NATAP'S NATIONAL AIDS TREATMENT ADVOCACY PROJECT

POSITIVE + INFORMATION

Production by: **Jessie Gibson**
Josh Weisbrot
Prepaired and Published by :
Jules Levin

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

Summary of Highlights From Fall 2001 HIV Conferences

Selection of highlights from *NATAP Reports* of recent conferences and meetings which took place from October through December 2001: The *3rd Lipodystrophy Workshop* and this years annual *European HIV Conference (ECCATHI)*, both of which took place in Athens, Greece; and the 41st ICAAC HIV meeting in Chicago (Interscience Conference on Antimicrobial Agents and Chemotherapy).

IN THIS ISSUE:

The information in this newsletter is for educational purposes only. Please consult your physician before making any treatment decisions.

Lipodystrophy

Highlights From Lipodystrophy and Adverse Drug Reactions in HIV Workshop

(Athens, Greece October 2001)

Body changes, metabolic abnormalities (cholesterol, triglycerides, sugar), and bone problems appear to be multifactorial in causation. In other words, it is likely that there are many abnormalities and causes going on simultaneously in a patient's body that leads to these abnormalities being manifested. This is not a new finding but researchers continue to think that this is the case. More and better research is still needed to find out what the causes are exactly. This problem is very complex and may take a long time to sort out if, in fact, it can be sorted out. Still, slow incremental progress is being made in understanding different parts of the problem.

What Causes Body Changes?

We still don't have clear answers to this question. Research reported at the Workshop offers food for thought, but does not offer clear answers. Researchers reported that protease inhibitors can inhibit the processing of glucose and alter how it's processed. Some researchers believe the development of insulin resistance may lead to body changes. Body changes and insulin resistance appear to often occur somewhat simulateneously, but we don't know which causes which. Do body changes cause insulin resistance, or does insulin resistance cause body changes?

The question of what causes lipodystrophy may be more complicated still. Other factors such as fat metabolism may play a role in body changes and in improper processing of glucose. Do elevated cholesterol and triglycerides cause body changes? Research suggests that such abnormalities in cholesterol and tryglicerides may cause body changes, but again it remains uncertain which comes first -- the body changes or the elevations in cholesterol, triglycerides, insulin and glucose abnormality, and other lipid abnormalities. Fat accumulation in the belly may cause insulin resistance and may cause abnormalities in fat metabolism. A study in HIV+ men reported at the

Workshop by Steve Grinspoon from Harvard Medical School saw abnormalities in fat processing in patients with body changes after they were fed glucose. This suggests that abnormalities in processing fat are associated with abnormalities in processing glucose-elevated sugar, insulin resistance and may contribute to insulin resistance. Do body changes cause abnormal fat and glucose processing or do abnormalities in processing glucose and fat cause body changes? This study does not answer this question.

Researchers reported finding that indinavir can cause glucose increases in vitro (in the test tube), in animals, and in single doses in HIV negative individuals. The increase occurs quickly. In vitro and in rats, indinavir was found to reduce glucose transport, and this reduction increased as more indinavir was used. When an amount of indinavir was used that was about the same as a human dose a 50% reduction in glucose transport occurred. In rats, researchers found that indinavir increased insulin resistance. Insulin processes glucose in the body and insulin resistance reduces the ability to process glucose normally. 4 hours after stopping indinavir insulin sensitivity was restored.

At the 2000 Lipodystrophy Workshop, Mustafa Noor from UCSF reported on HIV-negative individuals receiving indinavir for 1 month. Glucose and insulin levels increased quickly and were maintained for the month. No lipid abnormalities were seen. At this year's Workshop, Noor reported on a new group of HIV-negative individuals receiving a single dose of 1200 mg of indinavir. Insulin disposal decreased by 34%.

Other PIs also appear to cause this but studies on them were just briefly mentioned. Researchers at the Workshop said other protease inhibitors, specifically amprenavir, nelfinavir, and ritonavir were found to have similar effects as indinavir but to a lesser degree. These are all preliminary studies conducted in the test tube, in animals, and HIV-negative persons, not in HIV-infected patients. Although patients developing body changes may experience insulin resistance or diabetes, and elevations in cholesterol and/or triglycerides, we do not know for sure if these developments cause body changes or if the body changes cause the abnormalities in sugar, cholesterol and triglycerides.

