NATAP'S NATIONAL AIDS TREATMENT ADVOCACY PROJECT

POSITIVE + INFORMATION

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IN THIS ISSUE:

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Reyataz

Reyataz, also called atazanavir (ATV) is a new protease inhibitor that was approved by the FDAin June 2003 and was available in pharmacies in July. In studies of 48 weeks or longer, researchers looked at average changes in cholesterol, triglycerides, or glucose, and did not see increases associated with taking Reyataz. In a phase II study comparing ATV to nelfinavir the achievment of lower lipid concentrations with ATV treatment was sustained through 108 weeks, and there was an improvement in hyperlipidemia and hypertriglyceridemia when nelfinavir was switched to ATV. In addition, ATV demonstrated no clinically important effect on insulin/glucose metabolism. This finding has the potential to avoid patients having to take lipid lowering therapies, and perhaps reducing the potential risks for future cardiovascular events and heart disease. Reyataz is taken once-a-day with food at a dose of 400 mg (two 200-mg capsules). It is recommended to be taken with food, as this enhances the amount of drug that enters the body and reduces the variation of drug levels between patients. Without a light meal Reyataz blood levels are lower and more variable, and potency may be inadequate. Reyataz capsules should be stored at room temperature, 77°F (25°C): excursions permitted to 59°-86°F (15-30°C).

In two important studies the ability of Reyataz to reduce HIV viral load and increase CD4 count was tested. One study compared Reyataz to efavrienz (Sustiva) in treatment-naïve patients; these are individuals who never received previous treatment for HIV. The second study compared Kaletra to 300 mg of Reyataz boosted by 100 mg of ritonavir in patients who had experience with multiple regimens and had resistance to protease inhibitors. A third study, also discussed below, reports on body changes (lipodystrophy) after individuals had been on Reyataz for 48 weeks.

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Fuzeon (T-20): A Fusion Inhibitor, the First Entry Inhibitor

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 is a new drug, the first entry inhibitor approved by the FDAin April 2003 and is available in pharmacies. Researchers are intensely trying to develop entry inhibitors. A number of large drug companies and Biotech companies have potential drug candidates in early stages of development. Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Schering-Plough, and other companies have research and development programs dedicated to finding entry inhibitor drugs for HIV. A second generation fusion-inhibitor, T-1249, is in early development. There is a chance that in several years we will have several entry inhibitors, which work at various steps in the process of HIV entry into CD4 cells. Perhaps several entry inhibitors will be used together in a single HIV therapy regimen.

Fuzeon is a fusion inhibitor, and for now the first and only entry inhibitor to become available to patients. Attachment and fusion are steps identified for HIV to enter cells. Of note, Fuzeon is potent against HIV, whether or not a patient has treatment experience or has never been treated for HIV.

continued on page 5...

In a large phase III study, ATV was compared to Sustiva (efavirenz). The study was designed only to show that ATV was not worse than Sustiva, not to prove that it was better. Such "non-inferiority" studies have recently become more often used in studies of new HIV therapies. Previous studies usually compared two drugs only by looking at the percent of patients achieving an undetectable viral load. However, this result is still reported in the ATV studies.

In the large phase III trial, 810 treatment-naïve patients were randomized to receive atazanavir 400 mg once daily or efavirenz (Sustiva) once daily; all patients also received AZT/3TC (Combivir). This trial compared ATV against a preferred standard of care, Sustiva. The study found that atazanavir is not inferior to efavirenz. As well, the effects on viral load and CD4 counts are reported below.

The main side effect associated with ATV is elevated bilirubin, a laboratory test that measures liver function. Elevated bilirubin may result in yellowing of the skin (called jaundice). This was reported by 6-8% of the patients in studies of Reyataz, and <1% to 3% of the patients in Reyataz studies experienced yellowing of the whites of the eye.

The FDAsaid in their review of ATV that Grade 3 - 4 elevations in bilirubin were rarely associated with any Grade 3 - 4 elevations in ALT or AST in studies; only 10 patients out of 660 in 3 large studies (034, 043, and 045) had both Grade 3 - 4 ALT or AST and Grade 3 - 4 total bilirubin elevations. Of these 10 patients, 5 reported hepatitis B/C at baseline, and 6 patients had concurrent Grade 3 - 4 transaminase and total bilirubin elevations. There was no evidence that these elevations in bilirubin were associated with a hepatotoxic process.

Reyataz Study in Treatment-Naïve Patients

The study participants' average HIV viral load was 85,000 copies/ml and the CD4 count was 280 cells. 42% of patients had viral load levels >100,000 copies/ml. So the patient group in this study had relatively advanced HIV.

Percent Below 400 and 50 Copies/ml at Week 48

	<400 copies/ml	<50 copies/ml
ATV/Combivir (AZT/3TC)	70%	32%
Sustiva/Combivir	64%	37%

In evaluating the response by the percent of patients achieving an undetectable viral load, the study found patients had similar responses to either Sustiva or Reyataz. You may notice that the response to this Sustiva-based regimen is inferior to that seen in previous studies of Sustiva. Scientifically we can only compare response rates within a study, not between different studies which may have involved different patients, procedures, and conditions. This study shows ATV not to be worse than Sustiva. When looking at the response in patients with greater than or less than 100,000 copies, no difference in the ATV or EFV arms was present whether evaluating by <400 or <50 copies/ml. The rise in CD4 counts was 176 for ATV and 160 for EFV treated patients.

Still this may cause some concern in the community. Some data has been presented to suggest that procedures used in this particular study could have resulted in a systematic increase in viral load measurements, thereby leading to the generally poorer response rates seen in both arms. At the July IAS Conference in Paris (July 2003), Bristol-Myers Squibb reported at their symposium that a combination of factors contributed to the lower viral response rates for HIV-RNA <50 copies/ml. However, the primary factor appears to be problems in using the wrong tubes during shipping and freezing. After re-analyzing blood samples in different tubes BMS reported response rates for both treatments were close to that seen in previous Sustiva studies. To view the BMS data, visit http://www.natap.org/2003/IAS/day20.htm. Further study of and use of ATV will resolve this uncertainty.

Grade 2-4 adverse event rates were low in both study arms. Jaundice (yellowing of skin) and scleral icterus (yellowing of whites in the eye), known side effects of ATV, were reported in 5% and 1% of patients, respectively. Markers of hepatic toxicity (ASTand ALT) were not different between the groups, nor were white blood cell counts or hemoglobin. Total bilirubin (a laboratory test) elevations > 2.5 x the upper limit of normal (ULN) were reported in 33% of ATV treated patients. Based on studies so far conducted and opinions from experts the elevated bilirubin levels are believed to be without health consequences and resolve promptly upon discontinuation of Reyataz.

Other side effects that occurred at similar rates for patients whether they received Sustiva or Reyataz: diarrhea 1-2%; nausea 13-14%; rash: 6% for Reyataz, 10% for Sustiva; headache 5%; dizziness; 2% Reyataz, 6% for Sustiva.

The lipid profile (cholesterol, triglycerides) for Reyataz has been seen so far in studies to be unlike other protease inhibitors, which can cause increases in total cholesterol LDL ("bad" cholesterol), and increases in triglycerides. Similarly, significant abnormalities related to diabetes, increases in glucose or insulin resistance, have not so far been seen in studies.

Fasting Lipid Profile at Week 48

	Total cholesterol	LDL	HDL	TG
Reyataz	+2%	+1%	+13%	-9%
Sustiva	+21%	+18%	+24%	+23%

Through 48 weeks of treatment, ATV did not result in increases from baseline in fasting LDL-cholesterol, total cholesterol, or insulin, and resulted in a statistically significant decrease of 9% in fasting triglycerides and a statistically significant increase of 13% in HDL-cholesterol ($p < 0.05$) for comparisons to baseline. Baseline LDL-cholesterol values assessed by NCEP (National Cholesterol Education Program) categories were comparable for ATV and EFV regimens. At 48 weeks, the proportion of ATV- treated fasting LDL-cholesterol concentrations outside the NCEP-defined desirable range was unchanged from baseline. Among ATV-treated subjects, LDL-cholesterol was >130 mg/dL in 13% of subjects at baseline and 13% at Week 48. LDL-cholesterol was >160 mg/dLin 2% and 3% of ATV-treated subjects at baseline and Week 48, respectively. In comparison, the proportion of EFV-treated subjects with LDL-cholesterol >130 or >160 mg/dL increased

from baseline. Nineteen patients (2%) were administered lipid reduction pharmacological therapy while on-study, five (1%) on ATV, and 14 (3%) on EFV.

Resistance to ATV

ATV appears to be effective in reducing viral load for patients with low to moderate protease inhibitor resistance, but as PI resistance increases ATV effectiveness is likely to decrease. If you have prior PI experience and PI resistance you should confer with your doctor about the potential for cross-resistance if you are considering switching to ATV. Studies suggest that the I50L resistance mutation is often present if viral failure occurs following initial treatment with ATV, and that I50L appears to be the main mutation selected by ATV itself. Individuals experiencing viral failure with this mutation but without others in the protease gene appear to be fully sensitive to other protease inhibitors. This is a preliminary finding, which requires further evaluation. There is no evidence of cross-resistance between ATV and amprenavir, despite the known relationship between the I50V mutation and amprenavir resistance.

Reyataz For Protease Inhibitor Experienced

Results have been reported after 24-weeks of study of 340 patients comparing a once daily regimen of atazanavir (ATV) boosted by a small dose of 100 mg of ritonavir (RTV) to Kaletra in patients who had previous experience with protease inhibitors and had viral failure of 2 or more previous regimens. The study found Kaletra and ATV 300mg plus RTV 100mg to be similar in viral load response after 24 weeks. Patients continue to be followed.

Boosting 300 mg of ATV with 100 mg of ritonavir significantly increases the amount of ATV in the blood. It results in more than double the overall drug levels of ATV over the 24 hour dosing period, and in 3 times higher levels than the standard dose of atazanavir 400 mg at trough (24 hours after taking drug). Kaletra is co-formulated, where 3 capsules contain 300mg of lopinavir and 100 mg of ritonavir. This study also included a third regimen for comparison: ATV 400 mg plus saquinavir 1200 mg taken once daily, but this regimen was found to be not as good at suppressing viral load as the other two regimens in the study. The study examined a comparison of viral response, lipids, safety and tolerability. 35% of patients in the study had 4 or more protease inhibitor mutations; 40% of patients had 4 or more NRTI mutations.

Sensitivity to protease inhibitors (2.5 x IC50 of control strain) ranged from 56% to 83%, with 23% of the treated subjects highly resistant (> 10 x IC50 of control strain) to NFV and 21% of the subjects highly resistant to RTV. 74% and 75% of subjects were susceptible to ATV and LPV, respectively. Susceptibility to ATV or LPV was comparable across the treatment regimens. The majority of randomized subjects had recently taken a NRTI (96%) or NNRTI (60%), whereas only 34% had taken a PI. For randomized subjects, the mean exposure to any PI, NRTI, or NNRTI therapy was 138, 280, and 85 weeks, respectively. The FDA said, 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).

The study results after 24 weeks on therapy showed similar antiviral effectiveness of Kaletra and ATV/r; patients taking ATV/r appear to have a better response regarding total cholesterol and triglycerides compared to patients taking Kaletra. Fewer patients treated with ATV/r took lipid lowering drugs than those on Kaletra.

45% of patients taking ATV/r experienced grade 3/4 elevations in bilirubin, 6% of patients experienced jaundice, and 3% experienced scleral icterus.

There was no difference in grade 3/4 laboratory abnormalities of ALT (SGPT) or AST (SGOT) of note between the Kaletra and ATV/r regimens: grade 3/4 ALT elevations were 3% for patients taking ATV/r and 3% for Kaletra; AST grade 3/4 elevations were 3% for ATV/r and <1% for Kaletra.

Viral Load Response at Week 24 (Intent-To-Treat analysis)

	<400 copies/ml	<50 copies/ml
ATV/r 300/100	64%	39%
Kaletra (LPV/r)	62%	42%
ATV/SQV 400/1200	44%	23%

There were an equal number of patients discontinuing from the Kaletra regimen (n=6, 5%), and from the ATV 300/RTV 100 arm (n=7, 6%); 14 patients (12%) discontinued from the ATV400/SQV1200 regimen.

Lipids at Week 24

	TC	LDL-C	HDL-C	TG
ATV/r	-8%	-10%	-7%	-2%
ATV/SQV	-9%	-11%	-1%	-14%
Kaletra	+3%	-4%	0%	+31%

TC=total cholesterol; LDL-C is the “bad cholesterol” and increases are associated with increased risk for heart disease; HDL-C is the “good cholesterol” and decreases are associated with risk for heart disease. Increases in triglycerides (TG) may be associated with increased risk for heart disease. It is important to bear in mind that in general it can take years for lipid abnormalities to lead to the development of heart disease. The presence of other risk factors plays an important role in contributing to the risk for heart disease and in how quickly heart disease can develop. Here are several key risk factors: smoking cigarettes, family history, diet rich in fats and salt, and a sedintary lifestyle.

