copies/ml (45% vs 26%).

53% of patients who had previously used 10 ART drugs or less were able to achieve <400 copies/ml, while 29% of patients who had previously used 11-13 drugs had <400 copies/ml, and 9% of patients who had used >14 ART drugs had <400 copies/ml.

Addressing barriers to using Fuzeon
Fuzeon is used for patients with limited treatment options due to its self-injected administration and injection site reactions. As well, Fuzeon must be properly prepared and injected to be effective, and proper training on its administration is crucial. The difficulties in administration can discourage patients from using Fuzeon. But, for patients with limited treatment options, it is important to give due consideration of Fuzeon. Because of its difficult administration, patients may delay using Fuzeon. However, its usefulness, antiviral effectiveness and potency, may be diminished if its use is delayed too long--waiting too long may put the patient's health at risk. After reading this entire section on Fuzeon, you should have a better understanding of the factors to consider when deciding whether to use Fuzeon.

At the Roche Fuzeon press conference in Bangkok, Roche presented data from a survey they conducted. For every 10 patients in need of using Fuzeon, 4 of them were not offered it because their doctor decided the patient was not appropriate for the drug most likely because Fuzeon is a self-injectable and can cause injection site reactions. Perhaps these doctors felt the patient will not want to self-inject and put up with the site reactions. But perhaps the doctor is wrong, and should not be making the decision for the patient. In addition, Roche reported the survey found that of the remaining 6 of 10 patients, three patients decided they did not want to use Fuzeon. Of the three patients who did in fact start Fuzeon therapy, 1 discontinued. And two of the ten patients remain on fuzeon. As part of the panel at the press conference was a nurse in New Jersey who holds a regular support group that educates patients about how to administer & use Fuzeon, and provides support in initating therapy and while on therapy. He described how he is successful in getting patients who truly need to be on Fuzeon in supporting their initiation of therapy by educating them and giving emotional support. The Roche survey also found that doctors, perhaps due to time constraints, on average spend just too little time with patients suggesting that there is inadequate due consideration by the patient and the doctor in making the decision whether or not to use Fuzeon.

At Bangkok researchers reported on a program to address barriers to use of Fuzeon: **"A Fuzeon Empowerment Program: do not enter"**

D Varsalone (New Jersey Community Research Initiative, Newark, NJ) reported that "Injection phobia", generally defined as the inability to receive an injection, has been estimated to occur in 7% to 22% of the general population. They identified these challenges to the acceptance of Fuzeon:

- injection phobia
- self-injection anxiety
- lack of communication about Fuzeon between medical providers and patients
- patient agreement to take Fuzeon before prepared to do so
- loss of morale owing to patient perception of Fuzeon as being 'end of the line"

Varsalone went on to say that many of these patients would benefit from a new therapeutic drug class, and these barriers to Fuzeon acceptance therefore constitute a significant barrier to effective ART (antiretroviral therapy).

The Enfuvertide (Fuzeon) Empowerment Program was established to address these barriers and provide education and support to patients on Fuzeon and others with an interest in assisting patients to achieve best results on this drug.

Skilled nurses are utilized to provide educational sessions to: Fuzeon-experienced patients; Fuzeon injection partners; physician-approved candidates; interested patients or healthcare providers. The groups meet every other week, or more if required. The group empowers patients to make educated decisions, improve self-injection techniques, address issues of injection site reactions, to optimize adherence to Fuzeon, and address Fuzeon reconstitution problems.

You can get more information at - The Fuzeon Answer Center is a 24-hour hotline to answer questions and help guide patients with injection concerns, 1-877-4-Fuzeon (1-877-438-9366); during peak hours (7am-7pm) a healthcare professional answers calls and during non-peak hours call back by pager is available.

Fuzeon Study Toro I & II Study Results

Phase III studies of Fuzeon were TORO I and II.

661 highly treatment experienced patients were randomized to receive Fuzeon plus optimized therapy background and 334 patients were randomized to receive optimized therapy background. Treatment history of patient and resistance testing was used to select an optimized treatment background. The patients had advanced HIV and limited treatment options, as you can see.

Baseline characteristics of patients included:

- median HIV viral load: 5.2 log (>100,000 copies/ml)
- median CD4 count: 88-97 cells
- median number of prior ARVs: 12
- median years since initiating ARVs: 7
- Prior AIDS defining events: 79-86% of patients
- median duration of prior NRTI therapy: 6.3 yrs
- median duration of prior NNRTI therapy: 1.5 yrs
- median duration of prior PI use: 3.8-4 yrs

Summary of 96-week follow-up study results reported in Bangkok—

1. Early response (week 4) to therapy. Change from baseline at week 4 in viral load: -1.54 log for Fuzeon+OB vs –0.89 log for OB. The percent of patients <400 copies/ml: 16% for Fuzeon+OB vs 9% for OB. Median time in days to 1 log or more decrease in VL from baseline: 8 days for Fuzeon vs 92 for OB. Median time to <400 copies/ml: 99 days for Fuzeon.

2. Mean change in CD4 count from baseline: +166 cells for Fuzeon+OB (on-treatment) at week 96. Mean change in HIV viral load (on treatment): -2.07 log at week 96.

3. At week 96, 47% of patients withdrew, and 52% remained on treatment: 10.2% for insufficient therapeutic response; 7.2% for injection site reactions; 12.1% for adverse events.

4. At 96 weeks, 26% of patients had <400 copies/ml (ITT, D/C, SW or missing). This compared with 37% at week 24, 34% at week 48. For patients who received only optimized background therapy, not Fuzeon, 16% and 13% had <400 copies at weeks 24 & 48, respectively. Patients on average switched as soon as week 16 to add Fuzeon.

5. Patients with HIV RNA <50 copies through 96 weeks: Fuzeon+optimized background therapy—23% at week 24, 23% at week 48, and 17% at week 96. Patients who only received optimized background at initial part of study—9% had <50 copies at week 24 & 9% had <50 copies at week 48. (ITT, D/C, SW or missing)

6. Patients with CD4 increase >50 cells over 96 weeks (ITT, D/C, SW or missing): Fuzeon+optimized background: 49% at week 24, 51% at week 48, and 39% at week 96. For patients who received only optimized background, 21% at week 24 & 16% at week 48.

7. Patients with CD4 increase >100 cells over 96 weeks: (same ITT analysis)—patients receiving Fuzeon+OB, 30% at week 24, 38% at week 48, and 31% at week 96. Patients receiving only OB, 13% at week 24, 10% at week 48.

8. Upper respiratory infection: 12.2% after 1 year on therapy, year 2: 7.1%, total: 19%. Pneumonia 2.7% after 1 year on Fuzeon, 1.2% year 2, 3% total. Fatigue: 20% year 1, 3.3% year 2, 24% total.

9. Injection site reactions: 70-80% of patients reported mild tenderness, 20% moderate pain, a few percent severe pain—analgesics required or limited usual activities.

Waiting too long to use Fuzeon may reduce its effectiveness

The presenter suggested that the TORO I & II study data reported below supports not waiting 'too long' to initiate Fuzeon. CD4 increase & viral load response was reduced in patients who deferred Fuzeon due to randomization in the study. The presenter is suggesting that as you accumulate more drug resistance and the available drugs are not as effec-

tive the addition of Fuzeon is less effective. ***It is important to have drugs that are effective to start along with Fuzeon.*** Data shows that using Kaletra improves response to Fuzeon. Now that tipranavir is available this becomes an important option for combining with simultaneous initiation of therapy with Fuzeon. The simultaneous use of two very active agents will no doubt be more durable than the sequential use of any of them.

Patients who switched from optimized background regimen to fuzeon + optimized background regimen (switch patients): study results

Who Are Switch Patients:
Patients failing on the optimized background (OB) arm who were not receiving Fuzeon were permitted to switch to a Fuzeon containing regimen at virologic failure (after week 8) or at week 48. Reoptimization of OB was permitted. Median time to switch 16 weeks.

Mean HIV RNA Change from Original Baseline
Switch Patients: about 1 log HIV viral load reduction at week 96 from baseline
Fuzeon+OB: about 2 log reduction in VL at week 96 from baseline

Delaying initiation of Fuzeon & potent initial regimen led to drug resistance to future regimens
At ICAAC (October 2004), TORO investigators reported that one year after switching to Fuzeon, 22% of delayed Fuzeon users achieved an HIV-1 RNA level less than 400 copies/mL compared with 32% of immediate Fuzeon users ($P < .05$). They also performed an analysis that found that patients who were randomized to the Fuzeon arm lost fewer treatment options than patients assigned to begin OB alone. Of those individuals who began an OB regimen (without Fuzeon) that contained at least 1 active drug by genotypic testing at baseline, 54% who experienced subsequent virologic failure lost sensitivity to at least 1 active component of their combination in the process. Virologic failure of these regimens leads to further drug resistance and inferior responses to subsequent regimens, even when including Fuzeon.

Good CD4 & viral load reductions at week 12 after initiating fuzeon therapy predicts durable outcome & motivates patients. At ICAAC TORO investigators also reported an analysis of early responses to Fuzeon in TORO. Early responses to antiretroviral (ART) therapy are known to predict longer term outcome in ART-naïve patients, but for more experienced patients the predictive nature of this early response is less understood. It is well established that a good viral load reduction several weeks after initiating HAART indicates a good response to HAART. It is also well established that following this early response an undetectable viral load (<50 copies/ml) one year after initiating therapy predicts a good long-term response to HAART that has lasted so far in followup of patients with modeling for at least 10 years. Of course these positive outcomes are premised on full adherence all along the way, but particularly in the first year of therapy.

As mentioned above, TORO 1 and TORO 2 involved patients in whom Fuzeon was added to baseline therapy at week 8 for patients with virologic failure. Week 12 of TORO was chosen as an early response time point. Post-hoc analyses were performed to correlate responses at weeks 24, 48 and 96 with the week 12 response. Week 12 responses for this analysis were a reduction in viral load of ≥1 log and/or an increase in CD4 of at least 50 cells. The week 12 response with Fuzeon was found to be predictive of future outcome; over 85% of patients who experienced a ≥50 CD4 cell increase at week 12 maintained this to week 96. The percentage of patients with viral load <400 copies/mL was 60% in patients who had achieved a viral load reduction of ≥1 log at week 12, compared to 3% in patients who had not achieved that reduction. Nevertheless, even in patients who did not achieve both a 1 log decline and a 50 cell increase by week 12, about a third of patients still had a robust immunologic response of at least 50 cells with the use of an Fuzeon-based regimen. The authors conclude that week 12 responses of these magnitudes in patients with advanced disease may have significant implications for motivating patients for long-term adherence to ART, especially for a drug that has the additional burden of twice daily subcutaneous injection.

MEAN CD4 Cell Count Change from Original Baseline
Switch patients: increase of about 100 cells at week 96 from baseline
Fuzeon plus OB: about 166 cell increase from baseline to week 96

Adverse Events (related & unrelated between weeks 48 & 96 (Fuzeon+OB)

This table shows that patients who received Fuzeon+ OB from the start of the study experienced less adverse events after 1 year of taking Fuzeon. Comparing the incidence of adverse events in year 1 to year 2: less patients were experiencing these events during year 2. This is likely due to constitutional systemic improvement due to improved CD4s & viral load.

	Year 1	Year 2	Total
Upper respiratory tract infection	12%	7%	19%
Sinusitis	8%	3%	11%
Bronchitis	7.6%	3%	10.7%
Cough	8.7%	3%	12.7%
Diarrhea	32%	5%	37%
Pyrexia	12%	4%	17%
Arthralgia	8%	3%	11%
Oral candidiasis	8%	3%	11%
Fatigue	20%	3%	24%
Dermatitis	10%	3%	12%

New HIV Antiretroviral Drugs in Early Development

New Drugs in Development
Reverset (NRTI)
SPD-754 (NRTI)
GW678248 and GW695634 (NNRTIs)
TMC-114 (protease inhibitor)
GW873140 (CCR5 receptor antagonist)
SCH-D (CCR5 receptor antagonist)
BMS-488043 (attachment inhibitor)
TNX-355 (attachment inhibitor)
TMC-125 (NNRTI)
MIV-310 (NRTI)
L-Fd4C (NRTI)
Racivir (NRTI)
AMD-070 (CXCR4 receptor antagonist)
Integrase inhibitor from Merck
PA-457: maturation inhibitor
Capravirine (NNRTI)

It appears that a lot of new drugs are in the pipeline but not much new around the corner except for tipranavir. There appears to be much early exciting data on a range of novel agents, not just those targeting the various steps required for attachment of HIV to the cell (entry inhibitors).

All in all there is a rosy picture emerging of antiretroviral opportunities for the next couple of years with the drugs acting outside the cell holding potential for effective drugs with less toxicity or a different toxicity profile, which could dramatically alter the way HIV is treated.

TMC-125: new NNRTI inhibitor; Early Studies Show Effectiveness for Patients with NNRTI Resistance

Both TMC drugs (TMC125 & TMC 114) have been moving along slowly, but appear to be moving more quickly now through the study process. TMC125 is a new next generation NNRTI and from Tibotec-Virco and Johnson & Johnson, and has shown in early studies to have antiviral activity against HIV with or without NNRTI resistance. After 7 days of monotherapy with TMC125, treatment-naïve patients saw a -1.99 viral load reduction. This drug is expected to be effective for patients with drug resistance to the currently available NNRTIs, nevirapine (Viramune) and efavirenz (Sustiva). Currently, phase II dose finding studies are in progress and large phase III studies are planned for 2005. Patients with extensive resistance are being recruited for ongoing studies. For information on study sites for TMC125 & TMC114, go to www.clinicaltrials.gov and enter either TMC114 or TMC125 for the query. A list of all sites along with contact information can be found at this site and on the NATAP site.

Ultimately, it's results from ongoing studies in patients that will reveal the drug's antiviral effectiveness, but here are test tube resistance study results. In vitro studies show that when the K103N mutation was present alone, this is the signature mutation for efavirenz, there was little or no resistance to TMC125. When NRRTI common single mutations were present (Y181I, Y181V, F227C), a study found that a few viruses out of 50 had 10-fold resistance to TMC125. Test tube viruses with the double mutant K103N + Y181C, developed resistance to TMC125, while study of other double NNRTI mutants showed some resistance to TMC-125 but more extensive resistance to efavirenz. Mutations at positions 101, 179, 181 and possibly 227 and 230 may play a role in decreased susceptibility to the drug, and the triple mutation K103N, L100I with Y181C or T386A appears to produce >10 fold resistance to the drug.

A small short-term study in HIV-infected patients with NNRTI-resistance (efavirenz, nevirapine, delavirdine) has been conducted. Tibotec-Virco investigators reported that mutations found in the 16 study patients were K103N, Y181C, Y188L, G109A/S, L100I (all NNRTI mutations) and combinations of these; so the patients had double NNRTI mutation combinations. This was an early open-label phase IIAstudy in 16 HIV-infected men who were failing NNRTI therapy and had efavirenz resistance. 80% of patients were taking nevirapine and 20% efavirenz. The patients received 900 mg TMC125 twice daily instead of the failing NNRTI but continued to take the same NRTIs for 7 days. After 7 days patients changed their NRTIs. Average patient CD4 count before switching to TMC125 was 389, viral load was 10,000 copies. Before starting TMC125 the average resistance to efavirenz (change in IC50) was 111-fold while resistance to TMC125 ranged between 0.5 to 8 fold.

On day 8 the average viral load reduction was -0.86 log (range: -1.95 to +0.09). The response may be muted because patients were ART experienced and had drug resistance. In addition they did not change underlying drugs for which they probably had some resistance. 12 patients (75%) had a decrease in viral load of at least 0.5 log and 44% (7) of patients had a decrease of at least 1 log. Investigators reported 11 patients reported adverse events and TMC125 was well tolerated and safe in this early study. Of note, tolerability appeared good and there was no apparent association between viral response and baseline resistance. The most commonly reported side effects were diarrhea (5) and headache (4) and were reported to be mild in severity. This study is small and preliminary, so further studies are needed to characterize the effectiveness and side effect profile of this drug in patients with NNRTI resistance.

TMC-114, New Protease Inhibitor for PI-Resistant HIV

At the 11th CROI, researchers presented results from a study in patients and TMC114 showed impressive short term virologic response in patients on failing PI regimens who had their PI switch to one of 3 different doses of TMC114, boosted with RTV (300mg/100mg BID, 600mg/100mg BID or 900mg/100mg once daily) compared to a control group who remained on their failing PI. In this randomized phase 2a controlled study, 38 patients were enrolled and viral load response was monitored over 14 days. At day 14, viral load declines averaged 1.2 to 1.5 logs in the 3 TMC114 groups with maximal declines of up to 2.5 log seen. Of note, the

reduction in viral load was unaffected by phenotypic resistance to all licensed PI's or baseline viral load. No tolerability data was presented. We look forward to the further development of this drug, particularly in patients with PI-resistance.

Another poster presentation on TMC114 examined the resistance profiling of the drug against 1600 PI clinical resistance isolates. The isolates were grouped as >4-fold resistant to 1, 2, 4, 5, 6 or 7 currently available PI's and TMC114 performed well in vitro against all of these isolates demonstrating at most a <4-fold change to isolates resistant to all 7 drugs or with 3 major PI mutations.

Reverset: New Nuke in Early 10-Day Study for Nuke Resistant HIV Reduced Viral Load by 0.8 Log

Reverset (D-d3FC; DPC 817) is a novel nucleoside (NRTI, nuke) analogue (D-D4FC) with in vitro activity against HIV-1 strains that are resistant to AZT, 3TC, and perhaps tenofovir. Reverset is being developed by Pharmasset. In vitro (test tube) experiments of Reverset only showed 3-fold resistance to the tenofovir K65R mutation suggesting it should be effective in tenofovir failure in the presence of K65R.

There was no Reverset resistance in vitro when evaluated against TAMs including these mutant viruses some of which have multiple AZT-related mutations: L74V, M184V, T215Y, M41L/T215Y,D67N/K70R/T215Y/K219Q, D67N/K70R/M184V/T215Y/K219Q, D67N/K70R/K103N/T215Y, M41L/D67N/M184V/T215Y+5 others, M41/K103N/M184V/T215Y+10 others. However, the multi-nucleoside resistance patterns (69insert and Q151M complex) appear in vitro to cause resistance to Reverset.

It has been difficult to select for resistance in vitro. After 15 or more in vitro passages in 4 studies several viruses with >9-fold resistance have been produced. Two of the mutant viruses have the K65R mutation along with several other RT mutations. In vitro there is no mitochondrial toxicity noted in the studies that have been performed, nor in PBMCs. The drug has a long intracellular half-life of 17 hours allowing for once daily dosing. Rob Murphy reported a phase I, monotherapy study in antiviral naïve subjects at CROI.

Murphy reported favorable data at CROI from a dose ranging study in which 30 treatment-naïve patients were randomized equally to one of three doses of RVT (50mg, 100mg or 200mg) versus placebo. Subjects were dosed for 10 days with 4 weeks of follow up, they had >50 T4 cells (median was 468), >5,000 copies/mL HIV RNA (median 4.29 log10 copies/mL) and included 6 women. Study drug was given in a blinded manner and viral loads declined in all treatment groups, with average declines of 1.2 to 1.7 logs by day 10. The plasma half-life was measured at 5.2 hours and no nRTI-associated resistance emerged during the course of the study. With increasing dose the Cmax also rose from 2.3 to 5.4 to 9.8 ng/mL and the AUC increased from 11.9 to 31.7 to 74.6ng/mL. Despite this no serious adverse events were reported and there appeared to be no differences between drug and placebo in terms of minor adverse events most of which consisted of flu-like symptoms, common at the time of the year the study was undertaken. Questions to the speaker included if the drug passed the blood brain barrier, for which no data exist. Pigmentation of the nose, which appears in female dogs, has not yet been reported in human studies. We anticipate clinical trials in patients with various patterns of nRTI-associated resistance.