Interestingly, in preliminary studies in vitro (in the test tube), researchers from Bristol-Myers Squibb found that atazanavir, their new PI, did not inhibit glucose transport, while ritonavir and other protease inhibitors did. Additional testing found atazanavir had lesser effects on glucose and fat cell related processing than other protease inhibitors. The processing of fat cells may be related to the abnormalities of cholesterol and triglycerides we see with the use of protease inhibitors. Results from studying atazanavir for 1 year in HIV-infected patients show cholesterol and triglycerides do not become elevated (this study is discussed below). Elevations in lipids (cholesterol, triglycerides) may be associated with body changes. So, perhaps atazanavir will not lead to body changes and insulin resistance, or perhaps if they occur it will be much more slowly. But it is too early in the study of atazanavir to be sure. A 1 year long study is too short a time to detect if body changes will occur. But after studying atazanavir for 2 years and more and after it's use in patients in the real world we will have a better sense of its effect on lipodystrophy and glucose.

Amprenavir and Effects on Metabolics & Lipoatrophy

At the 3rd Annual Lipodystrophy Workshop in Athens in November 2001, Michael Dube, MD, a researcher with the ACTG and a treating physician at Indiana University reported finding no significant change in fasting glucose or fasting insulin in patients receiving an amprenavir regimen. Insulin sensitivity (resistance) did not fall significantly by week 8 or week 24, but was decreased at week 48. Six patients experienced new or worsening glucose tolerance by week 24, but fasting hyperglycemia (too much sugar in blood) did not occur. Interestingly, patients did gain a good deal of weight in the trunk as well as in the periphery. This may be good for the development of lipoatrophy (fat loss), as patients in this study did not develop lipoatrophy, but instead gained body weight. Dube did not objectively measure visceral fat (fat accumulation in the belly).

Most of the patients in the study were hispanic (10 hispanic, 2 black, 2 white), which raised some questions about how applicable these study results are to non-Hispanics. Interestingly, Hispanics tend to be more likely to develop diabetes. Cholesterol and triglycerides increased significantly, triglycerides by 90%. This result drew attention because early preliminary studies on amprenavir suggested that cholesterol and triglyceride elevations may not occur as much as seen with some other protease inhibitors. However, the study was only 48 weeks long. Although the data at week 48 is encouraging in terms of not developing lipoatrophy, it is preferable to see longer term data, as lipoatrophy can develop in year two of therapy or beyond. Week 48 body image questionaires filled out by patients showed either no changes or increases in the amount of flesh in the face and limbs, no fat loss. An interesting finding in this study was that insulin resistance appeared late following weight gain, particularly trunk fat, but loss of limb fat or facial lipoatrophy did not occur. These late changes appear to be related to increased adiposity (fat in belly) rather than a direct drug effect. So, does insulin resistance cause fat accumulation or fat loss? This study doesn't answer these questions.

Again, since the study was conducted in Hispanics are the results applicable to whites and blacks? Researchers I spoke with at the conference feel the insulin resistance (not developing insulin resistance) results seen here are encouraging and credible, but preliminary. They would like to see further confirmatory study. Although the study is small the metabolic testing was intensive.

Fat Loss Occurred Less in Efavirenz Regimen Than Indinavir Regimen

At the Lipodystrophy Conference in Athens, the DuPont company and Karen Tashima of the University of Pittsburg reported on a study looking back at patients in the major big efavirenz study (trial #006) comparing efavirenz to indinavir. The 006 study was conducted a few years ago. Study 006 compared efavirenz + AZT/3TC to indinavir + AZT/3TC to efavirenz +indinavir in treatment naive patients. Abdominal CT-scans were used to look at fat changes at their next scheduled visit with a 1-year follow-up scan. An independent,

central reader read all scans in a blinded fashion. The average time from study start to first scan was 738 days and to the follow-up scan, 1106 days. So there were about 400 days between the first and second CT-scans. There are other techniques for evaluating fat loss in arms and legs. Evaluating fat loss in the face is difficult and I don't believe any techniques have been well developed yet.