The study looked at the number of patients that used any lipid lowering drugs, such as Lipitor. 15% of patients taking Kaletra, 7% of patients taking ATV/r, and 15% taking ATV/SQV took lipid lowering drugs. Diarrhea was reported by 3% of patients taking ATV/r, and 11% of patients taking Kaletra. There were no other differences of note between the two-drug regimens reported regarding grade 2-4 adverse events. The rate of withdrawal by patients from the study was low: 3% in the ATV/r group and 2% in the Kaletra group.

Potential Effects on Heart Rhythm

It is generally recommended that atazanavir be used with caution in patients with preexisting abnormalities of the heart rhythm. Until more is known about the interaction of atazanavir and other medications, it is also recommended that certain cardiac medications be administered with caution or at reduced dosages in patients receiving ATV.

Atazanavir and PI's have been found to be associated with asymptomatic slowing of electrical impulses through the heart's pacemaker system (increased PR interval). In clinical trials, measurable slowing, called asymptomatic first-degree AV block, was observed in 5.9% of atazanavir-treated patients (n=920), 5.2% of lopinavir/ritonavir-treated patients (n=252), 10.4% of nelfinavir-treated patients (n=48), and in 3.0% of efavirenz-treated patients (n=329).

QTc is another measure of the time it takes an electrical impulse to pass through the heart. QTc prolongation can increase the risk of serious heart rhythm disturbances. However, ATV has not been found to have a clinically meaningful effect on QTc. Oral doses of 400 mg and 800 mg were compared with placebo; there was no concentration-dependent effect of atazanavir on the QTc interval. In 1,793 HIV-infected patients receiving antiretroviral regimens, QTc prolongation was comparable in atazanavir and other comparator PI regimens. No atazanavir-treated healthy subject or HIV-infected patient had a QTc interval >500 msec.

Thus far, there have been no cases of severe heart rhythm block. Because of limited clinical experience, atazanavir should be used with caution in patients with preexisting conduction system disease (eg, marked first-degree AV block or second-or third-degree AV block). In a pharmacokinetic study between atazanavir 400 mg once daily and diltiazem (a blood pressure and hearth rhythm medicine) 180 mg once daily, a CYP3A substrate, there was a 2-fold increase in the diltiazem plasma concentration and an additive effect on the PR interval. When used in combination with atazanavir, a dose reduction of diltiazem by one half should be considered and ECG monitoring is recommended.

In a pharmacokinetic study between atazanavir 400 mg once daily and atenolol 50 mg once daily, there was no substantial additive effect of atazanavir and atenolol on the PR interval. When used in combination with atazanavir, there is no need to adjust the dose of atenolol. Pharmacokinetic studies between atazanavir and other drugs that prolong the PR interval including beta blockers (other than atenolol), verapamil, and digoxin have not been performed. An additive effect of atazanavir and these drugs cannot be excluded; therefore, caution should be exercised when atazanavir is given concurrently with these drugs, especially those that are metabolized by CYP3A (eg, verapamil).

Body Changes After 48 weeks on Reyataz or Sustiva

The effects on body changes (lipodystrophy) by Reyataz was evaluated in a study, and results after 48 weeks on Reyataz therapy were reported in July 2003 at the Lipodystrophy Workshop. This study compared ATV to Sustiva, which is described above. Patients were taking Reyataz plus AZT/3TC or Sustiva plus AZT/3TC. After 48 weeks on either treatment, on average fat loss (lipoatrophy) was not detected for patients in either regimen in the limbs, the trunk, or total body fat using objective DEXAtesting. Bear in mind that fat loss often occurs after one year on therapy. We need to wait for the study report after 2 years on therapy.

The study used objective imaging tests before patients took Reyataz or Sustiva and after 48 weeks of treatment. CT scans (computerized tomography) and DEXA (dual energy x-ray absorptiometry) were used to assess body changes. The body changes evaluated included visceral adipose tissue (VAT: belly fat), subcutaneous fat (SAT: peripheral fat--legs, arms, face), total adipose tissue (TAT), appendecular fat (limbs), truncal fat (trunk is between hips and shoulders), and total body fat.

DEXA scans performed at baseline and Week 48 for treated subjects enrolled in the metabolic substudy identified the following:

- Mean increases from baseline at Week 48 were small and comparable between regimens in appendicular (limbs) fat (3% ATV, 3% EFV), truncal fat (5% ATV, 8% EFV), and total body fat (5% ATV, 5% EFV).
- No changes from baseline in the ratios of appendicular-to-total fat and truncal-to-total fat were observed on either regimen.

Cross sectional CT scans performed at baseline and Week 48 identified the following:

- Mean increases from baseline at Week 48 were comparable between regimens in VAT (40% ATV, 29% EFV), SAT (19% ATV, 5% EFV), and TAT (23% ATV, 11% EFV). Modest increases in VAT and TAT were observed on both regimens.
- No change from baseline in the ratio of VAT-to-TAT (which remained at 0.3) was observed on either regimen.

Average weight gain from baseline at week 48 was 4.4 lbs for patients on ATV and 0 lbs for patients on Sustiva. Patients taking ATV are expected to be followed for a second year.

In addition to the objective measurements of fat redistribution provided in Study 034, the general safety database for ATV provides estimates of the incidence of lipodystrophy events. It is recognized that passive collection (doctor assessment) of lipodystrophy events on case report forms without standardized criteria or a case definition does not provide a rigorous assessment of ATV's effect on body fat. Through approximately two years of treatment with ATV in combination with d4T and/or ddI, the frequency of lipodystrophy was 16% to 18% for patients receiving 400 mg of ATV. This was comparable to the rates observed after 95 weeks in Studies 007/41 and 008/44 comparing ATV to nelfinavir, with d4T/ddI in treatment-naIve patients.

Fuzeon (T-20): A Fusion Inhibitor, the First Entry Inhibitor, cont'd.

Small studies show that Fuzeon reduces HIV viral load by about 1 to 1.5 log when used as monotherapy in short-term trials of treatment-naïve individuals. It is effective for patients with resistance to the currently available HIV drugs. Patients with resistance to PIs, NRTIs, and NNRTIs should not have any resistance to Fuzeon as this drug functions at a different stage of the HIV replication process. Fuzeon, like previous anti-HIV drugs, has been found to be most potent and effective in suppressing HIV when used along with 2 or more drugs in a regimen to which a person is also sensitive. Studies in patients with advanced HIV and drug resistance to protease inhibitors, NRTIs, and NNRTIs show that composing the best regimen available from current drugs and then adding Fuzeon significantly reduces HIV viral load and increases CD4 counts compared to a regimen that includes the best available drugs without Fuzeon.

Because Fuzeon is somewhat complicated to administer, the drug is recommended for use by patients with few treatment options. So far in studies, the main side effect from the drug is injection site reactions, described below. Before describing results from the two large studies so far conducted here is an explanation of how entry and fusion inhibitors work.

Currently approved classes of anti-HIV drugs -- protease inhibitors, NRTIs, NNRTIs-- inhibit the HIV replication process after HIV enters the CD4 cell, where HIV reproduces itself and churns out new infectious viral particles that enter new cells. Many HIV-infected individuals have developed resistance to these classes of drugs. But, they should not have resistance to Fuzeon. Fuzeon prevents HIV from fusing with and entering the CD4 cell. Researchers have discovered that there are several steps for the virus to enter the CD4 cell, attachment and fusion. Attachment is the first step, and there are two parts to attachment: HIV's gp120 molecule binding to a CD4 receptor on a CD4 cell, and secondly to a necessary "coreceptor" molecule on the cell surface (CXCR4 and CCR5 are the most common) that must be present on the cell surface for proper attachment. Drugs inhibiting this binding are called attachment inhibitors.

After attachment HIV fuses with the CD4 cell and dumps the enzymes it needs for reproduction into the CD4 cell. These enzymes include the reverse transcriptase, integrase, and protease enzymes. Once gp120 binds to the CD4 receptor and a coreceptor, gp120 flips back out of the way, exposing the virus' previously hidden harpoon molecule, gp41. gp41 is then free to pierce the cell and bring it in close enough to allow virus-cell fusion. Drugs targeting these last steps are called fusion inhibitors. T-1249 is a second generation fusion inhibitor and a "cousin" of T-20, which is being developed by the same companies, Roche and Trimeris. In preliminary studies, T-1249 has been shown to be more potent than T-20 and effective in suppressing HIV that is resistant to T-20 (Fuzeon). Further study is in progress, and Phase II studies of T-1249 are expected to start in early 2004.

Fuzeon has been studied in 1000 patients in two large phase III studies. The 1000 patients in the TORO I and II studies were highly treatment experienced with all 3 HIV drug classes and had a good deal of HIV drug resistance. The studies were open-label, randomized, multicenter, international trials where patients were randomized to Fuzeon and an optimized background regimen, or just an optimized background regimen without Fuzeon. Genotypic/phenotypic resistance testing was used to select the optimized background regimens. Patients were permitted to switch to Fuzeon at virologic failure or at week 48.

Before starting study treatments the average patient viral load was over 100,000 copies/ml and CD4 count was 90. The average number of previous anti-HIV drugs used was 12. It had been 7 years since patients had started HIV therapy. Patients had on average 4 years of PI use, 6 years of NRTI use, and 1.5 years of NNRTI use. At week 24, patients receiving Fuzeon had –1.52 log reduction in viral load compared to –0.73 log in patients not receiving Fuzeon.

Viral Responses at Week 48

	Fuzeon +OB	OB
<400 copies/ml	30%	12%
<50 copies/ml	18%	7.8%
dropped > 1 log	34%	17%

The viral load responses were about the same at week 48 as at week 24 of the study, showing the response was durable. The time to virologic failure was 32 weeks for the Fuzeon regimen compared to 11 weeks for the optimized regimen only arm. Participants in the T-20 arm reported greater improvements in constitutional symptoms, such as fatigue, diarrhea, and headache, compared with patients not receiving Fuzeon. The increase in CD4 count from baseline was 71 cells at week 24 for patients receiving Fuzeon+optimized background compared to 35 cells for patients receiving optimized background alone. At week 48 the increase in CD4 count was 91 from baseline for patients receiving Fuzeon. Patients in the study responded better to the Fuzeon regimen if CD4 count was >100, viral load was <100,000 copies/ml, had prior use of <11 antiretroviral medications, and had 2 or more active HIV drugs in the optimized background regimen. Patients who met this criteria had better outcomes: 80% had <400 copies/ml at week 24 vs 50% for patients not receiving Fuzeon. Patients with 3 positive prognostic indicators had 59% <400 copies/ml compared to 34% for patients who did not receive Fuzeon. Patients also responded better if they had never had previously used Kaletra and had fewer PI mutations. This raises the question, when is the optimal time to use T-20?

Injection Site Reactions

Injection site reactions are common. In the study most patients reported discomfort, red bumps or nodules at the site of injection, and induration (hardening of skin at site of injection). About 50% of patients reported mild tenderness at the sites of injection for Fuzeon. About 20% reported moderate pain. About 1-2% reported severe pain requiring analgesics or limiting usual activities. Perhaps the severity or risk of experiencing an ISR can be reduced by proper drug administration. Roche has developed educational materials instructing how

Fuzeon should be injected; both doctors and patients should use these educational materials. Proper drug administration technique is crucial for success with Fuzeon. Improper injection of the drug, like forgetting to take your pills, may allow drug resistance to develop.

Fuzeon is stored at room temperature, 77°F (25°C): excursions permitted to 59°-86°F (15-30°C). Reconstituted solution should be refrigerated at 36°-46°F and used within 24 hours.

The adverse event profile reported is similar for both treatment groups in the study except for injection site reactions. There was more sinusitis, peripheral neuropathy, and weight decrease reported for the patients receiving Fuzeon. There also was a higher incidence of bacterial pneumonia for patients receiving Fuzeon+OB vs OB alone (6.6% vs 0.6%). The incidence of bacterial pneumonia was 9-10% for patients with <200 CD4s.

The study authors added that Fuzeon "did not exacerbate most of the known toxicities associated with most ARVs". This is in part referring to metabolic abnormalities. An analysis is ongoing to examine body changes and metabolic abnormalities in this study. But the study authors suggest they do not see major exacerbation of metabolics associated with Fuzeon, this is preliminary and speculative until we see the data. Hyper-sensitivity reactions have been attributed to Fuzeon (1% or less) and in some cases have recurred upon re-challenge.