At the Glasgow meeting in November 2004, Murphy reported an update on the treatment-experienced patients. 8 treatment-experienced patients have received Reverset in a 10-day study and this was reported at Bangkok. Reverset was added to the patient's current failing regimen. The mean baseline viral load was a relatively low 4.11 log. The mean day 11 viral load reduction was -0.8 log. About 75% (7/8) of patients had ≥0.5 log reduction in viral load, and 50% of patients achieved <400 copies/ml after 10 days. Murphy reported viral response to Reverset for patients with the following baseline resistance. 5 patients had 3TC resistance (M184V), and their viral load reduction was similar after 10 days to the -0.8 log achieved overall by the 8 patients in the study. For 4 patients who had 3 or 4 TAMS, viral load reduction was about -0.4 log, which Murphy said was a 'respectable' reduction in viral load. Only 1 of the 8 patients in the study did not have a reduction in viral load in this study, and that patient had 4 TAMS. Another patient with the same TAMS had one of the better virologic responses in the study. A large phase IIb study is ongoing and enrolling patients now in Europe.

At Glasgow Murphy provided an update on the L form of this drug, **L-Fd4C**, also called ACH-126,443 or Elvucitabine. A previously done study was discontinued because although treatment-experienced patients achieved a 0.5 log viral load reduction about 20% of the patients experienced grade 3-4 hematologic toxicity. The drug was probably dosed too high in that study. Increases in lactic acid production were seen in at least one cell line in vitro. The intracellular half-life of this drug is 175 hours so there is a potential for once or twice weekly dosing. The drug is however going to be studied again but at lower doses and at less frequent dosing intervals.

MIV-310 (FLT, alovudine) is an old drug that's been around since the early 1990s. when it originally was studied there was a lot of hepatotoxicity associated with it (there were 3 deaths), but is also probably dosed too high or too often. It has a good resistance profile. This drug is a thymidine analogue, like AZT. Previously reported week 4 antiviral activity data from a study in 15 patients showed that in patients with 2-5 TAMs 1.9 log viral load reductions were seen. 8 of 11 patients not on D4T achieved <400 copies/ml but patients who were taking d4T did not do as well with 0.6 log viral load reductions. This drug is now in development by Boehringer Ingelheim.

Racivir is similar to 3TC & FTC. It is being developed by Pharmasset and is in phase II study now. It has in vitro activity against wild-type & AZT resistant HIV and against HBV. It has an 11-15 hour intracellular half-life. No mitochondrial toxicity has been seen in laboratory study. It shows potent antiviral activity in vitro. In vitro there were no safety concerns. At CROI, results were reported from a phase II study in 18 treatment-naives who received Racivir once daily for 14 days at

doses of 200, 400 or 600 mg plus d4T+efavirenz. Mean viral declined by 2.0 to 2.40 log copies/ml at the end of treatment on day 14. Of note, after stopping therapy viral levels remained suppressed for 2 more weeks. One week later viral levels started to increase. Therapy was well tolerated. A phase II studyfor 60 patients is enrolling now will assess safety, tolerability and antiviral activity in HIV/HBV+ individuals with 3TC resistance. Recently Pharmasset entered into an agreement with Roche to develop a polymerase inhibitor drug PSI-6130 for treatment of HCV.

AMD-070 is a CXCR4 inhibitor. It is the follow-up drug to AMD 3100 which was administered by infusion. AMD 070 is orally administered, bioavailable has been observed in animals. Phase I study has been conducted in humans with doses 50, 100, 200 and 400 mg tested. The drug was generally safe in animals, with mild headache in man. Phase II study with multi-dosing is proceeding in the ACTG.

Integrase inhibitor from Merck. Finally Merck is moving into patients with an integrase inhibitor drug. Safety, anti-viral activity, and tolerability will be examined in a phase II study in patients planned for 2005 in the ACTG. Initially treatment-naive will be studied followed by treatment-experienced patients. Study data in patients from the forerunner compound '870810' in patients will be presented at CROI in early 2005. Animal toxicity was found with '810' so the follow-up compound is being studied which is more potent and has better PK qualities. It will be studied with twice daily dosing and no food restrictions. Key drug interaction studies have been conducted.

Capravirine is an NNRTI that is being developed for patients with NNRTI drug resistance. Early studies of this drug suggest it might suppress HIV with resistance to currently available NNRTIs, efavirenz and nevirapine. Pfizer is planning studies now to explore Capravirine's antiviral activity in patients with NNRTI drug resistance.

HIV Maturation Inhibitor PA-457: New Oral Drug, Early Study Results Presented at Bangkok IAC

PA-457 is the first in a new class of antiretrovirals called Maturation Inhibitors directed against a novel viral target recently discovered by Panacos scientists. Because PA-457 has a different target than approved HIV drugs, it retains activity against virus isolates resistant to currently available treatments including reverse transcriptase inhibitors and protease inhibitors.

The company summarized the results from the Bangkok studies and their conclusions about the future use of this drug. The safety and pharmacokinetics of PA-457 were examined in uninfected, healthy male volunteers following a single oral dose of 25 mg, 50 mg, 100 mg or 250 mg in a dose escalation protocol. At each dose level, six subjects received PA- 457 and two additional individuals received placebo. PA-457 was well tolerated at all doses, with good oral bioavailability and favorable pharmacokinetics. All doses produced mean circulating plasma levels which exceeded the target therapeutic concentration, and at doses of 50 mg or greater PA-457 levels continued to exceed the target concentration 24 hours after administration. These results suggest that PA-457 will be suitable for once daily oral dosing.

Based on the promising results of the first clinical study, Panacos has now advanced PA-457 into a multiple dose Phase 1 study to examine the safety and pharmacokinetics of the compound administered once daily to uninfected, healthy volunteers for 10 days. PA- 457 is expected to begin Phase 2 testing in patients soon". In the same presentation, Dr. Martin summarizes results of pre-clinical studies that suggest PA-457 is unlikely to exhibit drug-drug interactions when used in combination therapy with approved HIV drugs.

In cell culture studies, PA-457 shows activity against drug-resistant HIV strains that is comparable to that against wild type virus, strongly supporting the compound's potential value for treating strains of the virus that are resistant to approved drugs. Dr. Allaway also describes the results of a collaborative study with scientists from the Gladstone Institute (San Francisco, CA), demonstrating that PA-457 is a potent inhibitor of HIV replication following oral administration in the SCID-hu mouse model of HIV infection. In this study, PA-457 exhibited similar potency to the approved HIV drug EPIVIR(R) (lamivudine or 3TC).

SPD754: New NRTI in Early Development Stages

New study data was presented at CROI on SPD754, a new NRTI in very early stages of development from Shire Pharmaceuticals. This drug appears to have no laboratory induced mitochondrial toxicity. The aim of this study was to evaluate the interaction due to phosphorylation between SPD754 600mg BID and lamivudine (3TC) 150 mg BID. In a study of 21 healthy volunteers who were given each drug separately or in combination in a 3-way study of 4 days treatment with 7 days washout, no effects were seen on plasma concentrations. However, when the intracellular drug levels were examined there was 6-fold reduction in SPD754 levels by the co-administration of 3TC which did not occur in the opposite direction. The data suggest that it is imperative to evaluate triphosphate concentrations of agents to assess drug-drug interactions prior to commencing clinical efficacy studies if the activity of the drug could potentially be affected by co-administration. It was pointed out, however, that since SPD754 is targeted at viruses which are already resistant to 3TC, this particular interaction should not per se affect the development of the compound. A study of SPD75, at dose from 400mg to 1600mg daily, in 63 patients some of whom had baseline thymidine analogue mutations showed no evolution of new resistance mutation after 10 days monotherapy and substantial viral load reductions of -1.18 to -1.65 log copies/ml. No adverse events were reported. In addition a 52-week safety study in cynomolgus monkeys demonstrated no significant toxicity, although some hyperpigmentation developed as well as mild gastrointestinal side effects.

GW695634: New NNRTI for Resistance in Early Development

At the Bangok IAC, GlaxoSmithKline researchers reported early data on a new NNRTI GW695634, which is a prodrug of the active compound GW678248, a new NNRTI in development for treating HIV. GW678248 is active in vitro, in the test tube, (IC50≤2 nM) against NRTI-resistant mutants and NNRTI-resistant mutants (IC50≤7 nM). In a panel of patient isolates (blood samples) from NNRTI-experienced patients that showed efavirenz and/or nevirapine resistance, >80% of the viruses were susceptible to GW678248 with ≤10 fold change in IC50 value. The drug has the potential to be an effective therapeutic option for treatment-experienced patients.

Data was presented from an early study designed to establish initial safety, tolerability and pharmacokinetics of GW695634 and GW678248 in healthy subjects; also to study the effect of food on the relative bioavailability of 695634 and 678248, and to support the dose selection for future clinical studies. The study enrolled healthy male subjects in a double-blind, randomized, parallel, placebo-controlled, single-ascending dose study of 695634. Study doses were 10mg, 25mg, 75mg, 200mg, 400mg, 600mg, and 800mg. At each dose level, 10 subjects were enrolled with 8 receiving GW695634 and 2 receiving placebo. To study the effect of food on the relative bioavailability of 695634 and 678248, the 200mg dose was given on a second occasion with a standard high fat meal.

Study authors reported that GW695634 was generally well tolerated. No serious adverse events, deaths, or withdrawals due to AEs occurred during the study. The most commonly reported AEs were rash (14 subjects; 18%), headache (10 subjects; 13%), erythema (8 subjects; 11%), skin irritation (5 subjects; 7%), skin laceration (4 subjects; 5%), pharyngolaryngeal pain (4 subjects; 5%), and increased serum ALT values (4 subjects; 5%). Authors reported that the subjects who experienced rash (14 subjects), erythema (8 subjects), and skin irritation (5 subjects) had these due to ECG electrode site irritation and not due to the drug in the opinion of the investigator.

All AEs were reported mild to moderate in intensity; no severe AEs were reported; no notable trends in AEs were observed with increasing doses of 695634. No notable trends in laboratory values were observed.

Changes from placebo in QTc were generally small (-4.436 to +2.161 msec) for the overall population. There were no QTc, QTcF, QTcB, or QTcl abnormalities of >60 msec duration, missed heart beats.

Authors concluded 695634 can be administered with or without food.

At ICAAC (October 2004) additional study data on this new NNRTI was presented. 39 healthy male volunteers received, every 12 hours for 10 days, increasing doses of GW695634 starting with 100 mg and ending with 400 mg. Screening for adverse events, clinical laboratory evaluations, vital signs, and ECGs were performed, along with pharmacokinetic measurements. Thirty-four of the 39 subjects completed the study.

GW695634 was generally well tolerated. No serious adverse effects occurred during the study. Five study discontinuations due to side effects occurred, with reported symptoms of rash (3), abdominal pain (1), ECG abnormality (1) and mouth ulcerations.

The study concludes that doses of 200 mg and 300 mg once very 12 hours would be sufficient for many NNRTI-resistant viruses, while 400 mg once every 12 hours would be needed for highly resistant viruses. Due to these study results and the drug showing potency in vitro against NNRTI-resistant HIV clinical efficacy studies of GW695634 in NNRTI-experienced are ongoing.

Double PI Regimens

- Reyataz (atazanavir) Update: FDA approves ATV/r in treatment and protease inhibitor experienced patients based on new data reported below comparing ATV/r to Kaletra
- Context Study: fosamprenavir/r vs Kaletra in treatment-experienced
- Saquinavir/r 1000/100 twice daily & 1600 or 2000/100 once daily
- SOLO Study final results: fosamprenavir/r vs nelfinavir in treatment-naïve
- Kaletra Report: 6 years follow-up; Kaletra monotherapy as first-line or simplification therapy

Reyataz and Reyataz/ritonavir

Study 045 reports viral load response of Reyataz/ritonavir once daily (300/100 mg) in treatment and protease inhibitor experienced patients.

Reyataz was the first once daily protease inhibitor to become available. It was approved by the FDAin the Summer of 2003 to be taken as 400 mg (two 200 mg pills) once daily. It is relatively easy to tolerate, and has a low pill burden. Perhaps it's most appealing attribute is that it has a favorable effect on fat lipids (cholesterol, triglycerides) and glucose. Treatment-naïve patients do not in general experience lipid elevations when using Reyataz. Treatment-experienced patients who already have elevated lipids often experience improvements in lipids after switching to a Reyataz-based regimen. In a study patients who were on nelfinavir and experiencing elevated lipids switched to Reytaz 400 mg once daily and saw improvements in their lipids.

At the 6th International Congress on HIV Drug therapy in Glasgow (November 2004), updated 96 week results were reported. The primary study analysis for '045'was at week 48. At week 48 in study 045 treatment-experienced patients receiving Reyataz/rtv experienced declines of 8% in total cholesterol, 14% in fasting triglycerides, and 10% in fasting LDL (bad cholesterol). At week 96, the mean change in total cholesterol was -7% from baseline for patients taking Reyataz/r,

-11% in LDL-cholesterol, -5% for HDL-cholesterol, and -2% in triglycerides. As well, 48-week study results reported that using Reyataz can reduce the need to use lipid lowering drugs for patients with elevated lipids: 6% of patients receiving Reyataz/r in study 045 were taking lipid lowering agents before the study and only 8% needed lipid lowering agents while on reyataz/rtv in the study. At week 96, 9% of patients taking Reyataz/r were using lipid lowering agents.

For patients without diabetes, Reyataz does not appear to increase glucose for many patients. The effect of Reyataz in patients who have developed diabetes or insulin resistance is uncertain and further study is needed. See the section in this newsletter on Insulin Resistance and Diabetes for further discussion about study results observed regarding the effect of Reyataz on glucose.

The main side effect observed associated with Reyataz is asymptomatic elevations in indirect bilirubin, but in studies this has not lead to discontinuation of Reyataz. The hyperbilirubemia is reversible upon discontinuation of Reyataz. This may be accompanied by yellowing of the skin or whites of the eyes and alternative antiretroviral therapy may be considered if the patient has cosmetic concerns. 35-47% of patients in studies of Reyataz without ritonivir boosting experienced elevations in total bilirubin (≥2.6 x ULN); jaundice was reported by 7%, and 1-3% of patients reported yellowing of the eyes.

Reduced blood levels of atazanavir are expected if antacids, including buffered medications, are administered with Reyataz. Reyataz should be administered 2 hours before or 1 hour after these medications.

Reduced blood levels of Reyataz are expected if H2-receptor antagonists (eg, Tagamet, Zantac), and proton-pump inhibitors (eg, Nexium) are administrated with atazanavir. The FDA recommends against concomitant use of Reyataz and proton-pump inhibitors. Coadministration of Reyataz with proton-pump inhibitors is expected to substantially decrease Reyataz blood levels and reduce its therapeutic effect.

When Combining Reyataz with Efavirenz
The FDA recommends this dosing regimen: Reyataz/ritonavir/efavirenz 300/100/600 mg once daily applies to treatment-naïve subjects. Appropriate dosing recommendations for efavirenz and Reyataz in treatment-experienced subjects have not been established.

When Combining Reyataz with Tenofovir (Viread)
Tenofovir decreases the AUC (area under the curve) also referred to as the drug level of Tenofovir in the blood during the 24-hour dosing period; and Cmin (minimum concentration) of Reyataz. When coadministered with tenofovir, it is recommended that Reyataz 300 mg is given with ritonavir 100 mg and tenofovir 300 mg (all as a single daily dose with food). Reyataz without ritonavir should not be coadministered with tenofovir.

Reyataz was approved by the FDA in the Summer of 2004 to be taken as 300 mg once daily along (two 150 mg pills) with low-dose ritonavir (one 100 mg pill) to boost Reyataz levels. Most doctors are using 300/100 in treatment-naïve and experienced patients because the 300/100 regimen achieves higher levels of Reyataz in the blood and is likely to be more potent. Importantly, for treatment-experienced patients only the 300/100 dosing regimen is recommended by the FDA because patients with prior experience need a more potent regimen. The effect of Reyataz 300/100 on lipids has not been extensively studied, but anecdotal reports are that lipids often improve dramatically after switching to the Reyataz 300/100 regimen.

Food Effect: Reyataz should be taken with a light meal
Administration of Reyataz with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400-mg dose of Reyataz with a light meal (357 kcal, 8.2 g fat, 10.6 g protein) resulted in a 70% increase in AUC (blood level of drug) and 57% increase in Cmax (peak drug level) relative to the fasting state. Administration of a single 400-mg dose of Reyataz with a high-fat meal (721 kcal, 37.3 g fat, 29.4 g protein) resulted in a mean increase in AUC of 35% with no change in Cmax relative to the fasting state. Administration of Reyataz with either a light meal or high-fat meal decreased the coefficient of variation of AUC and Cmax by approximately one half compared to the fasting state.

Reyataz Resistance: implications for using Reyataz as first-line protease inhibitor
The 50L mutation associated with Reyataz (atazanavir or ATV) is unique to this PI and appears in vitro to not cause resistance to the other PI's. In fact, in lab testing patients blood samples with the 50L mutation tend to be hypersusceptable to the other PI's. But the I50L mutation confers resistance to Reyataz.

Preliminary study results suggest that PI naïve patients who start a Reyataz regimen appear to be sensitive to other PIs if they develop viral failure to the Reyataz regimen. However, if the treatment-naïve patient also develops another primary PI mutation, the patient may have some resistance to another PI.

Researchers from BMS reported at the 2004 Resistance Workshop in the Canary Islands on the resistance profile of patients failing ATV regimens from various BMS trials. The investigators report that 50L is more commonly seen in PI-naïve patients who fail ATV as their first PI. In the 034 trial of PI-naive patients treated with unboosted ATV, 83% (5/6) who failed with PI resistance had the 50L mutation. In contrast, in PI-experienced patients treated with an ATV-containing regimen, the 50L mutation was seen less frequently. In the various trials of treatment-experienced patients, the 50L was observed in 0% to 35% of patients failing with new PI-resistance. In PI-experienced patients with preexisting PI resistance, the determinates for the development of 50L versus non-50L resistance pathway remain unclear -- nor is it clear what the PI sequencing implications are after failure with 50L versus a non-50L pathway.

Further studies are needed to confirm these findings. As well, the resistance profile of patients in Reyataz studies will be helpful to see so we can understand better how to treat Reyataz viral failures.

Reyataz/ritonavir is Approved by the FDA in Treatment-Experienced Patients (Study 045)

Once daily Reyataz 300 mg boosted by 100 mg ritonavir is a potent and tolerable option for patients with HIV drug resistance. Reyataz has favorable effects on fat lipids (cholesterol, triglycerides) in treatment-naives and experienced, and a favorable profile on glucose in treatment-naives. Reyataz should be taken with a light meal (about 400 calories). The drug should be stored at average room temperature. Study 045 compared Reyataz 300/100 to Kaletra (lopinavir 300/ritonavir 100) and also to a Reytaz + saquinavir regimen in treatment and protease inhibitor experienced patients. However, the Reyataz/saquinavir regimen did not perform well in the study and is not recommended for use. The study results are reported below. Study results were reported at the 11th CROI in February 2004.

In study 045, patients had failed at least two regimens containing medications from the three ARV drug classes available at the time of enrollment. The 48-week trial evaluated the efficacy and safety of Reyataz 300 mg + ritonavir 100 mg once daily or Reyataz 400 mg + saquinavir 1200 mg once daily compared to Kaletra (lopinavir/ritonavir 400/100 mg) twice daily each with tenofovir and a nucleoside reverse transcriptase inhibitor in treatment-experienced patients.

The FDA approved ATV/rtv for use in treatment-experienced patients in July 2004. Along with the approval they reported additional information. The FDA reported an analysis of viral responses to ATV/r and Kaletra based on the amount of resistance patients had prior to the study--see analysis below.

Reyataz/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in change from baseline in HIV RNA level (viral load). The HIV RNA change from baseline was -1.58 log10 copies/mL for Reyataz/ritonavir and -1.70 log10 copies/mL for lopinavir/ritonavir.

Study 045 was not large enough to reach a definitive conclusion that Reyataz/ritonavir and lopinavir/ritonavir are equivalent on the secondary efficacy outcome measures of proportions below the HIV RNA lower limit of detection. The proportion of patients with HIV RNA < 400 copies/mL and < 50 copies/mL at week 48 was 55% and 38% for Reyataz/ritonavir and 57% and 45% for lopinavir/ritonavir, respectively.

Reyataz Affect on Lipids & Body Changes

The results of studies show that lipids (cholesterol, triglycerides) and glucose do not appear to increase for most people taking Reyataz. In one study, patients switched from nelfinavir (Viracept) to Reyataz and lipids significantly declined. In the clinic doctors report anecdotally that patients with elevated lipids on HAART who switch to a ATV regimen experience improvements in lipids, sometimes dramatic improvements. At the Paris Lipodystrophy Workshop in 2003, 48-week study data was presented regarding the development of lipodystrophy (body changes) from a large trial comparing Reyataz 400 mg once daily to efavirenz (Sustiva) and all participants received AZT/3TC. Objective testing was used to evaluate body changes: CT scans (computerized tomography) and DEXA (dual energy x-ray absorptiometry. After 48 weeks on therapy the DEXA results showed that on average there was no loss of fat in the body compartments examined for either EFV or ATV treatment arms: appendicular (limbs), truncal (waist to shoulders), total fat. On average study patients receiving Reyataz did not experience body changes, this does not mean necessarily that no one experienced fat loss. Follow-up data beyond 48 weeks has not yet been reported. There is limited data regarding lipids for patients taking Reyataz boosted by 100 mg daily of ritonavir, but clinical use and study data suggest lipids ought to improve for many patients using the ritonavir boosted Reyataz regimen.

Study 045 Results

Baseline Characteristics of Study Patients

Before entering the study, patients prior experience with ART is in table. The sensitivity of study patients prior to starting study drugs appeared relatively comparable.

Average Prior Treatment Experiance (yrs)

	PI	NNRTI	NRTI
Kaletra	2.6	1.3	5.1
ATV/r	2.6	1.5	5.2
ATV/sqv	2.4	1.6	5.2

Phenotypic Sensitivity

Prior to the study patients were required to have failed two HAART regimens including at least 1 PI regimen. Many patients had failed nelfinavir as their PI and switched to efavirenz. The majority of study patients had recently taken NNRTI (60%) whereas only 34% had taken a PI. 56% to 83% of patients were sensitive to specific protease inhibitors (≤2.5 x IC50): 55-57% sensitive to NFV; 80-86% sensitive to amprenavir; 63-67% sensitive to ritonavir; 83% sensitive to saquinavir. 20-23% of the treated subjects were highly resistant (>10 x IC50 of control strain) to NFV and 21% of the subjects highly resistant to ritonavir. 6% were highly resistant to amprenavir; 8% were highly resistant to saquinavir; Seventy-four percent (74%) and 75% of subjects were susceptible to ATV and LPV, respectively. The FDA added: An important caveat regarding interruption of baseline PI susceptibility data is that only 34% of randomized subjects were taking a PI at study entry. This would lead to PI susceptibility measurements that are overstated (ie, resistance, therefore, being understated).

There were about 120 pts in each treatment arm.

Viral Load Response at Week 48

	<400	**<50**	**CD4**	**Disct for Viral Failure**
Kaletra	57%	45%	+120	5%
ATV/r	55%	38%	+110	14%
ATV/sqv	38%	28%	+72	10%

At week 96, 42% taking ATV/r & 43% taking LPV/r had <400 copies/ml; 30% taking ATV/r & 33% taking LPV/r had <50 copies/ml.

	T chol	Fasting TG	Fasting LDL-C	HDL-C
Kaletra	+9%	+30%	+1%	+7%
ATV/r	-7%	-4%	-10%	-5%
ATV/sqv	-4%	-14%	-3%	+4%

	Diarrhea	ALT/AST	Bilirubin	
		G3/4	G3	G4
Kaletra	11%	3%	<1%	0%
ATV/r	3%	3%	39%	9%
ATV/sqv	6%	-3%	20%	2%

At week 96, 53% taking ATV/r had grade 3-4 total bilirubin elevations.

While Kaletra is associated with diarrhea, due to elevations in bilirubin ATV is associated with jaundice or yellowing of the eyes. In study 045, there were no treatment discontinuations for patients due to elevated bilirubin. Total discontinuations prior to week 96 were 44% for ATV/r & 35% for Kaletra. Serious adverse events occurred in 13% taking ATV/r, and 11% for LPV/r. More patients taking Kaletra experienced diarrhea (11% vs 3%); but jaundice (6% vs 0%) and yellowing of eyes (3% vs 0%) were associated with ATV/r.

Withdrawal due to Adverse Event

ATV/r: 5%
LPV/r: 4%
ATV/sqv: 7%

Use of Lipid-lowering agents

	Before Study	On study
ATV/r	6%	8%
LPV/r	5%	19%
ATV/sqv	7%	12%

Use of Anitdiarrhial

ATV/r: 6%
LPV/r: 24%
ATV/sqv: 3%

Viral Load Response by Number and Type of Baseline PI Mutation for Antiretroviral-Experienced Patients in Study 045 (As-Treated Analysis)

Upon granting approval for use of ATV/r in treatment-experienced patients, the FDA reported viral responses based on baseline protease inhibitor resistance. The number of baseline resistance mutations affects the viral response to your next PI regimen. In patients with some prior PI resistance the FDA analysis found similar viral responses to Kaletra and ATV/r. In patients with extensive PI resistance-- 5 PI genotypic mutations or 5-fold phenotypic resistance, Kaletra appeared more potent; this analysis was based on a small number of patients. See below for a full discussion of the results and to see the actual data.

Response by PI Mutations

The FDAprovided a table with information regarding HIV RNA response at week 48 by number and type of baseline protease inhibitor mutations and baseline phenotype in treatment-experienced subjects from Sudy 045.

In summary, the HIV RNA response rates (< 400 copies/mL) were 75% for both Reyataz/ritonavir and lopinavir/ritonavir in patients with 0-2 baseline primary protease inhibitor mutations. In patients with 3-4 baseline primary protease inhibitor mutations the response rates were 41% and 43% for Reyataz/ritonavir and lopinavir/ritonavir, respectively. In patients with 5 or more baseline primary protease inhibitor mutations the response rates were 0% (0/9) and 28% (5/18) for Reyataz/ritonavir and lopinavir/ritonavir, respectively.

Virologic Response= HIV RNA<400 copies/ml(b) by Baseline PI Mutation Profile

Number & type of baseline PI mutations (a)

	ATV/rtv n=110	LPV/rtv n=113
3 or more primary PI mutations including (c):		
D30N	75% (6/8)	50% (3/6)
M36I	20% (3/15)	33% (6/18)
M46I/L/V	24% (4/17)	23% (5/22)
L54V/L/T/M/A	31% (5/16)	31% (5/16)
A71V/T/I	34% (10/29)	39% (12/31)
V77I	47% (7/15)	44% (7/16)
V82A/F/T/S/I	29% (6/21)	27% (7/26)
I84V	13% (1/8)	33% (2/6)
N88D	63% (5/8)	67% (4/6)
L90M	10% (2/21)	44% (11/25)

Number of Baseline Mutations (a)

	ATV/r	LPV/r
All patients as-treated	58% (64/110)	59% (67/113)
0-2 PI mutations	75% (50/67)	75% (50/67)
3-4 PI mutations	41% (14/34)	43% (12/28)
5 or more PI mutations	0% (0/9)	28% (5/18)

a- Primary mutations include any change at D30N, V32, M36, I47, G48, I50, I54, A71, G73, V77, V82, I84, N88, and L90.
b- Results should be interpreted with caution because subgroups were small.
c- There were insufficient data (N<3) for PI mutations V32I, I47V, G48V, I50V, and F53L.

Baseline Phenotype by Outcome, Antiretroviral Experienced Patients in Study 045, as-Treated Analysis

Virologic Response=HIV RNA<400 c/ml (b)

Baseline Phenotype(a)	ATV/rtv N=111	LPV/rtv n=111
0-2	71% (55/78)	70% (56/80)
>2-5	53% (8/15)	44% (4/9)
>5-10	13% (1/8)	33% (3/9)
>10	10% (1/10)	23% (3/13)

a- Fold change in in vitro susceptibility relative to wild-type reference.
b- Results should be interpreted with caution because the subgroups were small.

908 (Fosamprenavir)/RTV

'908' is short for fosamprenavir, which is the new formulation of amprenavir (Agenerase). 908 (brand name: Lexiva) was FDA approved about one year ago. The new version, fosamprenavir, has been reformulated and appears to be associated with fewer clinical adverse events than amprenavir, improved tolerability and GI side effects, and a significantly lower pill count. 908 now comes in 700 mg capsules. As well, 908 has no food or fluid restrictions.

In treatment-naïve patients, 908 has been studied in clinical trials as once daily (QD) dosing with ritonavir (RTV), or twice daily (BID) dosing with or without RTV. Fosamprenavir is effective as a once daily therapy for treatment naïve individuals. For treatment-experienced patients it is taken only as a twice daily regimen.

908 has a distinct resistance profile that offers opportunities for treatment sequencing. Similar to Kaletra PI resistance so far has not been seen when fosamprenavir is boosted with low-dose RTV. 908 boosted with low-dose ritonavir is a potent protease inhibitor therapy and relatively tolerable. 908 appears to have similar elevations in lipids (cholesterol, tryglicerides) as nelfinavir; study results are presented below.

Reported below:

- SOLO Study examines once daily fosamprenavir in treatment-naïve patients

- CONTEXT Study examines twice daily fosamprenavir in treatment-experienced patients

908/r: 48 Week Results in PI-Experienced
(CONTEXT study)

Below you will find study results of an analysis of viral response to 908/r in PI-experienced patients based upon prior genotypic and phenotypic resistance for the patients in the CONTEXT Study. This study was presented at the IAC Bangkok 2004.

The CONTEXT Study looked at 908 (fosamprenavir, a/k/a Lexiva) boosted with ritonavir both as a once or twice daily regimen and compared it to Kaletra in patients with resistance to protease inhibitors. This study is a first-time comparison of the two PI therapies.

Background on Resistance. Kaletra contains in one pill 300 mg of lopinavir and 100 mg of ritonavir to boost lopinavir blood levels. Kaletra has been approved for over 5 years and studies so far do not show resistance to protease inhibitors after patients develop viral failure when taking Kaletra. Fosamprenavir boosted with low dose ritonavir has been studied for less time, about 1 year, but also so far no resistance to other protease inhibitors has been observed after a patient experiences viral failure.

This is the history of drug resistance observed. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V, as well as mutations in the p7/p1 and p1/p6 Gag and Gag-Pol polyprotein precursor cleavage sites. A few small studies found that the presence of I50V may cause cross-resistance to Kaletra. Some of these amprenavir resistance-associated mutations have also been detected in HIV blood samples from antiretroviral-naive patients treated with Lexiva. Of the 488 antiretroviral-naive patients treated with Lexiva or Lexiva/ritonavir, 61 patients (29 receiving Lexiva and 32 receiving Lexiva/ritonavir) with virological failure were genotyped. Five of the 29 antiretroviral-naive patients (17%) receiving Lexiva without ritonavir had evidence of genotypic resistance to amprenavir: I54L/M (n = 2), I54L + L33F (n = 1), V32I + I47V (n = 1), and M46I + I47V (n = 1). No amprenavir-associated mutations were detected in antiretroviral-naive patients treated with Lexiva/ritonavir. CONTEXT Study results related to resistance are discussed below.

CONTEXT Study
315 patients who had failed 1-2 protease inhibitors with current treatment failure (HIV RNA >1000 c/ml at screening) were randomized to receive 2 N(t)RTIs along with:

- 908/r 1400/200 mg QD (2 908 + 2 RTV pills, once daily)
- 908/r 700/100 mg bid (1 908 tablet + 1 RTV pill, twice daily)
- LPV/r 400/100 mg bid (3 Kaletra pills, twice daily)

48 week results from this study had been previously reported. But results from the Virology Substudy were newly reported at Bangkok, and these may provide added guidance in selecting treatment.

Brief Summary of Results:

- 908/r appeared to perform similarly to Kaletra in this study
- Patients receiving 908/r twice daily: 58% had <400 copies/ml; 46% < 50 copies/ml
- Patients receiving Kaletra (LPV/r) twice daily: 61% had <400 copies/ml; 50% had <50 copies/ml (ITT RD=F).
- FDA said non-inferiority of 908/r compared to Kaletra at 48 weeks using the primary endpoint could not be established
- There were 27% virologic failures in each arm.
- At week 48 viral load reduction for patients taking 908/r twice daily was on average -1.53 log c/ml and -1.76 for patients taking Kaletra.
- 908/r once daily did not perform well in this study in PI-experienced patients, so it is not recommended for use in PI-experienced; but it is approved to be used in PI-naïve patients.
- Below, in this article, you'll find a Virology substudy which compares the two regimens, 908/r & Kaletra, regarding virologic responses in the presence of prior common PI resistance mutations: D30N, M46/I/L, L90M, V82, I84V
- There were more grade 3 & 4 triglycerides elevations in the patients taking 908/r than Kaletra (11% vs 6%); no difference in cholesterol in this study. Overall, grade 2-4 adverse events were comparable between the two regimens, but there appears to have been a bit more GI side effects associated with Kaletra.

Basline Demographics

	908/r bid n-107	LPV/r bid n=103
Females	13%	17%
Median age	40	41
Wh, Bl, Hisp (%)	70/21/8	57/32/11
Hep B, C	4%/15%	5%/17%
CDC Class C	32%	34%
Med HIV RNA	4.13 log	4.13 log (aprx. 10k copies/ml)
Med CD4 count	292	234

Prior Art Exposure

This data suggests that patients receiving 908/r had more prior ART experience than patients receiving LPV/r.

	908/r bid	LPV/r
median duration of prior PI (wks)	149	130
≥2 prior PIs taken % of subjects	49%	40%
≥3 prior PIs taken	4%	40%
median duration prior NRTIs (wks)	257	210
≥3 prior NRTIs taken % of subjects	79%	64%
median duration prior NNRTIs (wks)	84	78
≥2 prior NNRTIs % of subjects	14%	8%

Baseline Resistance

Although patients receiving 908/r appeared to have more ART experience, the following data does not necessarily suggest much difference in drug resistance between patients receiving 908/r and LPV/r, although patients receiving 908/r had more phenotypic PI resistance (16% vs 9%) and more often had NRTI mutations (38% vs 24%).

Mean (median)

	908/r bid	LPV/r
# Primary PI Mutations	0.9 (1)	1 (1)
>3 Primary PI Mutations	8%	11%
# Secondary PI Mutations	2.8 (3)	3 (3)
Phenotypic Resistance to all PIs (>2.5-fold)	16%	9%
NRTI Mutations	2.6 (3)	2.4 (2)
# TAMS	1.7 (2)	1.4(1)
>3 TAMS	38%	24%
M184V	49%	56%

TAM=thymidine analogue mutation

Week 48 Results

Proportion of Subjects with Plasma HIV RNA Levels <400 and <50 Copies/ml

908/r QD is not recommended for PI-experienced patients (HIV RNA <400 c/ml- 50%; HIV RNA <50 c/ml- 37%)

	908/r bid n=107	LPV/r n=103
Responder (ITT RD=F)		
HIV RNA <400 c/ml	58%	61%
HIV RNA <50 c/ml	46%	50%
Virologic Failures		
HIV RNA >400 c/ml	27%	27%

Safety

Grade 2-4 drug related AEs were comparable between 908/r bid & LPV/r bid.

Upper GI-Events

nausea: 908/r: 3% LPV/r: 9%
vomiting: 908/r 3% LPV/R: 5%

No grade 3/4 total cholesterol elevations were observed in either treatment group.

Grade 3/4 lipase elevations: 908/r bid- 5%, LPV/r: 12%

Grade 3/4 triglycerides elevations: 908/r bid- 11%, LPV/r- 6%

Virology Substudy

The Virology Substudy objective is to identify statistically robust phenotypic and genotypic clinical cut-offs for 908/r. Virologic response: <400 c/ml at week 48

Virology population:

- all subjects who received at least one dose of randomized PI
- subjects were excluded if the study drug was discontinued for reasons other than virologic failure (eg- adverse events).
- 908/r bid n=92, LPV/r bid n=88

Virology Substudy Analysis

Phenotypic Clinical Cut-off:

A statistically robust phenotypic cut-off could not be established due to the distribution of the baseline data.

Genotypic Based Analysis:

The most robust differentiation between virological response & failure was associated with the presence at baseline of-

- 3 primary PI mutations (p= 0.009)
- 6 or more primary/secondary PI mutations (p=0.007)
- 4 or more Marcellin et al mutations (p<0.001)

(L10F/I/V, K20M/R, E35D, R41K, L63P, V82A/F/T/S, I84V)

% Response at Week 48 (<400 copies/ml) by Presence of Primary PI-mutations at Baseline

Most patients had >1 PI resistance-associated mutation at baseline, and not all patients had a fully active NRTI backbone.

In a press release, GSK said these were the most common PI associated mutations seen at baseline among the 210 patients included in the study:

L90M in 63 patients (30 percent)
M46I/L in 48 patients (23 percent)
D30N in 45 patients (21 percent)

Genotypic Resistance 908/r: I54L/M, V32I, I50V, I84V. LPV/r: Abbott algorithm.

Baseline Mutation

	908/r bid	**LPV/r bid**
D30N	21/25 (95%)	17/18 (94%)
M46I/L	11/22 (50%)	12/24 (50%)
L90M	16/31 (52%)	17/28 (61%)
V82A/F/T/S	2/9 (22%)	6/17 (35%0
I84V	1/6 (17%)	2/5 (40%)

It is unknown what effect therapy with Lexiva will have on the activity of subsequently administered protease inhibitors. Clinical relevance of resistance data is currently being evaluated.

The likelihood of a successful response in patients with baseline L90M or M46L is reduced.

M46I/L at Baseline & Recieved 908/r BID: Characteristics of Responders vs Non-Responders

<400 c/ml (responders), n=11
>400 c/ml, n=11 (nonresponders)
(mean numbers)

- Responders had 2 primary PRO mutations, while non-responders had 3.

- Respondershad 5 primary & secondary PRO mutations, while non-responders had 7.

- Responders had 4 total number of RT mutations, while non-responders had 5.

- Responders had 1 PI-fold resistance, while non-responders had 5-fold PI resistance.

- Responders had 2-- number of susceptible concomitant NRTIs, while non-responders had 1.