Kaletra Update

Viral load and CD4 response after 4 years follow-up

Abbott Labs has reported the 4-year follow-up of treatment-naive patients in the longest study of Kaletra so far. The results show that Kaletra is potent and durable in its antiviral effectiveness. The patients in the study show continued high response rate (70% with HIV viral load <50 copies/mL by intent-to-treat analysis). Patients also received d4T and 3TC in the study. 100 patients originally started this study and 72 remain in the study. The average increase in CD4 count for patients is 500 cells. Of note, 59 of the 72 patients have shown an increase in CD4 count of 500 cells or more. CD4 counts have continued to increase through the 4 years. For patients on the study at week 216 (4+ years), increases in CD4 cell count were largest during the first 48 weeks of study (230 cells). An increase of 141 cells was observed during the fourth year of study (between weeks 156-216) following annual increases of 56 and 72 cells during the second and third years of study (Weeks 48-156). Patients starting in this study with <50 CD4s had an average increase of 489 cells over the 4 year follow-up. GI upset being the most common side effect associated with Kaletra, 27% of patients reported diarrhea after starting Kaletra. Kaletra is also associated with elevations in cholesterol and triglycerides. In this study 22% of patients reported incidence of cholesterol >300, and 22% reported triglycerides >750 mg/dL during the 216 weeks. The poster reports 7% of participants discontinued due to drug-related adverse events.

In over 500 treatment-naive patients enrolled in Phase II/III trials with Kaletra for an average duration of 97 weeks (range, 0-250 weeks) who experienced viral failure, no genotypic or phenotypic resistance to Kaletra has been observed.

In Study 863, Kaletra was compared with nelfinavir (Viracept), plus d4T/3TC, in 326 treatment-naïve patients. Through 96 weeks of therapy, no evidence of primary resistance to Kaletra (defined as any primary or active site mutation) was detected in any of 51 Kaletra-treated patients with detectable viral load for whom genotype was available. 48% of isolates from nelfinavir-treated patients with viral failure displayed primary resistance to nelfinavir (emergence of D30N and/or L90M) or displayed substantially reduced (> 6.8-fold) susceptibility to nelfinavir in the absence of either primary mutation. 51/74 patients taking Kaletra and 96/113 (85%) of patients taking nelfinavir had a genotype test available. 0% taking Kaletra had PI resistance vs 48% (46/96) taking nelfinavir. Regarding 3TC resistance, 37% (19/51) of patients taking Kaletra vs 82% (79/96) of patients taking nelfinavir had 3TC resistance.

2 Kaletra High-Dose Regimens in Protease-Inhibitor Experienced: short-term results

In patients who have failed multiple antiretroviral regimens and have multiple protease inhibitor experience, high-level drug resistance is likely. Abbott reported preliminary results from evaluating increased doses of Lopinavir/ritonavir (Kaletra) to achieve higher lopinavir (LPV) concentrations and overcome Kaletra and PI resistance. The study examines the pharmacokinetics (PK), drug levels in the blood, of two high-dose Kaletra regimens.

31 multiple protease inhibitor experienced patients with <200 CD4s received 1 of 2 high-dose Kaletra regimens—either LPV/r 400/300 mg twice daily or 667/167 mg twice daily (each regimen was 5 capsules). The standard Kaletra (lopinavir/r) dose regimen is 400/100 mg twice daily.

After 4 weeks the viral load reduction was about the same in both groups, -1.2 to –1.5 log. The 667/167 regimen increased lopinavir blood levels 73% to 88%. The 400/300 regimen increased lopinavir levels 47% to 59%.

Compared to Kaletra (400/100mg), when using the 667/167mg dose Kaletra Cmax (peak lopinavir levels in blood) was 73% higher, AUC (drug levels over entire 12-hour dose period) was 88% higher, and Ctrough (lowest drug level before next dose) was 73% higher. When using the 400/300mg dose, Kaletra Cmax was 47% higher, AUC was 59% higher, and Ctrough was 56% higher.

Ritonavir blood levels were 3 times higher using the 400/300 regimen compared to the 667/167 regimen and 6 times higher than using the standard 400/100 Kaletra regimen. Patients will continue to be studied for 1 year of treatment for pharmacokinetic and pharmacodynamic relationships and tolerability.

Three patients discontinued from the study prior to week 3 due to adverse events: fever, nausea and vomiting, asthenia (weakness), vomiting, and dizziness.

Kaletra Once Daily

Previously, a study in 38 treatment-naïve patients compared Kaletra (800/200mg) once daily to Kaletra standard dose (400/100mg) twice daily. After 72 weeks of therapy 74% in the once daily Kaletra group vs 58% in the twice daily Kaletra group had <50 copies/ml of viral load (ITT non-completer=failure). Because this study was small you can safely say the viral responses appeared comparable in this study. 2 of 19 patients in the once daily group discontinued vs 6 of 19 in the twice daily group. On average the Kaletra blood level was lower at the end of the dosing period (trough) for patients on the once daily regimen than the twice daily regimen. The drug level at trough is considered an important factor in predicting the long-term success of drug therapy. There were a number of individuals with lower troughs in the once daily group, while none of the patients receiving the twice daily regimen had low trough levels. Also, there may be more variability in Ctrough for patients on the once daily regimen.

Abbott reported at the IAS Conference July 2003 preliminary results from a small pharmacokinetics study in 190 HIV-infected treatment-naïve patients, examining if Kaletra blood levels are adequate using a once daily regimen. Patients were randomized to Kaletra, dosed with food (N=190) as 800/200 mg once-a-day or 400/100 mg BID, the standard dose of Kaletra. Each treatment arm also received tenofovir (300 mg) and FTC (200 mg). Both of these drugs are also taken once daily. 115 patients received Kaletra 800/200mg, vs 75 who received Kaletra 400/100mg. Average CD4 count was about 220, and avg viral load was 50,000 copies/ml.

Kaletra (LPV/r 800/200 mg) once daily produced a slightly higher LPV Cmax (peak drug level), similar AUC-24 (154.5 vs 182.2 µg.h/mL) and lower Ctrough (3.0 vs. 6.5 µg/mL) vs Kaletra (LPV/r 400/100 mg) twice daily. Viral load reduction from baseline to week 4 was similar for QD (-2.1 log) vs. BID (-2.0 log). Efficacy and safety of Kaletra (LPV/r) twice daily and once daily dosing will be assessed as study participants are followed for a longer duration of 48+ weeks in this study. Although the once daily regimen may work well in the treatment-naïve patients, one would have more concern for failure among the treatment experienced patients with PI resistant virus. Having a lower Ctrough may raise concern about developing resistance. One would like to know how the Ctrough levels of Kaletra once daily correlate with the IC90 and IC50 of the virus.

Tipranavir: New PI for Resistance

Tipranavir is a new protease inhibitor in large phase III studies, the last stage before the Food and Drug Administration reviews it for approval. So far in phase II studies this drug has shown itself to be effective in reducing HIV viral load and increasing CD4 counts for patients with high-level resistance to the currently available protease inhibitors. Tipranavir will be boosted with a low dose of ritonavir. Studies suggest that a number of PI mutations including primary PI mutations are required before a patient develops resistance to tipranavir.

The large phase III RESIST Trials are ongoing and the manufacturer, Boerhinger-Ingleheim, is conducting an expanded access program for patients unable to enroll in the RESIST Studies.

Results from a phase II study in 216 patients have been reported. Patients in the study had low CD4 counts and much PI resistance. To enter the study patients were required to be triple-class experienced failing 2 or more PI-based regimens; to have one or more primary PI mutations (30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M); but not more than one of 82L/T, 84V, or 90M. This study suggested that the L33F mutation may also be a major predictor of resistance along with 82, 84, and 90 mutations. The average CD4 count was 150 cells and the average HIV viral load was 30,000 copies/ml (range 400-2.6 million).

Genotypic and phenotypic resistance testing on study participants before they started tipranavir showed study patients had extensive resistance to currently available protease inhibitors, but not to tipranavir. This suggests that although patients in this study are resistant to protease inhibitors they should be responsive to tipranavir. Using the Visible Genetics Trugene Genotypic Test, patients had 27-fold resistance to Kaletra, 60-fold to amprenavir, 66-fold to saquinavir, 85-fold to indinavir, 95-fold to nelfinavir, and 86-fold to ritonavir. Using the Virco antivirogram assay to test for phenotypic resistance, patient samples were fully sensitive to tipranavir (1.1 fold) but had on average greater than 40-fold resistance to Kaletra, 8.7-fold resistance to amprenavir, 7-fold to saquinavir, 12-fold to indinavir, 37-fold to nelfinavir, and over 40-fold to ritonavir.

Study investigators reported viral load changes during the first 14 days of the study before background nukes were switched, which gives a better sense of the effect of tipranavir. Viral load was reduced by -0.87 to -1.18 log. After day 14, 20% of patients changed their background nukes. Researchers reported that at day 56 viral load reductions were maintained at about 1 to 1.2 log below baseline.

Of note, viral load reductions were similar for patients regardless of how many PI mutations they had until they had 20 or more PI mutations. All patients had at least 5 PI mutations. Patients were classified by whether they had 6-10 mutations, 11-15 mutations, 15-20 mutations, or greater than 20 mutations. Regardless of how many mutations patients had, on average the reductions in viral load from baseline were at least 0.8 log and ranged as high as 1.2 log, but only in the 500/200 and 750/200 dose groups.

10% of patients had grade 3/4 ALT lab abnormalities by day 28. But 14 of 19 patients who had grade 3/4 ALT elevations had grade 1 or greater elevation before starting tipranavir. 15% of patients had grade 3/4 elevations in triglycerides, but 0% had grade 3/4 elevations in cholesterol. 5% of patients discontinued therapy due to study drug related adverse events up to week 24.

Fosamprenavir: New Version of Amprenavir (Agenerase)

Fosamprenavir (908) is an improved version compared to the older formulation called amprenavir. The pill count is significantly reduced. 908 pills are 700 mg in contrast to 150 mg pills of the older version of amprenavir. 908 can be taken with or without food or fluid. The GI side effects from the old version were difficult and therefore reduced tolerability. The new version, 908, has much less GI side effects, as you will see from the study data reported below. Fosamprenavir has been studied in two large trials (SOLO and NEAT) in treatment-naïve patients, in which fosamprenavir was compared to nelfinavir. A third study (CONTEXT) examines fosamprenavir boosted with a low-dose of 200 mg ritonavir dosed once and twice daily and compared to Kaletra. The results from these studies are described below. The application for approval has been submitted to the FDAand approval is expected by the end of 2003.

These 3 studies illustrated several interesting points:
1) As seen with the use of Kaletra, GSK researchers found that none of the patients taking 908/r QD (0/32) who were evaluated in the resistance substudy of the SOLO study developed primary or secondary protease mutations, while 50% (27/54) of the patients taking NFV did develop primary or secondary protease mutations.
2) The viral response in the CONTEXT Study to 908/r (1400/200mg) twice daily was similar to Kaletra twice daily, but in these PI-experienced patients the 908/r once daily regimen appeared inferior. This study was designed as a non-inferiority study and the primary endpoint of the study was time-averaged change in viral load (AAUCMB). The FDA said that by the statistical endpoints at week 48 established for the study, 908/r BID or QD could not be proved to be non-inferior to Kaletra.
3) 908/r taken once daily (1400 mg 908 plus 200 mg ritonavir) appears to be an effective regimen in treatment-naïve patients based on the results from the SOLO Study, but in PI-experienced patients the CONTEXT study showed that twice daily 908/r and Kaletra regimens performed better than the 908/r once daily regimen.
4) In the NEAT and SOLO Studies 908 had less incidence of diarrhea than in patients taking nelfinavir, and GI related side effects for patients taking 908 were mild. Elevations in cholesterol were similar between nelfinavir and 908 (1400 mg twice daily) in the NEAT Study. LDL and total cholesterol increased similarly for both groups over the 48 week study, and triglycerides increased more for patients on nelfinavir than on 908. In the SOLO Study where 200 mg of ritonavir was added to 1400 mg of 908 there was an increased incidence of grade 3/4 triglycerides (6% for patients taking 908/r).

These studies are reviewed in detail below.

Recently, an ACTG study arm was prematurely discontinued due to strong drug interactions between Kaletra and 908. Further PK studies are in order before these two drugs may be given together.

CONTEXT Study (908 once or twice daily vs Kaletra)

The CONTEXT Study examines 908 once and twice daily boosted by low-dose 200 mg ritonavir in comparison to Kaletra twice a day in treatment experienced patients. This study was designed to see if 908 once or twice daily was not inferior to Kaletra (non-inferiority design). Study results were reported by press release from Vertex Pharma and by GlaxoSmithKline at the June Summer Summit community conference. The FDA said that in an evaluation of time-averaged change in viral load (AAUCMB), which was the primary endpoint of the study and now the standard measure used by the FDA for antiviral licensing, non-inferiority of 908/r BID and 908/r QD compared to LPV/r BID could not be established at 48 weeks. In an analysis of the proportion of patients with viral load below 400 copies/mL, 908/r BID (58%) and LPV/r BID (61%) demonstrated similar levels of antiviral activity. The proportion of patients who achieved vRNA below 50 copies/mLat 48 weeks was also similar in the 908/r BID (46%) and LPV/r BID (50%) arms.

In the CONTEXT Study PI-experienced 315 patients with current treatment-failure were randomized to:
- 908/r 1400mg QD plus RTV 200mg QD
- 908 700mg BID plus RTV 100mg BID
- Kaletra (lopinavir 400mg plus RTV 100mg BID)

Prior ART Experience
Researchers reported median duration of prior protease inhibitor use was 149 weeks in 908/r QD arm, 149 weeks for 908/r BID arm, and 130 weeks for Kaletra arm. Patients previously taking 2 or more protease inhibitors: 57% for 908/r QD, 49% for 908/r BID, and 40% for Kaletra.

Median duration of prior NRTIs: 234 weeks in 908/r QD, 257 in 908/r BID, 210 weeks in Kaletra group. Percent of patients previously taking 3 or more NRTIs: 70% in 908/r QD, 79% in 908/r BID, and 64% in Kaletra.

Median duration of prior NNRTIs: 87% in 908/r QD, 84% in 908/r BID, and 78% in Kaletra. Percent of patients previously taking 2 or more NNRTIs: 11% for 908/r QD, 14% for 908/r BID, 8% for Kaletra.

Overall, patients assigned to take Kaletra during the trial had slightly less experience with ART drugs.

Results
Mean Viral Load Reduction (AAUCMBs) at Week 48:
- 908/r QD: -1.49 log
- 908/r BID: -1.53 log
- Kaletra BID: -1.76 log

Percent of Patients <400 copies/ml (ITT Rebound or Discontinuation=Failure) at Week 48
- 908/r QD: 50%
- 908/r BID: 58%
- Kaletra BID: 61%

Proportion of Patients <50 copies/ml (ITT RD=F) at Week 48
- 908/r QD: 37%
- 908/r BID: 46%
- Kaletra BID: 50%

Reasons for Failure

	908/r BID	Kaletra
Viral Failure	27%	27%
• RNArebound	9%	17%
• D/C due to Protocol defined VF	8%	<1%
• never achieved VL suppression	9%	9%
Non-Viral Failure	15%	12%
• adverse events	5%	7%
• lost to followup	7%	3%
• consent withdrawn	0%	2%
• protocol violation	<1%	0%
• death	<1%	0%

NEAT Study (908 1400 mg twice daily vs nelfinavir twice daily)

In the NEAT Study, 908 without ritonavir given 1400 mg twice daily was compared to nelfinavir 1250 mg twice daily, and as evaluated by percent of patients <400 and <50 copies/ml 908 performed better.

The NEAT Study examined 251 ART-nave patients who received open-label 908 1400 mg twice daily vs nelfinavir 1250 mg twice daily. All study participants also received abacavir (Ziagen) 300 mg twice daily plus 3TC 150 mg twice daily. The patient population in the study was diverse: 25% white, 31% black, 43% hispanic. 55% of study participants were identified as contracting HIV by heterosexual contact, 39% as men who have sex with men, and 6-10% IDU.13% of patients had hepatitis C and 5% hepatitis B. The patients had fairly advanced HIV, as the average CD4 count was 212, and the average viral load was 66,000 copies/ml; 18% had <50 CD4s and 46% had HIV viral load >100,000 copies/ml.

Results

In this study efficacy was evaluated by how many patients had viral failure and non-viral failure (adverse events) for each study group. More patients taking nelfinavir experienced viral failure (28% vs 14%) by week 48. Viral load rebound was seen in 10% in the 908 group vs 14% in NFV group. 4% prematurely discontinued in 908 group vs 13% in NFV group due to insufficient viral load response. Patients taking nelfinavir had a higher incidence of diarrhea (18% vs 5%).

Non-virologic failure or discontinuation was equal for both arms (20% vs 21%). Failure due to adverse events was equal, 5-6% in each treatment group. Additional reasons for non-viral failure were lost to follow-up, consent withdrawn, clinical progression, death, other unidentified reasons, and missing data. There were no differences between the treatment groups.

Viral Load Response at Week 48

As you can see, a higher percent of patients receiving 908 than nelfinavir had <400 copies/ml (66% vs 51%) and <50 copies/ml (55% vs 41%). Patients with high viral load were more likely to achieve undetectable viral load with 908 than with nelfinavir.

Percent <400 Copies/ml at Week 48

(ITT: Intent-To-Treat – Rebound or Discontinuation=failure)

	908 1400mg BID	NFV 1250mg BID
All	66% (n=166)	51% (n=83)
<100,000 c/ml	65% (n=93)	63% (n=46)
>100,000 c/ml	67% (n=73)	35% (n=37)
>500,000 c/ml	65% (n=23)	31% (n=16)

Percent of Patients <50 copies/ml at Week 48 (ITT RD=F)

	908 BID	NFV BID
All	55%	41%
<100,000 c/ml	56%	54%
>100,000 c/ml	55%	24%
>500,000 c/ml	52%	19%

CD4 count increased about the same: 201 in 908 group and 216 in NFV group. Viral load decreased –2.32 log in NFV group and –2.41 in 908 group.

Drug-Related Adverse Events

Diarrhea:	18% taking NFV vs 5% taking 908
Drug hypersenstivity:	9% taking 908 vs 5% taking NFV
Rash:	7% taking 908 vs 2% taking NFV
Nausea:	5% 908; 4% NFV
Vomiting:	2% 908 vs 4% NFV

Fasting Lipids

There did not appear to be much difference between 908 and nelfinavir in their effect on cholesterol, but triglycerides increased more in the NFV group. HDL is "good" cholesterol; LDL is "bad" cholesterol.

Mean Cholesterol and Median Triglycerides Values (mg/dL)

	Baseline		Week 48		NCEPCut-off
	908	NFV	908	NFV	
HDL	37	36	49	44	39
LDL	86	89	119	122	100
Total chol	152	153	197	203	240
TC/HDL*	4.3	4.3	4.3	5.0	6.5
TG	150	154	151	200	200

*total cholesterol-HDLratio is used to evaluate cardiovascular risk

Grade 3/4 lab abnormalities were comparable between treatment groups: ALT 5-6%, AST 6%, triglycerides 0-1%, cholesterol 0%, glucose <1%-0%.

SOLO Study (908/r once daily in treatment-naïve)

In the SOLO Study 908 1400 mg plus 200 mg ritonavir taken once daily was compared to nelfinavir 1250 mg twice daily; as evaluated by percent <400 and <50 copies/ml, nelfinavir responses were better in SOLO than that seen in the NEAT Study, and 908 responses were similar to that seen in the NEAT Study.

606 treatment-naïve patients were randomized equally to 908 1400 mg plus 200 mg ritonavir once daily, or nelfinavir 1250 mg twice daily. All patients also received abacavir 300mg plus 3TC 150 mg.

About 27% of study participants were female; 51% of the total number of the participants were white, 38% black, 7% his-

panic. 7% had hepatitis B, 18% had hepatitis C. Patients in this study also had low CD4 counts. Average HIV viral load was about 63,000 copies/ml and CD4 count was 170. 20% had <200 CD4 count.

Results

In contrast to the NEAT Study there was less viral failure in this study in both study groups, 4% in the 908/r QD arm vs 15% in the NFV BID arm. This compares to 14% (908) vs 28% (NFV) in the NEAT Study. 3% had viral rebound in the 908/r arm and 7% in the NFV arm. 1% in the 908 arm never achieved viral load suppression vs 8% in the NFV arm. Patients taking nelfinavir were more likely to experience diarrhea (16% vs 9%). Premature discontinuations: adverse events 8% in 908 arm, 5% in NFV arm; lost to follow-up 6% in 908, 3% in NFV; consent withdrawn 5% 908, 3% NFV; other 5% 908, 3% NFV.

Resistance

It appears that, similar to findings reported regarding PI resistance in patients failing Kaletra, no protease mutations were found in patients experiencing virological failure on 908/r. A statistically significant difference between the 908/r and NFV arms was observed in terms of protease (0 vs 50%, p<0.0001) and RT (13% vs 56%, p<0.0001) mutations.

At the first time point checked 0/32 patients taking 908/r QD had a primary or secondary mutation detected vs 27/54 patients taking NFV. 4/32 (13%) of patients taking 908/r QD had 3TC resistance vs 30/54 (56%) taking NFV. 0/32 patients taking 908/r had abacavir resistance (K65R, L74V) and 2/54 (6%) taking NFV had abacavir resistance (2 K65R, 1 L74V).

Viral Load Response At Week 48

Nelfinavir (NFV) performed better in SOLO than in NEAT. In NEAT, the patients on NFV had 51% <400 copies/ml and compared to 65% in this study; and patients had 41% <50 copies/ml in NEAT compared to 52% in SOLO.

Percent <400 copies/ml at Week 48, (ITT missing=failure)

	908/r QD	NFV BID
All	68%	65%
>100,000 c/ml	66%	60%
>500,000 c/ml	71%	53%

Percent of Patients with HIV RNA <400 c/ml at Week 48 By Baseline CD4 Count (ITT m=f)

	908/r QD	NFV BID
All	68%	65%
<200 CD4	68%	62%
<50 CD4	69%	54%

Percent with HIV RNA <50 copies/ml at week 48, (ITT m=f)

908/r BID	56%
NFV BID	52%

CD4 increase was similar in both arms; an average of +396/ul cells for patients on 908/r and +385/ul for NFV.

Adverse Events (drug related of at least moderate severity)

Diarrhea: 9% on 908/r QD vs 16% on NFV
Nausea: 7% on 908/r vs 5% on NFV
Vomiting: 6% on 908/r vs 4% on NFV

There were no differences between treatment groups regarding other adverse events: fatigue, headache, increased ALT (2%), abdominal pain (2%), rash (2%).

Grade 3/4 Lab Abnormalities

Liver enzymes: ALT:	8% in both groups; AST: 6-7%
Triglycerides:	6% in 908/r QD group vs 2% in NFV group
Cholesterol:	<1% in 908/r group vs 0 in NFV
Glucose:	<1% in 908/r vs <1% in NFV group

Lipids

Fasting triglycerides: increased from mean levels of 150 mg/dL in 908/r patients at baseline to about 250 mg/dL at week 48. For NFV TG increased from 150 mg/dL at baseline to 200 mg/dL at week 48. NCEP cut-off is 200 mg/dL. The NCEP cut-off is the acceptable level.

Fasting total cholesterol: mean values increased the same for both groups from 150 mg/dl at baseline to about 220 mg/dLat week 48. NCEP cut-off is 240 mg/dL.

Fasting LDL (bad cholesterol): mean values increased the same for both groups from 100 mg/dL at baseline to about 125 mg/dL at week 48. NCEP cut-off is 160 mg/dL.

HDL Cholesterol: The NCEP cut-off is 40 mg/dL. At baseline, 40% taking 908/r and 32% taking NFV had >40 mg/dL; at week 48 75% taking 908/r and 69% taking NFV had >40 mg/dL. Above 40 mg/dL is good.

Kaletra vs Saquinavir 1000mg plus 100mg Ritonavir

As you can see there are a number of boosted protease inhibitor regimens being developed, and they all are being studied as once-daily regimens. At the IAS Conference in Paris in July two studies reported on using saquinavir/ritonavir twice daily and once daily. In both of these studies the currently available formulation of saquinavir was used. The studies used Fortovase but the twice daily study permitted a switch to Invirase if there was a tolerability issue. Roche has announced that they are developing a 500 mg capsule of Invirase rather than the current 200 mg capsules used for Fortovase and Invirase. Eventually, the 200 mg capsules are expected to be eliminated and the new 500 mg capsule will be substituted, once the proper studies are completed and the FDA approves it for use. Use of the new 500 mg capsule will reduce the pill count and make the regimens more convenient.

The Maxcmin2 Study compared Kaletra to saquinavir/ritonavir (1000/100 mg) in a cohort of 330 diverse patients. Both regimens were taken twice daily. About 27% of patients in the study were treatment-naïve, and 29% of the treatment experienced patients were PI-naïve. Only about 32% of the patients had failed PI regimens. Before starting the study HIV viral load on average was 25,000 to 40,000 copies/ml, and CD4 counts were 240 cells. 67% of patients previously used NRTIs, about 32% NNRTIs, and 52% protease inhibitors.