M46I/L at baseline: response in the presence/absence of baseline resistance

	Genotype		Phenotype		Combined		Odds Ratio
Evidence of Resistance	Yes	No	Yes	No	Yes	No	95% CI
908/r	20%	59%	25%	80%	23%	89%	0.038
(>2.5-FC)	1/5	10/17	3/12	8 /10	3/13	8/9	(0.0008, 0.55)
LPV/r	22%	67%	29%	100%	33%	100%	
(>2.5 FC)	2/9	10/15	5/17	7/7	6/18	6/6	-
LPV/r	22%	67%	14%	65%	18%	77%	0.067
(>10 FC)	2/9	10/15	1/7	11/17	2/11	10/13	(0.005, 0.65)

L90M at Baseline & Recieved 908/r BID: Responders vs Non-Responders

- Responders had 1.5 number of primary PRO mutations, while non-responders had 2.

- Responders had 5 primary & secondary PRO mutations, while non-responders had 6.

- Responders had 4 total number of NRTI mutations, while non-responders had 5.

- Responders had 1 fold PI resistance, while non-responders had 5 fold PI resistance.

- Responders had 1-- number of susceptible concomitant NRTIs, while non-responders had 1.

L90M baseline: response in the presence/absence of baseline resistance

	Genotype		Phenotype		Combined		Odds Ratio
Evidence of Resistance	Yes	No	Yes	No	Yes	No	95% CI
908/r	22%	64%	17%	72%	20%	81%	0.056
(>2.5-FC)	2/9	14/22	2/12	13/18	3/15	13/16	(0.007,0.43)
LPV/r	17%	73%	23%	93%	23%	93%	0.021
(>2.5 FC)	1/6	16/22	3/13	14/15	3/13	4/15	(0.0005,0.29)
LPV/r	17%	72%	20%	70%	14%	76%	0.052
(>10 FC)	1/6	18/22	1/5	18/23	1/7	16/21	(0.001,0.65)

908/r Once Daily (1400/200) vs Nelfinavir Twice Daily (bid) (old formulation, more pills), 48 Weeks & 96 weeks

At the Bangkok IAC 48 & 96 week results were presented from the SOLO Study. The I50V drug resistance mutation is associated with resistance to fosamprenavir, and studies have found that development of this mutation may reduce response to Kaletra.

SOLO: 48-week efficacy and safety comparison of once-daily (QD) fosamprenavir/ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients

908/r QD in Treatment-Naïve 96 weeks Followup of SOLO
At the Intl AIDS Conference in Bangkok Joe Gathe, MD reported results from a 96-week followup study of SOLO. In SOLO 650 treatment-naïve patients were randomized to 908/r 1400/200 mg QD compared to nelfinavir bid plus abacavir/3TC. The followup study reports 96 weeks data.

Patients were randomized to receive either FPV 1400 mg QD (two 700 mg tablets) plus RTV 200 mg QD (two 100 mg capsules), or NFV 1250 mg BID (five 250 mg tablets). A new formulation of 625 mg tablets of Viracept was recently made available, which reduces the 'pill count' making NFV easier to take. Both treatments were administered with ABC and 3TC BID. Patients were stratified according to screening viral load: 1000-10 000, > 10 000-100 000 and > 100 000 copies/ml.

No FPV/r QD recipients developed protease inhibitor mutations and significantly fewer recipients developed nuke mutations throughout the 48 weeks of treatment. The once daily 908 regimen has no food restrictions, a low daily pill burden (4 tablets), once-daily dosing and a favorable lipid profile.

The study population had relatively advanced HIV, was ethnically diverse and included a relatively high proportion of females (27%). The patients in this study had relatively advanced HIV. Median viral load level was 63,000 copies/ml) and median CD4+ cell count of 170 was low. Of note, 20% of patients had CD4+ cell counts < 50, whereas 22% had a history of CDC Class C (AIDS) events.

Viral Load Reductions at Week 48
(intent to treat, rebound/discontinuation = failure; patients counted as failures if they discontinued regimen or study).

	FPV/r QD	NFV BID
<400 copies/ml	69%	68%
<50 copies/ml	55%	53%
Virologic failures	7%	17%
CD4 increase	+203	+207

Viral load Response (<400 copies/ml) For Patients with High Baseline Viral Load or Low CD4 Count

	FPV/r QD	NFV BID
<500,000 copies/ml	73%	53%
CD4 >50 (posthoc anal)	68%	72%
CD4 <50	73%	51%
(ITT RD=F)		

There were 23 NFV premature discontinuations as per protocol switch vs 1 for FPV/r. 6 never achieved viral load <400 in NFV vs 1 for FPV/r. Non-vrologic failure (premature discontinuation) was 24% for FPV/r vs 15% for NFV.

Although 41 subjects were classified as non-virological failures for premature discontinuation of study drug due to adverse events, the ITT RD = F efficacy analyses only considers the first reason for treatment failure. Overall, 44 subjects withdrew from the study due to an AE: 28 (9%) FPV/r recipients versus 16 (5%) NFV recipients. Adverse events that led to withdrawal from the study in at least 1% of subjects in either treatment group were: suspected ABC hypersensitivity (FPV/r QD n = 4;NFV BID n = 3), diarrhea (FPV/r QD n = 4: NFV BID n = 1) and nausea (FPV/r QD n = 4: NFV BID n = 1).

Viral Load Reductions (<400 copies/ml & <50 copies/ml, RD=F) in FPV/r QD in patients with Low CD4+ cell counts < 50 cells/l or High HIV RNA >100 000 copies/ml at entry

At the Bangkok IAC GSK reported a post-hoc analysis of viral response in patients with high VL and low CD4 count at study entry.

Definitions:
- Low CD4: <50 cells
- high Cd4: >50
- low VL: < 100,000 c/ml
- high VL: >100,000 c/ml.

Low CD4/low VL
- 48% taking NFV had <400 copies/ml
- 60% taking 908/r had <400 copies/ml

Low VL/High CD4
- 73% taking NFV had <400 copies/ml
- 68% taking FPV/r had <400 copies/ml

High VL/ Low CD4
<400 copies/ml: 74% 908/r, 44% NFV
<50 copies/ml: 51% FPV/r, 33% NFV

High VL/High CD4
<400 copies/ml: 67% 908/r, 71% NFV

There were no PI mutations among patients with viral failure taking FPV/r but 8-14% of patients receiving NFV experiencing viral failure had PI mutations except in the low VL/high CD4 group where 1% had PI mutations. There was a similar trend regarding nuke mutations: 0% in FPV/r viral failures except 6% in high VL, low CD4 group; 14-38% in NFV group, except it was 1% in lowVL/high CD4 group.

Safety Analysis:
Overall, 41% of patients receiving FPV/r QD and 39% receiving NFV BID experienced grade 2-4 adverse events considered to be drug-related. Both regimens were generally well tolerated. Diarrhea was more common on NFV BID than on FPV/r QD (16 versus 9%; P = 0.008). Fasting lipid profile results were generally favorable in both treatment arms. FPV/r QD maintained plasma amprenavir (APV) trough concentrations above the mean phenotypic drug-susceptibility (IC50) for wild-type virus for APV.

The overall incidence of patients discontinuing ABC for a suspected hypersensitivity reaction was the same in both treatment groups (FPV/r QD: 8%; NFV BID: 8%). Subjects who discontinued ABC for suspected hypersensitivity reactions were allowed to continue on study with their randomized PI and substitute another NRTI for ABC.

Liver Enzymes
Incidences of treatment-emergent grade 3/4 clinical chemistry and hematology abnormalities were generally low and comparable between treatment groups, although the incidence of grade 3 elevations in triglycerides and serum lipase was slightly higher in the FPV/r QD group. Serum lipase elevations were observed in both groups and were predominantly asymptomatic. Elevations in liver enzymes were more commonly observed in patients entering the study with evidence of co-infection with hepatitis B and/or C: grade 3/4 ALT increases were observed in 3% (FPV/r QD) and 4% (NFV BID) of subjects without co-infection compared with 24% co-infected with hepatitis B and/or C in both treatment groups.

Lipids
A greater but insignificant median increase from baseline in triglycerides was observed in the FPV/r QD group (baseline 116 mg/dl; change + 58 mg/dl) compared to the NFV BID group (baseline 130 mg/dl; change + 41 mg/dl). Median baseline cholesterol values were: total 162 and 158 mg/dl; LDL 96 and 94 mg/dl and HDL 37 and 36 mg/dl for the FPV/r QD and NFV BID arms, respectively. Although median increases in total, LDL and HDL cholesterol were observed in both groups, there was no appreciable change in the total/HDL cholesterol ratio during the course of the study in either treatment group (median 4.3 for FPV/r QD and 4.5 for NFV BID at baseline vs 4.8 in both groups at Week 48). All median fasting cholesterol levels at Week 48 remained below (total, LDL) or above (HDL) the recommended NCEP intervention guidelines.

96-Week Follow-up Study Results: SOLO Study- 908/r 1400/200 mg QD vs Nelfinavir BID
This analysis reports 96-week data for ART-naïve patients who completed at least 48 weeks on a 908/r 1400 mg/200 mg QD regimen in SOLO and continued this 908/r QD regimen. In SOLO, patients received a background regimen of abacavir (ABC) 300 mg BID and lamivudine (3TC) 150 mg BID. Once subjects enrolled in this follow-up study, background regimens were at the discretion of the investigator and subject to change or optimization at any time. As reported separetly (see Lipodystrophy Workshop report in this newsletter) only 4-5% of patients in this study developed fat wasting (lipoatrophy). This appears likely to be as a result of using abacavir+3TC as the nuke backbone.

322 subjects were randomized to and received 908/r QD in SOLO. Of these, 231 subjects completed SOLO on a 908/r QD regimen and 220 enrolled in this follow-up study. Because the data cut was taken at a specific time point, not all subjects had reached Week 96 as of the cut-off date: 115 patients were available for the Week 96 analysis.

Baseline Demographics
908/r, n=210

Females: 28%
Median age: 36 yrs
White, Black, Hispanic: 49%, 39%, 8%
Heterosexual contact, MSM: 49%, 37%
Hepatitis B, C: 9%, 12%
CDC Class C: 21%
Median viral load: 4.82 log
HIV RNA >100,000: 45
Median CD4: 168
CD4 <50: 20%

175/210 (83%) subjects in the 908/r QD population entered this followup study on an ABC/3TC background. Of those, 94% (164/175) remained on ABC/3TC as of data cut-off.

Viral Response <400 & <50 (observed)
Responses seen at week 48 in SOLO were maintained. At Week 96, 96% (109/113) and 86% (97/113) of subjects with data had viral load <400 copies/mL and <50 copies/mL, respectively. Median CD4+ cell count at Week 96 was 461 (range 103-1333), with median change from baseline increasing from +205 cells at wk 48 to +263 at Week 96.

Resistance
11 subjects in the follow-up study met the criteria for inclusion in the virologic failure (VF)/ongoing replication population (>1000 copies/mL at two consecutive time points) as of the cut-off date. 10/11 remained on ABC+3TC background, while the other subject switched to a AZT + 3TC background at Week 2.

5/11 subjects were new failures in the follow-up study. The other 6 subjects had been previously classified as failures in SOLO and either resuppressed or stayed on a failing regimen in APV30005.

There were no primary PI mutations and only one reverse transcriptase mutation, a M184m/v mixture. 9/11 subjects had susceptibility data, and no phenotypic resistance was observed for any PI or RTI. A small shift was detected for 3TC in the subject with M184m/v, indicating the mixture was predominantly wild-type.

Safety
Median duration of exposure to 908/r QD was approximately 92 wks (range 53-121 wks).

Drug-related Grade 2-4 AEs were reported by 41% of subjects on 908/r QD throughout SOLO and the follow-up study. There were no new cases of drug-related Grade 2-4 drug hypersensitivity or diarrhea and only 1 new case of drug-related Grade 2-4 nausea reported during the follow-up study.

After Week 48, few subjects experienced new Grade 3/4 laboratory abnormalities in this study:
- Grade 3/4 ALT elevations (2%)
- Grade 3/4 AST elevations (<1%)
- Grade 3/4 triglyceride elevations (1%)

Mean Change From Solo Baseline in Lipids
Baseline lipids in SOLO were normal.
Triglycerides increase: +77
Total cholesterol increase: +49
HDL (good) Cholesterol increase: +12

Fasting HDL cholesterol levels continuously improved to a mean percent increase from baseline of +36% at Week 96.

There was no clinically relevant mean percent change from baseline observed for the TC/HDL-C ratio (+2.5% at Week 96).

At Week 96, small mean changes from baseline were observed in fasting glucose (+10 mg/dL), and mean decreases from baseline were observed for ALT (-7 µ/L) and AST (-14 µ/L).

New use of anti-hyperlipidemics in the follow-up study (after Week 48) was reported by only 5 subjects (2%).

Saquinavir/ritonavir Twice & Once Daily

The U.S. FDAapproved Invirase (saquinavir) 1000 mg for use in combination with low-dose ritonavir 100 mg twice daily plus other antiretroviral drugs in December 2003. The twice daily administration of Invirase in combination with ritonavir is supported by safety data from the MaxCmin 1 study and pharmacokinetic data. Invirase was the original formulation of saquinavir but its use was replaced by Fortovase, the second formulation of saquinavir, but Invirase remained available in the pharmacy. Recent research found that Invirase when boosted with low-dose ritonavir is at least as effective as RTV boosted Fortovase, or more effective. As well, Invirase has less GI side effects than Fortovase.

As well, early studies have been conducted using saquinavir once daily, and these preliminary results show promise. 24-week study results are shown below from the Staccato Study. The dosing regimen remains uncertain as both 1600 and 2000 mg of saquinavir are being considered for the once daily regimen, along with low-dose ritonavir to boost saquinavir levels. But, the thinking is that 2000 mg will be the dose selected.

The U.S. Food and Drug Administration (FDA) has granted priority review status to the New Drug Application (NDA) for a 500 mg tablet formulation of its HIV protease inhibitor, Invirase. If approved, the new formulation of Invirase will simplify dosing regimens by reducing pill count for each dose by more than half (from five pills to two, twice-daily). Roche is conducting The Gemini Studies which will compare once daily SQV/r to Reyataz/r and twice daily SQV/r to Kaletra.

Twice daily SQV/rtv appears to be a potent protease inhibitor treatment option based on the limited studies so far conducted. More research is needed to better characterize the regimen's effect in treatment-naïve and particularly in experienced patients. Saquinavir is associated with a degree of lipid elevations similar to all protease inhibitors except Reyataz, which is not in general associated with lipid elevations.

MaxCmin1 Study: SQV/rtv 1000/100 mg twice daily vs IDV/rtv

This trial assessed the rate of virological failure at 48 weeks in HIV+ adults assigned indinavir/ritonavir (IDV/rtv; 800/100 mg 2 times daily) or saquinavir/ritonavir (SQV/rtv; 1000/100 mg 2 times daily) in an open-label, randomized (1 : 1), multicenter, phase 4 design.

306 patients began the assigned treatment. At 48 weeks, virological failure was seen in 43 (27%) of 158 and 37 (25%) of 148 patients in the IDV/rtv and SQV/rtv arms, respectively. The time to virological failure did not differ between study arms. When switching from randomized treatment was counted as failure, this was seen in 78 of 158 patients in the IDV/rtv arm, versus 51 of 148 patients in the SQV/rtv arm (P = .009).

A switch from the randomized treatment occurred in 64 (41%) of 158 patients in the IDV/rtv arm, versus 40 (27%) of 148 patients in the SQV/rtv arm (P = .013). Sixty-four percent of the switches occurred because of adverse events. A greater number of treatment-limiting adverse events were observed in the IDV/rtv arm, relative to the SQV/rtv arm.

In conclusion, RTV-boosed SQV and IDV were found to have comparable antiretroviral effects in the doses studied.

MaxCmin2 Study: Kaletra vs saquinavir/ritonavir; final 48-week results

Final 48-week study viral response results have been reported from this study. Patients assigned in this study to Kaletra (LPV/r) or saquinavir/ritonavir (1000/100 mg twice daily) had similar baseline characteristics. About 27% of patients in the study were treatment-naive. The rest of the patients were treatment-experienced. About 32% of the patients were PI-failures. About 29% were PI-naive.

After 48 weeks on the assigned treatment, patients on Kaletra had 60% <50 copies/ml vs 53% for the patients taking saquinavir/r. The risk of protocol-defined virologic failure was higher in the SQV/r arm compared to the LPV/r arm in the ITT/e (p=0.0009) analyses, but not in the on-treatment-analysis. The rates of failure appear to be driven by higher rates for switching regimens due to non-fatal adverse events in the SQV/r arm (13/167, 7.8% vs 20/172, 11.6%), and by patient choice/non-compliance (5/167, 3.0% vs 14/172, 8%). Tolerability to saquinavir is expected to improve once the newly formulated Invirase 500 mg tablets are available. Fortovase was used in this study, this formulation is generally considered to have more GI side effects than Invirase (hard-gel formulation of saquinavir), although patients were permitted to switch to Invirase during the study.

The primary population for the analysis was the intention-to-treat/exposed (ITT/e) including all randomized patients that had taken at least one dose of the assigned treatment. ITT/e/discontinuation=failure analysis were also performed as were analysis including only patients that remained on the assigned treatment (on-treatment, OT, analysis).

At week 48, 65% vs 57% (ITT/e), 60% vs 53% (ITT/e/s), and 70% vs 75% (OT) in the LPV/r and SAQ/r arm, respectively, had a HIV-RNA <50 copies/ml (p>0.05 for all comparisons).

Baseline characteristics of patients. HIV-RNA was 4.4 to 4.6 log (25,000 to 40,000 copies/ml). 21-22% had <400 copies/ml. CD4 count was 239-241. CD4 nadir was 100-101. Prior use of NNRTIs: 29% (LPV/r) and 35% (SAQ/r). Prior use of PI: 52% and 52%. No difference was observed between the two arms in baseline characteristics.

Discontinuation of the assigned treatment occurred in 69/324 (21%) patients; 13% in the LPV/r versus 29% in the SAQ/r arm (p=0.001) for non-fatal adverse events. In 48% of cases discontinuation was due to a non-fatal adverse event.

Pill count. For patients taking saquinavir regimen, there were 6 capsules taken twice per day; 5 saquinavir capsules plus 1 ritonavir capsule. The pill count will improve after FDA approval of the 500 mg invirase tablets. Patients taking lopinavir/r took 3 capsules twice per day.

No difference was seen in immunologic response between the two arms.

No difference in risk of grade 3 and/or 4 adverse events was seen between the two arms.

Once Daily PI Regimen 1600/100 Saquinavir-hgc/ritonavir or 2000/100: 24 week results: Staccato Study
A study was conducted in Thailand and found that once daily SQV-hgc (Invirase) with a d4T/ddI backbone showed good efficacy over 24 weeks, with more than 90% of patients achieving an HIV RNA level <50 copies/ml and CD4 increase of >100 cells. Although adverse events were common, they were mostly mild and self-limiting, with no patient experiencing severe or life threatening adverse events. This study was presented at Bangkok IAC by Ananworanich and colleagues (HIV NAT, Bangkok, Thailand).

Saquinavir blood levels are higher in Thais compared to Americans so Roche is planning a study comparing 2000/100 mg SQV/r to Reyataz/r (300/100mg) in 180 treatment-naives and they believe this dose regimen will be preferable to 1600/100 due to higher SQV blood levels based on good tolerability observed in a PK study of 2000/100. As well, Roche is planning a study comparing 1000/100mg SQV/r bid to Kaletra in 300 treatment-naives.