There was not much difference between the patients in the two treatment groups with regards to these baseline characteristics before starting the study.

After 48 weeks on the assigned treatment (ITT, switch=failure), 60% of the patients on Kaletra had <50 copies/ml vs 53% of the patients taking saquinavir/r. The risk of virologic failure was higher in the SAQ/r arm compared to the LPV/r arm in the ITT/exposed/switch≠failure (p=0.0009) analyses, but similar in the on-treatment analysis (patients who remained on assigned regimen).

The rates of failure appear to be driven by higher rates for switching regimens due to non-fatal adverse events in the saquinavir/r arm (7.8% vs 11.6%), and by patient choice/non-compliance (3% vs 8%). An analysis of changes in lipids (cholesterol, triglycerides) was not presented. The side effect profile in this study seems to be relatively similar between the two arms with the expected problems of diarrhea (mainly SAQ/r arm), bloating, and nausea (mainly LPV/r arm) predominating.

The lead investigator for the study, Mike Youle (Royal Free Hospital, London, UK) suggests the pill burden may have played a role in the difference in response rates between the two regimens, since there were eleven patients in the SAQ/r arm who opted not to take their randomised treatment versus 4 in the LPV/r arm. In addition, 47 subjects in the SAQ/r arm (27%) permanently switched to another therapy but only 3 of these were for virological failure (mostly for patient choice or non-compliance), and 22 patients (13%) on Kaletra permanently switched to another regimen. Since this was not a blinded study, the issue of pill burden could have played a part in explaining these findings. It is interesting to speculate whether the ITT analyses would be different if the new 500mg formulation of saquinavir had been used in this study. Several trials have shown that pill burden is a major factor in the willingness of patients to take particular regimens and much effort is being put into reducing the burden. However, we don't know for sure what effect pill burden had; patients may have switched due to SAQ/r being less tolerable.

A small observational study of 46 patients reported on the use of saquinavir/ritonavir once daily. The dose regimen was saquinavir 1600 mg boosted by 100 mg of ritonavir plus two nucleosides. Average CD4 count was 129 and HIV viral load was 109,000 copies/ml. The results are preliminary, as not too many patients have completed the study yet. At week 52, 19 patients were available to analyze viral load response and 55% had <50 copies/ml. The average viral load reduction was –1.78 log at week 52. The average CD4 count was 350. Nine patients interrupted treatment because of grade 1-4 adverse events. Grade 3/4 adverse events developed in 8 patients, and study investigators said it was probably treatment-related only in 2 (indigestion and diarrhea).

Tenofovir (Viread)

This drug was FDA approved almost two years ago but interesting new information has been reported. The drug is appealing because it is taken once daily by one 300 mg pill and is taken with or without food, making it convenient and easy to take. As well, the drug appears relatively tolerable for most patients. It has been used as a substitute for an NRTI in a protease inhibitor or NNRTI based regimen. For example, in the study described immediately below treatment-naïve patients received tenofovir plus 3TC and Sustiva while the other treatment group in the study received d4T plus 3TC and Sustiva.

Tenofovir is effective as a first-line regimen, and is effective in subsequent regimens. The drug can be effective for patients with nuke (AZT & d4T) experience and resistance. Tenofovir effectively reduces viral load until several AZT mutations are present (see resistance section below). Tenofovir has been shown to reduce viral load on average -0.6 log in treatment-experienced patients, and -1.5 log in studies of treatment-naive patients.

At the IAS Conference researchers reported 96-week results from Study 903 in 600 treatment-naïve patients, which show that tenofovir has sustained potent antiviral effect. The study results showed a similar renal (kidney) safety profile between the d4T and tenofovir regimens.

Resistance

The following information was found in looking at 333 patients in tenofovir Studies 902 and 907. Patients had extensive NRTI resistance (5 years of prior nuke experience). 71% of the patients had a "thymidine analog mutation" ("TAM" or AZT resistance mutations which may also cause d4T resistance: 41, 67, 210, 215).

- when no TAM or other mutation was present average patient viral load reduction was 0.8 log
- when 1 or 2 TAMS were present viral load reduction was 0.7 log
- when 3 or more TAMS were present plus the M41L or the L210W the viral load reduction was only 0.25. The presence of the 41 or 210 with 3 TAMS severely reduces antiviral response to tenofovir
- 3 or more TAMS are present without the 41 or 210 the viral load reduction on average was 0.7
- the following nucleoside analog mutations (NAMS) also appear to have an effect in reducing response to tenofovir: 39, 43, 208
- the presence of the K65R is a predictor of poor response to tenofovir. Up until recently the K65R mutation has been found in only 2-3% of patients. This percent may increase if abacavir and tenofovir are used more widely
- M184V, the 3TC mutation may marginally improve TDF response (about 0.1 log)

Resistance to tenofovir is not easily developed. When tenofovir is taken as part of a first-line regimen, if viral failure occurs the K65R mutation may emerge. At the Resistance Workshop (Mexico, July, 2003) researchers discussed several studies examining the implications of resistance to tenofovir and the K65R. Presence of K65R might lead to reduced sensitivity to some other NRTI's. Bear in mind that viral failure to AZT results in NRTI resistance and can reduce sensitivity to other NRTIs. In other words, regardless of which NRTIs are used in a first-line regimen resistance of some sort develops after viral failure. The resistance pattern, however, differs

depending on which drugs are used. Resistance to abacavir is associated with the K65R and the 3TC mutation M184V. In a study of treatment-experienced patients who received tenofovir six patients had the K65R mutation and did not respond virologically after receiving tenofovir. The K65R is also associated with reduced sensitivity to ddI. Preliminary research suggests that combining tenofovir with AZT might delay development of the K65R mutation. In sum, the presence of the K65R mutation can cause some level of cross-resistance between certain NRTIs.

Tenofovir Study in Treatment-Naïve Patients

In Study 903 the viral failure rate was low. In the tenofovir group 29 individuals (9.7%) and in the d4T group 25 individuals (8.3%) were virological failures. This regimen is potent, as evidenced by the table below, and includes two other potent drugs, 3TC and Sustiva. D4T was taken twice daily in this study but is now available once daily. Sustiva is taken once daily.

Viral Response at Week 96 (ITT, missing=failure)

	<400 cps/ml	<50 cps/ml
Tenofivir/3TC/EFV	82%	78%
D4T/3TC/EFV	78%	74%

CD4 benefits have also been similar in the two groups, increasing about 260 cells by week 96. There were no differences reported between the two treatment groups regarding study discontinuations (15%), grade 3/4 adverse events (22%), and grade 3/4 laboratory abnormalities; ALT elevations were reported in 5%. There were no differences between the tenofovir and d4T groups in terms of abnormalities in serum creatinine and phosporous through 96 weeks of study. There were differences in body changes and metabolic abnormalities between the d4T and tenofovir groups.

2% of patients taking tenofovir regimen developed grade 3/4 triglycerides elevations vs 11% in the d4T group. There was little triglyceride elevation on tenofovir but there was an average increase of triglycerides of 100 mg/dL on the d4T regimen. Total cholesterol increased about 50 mg/dl for the d4T group and 30 mg/dL for the tenofovir group. LDL cholesterol, increased about 20 mg/dL for the d4T group vs about 10 mg/dL for the tenofovir group. These differences were significant. Patients taking the d4T regimen were more likely to use lipid-lowering drugs (10% vs 2%). Peripheral neuropathy occurred in 10% of patients on the d4T regimen vs 3% in patients on the tenofovir regimen.

Presence or emergence of lipodystrophy was determined by the subjective opinion of the investigator. Lipodystrophy was reported for 12% of patients taking the d4Tregimen compared with 1% for patients taking tenofovir. 1% of patients taking d4T developed lactic acidosis vs 0% taking tenofovir. Researchers measured total limb fat at week 6 by DEXA and found significantly less limb fat in patients taking d4T regimen. Patients taking tenofovir gained on average 6 lbs, while patients taking d4T showed a 4 lb weight increase after 24 weeks but this decreased almost back to their original weight by week 96 for a net increase of 0.8 lbs.

In several studies tenofovir has been shown to be effective against hepatitis B virus, as it reduced HBV viral load (HBV-DNA). However, tenofovir is not yet indicated for the treatment of chronic HBV infection and the safety and efficacy of tenofovir have not yet been established in patients co-infected with HBV and HIV. Exacerbations of HBV have been reported in patients after the discontinuation of tenofovir. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping tenofovir treatment.

Bone Effects

In preclinical animal studies using high doses of tenofovir bone abnormality was observed. In study 903, patients were treatment-naïve. 25% had bone loss before starting HAART, suggesting that HIV may be associated with bone loss and that HIV-infected individuals may have more risk factors for bone loss. Patients taking either d4T or tenofovir had bone loss, but after 48 weeks on study drugs patients receiving tenofovir had more bone loss than patients taking d4T. In speaking with Gilead officials they said that bone loss plateaus after 24 weeks on therapy and remains plateaued. After week 48, bone loss remains stabilized and the data suggests it's beginning to reverse reverse towards levels before starting therapy. In the Fall of 2003 final 3-year results of Study 903 will become available, and bone effects of treatment will be analyzed and reported.

In study 903 through 48 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At 48 weeks, percent decreases in BMD from baseline (mean ± SD) were greater in patients receiving tenofovir + 3TC + efavirenz (spine, -3.3% ± 3.9 ; hip, -3.2% ± 3.6) compared with patients receiving stavudine + 3TC + efavirenz (spine, -2.0 ± 3.5; hip. -1.8% ± 3.3). The proportion of patients who met a protocol defined value of BMD loss (5% decrease in spine or 7% decrease in hip) was higher in the tenofovir group than the stavudine group. In addition, there were significant increases in levels of four biochemical markers of bone metabolism (serum bone -specific alkaline phosphatase, serum osteocalcin, serum C- telopeptide and urinary N-telopeptide) in the tenofovir group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels were also higher in the tenofovir group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. There was one bone fracture reported in the tenofovir group compared with four in the stavudine group; no pathologic fractures were identified over 48 weeks of study treatment. The clinical significance of the changes in BMD and biochemical markers is unknown and follow-up is continuing to assess long-term impact.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at substantial risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be considered for HIV-associated osteopenia or osteoporosis. If bone abnormalities are suspected then appropriate consultation should be obtained.

Tenofivir-Abacavir-3TC: Don't Use This Regimen

Recently reported results from 3 studies found a high viral failure rate of 50% when the 3-drug combination of abacavir, tenofovir, and 3TC was given to patients. The precise reasons are as of yet unknown but it's suspected to be because the K65R drug mutation is associated with viral failure to both abacavir and tenofovir. Studies to better understand the high failure rate are ongoing. The recommendation is not to use this regimen until further evaluation is completed.

FTC: 60 Week Study Results; FTC/ddI/Sustiva Once Daily

FTC or Emtricitabine, a NRTI, like AZT, d4T, and 3TC, was very recently approved to be used in combination therapy for HIV in the USA by the Food and Drug Administration, and will be available in pharmacies soon. Based on studies conducted so far, FTC appears to be a relatively safe and potent drug to be used as part of a combination HAART regimen. However, FTC is a sister drug of 3TC; if you have already taken 3TC and have resistance to 3TC, you will have resistance to FTC. FTC is taken as a one 200 mg pill once daily. 3TC is also available now to be taken as one pill taken once daily. If you have not taken 3TC yet, FTC is a treatment option as part of a regimen. FTC may be taken with or without food. In clinical studies FTC potency, safety, laboratory abnormalities, and tolerability appear similar to that of 3TC. Adverse events in studies, so far, appear to be of mild or moderate severity. Diarrhea was observed in 24% of patients; nausea was observed in 14% of patients.

In a 60-week study reported at the IAS Conference in Paris, and described in detail below, once daily FTC was compared to twice daily d4T. FTC had superior potency and fewer adverse events. In this study FTC was combined with two other drugs both taken once daily: efavrienz (Sustiva; one 600mg pill) and ddI. In another study, also described below, patients who were on a 3TC-containing regimen and who had undetectable HIV viral load (<400 copies/ml) switched off 3TC to FTC. After 48 weeks patients on 3TC or FTC did equally well.

Resistance

FTC has the same M184V resistance mutation as 3TC. Gilead Sciences, the manufacturer of FTC, reports that HIV blood samples from patients containing the K65R mutation selected by abacavir, ddI, and tenofovir showed reduced sensitivity to FTC. In other words if you use any of these 3 drugs first and acquire the K65R mutation you may develop reduced sensitivity to FTC.