Once daily ritonavir-boosted saquinavir (SQV-sgc/r od) 1600/100 mg has previously been shown to be effective and have acceptable pharmacokinetic (PK) parameters in HIV+ patients.

SQV-hgc (Invirase) has been shown to have equivalent PK parameters to SQV-sgc (Fortovase) when used in combination with RTV. As well, the hgc does not require refrigeration. Saquinavir was originally formulated as a hard-gel capsule, but unfavorable pharmacokinetics (PK) limited its effectiveness.

There has been no data to date on the treatment outcome of once daily saquinavir hard gel capsule/ritonavir (SQV-hgc/r)-based HAART.

The first 167 ARV-naïve Thai patients enrolled in the Staccato Study between Jan 2002 to July 2003 and treated in the study for 24 weeks were included in this analysis. Patients also received d4T (30 or 40 mg twice daily) and ddI (250 or 400 mg once daily) according to weight. Intent to treat analysis was performed.

Seventy four (56%) men and 93 (44%) women participated, with a mean age of 34.8 years, median CD4 265 and median HIV RNA 4.7 log (50,000 copies/ml).

Results After 24 Weeks
HIV RNA levels of <400 copies/ml and <50 copies/ml were seen in 95% and 91% of patients, respectively (intent-to-treat analysis); p<0.001 and p<0.01 vs baseline, respectively.

There was a median reduction in viral load (HIV RNA) from baseline of 2.9 log (p<0.001).

The median CD4 count was 380. There was a median increase from baseline of 109 cells (p<0.001 vs baseline).

ARV-related adverse events were seen in 74 patients (44%):
- grade 1 (78%)
- grade 2 (22%)
- grade 3 or 4 (0%)

The most common ARV-related AEs were diarrhea (19%), nausea/vomiting (12%) and peripheral neuropathy (13%).

9% of patients switched from d4T/ddI to tenofovir/3TC. Nine (5%) patients temporarily stopped ARV therapy owing to hyperlactatemia 1, worsening neuropathy 1, suspected drug allergy 1, gastrointestinal symptoms 1, non-compliance 3, and herpes simplex infection 1. One patient stopped TDF/3TC because of dizziness, nausea and vomiting. In the patient with hyperlactatemia the d4T dose was reduced; in all other patients the original therapy was subsequently recommenced.

Kaletra Report

6-Year Follow-up of Kaletra from Study 720
Kaletra has been established as a potent protease inhibitor option for 6 years. It is recommended by the PHS Treatment Guidelines as the protease inhibitor option for initial therapy. Kaletra is also recognized and well established as a potent option for patients with extensive treatment experience. New PIs target Kaletra to study for comparison purposes. So far no protease inhibitor resistance has been observed in patients in studies who have experienced viral failure when using Kaletra first-line. Elevated lipids and GI (stomach) side effects (diarrhea, nausea) are associated with Kaletra use.

At the 6th International Congress on Drug Therapy in HIV Infection (November 2004, Glasgow, UK) 6 year followup study results were reported from Study 720. 100 ART-naïve patients received 1 of 3 dosage levels of LPV/r together with d4T 40mg bid and 3TC 150 mg BID given either after 3 weeks of monotherapy or from study entry. At week 48, patients converted to open-label LPV/r 400/100 mg BID dosing.

Brief Summary
- Through 6 years (312 weeks) of follow-up, antiretroviral-naive patients receiving LPV/r-based therapy exhibited sustained virologic responses, with 63% of patients demonstrating HIV RNA <400 copies/mL and 62% demonstrating HIV RNA <50 copies/mL by intent-to-treat (NC=F) analysis.

• On-treatment response rates were 100% and 98%, respectively.

• Mean CD4 cell count increased 529 cells/mm3 over 312 weeks of follow-up with consistent CD4 cell count increases regardless of baseline CD4 cell count.

• Through 312 weeks of follow-up, no primary protease inhibitor resistance mutations have been observed in subjects with HIV RNA >500 copies/mL any time at or after Week 24.

• Rate of study discontinuations due to LPV/r-related adverse events (13/100, 13%).

Results

6 years Follow up: efficacy, resistance, CD4 response

Efficacy

Viral Load Suppression Below the LOQ

Based on the ITT NC=F analysis through Week 312, 63% of patients had HIV RNA<400 copies/mL (on-treatment analysis: 100%) and 62% of patients had HIV RNA <50 copies/mL (on-treatment analysis: 98%). One patient had HIV RNA between 50 and 400 copies/mL, but demonstrated resuppression to <50 copies/mL at subsequent visits.

Analysis of Genotypic and Phenotypic Resistance

A total of 33 samples from 28 patients were submitted for resistance testing.

17 patients met criteria for loss of virologic response, and 11 patients had at least 1 "blip"(single HIV RNA value >500 copies/mL bracketed by HIV RNA values <400 copies/mL) after Week 24.

In 18 patients with available results, no lopinavir or stavudine resistance was observed, and 3 patients demonstrated lamivudine resistance. Correspondingly, no evidence of phenotypic resistance to any PI was observed.

6 patients demonstrated a substitution at a new position in protease during viral rebound (1 each at amino acids 15, 36, 43, 57, 63, 70). However, as demonstrated previously, none of these substitutions are primary protease inhibitor mutations, no impact on PI phenotypic resistance was observed, and all 3 patients who remain on study demonstrated HIV RNA <50 copies/mL at the most recent visit.

CD4 Cell Count Response

Among subjects with values at both baseline and Week 312 (N=63), the mean CD4 cell count increased from 280 cells/mm3 at baseline to 808 cells/mm3 at Week 312, an increase of 529 cells/mm 3.

CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count. Among patients with baseline CD4 cell count <50 cells/mm3, mean CD4 cell count increased from 23 cells/mm3 at baseline to 576 cells/mm3 at Week 312, an increase of 553 cells/mm3. There was a mean increase of 500 cells regardless of baseline CD4 count.

Safety

Patients enrolled 100

Discontinuations prior to Week 312: 37
Discontinuations probably or possibly related to study drugs
--AST/ALT increases 2
--Diarrhea 1
--Liver pain, enlargement, fatty deposits 1
--Arthralgia 1
--Elevated lipids 2
--Fat distribution abnormalities 5
--Death 1
Other reasons for discontinuation
--Adverse Event unrelated to study drugs (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification- 3
--Lost to follow-up 9
--Noncompliance 4
--Personal/other reasons (moved (3), drug addiction, "virologic success" (8))
--Patients on study at Week 312: 63

Most Common Adverse Events Through Week 312

	Incidence through wk 312
Diarrhea	28%
Nausea	16%
Lipodystrophy	13%
Abdominal pain	10%

Most Common Grade Abnormalities Through Week 312

	Incidence Through Week 312
Cholesterol (>300 mg/dL) non-fasting:	23%
Triglycerides (>750 mg/dL) non-fasting:	26%
AST/ALT (>5xULN):	11%

Distribution of Lipid Values at Week 312 (non-fasting)

	Prevalence at week 312
Total cholesterol	
<240	47 (75%)
>240-300	13 (21%)
300-400	3 (5%)
>400	0
Triglycerides	
<400	49 (78%)
400-750	10 (16%)
>750-1200	3 (5%)
>1200	1 (2%)

23 patients with grade 2 or higher lipid values initiated lipid-lowering agents, and all but 2 subsequently demonstrated grade 0-1 lipid values.

Kaletra Once Daily: 48 Week Results

Abbott has submitted an application to the FDAto use Kaletra once daily. This study was conducted to explore Kaletra taken once daily (800/200, LPV/r) compared to Kaletra taken in its usual way as 400/100mg twice daily in 190 patients. Patients also received tenofovir once daily and FTC once daily. After 48 weeks the percent of patients with <50 copies/ml was similar (70% for the once daily regimen vs 64% for the twice daily regimen, p=0.35; intent-to-treat analysis, noncompleters=failures). Noninferiority of the LPV/r QD regimen compared to LPV/r BID-based regimen (ITT NC=F) was confirmed by the

95% confidence interval for the difference (QD minus BID) in response proportions (-7% to 20%). Gastrointestinal events were the most common adverse events, with a higher rate of diarrhea in the QD arm (16% vs 5%). Lipid elevations were the most common laboratory abnormality. The discontinuation rates were similar in both the once & twice daily arms with more patients discontinuing in the once daily arm due to adverse events, and more patients discontinuing in the twice daily arm for nonadherence (1% vs 4%).

Kaletra Monotherapy for Naives & as Maintenance or Simplification Therapy: PILOT Studies

Kaletra monotherapy has been recently explored in two types of small pilot experimental studies in patients who are treatment-naïve and as a way to simplify HAART. Both types of studies were presented at Bangkok IAC. Abbott is conducting a larger international study to further explore the results from this pilot experimental study. Until we have further data these study results should be considered experimental.

Simplification to Lopinavir/r single-drug HAART: 24 weeks results of a randomized, controlled, open label, pilot clinical trial (OK Study)

In the poster presented at Bangkok by Jose Arribas from Spain, 42 patients had undectectable HIV RNA (viral load) on ART and were randomized to Kaletra monotherapy or Kaletra 3-drug HAART. There were 3 viral failures in the Kaletra patient group receiving Kaletra monotherapy vs none in those who continued on 3-drug HAART. All three viral failure patients restarted nucs & achieved undetectable HIV-RNA. Patients who were on Kaletra for longer duration before simplifying to monotherapy were more likely to stay undetectable & not to have viral rebound. My understanding is that DEXAs will be performed to evaluate if body abnormalities improve after switching to Kaletra monotherapy without nucs.

Patients were eligible for the study if they had no history of virological failure while receiving a protease inhibitor (PI), were receiving 2 nucs + L/r (400 mg bid) for > 1 month and had maintained serum HIV RNA < 50 c/mL for > 6 months prior to enrolment.

Treatment failure was defined as: 2 HIV-RNA > 400 c/mL 2 weeks apart, change in randomized therapy, treatment discontinuation or lost to follow-up.

Results

At baseline there were no significant differences between these two patient groups in median CD4 cells/mL (662 vs 585), CD4 nadir (146 vs 145), HIV log10 viremia prior to HAART (5.11 vs 4.85 log) or months with HIV RNA < 50 c/mL (11 vs 9).

Patients (%) with < 50/400 HIV RNA c/mL at 24 wk: 95/100% (Kaletra single-drug therapy) vs 100/100% (Kaletra 3-drug HAART) in the on-treatment analysis *and 81/86% (Kaletra single-drug therapy) vs 100/100% (Kaletra 3-drug HAART) in the intention to treat (non completer = failure).*

Treatment Failures

3/21 in Kaletra single-drug therapy group and 0/21 in Kaletra 3-drug HAART were treatment failures. All 3 patients had viral load reduced to undetectable after reintroduction of nucs to therapy.

Arribas concluded that, in contrast to previous trials of induction-manteinance strategy, a large proportion of patients simplified to Kaletra-sd remain with undetectable viral load after 24 weeks. Preliminary data show that failures of Kaletra-sd HAART are not associated with the development of resistance mutations.

PILOT Study of the Safety & Efficacy of LOPINAVIR/ritonavir (KALETRA) as Single Agent Therapy in HIV-1 ARV Naive Patients

Joe Gathe presented an update with the final 48-week analysis of his 'pilot' study of Kaletra as monotherapy in treatment-naïve patients. He emphasized this is a pilot study and not ready to be used in patients except in clinical studies.

Viral Suppression at 48 Weeks

	<400	<50
AT	100%	90%
ITT	67%	60%

Gathe provided background. LPV/r has ideal characteristics for single agent therapy: short-term activity comparable to triple HAART; 24 hour pharmacokinetics significantly above IC50 of WT virus-- ie, good drug levels); there has been no PI resistance observed at time of failure in naïve patients in Kaletra studies. Gathe said what motivated this study was restricted access to HIV therapy for economic factors. In the USA, ADAP funding has been inadequate. Numerous states have put into place access restrictions to HAART through ADAP due to funding restrictions. Texas, where Gathe is located, is one of those States. One drug therapy = only one co-pay.

This was a 48-week open label pilot study and 30 treatment-naïve patients were recruited from March 2002 to March 2003 from a single inner city clinic in Houston. Dosing of Kaletra was given by weight: <70 kg weight of patient—received 400/100mg bid (3 caps) and >70 kg weight—533/133mg bid (caps). Therapy intensifcation was allowed at any point with either tenofovir/saquinavir or saquinavir. Most study participants were men, 60% white, 20% Black, 20% Hispanic. The study patients had on the whole advanced HIV. Average HIV viral load 262,000 copies and CD4 count 169 cells before starting Kaletra. 70% of study participants had CD4 count <400, 43% with CD4 count <50 cells, and 57% had viral load >100,000 copies/ml.

Results

After 48-weeks on study patients discontinued for: lost to followup—2; adverse events—2; virologic failure—2; deported--1; hepatitis B—1. The patient who was deported at week 16 had a viral load reduction of 2.2 log (259,000 to 621).

Two patients discontinued therapy due to GI intolerance at W1 & W12. One patient was found to have active hepatitis B and had to add TDF/3TC at week 12.

Viral Responses (As-Treated analysis)
At week 12, the average viral load reduction was 2.09 log (n=28); at week 24 (n=21) viral load reduction was 2.57 log; and at week 48 (n=20), VL reduction was 3.71 log.
% of Patients <400 Copies at Week 48: As-Treated analysis (n=20) 100% of patients had <400 copies/ml; ITT analysis (n=20): 67% of patients had <400 copies/ml.
% of Patients <50 Copies at Week 48: AT analysis: 90% (18/20) of patients had <50 copies/ml; ITT analysis (18/30): 60% had <50 copies/ml.
Mean CD4 Count Increase (AT analysis)
The average CD4 increase was about 315 cells from baseline to week 48.

Gathe reviewed in detail the 4 patients who did not reach viral loads less than 50 and intensified therapy: after intensification 3 of the 4 patients achieved <50 copies/ml and the fourth patient had a baseline viral load of 500,000 copies/ml and at week 48 viral load was 395 copies/ml; the CD4 count was 16 at baseline and 268 cells at week 48.

Gathe said: why was intensification necessary in the absence of resistance? 3 thoughts: adherence; potency: no single agent will be able to control virus <50 in all patients particularly with VL >100,000 copies; bioavailability: p-glycoprotein issues, viral sanctuaries/reservoirs; resistance: developing outside of the areas analyzed by standard genotypic/phenotypic assays (ie, substrate resistance, gag cleavage sites); analysis has been hampered by inability to amplify the virus and lack of baseline samples.

Gathe Conclusions: there was a low patient discontinuation rate; no identifiable genotype/phenotype resistance in viremic subjects; success with intensification with nukes.

Sustiva (efavirenz) 3-4 Year Update

The Public Health Service HIV Treatment Guidelines recommend Sustiva as the first choice for an initial NNRTI regimen. Extended follow-up data were recently presented from the Dupont 006 study, the original large, phase 3 trial comparing efavirenz/AZT/3TC, indinavir/AZT/3TC, and efavirenz/indinavir. This was the first HAART regimen for many patients in this study, but 13-18% were previously treated with NRTI regimens. The efavirenz/AZT/3TC combination was consistently superior to indinavir/AZT/3TC through the study. *After 168 weeks or 3 years of therapy, half of the patients on efavirenz/AZT/3TC maintained viral load <50 copies/mL.* This is an intention to treat (missing = failure) analysis, which is the most rigorous way to evaluate the potency of a given therapy.

All HIV HAART medications are potentially associated with side effects. If trying to select an NNRTI-regimen bear in mind that Sustiva is associated with CNS-related side effects while nevirapine (NNRTI) is associated with hepatotoxicity. At a median duration of 180 weeks therapy on EFV+AZT/3TC grade 2-4 treatment-related adverse events reported by patients: 9% dizziness; 8% fatigue; 5% depression; 7% insomnia; 2% anxiety; 5% dreaming abnormal; 5% concentration impaired; 25% somnolence; 19% rash.

Over 1,200 patients were randomized to EFV+AZT/3TC, IDV+AZT/3TC or EFV/IDV. Of note, patients with high (>100,000 & >300,000 copies/ml) or low (<100,000 copies/ml) viral load did equally well on EFV+AZT/3TC; there were 37 patients with >300K, 64 with 100K-300K, and 200 with <100K at baseline. About 400 patients were still on study drugs at week 168, about 200 patients at week 210, 120 patients at week 231, with similar viral responses seen at week 168. Treatment-related grade 3-4 adverse events were more frequent in patients receiving IDV-therapy than in those receiving EFV-therapy (34% vs 23%).

Viral Response at Week 168

	EFV/AZT/3TC	IDV/AZT/3TC	EFV/IDV
% <400 c/ml			
@ wk 48	69%	50%	57%
@ wk 168	48%	30%	40%
<50 c/ml			
@ wk 168	43%	23%	31%
Viral failure			
@ wk 48	6%	12%	13%
@ wk 168	12%	15%	15%
Viral rebound			
@ wk 48	5%	10%	10%
@ wk 168	11%	15%	15%
% <400 c/ml if baseline HIV RNA			
<100,000 c/ml	47%	31%	45%
100K-300K	47%	28%	42%
>300,000	61%	25%	23%
Discontinued for adverse events			
@ wk 48	7%	15%	5%
@ wk 168	8%	19%	8%
Discontinued for other reasons			
@ wk 48	17%	23%	24%
@ wk 168	30%	35%	37%

Efavirenz (Sustiva) Associated with Psychiatric and Nervous System Adverse Events
On Aug. 13, the FDA made revisions to the safety labeling for efavirenz to warn of its psychiatric and nervous system adverse events associated with its use.

According to the long-term results of a study (Study 006) comparing efavirenz-containing regimens (n = 1008; 1.6 years) with control regimens (n = 635; 1.3 years), patients receiving efavirenz regimens experienced higher incidences of severe depression (1.6% vs 0.6%), suicidal ideation (0.6% vs 0.3%), nonfatal suicide attempts (0.4% vs 0%), aggressive behavior (0.4% vs 0.3%), paranoid reactions (0.4% vs 0.3%), and manic behavior (0.1% vs 0%) compared with control subjects.

Factors associated with increased risk of psychiatric symptoms included history of injection drug use, psychiatric history, and psychiatric medication use at study entry.

Study results also showed a significantly higher rate of nervous system symptoms in patients receiving efavirenz compared with control subjects (53% vs 25%). Symptoms included (but were not limited to) dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%).

After six months of therapy, incidence rates of new-onset nervous system symptoms were similar between the efavirenz and control groups.

Triple PI Regimens: Two PIs Boosted by Low-Dose Ritonavir

Triple protease inhibitors (PIs) regimens, two PIs boosted by low-dose ritonavir, are sometimes used as therapy for patients with extensive drug and PI resistance. The treatment approach of boosting two protease inhibitors with low-dose ritonavir has been studied to some degree but is still considered experimental. Still, for patients with extensive protease inhibitor this approach appears to have provided effectiveness in suppressing HIV. However, with the availability of tipranavir, the effectiveness and usefulness of dual boosted PIs becomes a question; there have not been studies to date comparing tipranavir to dual boosted PIs, and tipranavir appeared to be potent in the RESIST studies for patients with extensive resistance to PIs. As well, initial tipranavir phase III studies provide a broad characterization of antiviral activity while there is I think less characterization of anitiviral activity for dual boosted PIs.