In 14-day monotherapy studies of FTC for 100 HIV+ patients, HIV viral load was reduced by -1.5 to -1.9 log viral load in the blood. In vitro (in the test tube) FTC has demonstrated more potency than 3TC. Gilead reports FTC has a long half-life of about 10 hours in the blood resulting in steady state concentrations above the concentration needed to produce 90% inhibition (EC90) of HIV for up to 80 hours following dosing of 200 mg once daily. The steady state intra-cellular half-life, which may better reflect antiviral activity for nukes, is reported to be 39 hours compared to a reported 16 hours for 3TC. But these differences in vitro have not been firmly established to show superior viral suppression in patients.

FTC/ddI/efavirenz was a convenient, potent, and well tolerated once daily regimen with durable suppression of HIV through 60 weeks in this study. Results from a phase III study were reported at the IAS Conference in Paris in which 570 patients who had never taken HIV therapy before were taking FTC in a once daily regimen. FTC 200mg was taken once daily combined with efavirenz (Sustiva) taken once daily and ddI taken once daily. This regimen was compared to d4T taken twice daily, with the same drugs combined, Sustiva once daily and ddI once daily. The once daily FTC demonstrated superior suppression of HIV viral load and was better tolerated compared to twice daily d4T.

78% of patients receiving FTC arm vs 59% of patients in d4T group had <50 copies/ml. Viral failure rate was 11% in d4T group vs 3% in FTC group. Study discontinuation due to adverse event was 13% in d4Tgroup vs 7% in the FTC group. CD4 increase was 168 cells for FTC group and 134 for d4T. The incidence of the most frequent or relevant adverse events (all grades) was greater in the d4T group: diarrhea (34% vs 24%), nausea (24% vs 14%), neuropathy (13% vs 5%), symptomatic hyperlactatemia/lactic acidosis (3% vs 0%), parasthesis (12% vs 6%, p=0.023), abnormal dreams (19% vs 11%). The incidence of most of the other adverse events were comparabe in the d4T and FTC groups.

A study has been conducted to evaluate if patients on a fully suppressive HIV regimen with 3TC could switch to FTC. In previously reported study, patients were randomized to continue therapy with 3TC (150 mg bid) or to switch to FTC (200 mg QD). All patients were maintained on their stable background regimen. This was a 48-week open-label multi-center study comparing FTC to 3TC in combination with d4T or AZT and a PI or NNRTI in 440 patients who were on a 3TC containing regimen for at least 12 weeks prior to study entry and had HIV-RNA <400 copies/ml. Average baseline CD4 count was 527, and HIV viral load was 1.7 log (<50 copies/ml). Average duration of antiretroviral therapy (ART) was 27 months. After 48 weeks in study 67% in FTC group had <50 copies/ml vs 72% in 3TC group. Viral failure was 7% in FTC group and 8% in 3TC group. Study discontinuation due to adverse events was 4% in FTC group vs 0% in 3TC group. The side effects and lab abnormality profiles for FTC and 3TC appear similar.

TMC-114 and TMC-125

TMC-114 is a new protease inhibitor in early stages of development that is intended to be used by patients who have resistance to the currently available protease inhibitors. Results from ongoing studies in HIV-infected individuals with resistance to protease inhibitors show TMC-114 to be effective in short-term evaluation in these patients. TMC-114 was

given in a 14-day study to 50 patients who had experience with multiple protease inhibitors and PI-resistance. The average number of total protease gene mutations that patients in the study had was 15 (range 8-26); the average number of PI resistance-associated mutations was 6 (range 1-11), with an average number of primary PI mutations of 3 (range 0-5) (including D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V or L90M). Greater than 80% of subjects had more than one primary PI mutation.

TMC-114 was boosted by 100 mg of ritonavir and was looked at in this study as a twice or once daily regimen. The 50 patients had an average of 6 protease mutations and had extensive resistance. 46% of the patients were resistant to all currently available protease inhibitors. But patients had <2 fold resistance to TMC-114 before starting TMC-114 therapy in the study and after 14 days of receiving TMC-114 treatment. After 14 days the average viral load reduction for the patients in the study was -1.35 log. These study results are preliminary, and further studies are planned by Johnson & Johnson and Tibotec-Virco who are jointly developing both TMC-114 and TMC-125.

TMC-125 may be a next-generation NNRTI. Based on studies so far conducted, this drug appears to be promising for patients with resistance to NNRTIs, efavirenz and nevirapine. This new NNRTI is in dose ranging studies now, so they can decide upon which dose to use. TMC125 showed antiviral activity in patients with NNRTI resistance in a 7-day study, by reducing viral load by –0.89 log. 12/16 of the patients had 0.5 log or greater viral load reduction. 7/16 had >1 log viral load reduction. No serious adverse events were reported. In a laboratory study, TMC-125 was put into a test tube with viruses which were resistant to efavirenz and nevirapine. TMC-125 inhibited 80% of the viruses that were resistant. It appears as if TMC-125 will be studied as a firstline therapy for treatment-naïve patients, and for patients with NNRTI resistance.

Switch Studies for Lipoatrophy

Reported by Cecilia Shikuma, MD, University of Hawaii and the ACTG. Contribution by Jules Levin.

The MITOX and TARHEEL studies had previously presented short term data suggesting small improvement in subcutaneous fat as assessed by objective testing, DEXA(dual-energy x-ray absorptiometry) and mid-abdominal CTscans (cross-section computerized tomography scans), following NRTI switch to "more mitochondrial friendly" regimens. Much concern was voiced at that time as to whether such small improvements were clinically relevant and whether these improvements would continue to occur as time progressed. Andrew Carr, presenting for the MITOX Study Group presented 128 wk data on their subjects at the Lipodystrophy Workshop, 50 of whom had originally switched from d4T- or ZDV-containing HAART to abacavir (Ziagen) and 56 of whom had remained on d4T or ZDV in the original control arm but had been allowed to switch to abacavir after wk 24 of study. These patients had been on d4Tor AZTfor 6 years, and experienced a 50% loss in limb fat. Utilizing whole body DEXA, the original switch group continued to gain peripheral fat over the course of 2 years achieving a mean increase in limb fat of 1.26 kg from the original baseline of 3.7 kg (36%). The sole positive predictor of recovery found by these investigators was high BMI (body mass index). Interestingly, the gain in peripheral fat was primarily evident as leg fat with arm fat initially improving but then decreasing over this 2 year period. It should be noted that in the TARHEEL study, data at wk 48 in their 118 subjects who replaced d4T with either ABC or ZDV suggested that the most gain in peripheral fat, also assessed by DEXA, was in the arms rather than legs – median increases in actual (grams) and % change from baseline: arms (239, 35.3%), legs (269, 12.0%) and trunk (859, 16.4%). Neither group demonstrated increases in visceral fat. Facial fat loss and gain are more difficult to objectively evaluate, and were not evaluated in MITOX. In TARHEEL, patients were asked to self-assess body changes. After 48 weeks, the percentage of subjects reporting positive body changes for face, legs, arms, and buttocks were 27%, 20%, 22%, and 19%. The majority of the remaining subjects reported stabilization of their body fat. Similar to finding in MITOX, researchers found in TARHEEL that arm fat in DEXA before switching approached significance in predicting lipoatrophy regression. In other words, if you had less fat on your arms or were more skinny, you were more likely to develop fat loss.

The encouraging message in these 2 studies is that there appears to be continued improvement in subcutaneous fat gain over 2 years of followup. However this gain was modest and concerns remain as to whether full recovery is possible. Even if possible, it was suggested that recovery may perhaps take as long as it took to develop the lipoatrophy. Whether the favorable return in fat tissue will be seen over longer period of follow-up, and whether full reversibility will be possible in all patients or whether there is a "point of no return" are important future research questions.

Rosiglitazone Study For Lipoatrophy: Cautious Optimism

Written for NATAPby Michael Dube, MD, University of Indiana and the ACTG.

Preliminary study results, described below, suggest rosiglitazone may improve lipoatrophy (fat loss), but more study is needed. Ongoing studies may provide the answers.

Several studies have shown that the insulin sensitizers, antidiabetic drugs, metformin and rosiglitazone can improve insulin resistance. Metformin does not appear to improve lipoatrophy, but rosiglitazone might. In a recent study patients with HIV showed improved insulin sensitivity from rosiglitazone but no improvement in lipoatrophy (Yki-Jarvinen, ATVB 2003). Another study did indeed show improvement (Gelato M, JAIDS 2002).

At the Lipodystrophy Workshop, Colleen Hadigan from Harvard presented a placebo-controlled study of rosiglitazone in 28 subjects with lipoatrophy. In the initial 3 months of study, rosiglitazone was given at a relatively low-dose of 4 mg per

day or placebo. In the second 3 months rosiglitazone was given at a full 8 mg per day to all subjects (open-label phase). During the initial 3-month placebo-controlled phase, while total body fat increased as measured by BIA (generally considered to be less accurate than DEXA scanning) it did not increase by DEXA scanning. There was a non-significant trend for increased leg fat (arm fat was not reported due to technical difficulties). Subcutaneous fat (just beneath the skin) in the abdomen increased compared to placebo. Subcutaneous fat just below the skin in the abdomen may reflect fat changes in the periphery. Subjectively there was improvement in fat loss with rosiglitzone. But there was no significant increase in leg fat or total body fat by DEXAscanning in the open-label phase either. Rosiglitazone also increased cholesterol levels and adiponectin levels. Pioglitazone is in ongoing studies for lipoatrophy in Europe, and preliminary information is that it does not increase cholesterol levels. Adiponectin is a hormone known as an "adipocytokine" that is produced by fat cells and improves insulin sensitivity. So, increases in adiponectin are generally thought of as being "good" and decreases in adiponectin (such as has been reported by several groups, including Khatami [abstract 44], that are seen with central obesity and loss of peripheral fat) are "bad" because insulin resistance worsens and cardiovascular risk increases.

This study gives some hope that rosiglitazone might reverse fat loss but is certainly not definitive. This study enrolled patients who were insulin resistant and findings suggest lipoatrophy may improve due to taking rosiglitazone. The Yki-Jarvinen study did not enroll patients with insulin resistance and lipoatrophy did not improve. Taken together, these findings suggest rosiglitazone may only improve lipoatrophy in patients with insulin resistance. Again, larger studies are needed, but I think it would be fair to say that if there is benefit from rosiglitazone in lipoatrophy, its benefits are likely to be relatively small overall. More information is needed to determine who is likely to benefit from it most. Ongoing studies in Australia and the ACTG may eventually clarify some of these issues.

Risks Associated With Getting Infected With HIV Today

- *10% Rate of HIV Drug Resistance in Newly Infected: genotype resistance testing suggested for newly infected*
- *Super-Infection*
- *Persistence of Drug Resistant Virus*

Two studies reported recently at the Resistance Workshop on the rates of transmission of HIV drug resistance in individuals newly infected with HIV. One study reported on the rates in the USA and the second study reported on Western Europe. Individuals are infected with HIV primarily by sex or by injection drug use (IDU). A worrisome study reported that newly transmitted drug resistant virus can persist for a few years after an individual is infected. Response to HAART may be impaired if a person is infected with a drug resistant virus. Related to this were studies reported at the Resistance Workshop on the risk for getting super-infection. Super-infection occurs when a person with HIV is infected with a second but different strain of HIV. These studies and others suggest that even if you already have HIV it's still possible that by unsafe sex or sharing a dirty needle that you can get infected with a second strain of HIV. You can be super-infected with HIV that is drug resistant or may be more virulent. The studies suggest that the chance for being super-infected may be greater through sharing needles by IDU because infected blood flows directly into the blood stream of another person. HIV infection by sex may be more difficult because HIV has to pass through the mucous membrane and other barriers. All in all, these studies suggest getting HIV today presents several serious concerns. The worst case scenario is engaging in unsafe sex or sharing a dirty needle can result in a 10% risk of getting HIV which is resistant to HIV drugs; this drug resistance may persist for several years and then may remain below the surface and may impair response to HAART.

CATCH Study: Transmission of Drug Resistance in Europe

CATCH Study researchers reported at the IAS Conference that primary drug resistant mutations were detected in 9.6% of antiretroviral naive individuals. Regarding individual classes of HIV drugs, 6.9% had resistance to NRTIs, 2.6% had resistance to NNRTIs, 2.2% had resistance to protease inhibitors, and 1.7% had resistance to 2 or more classes of HIV drugs.

The reported frequency of transmitted drug resistance varies widely in different areas of the world or even in different cities in the USA. The CATCH Study (Combined Analysis of resistance Transmission over time of Chronically and acute infected HIV patients in Europe) combines results from 1,633 newly diagnosed patients from 17 countries in Western Europe with the aim of assessing the prevalence of primary drug resistance.

RT (reverse transcriptase) and protease sequences and clinical information was analyzed from 1,633 newly diagnosed (recently and chronically infected) patients. The prevalence of resistance was assessed over the period of 1996-2002 based on the IAS resistance table (March 2003). Interpretation of genotypic resistant profiles was performed with the use of Retrogram.

The prevalence among patients with seroconversion in the previous year was 10.9% versus 7.5% in patients who had been infected for over a year (p=0.06). The prevalence of resistance was significantly higher in subtype B (11.3%) than in non-B subtypes (3.3%); Odds Ratio=3.72.

Reduced sensitivity to HIV drugs was found in patients infected with resistant virus. Interpretation of genotypic resistance profiles showed reduced susceptibility for NNRTI in 26% of the patients with NNRTI resistant viruses. For NRTIs reduced susceptibility ranged from 17% for 3TC to 47% for AZT, over 40% for d4T, 20% for abacavir, and 30% for tenofovir. Reduced susceptibility to protease inhibitors ranged from 10% for saquinavir and saquinavir/ritonavir, 22% for nelfinavir, 12% for Kaletra, 21% for indinavir, and 12% for amprenavir/ritonavir.

Study authors concluded:
1) The prevalence of primary drug resistance is 10% in Europe.

2) Drug resistance was predominantly found among patients infected with subtype B (the prevalent type in the USA), due to longer history of treatment of patients carrying these viruses. The original source for subtype B virus is outside the USA and Europe.

3) However, transmission of drug resistant non HIV type B is occurring

4) Once transmitted, mutations may persist for prolonged periods of time. The small difference observed between acute and chronic infections confirms that mutations may persist.

5) The high prevalence of resistance indicates that baseline sequencing should be considered in newly diagnosed patients.

Transmission of Drug Resistant HIV in the USA

A study was reported by the Centers for Disease Control (CDC) at the Resistance Workshop on the "Prevalence of Mutations Associated with Resistance to Antiretroviral Drugs among Treatment-Naive Men and Women Newly Diagnosed with HIV in Ten Cities in the USA, 1997-2001" and this study found that 11.5% of recent infections were resistant to an HIV drug.

Previously a study reported and published by Susan Little (University of California at San Diego) looked at rates of transmission of drug resistance among men who have sex with men. The CDC study presented in a poster by DE Bennett looked at a more diverse group of 1,082 individuals: 46% Black, 27% White, and 22% Hispanic. 44% were heterosexual, 46% MSM, and 10% IDU. 19% had recent HIV-infection. The study examined 10 cities: San Francisco, San Diego, Denver, New Orleans, Miami, Grand Rapids, MI, Detroit, NYC, and Newark. In addition to the different patient population from Little's study, the cities are different than that which Susan Little examined in her study. These patients were newly diagnosed within the past 12 months. Recent HIV infection was defined as occurring within 4-6 months.

Prevalence of drug resistance among those tested for recent infection: 11.5% of recently infected were resistant to any drug, 8.8% to NRTI, 3.9% to NNRTI, 2.8% to PI, and 3.9% to 2 or more classes of drugs. Among those tested for recent infection but not recently infected the rates of resistance were lower: 7.4% were resistant to any drug; 6.1% were resistant to NRTI, 0.9% to NNRTI, 1.8% to PI, and 1.0% to 2 or more classes of drugs.

A look at trends since 1997 show an increase in the first few years and suggest perhaps a leveling off in more recent years. In 1997-98, 7.7% (n=39) of recent infections had drug mutations associated with resistance; in 1999 the rate was 12.5%, and in 2000-2001 it was 12.7%. Bennett and Little both feel these rates are likely to increase as more individuals exposed to drug resistant virus are captured in these studies.

Among men with drug resistance the rate increased from 4.4% in 1997-98 to 11% in 1999 and 10.2% in 2000-2001 (p=0.04). Among women 6% had drug resistance in 1997-98, 6.3% in 1999, and 5.3% in 2000-2001. These changes were not significant. MSM were more likely to have drug resistance (11%) than IDUs (8%), and heterosexuals (5%). Whites were more likely to have drug resistance than Blacks and Hispanics. These differences might reflect less access to health care and appropriate drug treatment, access to support for adherence, and access to support for risk reduction.

Amongst women, IDUs were more likely to have resistance than heterosexuals; Whites were more likely to have resistance than Blacks and Hispanics, but these differences were not significant.

Transmitted Drug-Resistance Persists

Susan Little reported at the Resistance Workshop on the persistance of transmitted drug-resistant virus among individuals with primary HIV-infection who deferred antiretroviral therapy. Ten subjects were identified an average of 55 days after their estimated date of HIV-infection. The average follow-up on these patients was 242 days (range 64-1019 days). The average HIV viral load was a high 340,000 copies/ml. Average CD4 count was 489. 9 of the patients had NNRTI mutations; 7 patients had the 103N mutation; 3 patients had NRTI mutations, they had a number of key NRTI mutations; 3 patients had protease inhibitor mutations, and 2/3 of these patients had numerous PI mutations. Of note, only 1 patient lost their mutation.

Little concluded that transmitted drug resistant mutations in all ARV classes persist for more than a year after HIV-infection. These mutations may last for a long time, perhaps 3 years or longer. But when they are no longer detectable by commercial resistance tests they are likely to remain at levels below detection. In addition, the mutations may remain longer in genital secretions than in blood, which may promote transmission of drug-resistant virus through sex.

News from 2003 CDC Prevention Conference: July 28, 2003, Atlanta

"Although we've made great progress in preventing HIV since the early days of the epidemic, new and significant challenges remain," Ronald O. Valdisseri, deputy director of the CDC's National Center for HIV, STD, and TB Prevention. Following are highlights reported at the Centers for Disease Control Prevention Conference in Atlanta, July 28, 2003.

Those most at risk for infection: People of color, young teens, drug users, and gay men who meet sex partners online.

Between 850,000-900,000 persons are living with HIV in America, one-quarter of whom are unaware of their infection. 20% of African-American and Latinos are not aware that effective HIV treatments are available -- suggesting more

needs to be done to raise awareness, since the promise of effective treatment could encourage people to get tested.

HIV from injection drug use has increased by 15% in youth and young adults, with the greatest increase in the 13 to 15-year-olds. This increase follows years of steady declines, and points to the need for preventive education efforts aimed at young injection drug users.

73% of African-American women do not believe they are at risk for HIV, although more than half had a history of other STDs.

CDC research with women of childbearing age shows that reducing mother-to-child HIV transmission, a major goal of the new CDC prevention initiative, in part depends on increasing awareness of the need to be tested and on availability of treatment if results are positive.

In two separate CDC surveys of recently pregnant women, greater than 20% of pregnant women are still not being tested for HIV, despite the recommendation that testing be part of prenatal care. Another CDC study found that 40% of American women of childbearing age are not aware of methods to protect newborns from HIV. The CDC said that knowing that effective treatments are available could motivate more women to be tested during pregnancy.

Foreign-born women are more than twice as likely to refuse HIV testing as women born in the U.S.

"Thanks to the availability of treatment regimens to prevent transmission, the number of infants born with HIV has fallen dramatically," Valdisseri said. "However, newborns still contract HIV from their mothers each year, a preventable tragedy."

The number of women tested in New York State rose dramatically in 2002 from 64% to 94%. Rapid HIV testing can provide accurate results in just over an hour for women whose HIV status is unknown when they enter labor. This allows the doctor to introduce treatment to the newborn before transmission. CDC researchers presented study results at the conference showing that a brief training session for healthcare workers can enhance interpretation of results of the new OraQuick rapid test. Healthcare workers without previous laboratory experience more accurately interpreted results after a 20-minute training session than health care workers who had only the manufacturer's written instructions to follow.

Partners of HIV-infected persons need better counseling, Valdisseri said. HIV-positive patients are often not counseled on ways to prevent transmission to their partners. Among those surveyed following a clinic visit, one-quarter said they had received general prevention information during the visit, and only 6% said specific sex activities had been discussed with them. Even a one-day training session could help HIV treatment providers talk with their patients about reducing risk behavior. Those who took part in the session said they felt more comfortable discussing high-risk behavior, including needle sharing and sexual behavior, with their patients.

New research indicates the internet is a new environment for unsafe sex. Among gay men, the numbers who met partners online are increasing. More than three-quarters of gay men who meet partners online are likely to report high-risk sex with those partners. 39% reported having unprotected anal sex with those partners.

New HIV diagnoses among gay and bisexual men in some states increased for the third consecutive year, the Centers for Disease Control and Prevention (CDC) announced. CDC also released preliminary 2002 data showing a slight increase in AIDS incidence, although AIDS deaths continue to decline.
Data from 25 states (* see below) with long standing HIV reporting show the number of new HIV diagnoses among gay and bisexual men increased by 7.1 percent, from 2001 to 2002, supporting recent findings that this population remains at high, and perhaps increasing, risk for HIV infection. HIV diagnoses for gay and bisexual men have increased by 17.7% since the lowest point in 1999. The data also show that HIV diagnoses in other vulnerable groups have remained stable since 2001. Earlier in the year at the Retrovirus Conference the CDC reported that among heterosexuals, HIV diagnoses rose 10%, from 4,973 to 5,468. The CDC cautioned that the new data reflect the number of people newly diagnosed, regardless of when they were infected, and increases may reflect increases in HIV testing as well as potential increases in new infections. The survey didn't include some states with high HIV prevalence, such as New York and California, so data may not be representative of a nationwide spike.

"These findings add to the growing concern that we are facing a potential resurgence of HIV among gay and bisexual men," Dr. Howard Jaffe, Director of the CDC said.

Dr. Jaffe also presented preliminary 2002 data on AIDS diagnoses and deaths in the United States. These data show a 2.2% increase in new AIDS diagnoses (42,136 diagnoses) and a 5.9% decline in deaths (16,371 deaths). The findings suggest a continuing plateau in the dramatic progress against AIDS following the introduction of highly active anti-retroviral treatment (HAART) in the mid-1990s. The lack of continued progress in reducing AIDS diagnoses is likely due to several factors, Dr. Jaffe said, including treatment failure, difficulty adhering to complex regimens, and late HIV diagnoses delaying initiation of treatment.

"The AIDS epidemic in the United States is far from over," Dr. Jaffe said. "While effective treatments are crucial in our fight against HIV, preventing infection in the first place is still the only true protection against the serious and fatal consequences of this disease." Dr. Jaffe also emphasized that CDC's Advancing HIV Prevention Initiative, focusing on HIV testing as a routine part of care, greater access to HIV testing, increased attention to prevention among people living with HIV, and reduced mother-to-child transmission, will help address these continued challenges.

* Alabama, Arkansas, Arizona, Colorado, Idaho, Indiana, Louisiana, Michigan, Minnesota, Mississippi, Missouri, New Jersey, Nevada, North Carolina, North Dakota, Ohio, Oklahoma, South Carolina, South Dakota, Tennessee, Utah, Virginia, West Virginia, Wisconsin, Wyoming

Internet and Sex: Opportunity for Prevention Messages

In a study reported at the Retrovirus Conference researchers found that the internet may play a role in HIV transmission. In the survey of 2,934 men who have sex with men and who frequent chat rooms on a general interest Web site, 84% said they met sex partners online and were more likely to have unprotected anal sex (UAS) than those who met partners in other ways (64% vs 58%, p=0.02). Most HIV+ men (80%) had HIV- partners and were 1.4 times more likely to report UAS than HIV- men.

Of the 10 men diagnosed with syphilis during the 6-month period, 9 met sex partners online and 4 reported being HIV+. Overall, 43% reported any illicit drug use and 34% reported drinking until drunk 1-3 days per week.

The study was conducted in June-July 2002 and participants completed an anonymous 6-item online questionnaire about sexual, drug- and alcohol- using behaviors during a recent 6-month period.

Similar to other high risk venues of the 1970s and 1980s (e.g., bath houses and back rooms), the internet appears to be a setting in which to meet new sex partners and potentially transmit HIV. The success in rapidly recruiting a large number of men reporting very high-risk sexual behavior from a single internet site suggests that this recruitment method can also be used to provide urgently needed safer sex messages.

Unsafe Sex is Common Among HIV-Infected Prisoners Shortly After Release

Study shows 31% of released prisoners infect their main sex partners with HIV

As many as 20% of HIV-infected persons in the U.S. enter and leave a correctional facility each year. To what extent HIV-infected prison releasees contribute to the spread of HIV in the communities to which they return is not well described. The author of the study, David Wohl, MD (University of North Carolina), noticed that there are many communities within the US in which the HIV infection rates and the incarceration rates are high.

This study found that immediately following prison release a significant proportion of HIV-infected former inmates engage in high-risk behaviors that may play a significant role in the transmission of HIV within the communities to which they return. There is an urgent need for the development of interventions to reduce HIV transmission risk behaviors of HIV-infected releasees.