A combination of 2 active PIs may extend the range of activity against HIV and increase regimen potency, and there is evidence from clinical trials that dual-PI-containing regimens may lead to greater antiviral efficacy and a more favorable treatment outcome in PI-experienced patients than a single-PI-containing regimen. However, not all protease inhibitors are appropriate for such a combination. It is important to note that you want to make sure the two main PIs don't interact with each other in a way that reduces the blood levels of the PIs to a level below that needed for efficacy. It is also important to consider potential additive toxicities. All the currently approved PIs are metabolized by cytochrome P450 (predominantly CYP3A4) (enzymes in the liver), and thus clinically relevant and sometimes complex drug-drug interactions can occur when these agents are coadministered. For example, coadministration of the fixed-dose combination of lopinavir/ritonavir (Kaletra) with amprenavir results in significantly lower plasma concentrations of both lopinavir and amprenavir in HIV-infected individuals than those observed in historical controls.

Two potentially useful regimens of two PIs boosted by low-dose ritonavir are discussed below. The new formulation of amprenavir, fosamprenavir (908), is not recommended for use with Kaletra due to dfficult interactions between the two drugs.

There is also interest in using these regimens in treatment-naïve individuals and as a second-line regimen, without nukes, as nuke-sparing regimens. This interest is based on the concern that nukes may be a significant cause for lipoatrophy, and perhaps a nuke-sparing regimen would not lead to lipoatrophy or might reduce the risk for developing lipoatrophy. Studies examining this approach are ongoing.

Reyataz+saquinavir boosted by low-dose ritonavir is interesting and the subject of several ongoing pilot studies in treatment-naïve individuals and as second-line regimens. As well, fosamprenavir/saquinavir boosted by low-dose ritonavir is of interest but fosamprenavir has a big interaction with SQV reducing SQV levels. At CROI results from several PK studies were presented suggesting the promise for these two regimens.

Reyataz (ATV) plus Saquinavir (SQV) Boosted by Low-Dose Ritonavir

Boffito reported at CROI on the PK (pharmacokinetics; a/k/a drug levels in blood) of the combination of atazanavir (Reyataz) plus saquinavir boosted by low-dose ritonavir (ATV/SQV/RTV) 300/1600/100 in 20 HIV+ patients (2 females; mean age 41 years; median CD4 442 cells/mm3). These results are experimental in that they examine the affect of this regimen on drug blood levels, but don't evaluate the affect of this regimen on viral load in patients.

They administered SQV/RTV 1600/100 mg once daily with a 20-g fat meal. On day 2, ATV 300 mg once daily was added to the regimen for 30 days. Safety analysis was performed at screening, Day 1, 11, 31, and follow-up. No significant changes in ALT, AST, glucose, total cholesterol and triglycerides were observed, whereas total and indirect bilirubin increased by 5 times after 10 days of ATV therapy (median, range: 36, 11-139, and 32, 9-128 mmol/L, respectively). Four patients developed scleral icterus and 2 jaundice. ATV concentrations were in accordance with the ATV concentrations observed in patients with ATV/RTV. The authors concluded that the addition of ATV to SQV/RTV increased SQV AUC, Cmax and Ctrough by 60%, 42% and 112% respectively ($p < 0.05$). RTV and ATV may have independent mechanisms of boosting SQV and other CYP3A4 substrates. (Reviewer's note: an optimal dose for this regimen remains to be worked out. Perhaps ATV/SQV/RTV 300/1000 or 1500/100 once daily may an option worth pursuing).

Saquinavir plus Fosamprenavir Boosted by Low-Dose Ritonavir

Boffito also reported on the PK of the combination of SQV/908/RTV (908 is fosamprenavir: new formulation of amprenavir) in 18 HIV+ patients (1 female; mean age 42 years). These results are experimental in that they examine the affect of this regimen on drug blood levels, don't evaluate the affect of this regimen on viral load in patients.

Patients were given SQV/r 1000/100 mg with a 20-g fat meal on day 1; on day 2 they were switched to SQV/fAPV/r 1000/700/100 mg twice daily, and on day 12 to 1000/700/200 mg twice daily. Safety analysis was performed at screening, on day 1, 11, and 22 and at follow-up. At screening, mean ±SD CD4 cell count was 442±233/mm3 and plasma HIV-RNA <200 copies/mL in all patients.

No significant changes in ALT, AST, glucose, or total cholesterol triglycerides were observed, with the exception of 1 subject who experienced a relevant increase in AST (379 U/L) and ALT (780 U/L) as a result of hepatitis C reactivation (hepatitis C virus PCR = 40,000 copies/mL) during the study period. Both regimens were reportedly well tolerated, with adverse events limited to a small number of study subjects who reported grade 1 or 2 nausea, fatigue, or diarrhea after the addition of fosamprenavir to the saquinavir/ritonavir regimen. SQV pharmacokinetic data on 17 patients are summarized. On day 11, SQV AUC0-12, Ctrough and Cmax showed a not statistically significant decrease. On day 22, SQV AUC0-12, Ctrough, and Cmax showed a not statistically significant increase. fAPV concentrations were not affected by SQV coadministration: all patients had an APV Ctrough >HIV WT-MEC (Geometric mean 1252 ng/mL day 11 and 1120 ng/mL day 22).

Boffito concluded: SQV/908/r was well tolerated. SQV AUC 0-12, Ctrough and Cmax decreased by 14%, 24%, and 9% on Day 11 using 100 mg of RTV, and increased by 12%, 3%, and 20% on Day 22 when using 200 mg of RTV. Based upon this small pk study the authors recommend when combining SQV/908/r to use a dose of 1000/700/200 BID; although if SQV plasma level monitoring is available to insure adequate concentrations, then a reduced RTV dose of 100 mg BID could be administered. (Reviewer's note: currently this PI combination would be 8 pills twice daily).

ART Hepatotoxicity

Hepatotoxicity generally refers to elevations in liver enzyme tests-- LFTs -- (ALT & AST). After starting HAART about 8% of patients may experience >5 times the upper limit of normal LFTs, and this is called hepatotoxicity. HCV & HBV coinfected individuals are more likely to experience elevated liver enzymes. The risk of harm to the liver when LFTs are elevated has not been well studied. Research suggests that 'persistent' elevations of ALT 150 IU/L or more may effect liver disease, but again this is not well characterized. One study found that persistent elevations of liver enzymes 5 times above the upper limit of normal appeared to affect liver disease progression. These situations may suggest that treatment for hepatitis may be in order.

All HIV drugs appear to be associated with the possibility of elevations in ALT/AST, but usually elevations are moderate. NNRTIs and PIs can lead to elevations in liver enzymes, and as mentioned about 8% of patients starting HAART experience hepatotoxcity. As well, d4T can be associated with elevations in liver enzymes. In the past the use of full dose ritonavir—600 mg twice daily or 400 mg twice daily—has been associated with higher rates of hepatotoxicty, but today no one uses full dose ritonavir. Nevirapine has been associated with liver toxicity. Low-dose ritonavir –-100 mg once or twice daily—is now commonly used in combination with other protease inhibitors to boost their drug levels, such as Kaletra (LPv/r), IDV/r, 908/r, SQV/r (1000/100 twice daily), and ATV/r. But data from several studies show that low-dose RTV used to boost other PIs do not have any additional affect on liver disease.

A number of studies find that HIV accelerates HCV and HBV progression to a swifter pace than for individuals who have HCV or HBV without HIV. Results from a few studies suggest that reducing viral load to undetectable and increasing CD4 count may have a beneficial effect on HCV disease progression, but this finding needs further study. At the EASL meeting (Spring 2004) Norbert Brau reported on a study conducted in Veterans Administration system finding that patients with undetectable HIV RNA who also were coinfected with HCV did not experience faster HCV progression than HCV monoinfected who did not have HIV. This is the first study to find this so I would call these findings suggestive. But they suggest that full suppression of HIV may assist in slowing liver disease progression compared to detectable HIV RNA.

The FDA issued a report in July 2004 regarding Nevirapine and hepatotoxicity. The FDA said-- Severe and life-threatening hepatotoxicity, and fatal fulminant hepatitis have been reported in patients treated with Viramune (nevirapine). Hepatic adverse events have been reported to occur more frequently during the first 18 weeks of treatment, but such events may occur at any time during treatment.

In controlled clinical trials, clinical hepatic events regardless of severity occurred in 4.0% (range 2.5% to 11.0%) of patients who received Viramune and 1.2% of patients in control groups. Transaminase elevations (ALT or AST > 5X ULN) were observed in 8.8% of patients receiving Viramune and 6.2% of patients in control groups in clinical trials.

Increased AST or ALT levels and/or co-infection with hepatitis B or C at the start of antiretroviral therapy are associated with a greater risk of hepatic adverse events. It appears that women and patients with higher CD4 counts (>250 cells in women and >400 cells in men) may be at higher risk for rash-associated hepatic events with Viramune. Women appear to have a three fold higher risk than men for rash-associated hepatic events (4.6% versus 1.5%). Patients with higher CD4 counts may also be at higher risk for rash-associated hepatic events with Viramune. In a retrospective review, women with CD4 counts >250 cells had a 9 fold higher risk of rash-associated hepatic adverse events compared to women with CD4 counts <250 cells (8.4% versus 0.9%). An increased risk was observed in men with CD4 counts >400 cells (4.5% versus 0.7% for men with CD4 counts <400 cells).

If patients present with a suspected Viramune-associated rash, liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from Viramune.

Mark Sulkowski (Johns Hopkins Medical School), wrote in an article published in Clinical Infectious Diseases (March 2004; 38:S90-S97), **"Drug-Induced Liver Injury Associated with Antiretroviral Therapy that Includes HIV-1 Protease Inhibitors"**:

....in the study by Wit et al., the use of low-dose ritonavir based ART (i.e., 200 mg/day) was not associated with any cases of grade 4 hepatotoxicity. Furthermore, in a randomized controlled trial that compared lopinavir therapy boosted

with low-dose ritonavir and nelfinavir, only 4.5% of lopinavir/ritonavir recipients developed an AST or ALT level >5 times the ULN, which was similar to the incidence observed in nelfinavir recipients (5.2%). Similarly, Vora et al. reported that the addition of low-dose ritonavir to indinavir therapy for 19 patients coinfected with HBV or HCV was not associated with significant increases in serum ALT or AST levels…..emerging data indicates that the use of low-dose ritonavir to "boost" the levels of other PIs (e.g., lopinavir or indinavir) is not associated with significantly higher incidence of severe hepatotoxicity than is observed with other PIs, such as nelfinavir.

Sulkowski reported in this study at the AASLD liver conference in November 2003: **"Hepatotoxicity and Protease Inhibitors: nelfinavir, Kaletra, IDV/r, SQV/RTV"**:

This study evaluated the incidence of severe hepatotoxicity, defined as a grade 3 or 4 change in ALT/AST levels following initiation of ART-containing PIs with or without low-dose ritonavir at Johns Hopkins urban HIV clinic. 77% of patients were African-American; 46% HCV+; 10% HBsAg+; median ALT was 30 IU/L; median CD4 count 166; patients were followed for median 224-365 days.

This study looked at 1061 patients starting a PI regimen: nelfinavir (605 patients); Kaletra (89 patients), indinavir/ritonavir 200-400mg (94 patients), and SQV/ritonavir 800 mg. with 400mg of ritonavir; for the purpose of evaluating the rates for developing severe hepatotoxicity.

The study authors found that the rates of severe hepatotoxicity occurred in patients receiving nelfinavir regimen at 11%, Kaletra (LPV/rtv 200 mg) 9%, IDV/RTV (200-400mg/day) 12.8%, SQV/RTV (400mg/day) 17.2%. Overall 12% of patients experienced hepatotoxicity when on a PI regimen in this study. Having HCV was associated with experiencing severe hepatotoxicity. Hepatotoxicity was defined as grade 3 or 4 changes in ALT/AST. For patients with normal ALT/AST at baseline grade 3 was 5 x the upper limit of normal and grade 4 was 10 x the upper limit of normal. For patients with elevated ALT/AST before the study grade 3 was defined as 3.6-5 x baseline and grade 4 as >5 x baseline.

HCV+ patients had a 2-fold higher risk for hepatotoxicty, but 83% of HCV+ patients did not experience hepatotoxicyty. Overall, the incidence of grade 3/4 hepatotoxicity was higher in HCV+ subjects (8.7%) compared to HCV negative subjects (4%). In multivariate Cox proportional hazard analysis, grade 3/4 hepatoxicity was independently associated with use of IDV/rtv (Relative Risk 2.97), SQV/rtv (RR 2.41), being HCV (RR 1.82), baseline CD4 count <200, and baseline HIV RNA level >10,000 copies/ml (RR 4.77).

The authors concluded the highest risk for grade 3/4 hepatotoxicity was observed in pts receiving SQV/rtv (800mg/day) and IDV/rtv (200-400mg/day). However, no increased risk of hepatotoxicity was detected in pts receiving NFV or LPV/rtv (Kaletra). In addition, while HCV+ pts had a 2-fold higher risk of hepatotoxicity, 83% of such patients did not experience toxicity, suggesting PIs should not be withheld.

Following initiation of PI-containing HAART, serum ALT levels remained less than 1.25 x the ULN of their pretreatment levels in 54% of LPV/rtv users, 62% of IDV/rtv users, and 54% of NFV users compared to only 42% of RTV/SQV users (p<.0001 for comparison of RTV/SQV to other PI regimens). Overall, severe (grade 3 or 4) hepatotoxicity was observed in 135 of 1061 (12.1%) of patients prescribed PIs.

Hepatotoxicity (any grade) was observed in 58% of HCV-infected persons compared to 41% of HCV-uninfected than (p<.0001). The detection of severe hepatoxicity was more rapid among HCV+ than HCV-uninfected patients. While 62% (84 of 135) of severe hepatotoxicity cases were observed in HCV-infected pts, 82.6% (400 of 484) of HCV-infected pts did not experience severe hepatotoxicity.

Report from the 6th Lipodystrophy Workshop: Heart Disease in HIV; Prevention & Treatment of Lipoatrophy

The 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV was held 25-28 October 2004, Washington DC, USA. Jacqueline Capeau (doctor and researcher, Medicine Saint Antoine, INSERM, Paris, France) provided an in-depth report on conference proceedings for the NATAP website including a discussion of lipids, heart disease, and body changes. Here is a summary of part of her report. The full report is available on the NATAP website.

Heart Disease in HIV. In the HIV population, patients with lipodystrophy and metabolic alterations (cholesterol, triglycerides, glucose) could probably be considered as presenting with the metabolic syndrome with a higher risk for cardio-vascular and liver complications than the general population. Even if some studies on these complications have been presented, more works are required in this population to correctly analyze the risk of complications and to try to prevent it. There appears to be a deleterious effect of some ART therapies through their dysmetabolic action and potential for affect on the walls of arteries. In addition, the altered lipodystrophic adipose tissue (body changes), which is involved in further metabolic alterations and insulin resistance, could play an important role in the CV risk. From a therapeutic point of view, interventions on lipid parameters may not be sufficient to reduce this risk. Even if thiazolidinediones (rosi- and pio-glitazone) have not shown a major impact on the correction of lipodystrophy, these molecules are working at the level of adipose tissue and the vascular wall and are studied in the general population for their ability to reduce insulin resistance and the progression of atherosclerosis and to reverse steatosis. In the general population, preventive treatment with thiazolidinediones or Metformin are evaluated in patients with a metabolic syndrome and give indirect evidence of decreased insulin resistance and cardiovascular risk. Therefore, it would be important to consider this class of molecules for their potential beneficial impact on insulin resistance, atherosclerosis and NASH (fatty liver) in HIV-infected patients with high CV and liver risks.

Can You Prevent or Reverse Lipoatrophy?
Written by Jules Levin

From his research and from other research David Nolan (Royal Perth Hospital, Western Australia) concluded in his presentation at the 6th Lipodystrophy Workshop that abacavir and tenofovir don't appear to lead to mitochondrial DNA (mtDNA) depletion, and don't appear associated with causing lipoatrophy or have a much lower risk for developing lipoatrophy. Loss of mtDNA has been found to be associated with fat wasting. It is believed that loss of mtDNA contributes to lipoatrophy. It has been suggested that protease inhibitors may play a role in contributing to body changes and metabolic disorders by reducing the expression of sterol-regulatory-element-binding protein-1c (SREBP-1c), which is an essential step in adipocyte (fat cell) differentiation. These findings suggest that synergistic action may occur in lipoatrophy. It is also important to point out that there is uncertainty about what causes lipoatrophy. Several other factors appear to perhaps contribute to lipoatrophy including having HIV itself, family genetics, insulin resistance/diabetes, and having hepatitis C or B. Being skinny or having low Body Mass Index prior to starting HAART may contribute to developing lipoatrophy as well as starting HAART when HIV is advanced (low CD4 count and high viral load).

There were two posters at the Workshop reporting on the proportion of study participants who developed body changes in the SOLO study. This study compared treatment-naïve patients receiving fosamprenavir/ritonavir once daily to nelfinavir twice daily. Body composition changes were evaluated by physician observation, weight, and waist-to-hip ratios at three visits. Of note the proportion of patients reporting lipoatrophy was only 4-5% in both treatment groups. This could be due to the fact that the NRTI regimen in the study was abacavir+3TC.

Sharon Walmsley reported 48 and 120 week results from SOLO. SOLO was a randomized study in 600+ ART-naïve patients comparing fosamprenavir/ritonavir once daily to nelfinavir twice daily. These are the first prospective body composition changes data from a controlled clinical trial for FPV/r. 48-week results were reported for FPV/r & NFV. The followup study extended to 120 weeks was reported only for FPV/r. All patients received abacavir+3TC as the NRTI component of the regimen.

Of patients reporting no fat wasting at baseline, and who had an assessment at week 48, only 4% (9/215 and 9/232) reported fat wasting at week 48 in both groups (FPV/r & NFV). And with followup to week 120 for patients taking FPV/r: 5% (8/161) reported fat wasting. This is similar to findings from the Gilead 903 Study in which patients received tenofovir+3TC and efavirenz where only 3% of study patients developed fat wasting. 3TC & FTC are very similar drugs.

In his study, David Nolan reported data suggesting that patients who started with abacavir or tenofovir don't experience mitochondrial DNA (mtDNA) loss in fat cells. Patients who started with AZT or d4T did experience mtDNA loss, but this improved after switching to tenofovir or abacavir. mtDNA loss was worse for d4T than AZT and occurred more quickly for patients taking d4T compared to AZT. Nolan suggests that you can minimize or prevent lipoatrophy by starting therapy with tenofovir or abacavir. And if you switch from AZT or d4T to abacavir or tenofovir you can improve mtDNA depletion. His research and clinical experience, and the MITOX & TARHEEL studies find that switching from AZT or d4T to tenofovir or abacavir improves mtDNA and lipoatrophy. But in the MITOX & TARHEEL studies many patients did not see improvement merely by their observation. Although studies find improvements in mtDNA, patients have not yet been able to say they see an improvement. It is possible that being able to see actual improvement may take additional time or it's also possible that lipoatrophy may not be reversible for most patients. We don't know the answer to this question yet. Nolan feels that after switching nukes cell death (apoptosis of fat cells) stops & mtDNA depletion returns to normal but lipoatrophic damages although improving remain. Tissue is damaged so the question is: can you develop new fat cells, can you recover from lipoatrophy? Nolan believes you can generate new fat cells. In healthy adults new fat cells can be generated. But can a lipoatrophic person regenerate fat tissue to a normal level, how much of this damage can be reversed? Among his patients fat recovery is occuriing but will they recover fat back to normal levels? Improvement continues in his patients. But, it's a process that may take years. How many years, we don't know. The question remains-- will they recover back to normal? Follow-up will tell.