The study was done in North Carolina, a state that does not perform mandatory testing for HIV infection upon entry into or exit from prison.

Over half (51%) of HIV-infected releasees stated they had sex soon after being released from prison. 64% of releasees said their main sex partner from before imprisonment did not have HIV; 24% of releasees reported having sex with their main partners soon after release. Half of the releasees were women.

At follow-up interviews after release from prison, 26% had already had unprotected sex with their main sex partner, Dr. Wohl reported. The average time between release and having sex was 6 days.

All of the subjects said they had told their main sex partners that they were HIV-infected, but only two thirds had told their other sex partners. Thirty percent of the subjects reported they believed it was "very likely" or "somewhat likely" that they would infect their main sex partner.

This was a prospective observational study. From May 01-Oct 02, 80 HIV-infected state prison inmates within 3 months of release were enrolled. Subjects were interviewed prior to release about pre-incarceration and expected post-release sexual and drug-related HIV transmission risk behaviors. Follow-up phone interviews were conducted 30-60 days following release. The average prison stay was about 1 or 2 years.

Of the 80 subjects enrolled (58% women, 87% non-white, 81% heterosexual, mean age = 36 yrs), 83% have been released. Pre-incarceration crack cocaine use was reported by 84% of subjects and 29% had injected drugs. Since release, 16% reported using street drugs at least once a week, 18% have used crack cocaine, and 8% have injected drugs. Post-release interviews have been conducted in 85% of those eligible an average of 36 days following release. Within 6 months of release, 2 subjects died and 4 were re-incarcerated.

Prior to incarceration, 74% of inmates had a main sex partner with whom 79% report unprotected sex during the year before incarceration (54% of main sex partners were HIV-uninfected). 75% of inmates had other sex partners in the year prior to incarceration (average number of other sex partners = 12, range 1 to 1,460) and 74% had unprotected sex with their other sex partners in the year before they entered prison (64% of the other sex partners were HIV-uninfected).

Results from Treatment Interruption Study by the NIH

Patients in this study who took structured treatment interruptions did not show benefit. Some of these patients experienced HIV drug resistance, no clear improvement in cholesterol or triglycerides, and had viral load rebound. This is one of a number of studies demonstrating the risks associated with treatment interruptions or drug holidays.

Researchers at the National Institutes of Health conducted a study to evaluate structured treatment interruptions. 50 patients were randomly assigned to receive HAART continu-

ously or to receive cycles of HAART for 8 weeks followed by 4 weeks without HAART. Patients were to receive 7 cycles of 4 weeks without HAART followed by 8 weeks with HAART, but the study was terminated prematurely because of the emergence of HIV drug mutations associated with resistance to HAART drugs in 5 patients. It has been suggested that repeated "autoimmunization" cycles (exposure to HIV sandwiched between HAART use) could ultimately lead to control of viral load during extended discontinuation of HAART. Results from other studies have suggested autoimmunization might be possible but study results have been inconsistent and have discouraged researchers from thinking this may be possible. Although this study was not designed to evaluate the potential role of autoimmunization in the control of levels of plasma HIV RNA, the data suggest that multiple interruptions of HAART do not result in immunological control of levels of plasma HIV RNAin patients with chronic HIV infection.

HIV-infected patients with a CD4 count >300 cells who were receiving at least a 3-drug HAART regimen with HIV viral load levels <500 copies/ml for >6 months and <50 copies/ml during screening were eligible for enrollment. Patients could not have a treatment history consistent with drug resistance; however, individuals who had received antiretroviral drugs before initiating HAART were eligible for inclusion in the study.

Drug Resistance
HIV drug resistance was found in patients taking interruptions whether they received an efavirenz or a protease inhibitor regimen, but there was no evidence of drug resistance in patients who received continuous HAART. Three of the 5 individuals in the interruption arm with evidence of emergence of resistance had received suboptimal therapy with antiretroviral drugs before the initiation of HAART.

New enrollment was terminated as a result of evidence for newly emergent resistance in 3 of 8 patients in the intermittent arm receiving an efavirenz-based regimen. Two patients had both K103N, which is associated with resistance to efavirenz, and M184V, which is associated with resistance to lamivudine, genetic mutations during the fourth or sixth cycle without HAART that were not present during previous cycles of SIT. One patient had an M184V mutation during the fourth cycle without HAART not present during previous cycles of SIT. Two patients randomly assigned to SIT who received a protease inhibitor based regimen had evidence of emergence of mutations associated with resistance to nucleoside reverse-transcriptase inhibitors during cycle 2 without HAART; one patient had an M184V mutation and one had a T215Y (AZT) mutation.

Viral Load
5 (26%) of 19 patients receiving long-cycle intermittent HAART and 2 (9%) of 22 patients receiving continuous HAART had plasma HIV RNA levels >50 copies/mL at week 48. Since the study was supposed to last 92 weeks, this question could not be evaluated because the study was prematurely terminated.

Lipids
There was no significant difference between patients taking interruptions or continuous HAART before starting the study or after 48 weeks of the study with respect to lipids (total cholesterol, triglycerides, and LDL cholesterol).

Liver Enzymes
Certain antiretroviral drugs are known to cause significant elevations in hepatic enzymes in HIV-infected individuals. Therefore, the effects of long-cycle intermittent therapy on serum levels of ALT or AST were evaluated. There were no significant differences in levels of ALT and AST in patients receiving intermittent versus continuous HAART determined at baseline or week 48.

The study authors concluded that there was a lack of clear benefit in terms of virologic and immunologic effects, and multiple markers of toxicity, after 48 weeks of structured treatment interruptions versus continuous HAART. The emergence of genetic mutations in HIV that are associated with resistance to antiretroviral drugs led to the premature termination of new enrollment in the study. Potential benefits to long-cycle intermittent therapy should be weighed against this risk. A reduction in markers of toxicity, such as lipids and liver enzymes, is one of the major reasons for patient and clinician interest in treatment interruption approaches. Therefore, the lack of an improvement in the patients taking interruption versus the continuous HAART groups in these levels at 48 weeks may be important for assessing the relative advantages of interrupting therapy.

Hepatitis C and B are Treatable

The NATAP Hepatitis Treatment Education Programs provide community workshops and forums throughout the USA, including its home, New York City. NATAP programs have been held in 12 cities throughout the USA in the past 10 months for over 4,000 individuals. Trainings are attended by health professionals, community service providers, and patients. NATAP HIV and hepatitis education programs are provided in English and Spanish. NATAP also provides printed hepatitis handbooks and the new NATAP Hepatitis C Review quarterly newsletter. Printed materials and forums are provided in Spanish and English, and all of our programs and services are provided free of charge. Please call NATAP to receive literature for you and your community-based organization and to inquire about our community education programs.

Unlike HIV, based on everything we currently know HCV is considered "curable" when successfully treated. Rates for successful treatment are described below.

Perhaps the biggest challenge today in HIV is hepatitis, both in the USA and in Europe. But hepatitis can be successfully treated. A number of studies suggest that the hepatitis C virus (HCV) is now the leading cause of death in HIV. 30% of the approximate 900,000 HIV-infected individuals in the USA have hepatitis C, and 7-10% have hepatitis B. In HIV clinics in Spain, I have been told by doctors that 80% or more of

patients have HCV. The prevalence of Hepatitis C is high among patients in methadone clinics and substance abuse facilities. HCV and hepatitis B (HBV) may be absent of perceived in symptoms until late stage disease, although some individuals experience a reduced quality of life (less vitality, and reduced social and work functioning). Therefore, everyone with HIV should be tested for HBV and HCV, particularly if there is a history of injection drug use or sex with someone who may have used injection drugs. Of note, it's estimated that 60-90% of individuals HIV-infected by injection drug use have HCV. Again, HBV as well as HCV can be successfully treated. The standard of care for hepatitis C is pegylated interferon plus ribavirin. There are several drugs available for treatment of HBV, including lamivudine (3TC), adefovir, and interferon. Although it's not approved by the FDAfor treatment of HBV, tenofovir has been shown in several small studies to have similar efficacy as adefovir against HBV. Entecavir has been shown to be potent and effective against HBV and is in the final stages of development. Large phase III studies are in progress, and the drug is expected to soon become available for treatment of HBV. Additional drugs are in earlier developmental stages for the treatment of HBV.

HIV can accelerate both HCV and HBV disease progression. Although it can take a number of years for a person with HCV or HBV monoinfection to experience disease progression, studies show that co-infected individuals with HIV and hepatitis can have hepatitis progression accelerated at least 2 times faster.

If a person has hepatitis they should consult with a doctor who specializes in treating hepatitis. Most HIV doctors do not specialists in hepatitis, and so should refer theirs patients. Certain diagnostic tests are recommended for the HCV-infected person. An HCV genotype (a blood test), HCV viral load, and a biopsy are all important diagnostic tests. Of note, liver enzyme values (ALT and AST) are not very reliable in assessing the stage of liver disease: the liver biopsy is the most effective in assessing the stage of liver disease. As well, the ultrasound imaging test is not used to identify the stage of HCV disease, but is used to detect more advanced liver disease.

Transmission of Hepatitis

HCV is transmitted by blood to blood contact. The main source for transmission of HCV is sharing dirty needles (needles infected with HCV), and sharing drug use paraphernalia including cookers, water, cotton, and tourniquets. HCV can be transmitted sexually but the risk is low. However the risk for sexual transmission of HCV increases under certain circumstances: when sex partners have a STD, herpes or open sores; risky sexual behavior like fisting and anal sex; sex during menstruation; when a person has multiple sex partners. The results of two studies suggest increased risk for sexual transmission of HCV among men who have sex with men. HBV can also be transmitted sexually and by sharing IV drug paraphernalia. Although unproven, it is suspected that sharing straws to snort drugs such as cocaine may facilitate transmission of HCV. HCV and HBV can be transmitted from pregnant women to newborns, but if a woman has HIV the risk for HCV transmission has been found in studies to increase 3 times.

Treatment

Interferon-based therapy is the treatment for HCV and the most effective therapy is combination therapy of pegylated interferon plus ribavirin. Pegylated interferon is a once weekly subcutaneous injection. Ribavirin are pills taken twice daily. There are two pegylated interferon drugs and two ribavirin drugs available. The results of 3 large studies in a total of about 3,000 HCV monoinfected patients show 54-61% achieve a sustained viral response (undetectable viral load) after 6 or 12 months combination therapy and 6 months of follow-up. Normalization of elevated liver enzymes usually accompanies a sustained viral response. Adherence of 80% or more has been shown to significantly increase response rates by as much as 50% for genotype 1 and 15% for genotype 2 and 3. Patients with HCV genotype 2 or 3 responded much better to therapy in these studies than patients with genotype 1. 80% of patients with genotype 2 or 3 achieved a sustained viral response, while 41-56% of patients with genotype 1 achieved an undetectable viral load.

Studies in HCV/HIV co-infected patients suggest that on average response to pegylated interferon plus ribavirin combination therapy is lower than in monoinfected patients. Of note, the only way to tell if a given individual will respond to therapy is to initiate treatment. After 12 weeks on therapy for the HCV monoinfected patient, if there is a significant reduction in viral load (at least 2 logs), then he has a good chance to achieve a sustained viral response. But if the patient shows little viral response (<2 log reduction in viral load) within 12weeks after starting therapy they are unlikely to achieve an SVR and can consider stopping therapy. This finding has not been confirmed in co-infected patients, as studies suggest that co-infected patients may respond slower to therapy. As well, a number of studies suggest that interferon may slow HCV disease progression, even if viral load does not decline. If the goal of therapy is to slow progression, as when a patient has stage 3 or 4 disease (transition to cirrhosis or cirrhosis), continued interferon therapy may be helpful for some patients. This is called Maintenance Therapy. Slowing progression of HCV may keep a patient alive and healthy enough to benefit from new HCV drugs being developed now for use in about 4 years.

Therapy for HCV can be difficult to tolerate. A constellation of side effects and toxicities can occur including anemia, fatigue, irritability, depression, and loss of appetite. Since HIV can accelerate HCV progression by at least 2 times faster than in HCV monoinfected patients, therapy may need to be started earlier in disease progression for HCV/HIV co-infected individuals. Therapy is time limited, 6-12 months. A monoinfected patient with genotype 2 or 3 may only require 6 months of treatment. Genotype 1 in monoinfected calls for 12 months therapy. The HCV/HIV co-infected patient should be treated for 12 months.

As mentioned above, it appears as though HCV is "curable", based on everything we now know. Studies in HCV monoinfected patients show that 95% of patients who achieve a sustained viral response following 6-12 months therapy plus a 6 month follow-up period have maintained undetectable viral load for as long patients have been followed, which is up to 11 years of follow up.