Insulin Resistance/Diabetes and HIV

Aging with HIV may be associated with diabetes & cognitive impairment

Judith Aberg, MD, (Bellevue Hospital/NYU Medical Center) reported on insulin resistance in HIV for NATAP at the 11th CROI; and on an interesting study of aging with HIV, which finds a potential association between diabetes and cognitive impairment. But first an introduction by Jules Levin.

Introduction
There was a presentation at CROI from the MACS study that looked at 1000 men, and found HIV-positive men were 3 times more likely than HIV-negative men to develop diabetes, and taking HAART appeared to increase the risk. Another study presented at the conference found Reyataz (protease inhibitor) did not lead to elevations in glucose (sugar) in healthy volunteers. Insulin resistance and diabetes have been found to be associated with increased risk for heart disease. As well, abnormalities in fat lipids (cholesterol, triglycerides) are associated with increased risk for heart disease. Also associated with increased risk for heart disease in HIV-negative individuals are body changes (fat wasting & fat accumulation in the belly), smoking cigarettes, not exercising, genetic predisposition, and diet.

Below is a discussion of several studies conducted by Bristol-Myers Squibb the results of which suggest that Reyataz has a favorable effect on glucose metabolism. In one study,

researchers from BMS gave healthy volunteers either Kaletra or Reyataz. Study subjects receiving Kaletra were 25-35% less able to process sugar/glucose compared to study subjects receiving Reyataz or placebo. Study subjects receiving Reyataz were not impaired in processing sugar/glucose. As well, study subjects receiving Kaletra had a 43% increase in triglycerides but healthy volunteers receiving Reyataz had no increase in triglycerides. These study results confirm what has already been observed in studies in vitro (test tube) and in limited study of HIV+ individuals without diabetes. In a second study, at the Bangkok IAC, BMS reported on an in vitro (in the test tube) study they conducted which compared the effect of Reyataz boosted with low-dose ritonavir to Kaletra on glucose metabolism. It appeared that Reyataz boosted with low-dose ritonavir maintained the favorable metabolic profile of unboosted Reyataz. Further studies in patients with and without diabetes need to be conducted to confirm these findings and to better characterize our understanding of the effect of Reyataz on glucose metabolism in different types of patients. For example, HIV+ individuals who already have diabetes may not be able to reverse their condition by using Reyataz, benefit may be provided to patients at earlier stages of impaired glucose metabolism. As well preventative benefit may occur for those who have a predisposition to insulin resistance but have not yet developed it. More comprehensive studies are needed to better understand the effect of Reyataz.

The future: HIV & Aging- New risk factors in HIV?
Dr. Aberg explains below insulin resistance and diabetes, reports the MACS study results, and reports on the HIV & Aging Study (a study examining aging and the impact of metabolic abnormalities). The impact on aging and its association with development of dementia in HIV is unknown. The investigators took a step further and asked whether the metabolic complications associated with HIV have even more of an impact on the aging HIV-infected population. The study found that 15% of HIV+ individuals >50 years of age had diabetes; and cognitive impairment was associated with having diabetes. See details of this interesting study below. Increased research efforts on HIV & aging should be emphasized as we all get older with HIV.

What is Insulin Resistance and Diabetes & Why is it Important? Written by Judith Aberg, MD
When one consumes carbohydrates, the body breaks it down into sugars, also called glucose. The body also produces insulin, which carries the sugar out of the bloodstream and into the tissue and cells. The body does this so that it tries to maintain our blood sugar in what we label as a normal range of blood sugar. Some people require higher amounts of insulin to maintain glucose in a normal range and this is called insulin resistance. Insulin resistance by itself is associated with vascular disease and over time may progress to diabetes where the body no longer can keep the blood sugar in the normal range. Mild diabetes can sometimes be managed by diet and exercise but frequently patients need to take pills or even shots of insulin to control the blood sugar. Uncontrolled diabetes may lead to kidney disease, blindness, neuropathies, vascular disease and even death. But even insulin resistance without diabetes can have major unhealthy effects including elevated blood pressure, abnormal lipids and coronary heart disease, which also can lead to significant illness and death.

HIV+ Men Were 3 Times More Likely to Have Diabetes than HIV-negative Men

Brown and colleagues presentented at CROI: **"Prevalence and Incidence of Pre-diabetes and Diabetes (DM) in the Multicenter AIDS Cohort Study".** They examined the prevalence of hyperglycemia (elevated blood glucose) in 1107 men enrolled in the Multicenter AIDS Cohort Study, using data from April 1999 through September 2002.

Hyperglycemia (pre-diabetes and DM) was defined as a fasting plasma glucose (FPG) >110 mg/dL, use of anti-diabetic medication, or self-reported diagnosis of DM. DM was defined as a FPG >126 mg/dL, use of anti-diabetic medication, or self-reported diagnosis of DM. Of the 1107 men, 563 were HIV- and 544 were HIV+ (423 on HAART).

Of HIV+ men on HAART, 14% had prevalent DM at baseline compared with 5% in the HIV-negative group (odds ratio = 4.4). Exposure to a HAART regimen including a PI (hazard ratio [HR] = 1.9, d4T (HR = 2.1) or efavirenz (HR = 3.9) were each significantly associated with a higher rate of incident pre-diabetes or DM compared to the HIV- group.

The study concluded that HIV+ men with HAART exposure have an increased prevalence and incidence of pre-diabetes and DM compared to men without HIV in this large study. Exposure to a HAART regimen—including PIs, d4T, or efavirenz—was associated with an apparent increased risk of hyperglycemia.

Aging & HIV: diabetes found to be associated with cognitive impairment in older HIV+ individuals:
perhaps, a new risk factor for older HIV+ individuals

At 11th CROI, (Shikuma et al, Universities of Hawaii & Johns Hopkins): **"Diabetes and Cognitive Functioning Among HIV Seropositive Patients. The Hawaii Aging with HIV Cohort".**

The impact on aging and its association with development of dementia in HIV is unknown. The investigators took a step further and asked whether the metabolic complications associated with HIV have even more of an impact on the aging HIV-infected population.

Participants were from one of two groups (under 40 or 50+ years old) within the HIV-positive arm of the Hawaii Aging with HIV Cohort. Evaluations included comprehensive neuropsychological testing. Three measures of cognitive functioning were constructed from combinations of scores on neuropsychological test results standardized within our sample: an overall measure of cognitive functioning, NPZ8; a measure of memory, NPZ3-memory; and a measure of psychomotor functioning, NPZ3-psychomotor.

Trained personnel obtained medical histories including established diagnoses for diabetes (DM) using a structured interview. Data from 169 participants (73 younger and 96 older)

were available for these analyses.

- Frequency of DM was 8.9% (15.6% among older and 0% among younger).

- DM was negatively associated with overall cognitive functioning ($F = 19.15$, $p < 0.01$), accounting for 11% of the variance in NPZ8 scores. DM was also negatively associated with psychomotor functioning ($F = 14.16$,pp < 0.01) accounting for 8% of the variance in NPZ3-psychomotor scores.

- There was no association between DM and NPZ3-memory scores.

- Controlling for age, ARV, current hypertension, current hypercholesterolemia, pack-years of smoking, ethnicity, and duration of HIV infection, did not substantially alter these results.

These data suggest that diabetes is associated with decreased overall cognitive performance and specifically psychomotor performance in patients with HIV. (note from Jules Levin: in HIV-negative individuals diabetes may be associated with similar effects).

These findings are driven exclusively by diabetes in older patients and thus, if confirmed, may represent a newly identified risk factor for older seropositive patients. This risk is independent of other vascular risk factors. The underlying mechanism is not clear. While speculative, this could be associated with metabolic dysfunction and abnormalities in glucose regulation. Further studies are needed exploring the effects of HIV and its therapies on the aging HIV-infected population as many have other traditional risk factors for metabolic and cardiac diseases and we will need to know how best to manage them.

In summary, a quote from a colleague of mine, Dr. Donald Kotler, "Insulin resistance kills. Why would anyone think having HIV would be protective?" Dr. Kotler's point is well taken. Although we do not know what the risk of progressing from insulin resistance to diabetes is among those infected with HIV, we do know insulin resistance without HIV is bad. Just as we cannot be passive and let individuals sit with high lipids and ignore markers for cardiac disease, we should be managing our HIV-infected patients with insulin resistance or diabetes as we would the general population. The question remains whether conventional therapies for diabetes will work similar in the HIV infected population and further studies are warranted exploring the pathogenesis and management of insulin resistance in this population.

Reyataz & Glucose Metabolism

Reyataz (atazanavir): did not impair sugar metabolism & raise triglycerides in healthy volunteers

Investigators from Bristol-Myers-Squibb presented at CROI: **"The Effect of Atazanavir vs Lopinavir/ritonavir (Kaletra) on Insulin-stimulated Glucose Disposal Rate in Healthy Subjects".**

A proposed mechanism for why protease inhibitors may be associated with the development of diabetes is via blockade of the glucose transporters that take the glucose from the bloodstream into the tissues.

Atazanavir (ATV), unlike indinavir, lopinavir, and ritonavir, appears not to block glucose transport through the glucose transporter-4 insulin-sensitive transporter in vitro. This study presented at CROI compared the effects of ATV and lopinavir/ritonavir (Kaletra, LPV/r) to placebo on insulin-stimulated glucose disposal rates in healthy volunteers.

LPV/r decreased the mean insulin-stimulated glucose disposal per unit of insulin (M/I) by 24% compared to placebo and by 23% compared to ATV. LPV/r decreased glycogen storage rate (GSR) by 35% compared to placebo and by 38% compared to ATV.

Study researchers concluded--ATV did not reduce insulin sensitivity and had no effect on insulin-stimulated glucose disposal or GSR. In contrast LPV/r induced insulin resistance and reduced the glucose disposal per unit of insulin and glycogen storage rate. These data are consistent with in vitro studies showing that ATV does not interfere with glucose transporter-4 activity and does not induce fasting hyperinsulinemia, substantiating the findings of clinical trials. In addition, fasting triglycerides were not affected by ATV but increased a mean of 43% on LPV/r. This is welcomed and supporting evidence that ATV is not associated with the metabolic complications as many of the other antiretroviral drugs are.

Reyataz (atazanavir) boosted by low-dose ritonavir (RTV) did not impair glucose metabolism in vitro

At the Bangkok IAC BMS researchers reported in vitro (test tube study) study results that 100 mg of RTV used to boost 300 mg of atazanavir (ATV) did not have a negative affect on sugar processing but lopinavir did. ATV as a single drug at ≤10 mM or combined with low concentration RTV up to 3 mM, which is about the Cmax (highest drug level after single dose) observed in patients treated with boosted ATV, has very little effect on insulin stimulated glucose uptake, whereas LPV as single drug at ≤3 mM or combined with low concentration RTV up to 3 mM affects insulin stimulated glucose uptake in vitro. This is a limited study as larger confirmatory study is needed in HIV+ patients followed over a longer period of time.

Since the majority of doctors are prescribing ATZ in combination with low-dose RTV (100 mg), concerns have been raised

that RTV might negatively impact the beneficial effects BMS has observed and reported regarding the effect of ATZ on glucose. To answer this question BMS researchers hypothesized that Reyataz combined with low concentrations (≤3 mM, which is the Cmax observed in patients) of ritonavir would demonstrate an in vitro profile similar to that of Reyataz alone in models of glucose uptake. Results of this study in the test tube were reported at the Bangkok IAC.

Effect of Low Concentrations of Ritonavir (≤2 mM) On Glucose Uptake in Rat Primary Adipocytes (fat cells)
BMS researchers reported results from a preliminary study finding that using low-dose ritonavir to boost ATV did not impair glucose metabolism any more than ATV without ritonavir. This study was not conducted in HIV+ patients so the findings need to be confirmed in patients. But these study results taken together with results from several other studies conducted by BMS suggest that ATV should have a favorable effect on glucose metabolism in patients with HIV who don't already have diabetes.

BMS researchers reported that at concentrations up to 3 mM there was no effect of RTV on insulin-stimulated glucose.

ATV, at therapeutic concentration, alone and in combination with RTV (2 mM) at concentrations observed with pharmacologically enhanced ATV did not inhibit glucose uptake in human primary adipocytes. At higher concentrations (doses) of 3-10 mM (concentrations seen in patients) there appeared to be a slightly greater affect on reducing glucose uptake but similar effect, and when concentration was increased to 30 mM there was only a less than 50% inhibition.

At concentrations of 3 mM or higher lopinavir strongly inhibited insulin-stimulated glucose uptake. When RTV was added (2 mM) to lopinavir no further inhibitory affect was seen.

Effect of adding Ritonavir to Atazanavir and Lopinavir on Glucose Uptake in Human Primary Adipocytes (fat cells)
At concentrations of RTV of 0, 1, 2, and 3 mM when added to ATZ and LPV, ATZ had higher insulin-stimulated glucose uptake at all of these concentrations than LPV/r. (n=6, ATV & LPV at 30 mM.

BMS researchers concluded:
(1) RTV at concentrations of ≤3 mM dose does not affect insulin-stimulated glucose uptake. Inhibitory effect is observed at 10 or more mM.

(2) ATV as a single drug at ≤10 mM or combined with low concentration RTV up to 3 mM, which is about the Cmax observed in patients treated with boosted ATV, has very little effect on insulin stimulated glucose uptake, whereas LPV as single drug at ≤3 mM or combined with low concentration RTV up to 3 mM affects insulin stimulated glucose uptake in vitro.

(3) Clinical correlation and confirmation studies in patients are needed and BMS said these studies are planned.

Trizivir + Tenofovir Compared to Combivir (AZT/3TC) + Efavirenz in Treatment-Naive: 48 Week Study Results

Both regimens, Trizivir+tenofovir & Combivir+efavirenz showed equal antiviral effectiveness, but Trizivir+tenofovir had better effect on lipids: small increases in lipids for Combivir/EFV and no increases on cholesterol or triglycerides for Trizivir+tenofovir.

Graeme Moyle and colleagues at London's Chelsea and Westminster Hospital randomized 56 treatment-naive people to Trizivir/TDF and 57 to Combivir/efavirenz. Each of these twice-daily regimens relies on only three pills, which may be taken with or without food. Trizivir is one pill taken twice daily and tenofovir is one pill taken once daily. Combivir is one pill taken twice daily and efavirenz is one pill taken once daily. Reflecting the Chelsea and Westminster population, most study participants were men. Most had moderately advanced HIV disease:

	Combivir efavfrenz (n=57)	Trizivir TDF (n=56)
Gender (% male)	87.5	95.0
Median CD4 count (cells/µL)	194	153
Mean viral load (log copies/mL)	5.26	5.13
	(about 182.000 copies/mL)	(about 135.000 copies/mL)

By week 48, 17 people (30%) had dropped out of the Trizivir/TDF arm and 16 (29%) gave up on Combivir/efavirenz. Toxicity compelled slightly more people (9, or 16%) to quit Trizivir/TDF than to shelve Combivir/efavirenz (6, or 11%), usually because of abacavir hypersensitivity in the Trizivir group (6, or 10.5%).

Only one study participant, a woman taking Trizivir/TDF, had a virologic failure. The regimen pushed her viral load under 50 copies/mL, but she had a rebound, possibly because of shaky adherence. The rebound brought with it three AZT-related mutations and the 3TC-inspired M184V change. A regimen of ddI, TDF, and lopinavir/ritonavir promptly squelched the rebound.

Putting RNAand CD4 response numbers side by side after 48 weeks, Moyle and confreres discerned no difference between the two regimens:

	Combivir/EFV (n=57)	Trizivir/TDF (n=56)
<50 copies/mL (%) missing or change = failure analysis	67	68
<50 copies/mL (%) missing or change = failure analysis, AZT switch permitted	71	70
<50 copies/mL (%) missing on treatment analysis	100	97.3
Mean decrease in viral load (log copies/mL)	3.5	3.4
CD4 count (DAVG cells/µL)	+119	+165

Neither of these regimens is perfect, to be sure, but does one outdo the other in any way? Trizivir/TDF's modest advantage in CD4 gains may mean nothing clinically. That group began with fewer CD4s, and people starting a potent regimen with lower T-cell tallies typically gain more than people starting with more CD4 cells.

The oldest drug in the mix, AZT, caused the most side effects (in 7 people or 13%), but there were also 6 suspected hypersensitivity reactions to abacavir in the Trizivir/TDF arm and 2 rashes among people taking efavirenz.

Fasting triglycerides edged up in the Combivir/efavirenz group and edged down in the Trizivir/TDF group, though that small difference lacked statistical significance. But the Combivir/efavirenz group gained 0.8 mmol/L (30 mg/dL) in total cholesterol, while the Trizivir/TDF group lost about 0.2 mmol/L (8 mg/dL), a highly significant difference ($P < 0.001$).

The bottom line, Moyle offered, is that Trizivir/TDF is a single-class regimen with similar potency to two-class standard therapy. It sure beats three nukes.

FDA Approves Two Convenient New Nuke Regimens: One Pill Once Daily of Abacavir + 3TC (Epzicom) and Tenofovir + FTC (Truvada) and Abacavir Once Daily

The Food and Drug Administration approved in September 2004 for the first time a single tablet that includes two nukes, which is taken once daily. These are called Fixed Dose Combinations (FDC) Epzicom is the brand name for one tablet taken once daily that includes abacavir (Ziagen) and 3TC (Epivir). Truvada is the brand name for one tablet taken once daily that includes tenofovir (Viread) and FTC (Emtricitabine). These therapies improve convenience but be sure to have a discussion with your medical care provider regarding if this therapy is suitable for your situation. It remains unsure what role these once daily FDCs will play for treatment-experienced patients. For patients with HIV drug resistance you may want to consider twice daily abacavir.

Previously abacavir was taken 300 mg twice daily. The FDA approved abacavir to be used once daily at a 600 mg dose at the same time they approved the two FDCs. Studies have been reported supporting the use of abacavir once daily. Pharmacokinetics study has supported that the drug levels support once daily use. A clinical trial of 770 antiretroviral-naïve patients was conducted comparing once daily 600 mg abacavir to 300 mg abacavir twice daily. Patients also received once daily 3TC and efavirenz. Baseline average viral load and CD4 was 80,000 copies/ml and 262 CD4s, and about 45% of patients had >100,000 copies/ml. After 48 weeks of treatment, 66% of patients receiving abacavir once daily and 68% receiving twice daily abacavir had <50 copies/ml viral load. Cd4 increases were comparable at about 200. Toxicity was similar; about 9% in the once daily and 7% in the twice daily groups had a hypersensitivity reaction, which is a bit higher than the 5% normally seen.

Tenofovir+ FTC Once Daily Compared with Combivir

HIV-infected people in the US may now choose from two once-daily fixed-dose nuke duos—Truvada (TDF/emtricitabine [FTC]) and Epzicom (abacavir/3TC). Whether one outperforms the other remains to be seen, but TDF+FTC outdid Combivir (AZT/3TC) after a planned 24-week interim analysis for a 96-week non-inferiority trial. This study compared the two single drugs FTC + tenofovir, not the fixed dose combination of Truvada, to the fixed dose combination of Combivir. Everyone in this 517-person multicenter trial reported by Brian Gazzard at ICAAC and Jose Arribas at Glasgow also took efavirenz.

These antiretroviral-naive people began therapy with a median viral load of 100,000 copies/mL and median CD4 counts of 233 cells/µL in the TDF/FTC group and 241 cells/µL in the AZT/3TC group. About 40% of the study patients had less than 200 cells/µL at study entry, and about 40% were black or Latino.

TDF+FTC/efavirenz proved more tolerable than Combivir/efavirenz. Study discontinuation was higher in the Combivir arm (21% vs 11%). This was driven by a higher adverse event rate in patients taking Combivir, (9% vs 3%, p=0.008) who withdrew due to adverse events. Withdrawal due to suboptimal viral response was 2% in FTC+TDF arm and 1% in CBV arm.

Adverse Events Leading to Study Drug: Discontinuation Through Week 24

Safety Population	**FTC/TDF (n=257)**	**CBV (n=254)**
No. w/ any Adverse Event	8(3%)	22(9%)
Adverse Event		
Anemia	0	14(5%)
Nausea	1(<1%)	4(2%)
Fatigue	0	3(1%)
Vomiting	0	3(1%)
Dermatitis (NNRTI)	2(1%)	0
Neutropenia	0	2(1%)

Kidney toxicity rates were low and similar in the two groups.

Maximum Confirmed Toxicity Grade (mg/dL)	FTC/TDF (n=257)	CBV (n=254)
1(>1.5 - 2.0)	0	1(1<1%)
2(>2.1 - 3.0)	0	1(1<1%)
3(>3.1 - 6.0)	0	0
4(>6.0)	0	0

% of Patients with undetectable HIV RNA at Week 24

The higher dropout rate in the Combivir group drove the worse 24-week viral response in that group, determined by the FDA-sanctioned time to loss of virologic response (TLOVR) algorithm:

Week-24 result:	TDF/FTC-EFV	Combivir/EFV	P
<400 copies/mL (%)	87	78	0.01
<50 copies/mL (%)	73	65	0.038
<50 copies/mL and >100,000 copies/mL at baseline (%)	67	54	0.021
Gain in CD4 cells/µL	129	111	0.074

In an on-treatment analysis, nearly everyone in both groups had a 24-week viral load under 400 copies/mL.

Gazzard and colleagues genotyped 10 people in the TDF/FTC arm and 8 in the AZT/3TC group who had a confirmed viral load above 400 copies/mL by week 24 or who quit the study early. None of them had AZT-induced mutations and none had the TDF-linked K65R. The only resistance mutations spotted were the 3TC- or FTC-induced M184V and mutations conferring resistance to efavirenz:

Resistance Development at Week 24

	FTC/TDF (n=244)	CBV (n=243)
Genotypes		
Wild-type	5(50%)	3(38%)
EFV-R alone	3(30%)	4(50%)
EFV-R + M184V/I	2(20%)	1(13%)
K65R	0	0
TAMs	0	0

All patients with confirmed >400 copies /mL of HIV RNAat Week 24 or early discontinuation analyzed. Patients with baseline NNRTI-resistance excluded from analysis (n-22)

Grade 3-4 Adverse Events Through Week 24

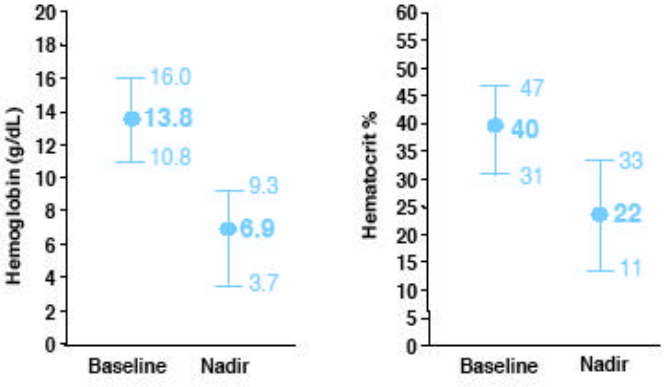
	FTC/ADV	CBV
# w/any AE	24 (9%)	38 (15%)
AE		
Anemia	0	10 (4%)
Neutropenia	1 (<1%)	3 (1%)
Diarrhea	3 (1%)	1 (<1%)
Fatigue	0	3 (1%)
Depression	1 (<1%)	2 (1%)

Grade 3 anemia: Hgb 6.0-6.9 g/dL; Grade 4 anemia: Hgb <6 g/dL.

Hemoglobin & Hematocrit Values for Patients Discontinuing CBV due to Anemia

For patients who discontinued CBV due to anemia, their median baseline & nadir (lowest value) for hemoglobin was 13.8 at baseline & 6.9 at nadir; for hematocrit it was 40 at baseline & 22 at nadir.

Median (Range) Hemoglobin and Hematocrit Values; Discontinuations due to Anemia on CBV arm (n=14)



Gazzard noted that most people had reached 48 weeks of follow-up at the time of his report, so final results should show up shortly.

HIV Superinfection May Reduce Response to HAART & Accelerate HIV Progression

Incidence of HIV Superinfection Following Primary Infection

There are a number of studies over the past two years suggesting rather strongly that superinfection is a real problem for HIV-infected individuals. Superinfection is when a person who has HIV gets infected with a second viral strain of HIV usually through sex or injection drug use. Researchers in San Diego (Little et al) reported on a study they conducted, results of which were reported at CROI 2004.

Anecdotal reports of HIV superinfection coupled with systematic investigations of chronically infected individuals who could not identify cases of superinfection prompted these researchers to investigate a group of newly infected individuals. The researchers retrospectively analyzed blood samples from 54 subjects enrolled in the San Diego and Los Angeles Acute HIV Infection and Early Disease Research Programs who deferred ARV treatment for 6 months or longer. Superinfection was suspected, and the researchers reported superinfection was confirmed by clonal (V3) and dye-primer (pol) sequencing and length polymorphism analysis (V1-2 and V4-5) (GeneScan, Applied Biosystems). They reported identifying 3 cases of superinfection, representing a rate of 6.5% per year. Superinfection occurred 5 to 13 months after the estimated date of initial infection. All 3 subjects were male whose risk factor was sexual exposure; each superinfecting

HIV strain was associated with a change in ARV susceptibility. Two were initially infected with drug-resistant HIV and then became superinfected with a wild-type strain, while the other was initially infected with a wild-type strain and then was superinfected with a drug-resistant strain. Within 6 months of acquiring the superinfecting strain, plasma viral loads increased (mean 1.6 log) and CD4 counts decreased (mean 132 cells/μL).

The investigators said that while initial co-infection cannot be ruled out, 4 independent lines of molecular investigation provide compelling evidence that these are cases of HIV-1 clade-B superinfection. The lab methods used may underestimate the true superinfection rate, the researchers said.

The researchers recommended that harm reduction counseling with patients is essential even if their risk exposures are with other HIV-infected people, as superinfection could have detrimental clinical consequences by accelerating disease progression and limiting future treatment options.

Transmitted HIV Drug Resistance May Reduce Response to HARRT

At the Resistance Workshop in July 2004, French researchers (Ghosen et al) reported on 10 patients in the French ANRS Primo Study who were found to have HIV resistant to HIV drugs during the primary infection period (shortly after infection).

Of the 5 patients who were not treated with HAART, 3 patients had resistance to one class of ART, 1 patient had resistance to 2 classes of HIV drugs, and 1 patient had resistance to 3 classes of HIV drugs. The resistance-associated mutations persisted in the blood and in PBMCs (peripheral mononuclear cells) throughout the followup period, which was 24 months.

Of the 5 patients receiving HAART, 1 patient had resistance to one class of HIV drugs, 2 patients had resistance to two classes of HIV drugs, and 2 patients had resistance to all 3 classes of HIV drugs. Two of these patients achieved undetectable HIV viral load at month 6 after starting HAART despite retaining archiving drug resistance mutations in PBMC HIV DNAfor up to an average of 24-months follow-up. Conversely, the 3 other patients experienced a slower decrease in HIV viral load in the blood, thus promoting the accumulation of additional drug-resistance mutations in the blood as soon as month 6 after starting HAART in 2 of the patients.

The authors concluded that drug-resistant HIV acquired at time of infection can establish itself as the dominant virus population and become archived in the latent cellular reservoir. This may result in sub-optimal response to HAART, promote the accumulation of mutations, and jeopardize already limited treatment options.

HIV Drug Resistance Found in 1 of 7 Treatment Naïve in the USA

At the ICAAC HIV conference (October 2004), a study conducted by GlaxoSmithKline and the University of Miami found worrisome rates of HIV drug resistance in HIV+ individuals who had never been treated for HIV before. Reduced sensitivity to NNRTIs was found in 18% of the 317 individuals studied in 40 cities. 6% were resistant to nevirapine and 9% to efavirenz. 8% of individuals had a nuke resistance mutation but only 0.9% had reduced susceptibility to NRTIs. 6% had reduced susceptibility to protease inhibitors, but only 2% had specific protease inhibitor mutations.

Ethnic differences in drug resistance were most pronounced between Hispanic or Asian patients and other groups (white, black). Hispanic and Asian patients had a lower prevalence of reduced susceptibility (6%) than whites or blacks, 27% and 23% prevalence. However, Hispanic patients showed a trend toward a higher prevalence of drug resistance mutations (17% vs 13% white, and 14% black), particularly NRTI mutations (14% vs 7% for other groups).

Troubling Persistence of Transmitted HIV Drug Resistance

Shedding light on another important aspect of HIV transmission, Susan Little reported at CROI 2004 on the persistence of transmitted drug resistant HIV in individuals with primary HIV infection who chose not to start antiretroviral therapy (ART). In 11 subjects at least one major drug-resistance mutation was identified, along with corresponding phenotypic resistance. In patients with resistance to NNRTI drugs (eg. Sustiva), it took an average of nearly 200 days for resistant virus to begin to be replaced by NNRTI-sensitive HIV, but resistance persisted for 9 of 11 subjects for months with complete disappearance of transmitted NNRTI resistance in only 1 subject, nearly 3 years after infection. HIV with NRTI resistance (eg. AZT) persisted for > 300 days. Protease inhibitor resistance persisted for more than 600 days, and complete reversion of genotypic resistance was observed in only one patient at 1019 days after infection. Despite the presence of drug-resistance mutations, which often impair viral fitness or ability to replicate, the replication capacity of these transmitted drug-resistant viruses was not impaired. This is likely due to selection at transmission for viruses that can replicate well. The durability of transmitted drug resistance raised troubling questions about the likelihood of therapeutic success for these individuals.

Depression & Not Taking HAART Increases Risk for AIDS-Related Death Among HIV+ Women in WIHS

- *women who had chronic depressive symptoms were more than twice as likely to die compared with those who had lim - ited or no symptoms*
- *but death was less likely among women who used mental health services*
- *women on a HAART regimen for a year or more were 90% less likely to experience AIDS-related mortality*
- *women in HAART were less likely to experience depression*

Judith A. Cook, PhD (University of Chicago) reported interesting results from this study in the July 2004 American Journal of Public Health. The study examined if there is an association between depressive symptoms and AIDS-related death after controlling for antiretroviral therapy use, mental health treatment, medication adherence, substance abuse, clinical indicators, and demographic factors. One thousand seven hundred sixteen HIV-seropositive women completed semiannual visits from 1994 through 2001 to clinics at 6 sites in the Women's Interagency HIV Study (WIHS): Brooklyn, NY; Bronx, NY; Chicago, Ill; Los Angeles, CA; San Francisco, CA; Washington DC.

Background: The existence of a potential association between women's depression and HIV disease progression is of interest to both health care providers and patients for several reasons. First, women's rate of depression is twice as high as that of men among the general population. Second, HIV-seropositive women who have high levels of depressive symptomatology are significantly less likely to use highly active antiretroviral therapies. Third, depression is associated with poor adherence to antiretroviral treatment regimens, which in turn is associated with poor disease outcomes, such as mortality. Finally, depression is a significant predictor of non–AIDS-related deaths (e.g., those caused by accident, drug overdose, violence, and non–AIDS-associated malignancies) among HIV-seropositive women.

Study Findings: After they controlled for all other factors, AIDS-related deaths were more likely among women with chronic depressive symptoms. Women who had chronic depressive symptoms were more than twice as likely to die compared with those who had limited or no symptoms, even after they controlled for clinical, substance use, and sociodemographic factors. Clinically significant depressive symptoms also were more likely among those women who reported illicit drug use and who had incomes below $12,000 per year. AIDS-related mortality also was more likely among those with low baseline CD4 cell counts, high viral loads, and HIV-related symptoms at baseline. Mortality was less likely among those who reported mental health service use and those who were on a HAART regimen or a non-HAART combination therapy. Women who were on a HAART regimen for a year or more were 90% less likely to experience AIDS-related mortality. Moreover, the proportion of women who reported recent depressive symptoms was lowest among those who were on a HAART regimen.

The authors concluded that the significantly lower proportion of women who had depressive symptoms among users of the most potent antiretroviral therapies shows the possible role of a HAART regimen in combating depression along with or in addition to the role of positive mental health in promoting use of a HAART regimen.

High Prevalence and Late Diagnosis of HIV Among Black Men Aged 40-54 in New York City

Researchers from the New York City Department of Health and Mental Hygiene reported these study results at the Intl AIDS Conference in Bangkok in July 2004.

The NYC Dept of Health conducted a study looking at the prevalence of HIV & AIDS among Black men in NYC, and found that the prevalence of HIV/AIDS is high in Black men aged 40-54, particularly in Manhattan, while Brooklyn has the greatest number of PLWHA. The high rate of concurrent diagnoses of both HIV & AIDS in 40-54-year-old Black men, especially among those born outside the US, indicates that many were long-infected but not tested until symptomatic. Late diagnosis may delay entry to primary care and preventive counseling, and puts health and response to HAART at risk.

Since New York City (NYC) began HIV reporting in June 2000, non-Hispanic Black men have comprised the largest group of people living with HIV or AIDS (PLWHA) and new HIV and AIDS diagnoses. Prevalence among Black men varies by age and geography, as do concurrent HIV/AIDS diagnoses, suggesting barriers to access to testing and care, officials said.

The study calculated prevalence of PLWHA as of December 31, 2001, by race/ethnicity, sex, and age, using census data and HIV surveillance data reported through September 30, 2003; and also examined geography, concurrent HIV/AIDS diagnoses, and foreign birth among Black men.

Results

Demographic data were available on 75,362 PLWHA (98.4%).

Prevalence was 1 in 100 citywide, 1 in 43 for Black men of all ages, and 1 in 15 for Black men 40-54 years old, the highest prevalence of all demographic groups (11,039/166,818, 6.6%; versus 2.3% of Black men of all ages).

Of 40-54-year-old Black male PLWHA diagnosed since June 2000 (n=1,523), nearly 1 in 3 had concurrent HIV/AIDS (31.4% of new HIV diagnoses).

While Brooklyn accounted for the greatest number of PLWHA in Black men aged 40-54 in New York City (n=3,258), *Manhattan had the highest prevalence, 1 in 8 (2,812/22,776, 12.3%; versus 1 in 21, 4.7% in Brooklyn).*

One in 10 of NYC's 40-54-year-old Black male PLWHA was

born outside the US: 70.4% in the Caribbean, 21.0% in Africa, and 8.6% in South America.

Non-US-born Black men aged 40-54 who were diagnosed since June 2000 were significantly more likely than those born in the US to have concurrent HIV/AIDS (56.8% versus 30.0%; p<0.001).

Safety and Tolerability of Vaginal Tenofovir gel (TFV) in HIV-Uninfected and HIV-Infected Women

Ken Mayer, MD reported the results of this study in an oral abstract at the Intl AIDS Conference in Bangkok (July 2004). One of the most compelling needs in HIV both globally in the USA is to find an effective microbicide that prevents HIV sexual transmission. The results from this study are a first step in making progress towards perhaps tenofovir gel providing an answer to this problem.

The purpose of this study was to determine if use of the gel is acceptable to men & women, to assess local & systemic toxicity, and to determine the highest tolerated combination of either 0.3% or 1% tenofovir gel (TFV) applied once or twice daily for two weeks in low-risk, sexually abstinent and active HIV(-) and then in abstinent and active HIV (+) women. TFV gel pharmacokinetics (PK) and effects on genital HIV shedding were also studied.

Rationale for the Use of Topical Tenofovir (PMPA, brand name Viread)

- PMPA is an adenosine nucleoside monophosphate (nucleotide) RTI
- Subcutaneous injection of 20-30 mg/kg of PMPA once daily for 4 weeks before or after intravenous SIV challenge protected 25/25 rhesus macaques (Tsai, 1995)
- Intravaginal application of 1% or 10% PMPA gel before or after vaginal SIV challenge also protected 100% of macaques (Miller, 1996)
- Animal toxicology studies of vaginal PMPA demonstrated a good safety profile.

The author's findings and conclusions:

- no life-threatening adverse events or deaths were observed
- 92% had at least one AE; 87% had a mild AE; 40% had at least one moderate AE; generally limited duration
- 70% had a genital tract AE; 32% a GI symptom
- rare severe adverse events (AEs) (1 possibly product-related)
- most AEs were mild and confined to the genital tract
- 50% developed at least one new pelvic exam or colposcopic finding while on study gel
- only one severe colposcopic finding
- erythema was the most common colposcopy finding
- about half of women tested had low, but detectable serum Tenofovir levels
- Tenofovir gel is acceptable to women
- Tenofovir vaginal gel used 1% BID was well-tolerated in abstinent and sexually active HIV(-) and HIV(+) women, with limited systemic absorption and with no clinically significant systemic toxicity detected and with possible beneficial effects on vaginal microflora
- extended safety and effectiveness studies are warranted, based on these initial data.

Vaginal Microflora

- 29 women had Asymptomatic Bacterial Vaginosis at Enrollment (Nugent's criteria)
- BV resolved in 14 of these women (48%)
- 1 of 39 women without BV at enrollment developed BV after 14 days of gel use
- 5% of women developed vaginal candidiasis after product use

The Most Common Adverse Events Were:

Genital pruritis (itching): 23%
Genital erythema (redness of skin): 18%
Applicator site bruising: 17%
Applicator site erythema: 17%
Vaginal discharge: 15%
Irregular menses: 13%
Metrorrhagia (bleeding from uterus): 11%

Gel concentration, sexual activity, and HIV status were not associated with a specific AE pattern.

Contributions to this newsletter were made by:

Judith Aberg, MD, Bellevue Hospital/ NYU Medical Center
Jacqueline Capeau, MD, Medicine Saint Antione, INSERM, Paris, France
Chris Pilcher, MD, University of North Carolina
David Margolis, MD, University of Texas Southwestern/Dallas VA Hospital
Mark Mascolini
Jules Levin, NATAP
Mike Youle, MD, Royal Free Hospital, UK
Graeme Moyle, MD, Chelsea & Westminster, UK
David Wohl, MD, University of North Carolina
Ronald Reisler, MD, MPH, Institutes of Human Virology University of Maryland Medical School
Andrew Zolopa, MD, Stanford University

The articles in this newsletter report the latest information from studies presented at these leading medical conferences held in 2004

CROI- 11th Annual Conference on Retroviruses & Opportunistic Infections (Feb 2004)

10th International AIDS Conference (Bangkok, July 2004)

Lipodystropohy Workshop- 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (Washington DC 2004)

ICAAC- 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC, October 2004)

Glasgow- 7th International Congress on Drug Therapy in HIV Infection (Glasgow, November 2004)

XIII International HIV Drug Resistance Workshop (Canary Islands, June 2004)

For more information please visit our website at http://www.natap.org, e-mail our staff at info@natap.org, or call: 1-888-26-NATAP