The CT-scans showed that subcutaneous fat, which is the type of fat lost in the periphery (face, arms, butt), was decreased in all of the 3 regimens but the fat loss was greater in the indinavir regimens than in the efavirenz regimen. This suggests that lipoatrophy (loss of fat in the periphery-face, arms, legs, butt) can occur with an efavirenz regimen but may be less likely to occur than with an indinavir regimen or perhaps another PI regimen. Several studies looking at abacavir and nevirapine regimens suggest these PI-sparing regimens appear less likely to cause body changes. But it appears body changes may occur regardless of the regimen used. No studies have yet to find that changing from a PI to a PI-sparing regimen reverses body changes that occurred while on the PI regimen.

One recent theory being highlighted now by Simon Mallal, a researcher in Australia, is that the combination of a PI and NRTIs may yield the worst fat loss. He believes that the combination of a PI and NRTIs may lead to body changes perhaps the quickest (in 1 year); double nukes alone will not lead to short-term body changes; and he believes a double PI regimen alone, such as ritonavir+saquinavir 600/400 mg bid, is less offensive. These beliefs are discussed by Mallal in a paper he has written for the journal called Antiviral Therapy, and it is based on data culled together from several studies conducted over the past few years. There has also been preliminary data presented suggesting that certain protease inhibitors may boost NRTI levels in blood or intracellularly. If the NRTI was associated with body changes, boosted levels could increase risk for body changes. These are all preliminary findings and theories, but they deserve further research exploration. ACTG studies are exploring NRTI-sparing regimens for the development of body changes.

Can We Reverse Lipodystrophy with Drugs?

Several studies reported on at the Workshop related to this question. Although some of the results were encouraging, the results are too preliminary to draw any conclusions. Improvements in fat loss were reported by patients and doctors, but more objective testing to evaluate this did not show improvement. Further studies are proceeding to look at these drugs. There was a presentation at the Lipodystrophy Conference in which 4 of 9 patients with lipodystrophy and insulin resistance reported improved facial fat loss and thinning of the extermities using rosiglitazone. Rosiglitazone is an anti-diabetic drug, which has been shown to improve lipoatrophy and insulin resistance in HIV- persons. But the reports of improvement were from patient and doctor reports. Studies using more objective tests evaluating changes in fat in the face, limbs, and belly are needed. Objective tests can measure fat changes in these areas of the body. Some of the objective measures in the study did not jive with the patient and doctor reports. But there is a feeling among some of the researchers that rosiglitazone may be helpful for reversing fat loss. In a preliminary study reported on at the Workshop, metformin (also a drug used to treat glucose abnormalities) reduced insulin resistance, fat in the belly, and glucose in patients with lipodystrophy and insulin resitance. However, there is a concern that metformin could cause fat loss (lipoatrophy). Pioglitazone is an anti-diabetic drug, which enhances insulin sensitivity and is thought may reverse fat loss in the face and other areas. This drug was given to patients with lipodystrophy. Objective testing with DEXA scans showed no improvement in fat in the arms and legs, although 4 of 9 patients reported improvements. Finally, a study was reported that gave acipomax to 7 patients with lipodystrophy, abnormal fat metabolism, elevated insulin, and insulin resistance. Acipomax is a drug that can improve fat metabolism abnormalities. Abnormal fat metabolism and insulin sensitivity were improved in these patients. So perhaps, acipomax might be useful in improving lipodystrophy and glucose abnormalities. But this study was small and the results are preliminary. Further studies are expected including a combination study of rosiglitazone and metformin.

Additional Highlights from the Lipodystrophy Workshop

Data was reported here associating nevirapine hepatic toxicity with nevirapine blood levels. It was suggested that this could be true with other drugs. It was also suggested that some degree of liver impairment, which could come from hepatitis C, may increase drug blood levels. These questions need to be studied better. Severe hepatitis may increase drug blood levels, but it is unsure what level of liver impairment is necessary to cause increased drug blood levels.

Kathy Mulligan reported on a study of the use of human growth hormone (HGH) using 3mg/day. HGH has been shown in a few studies to reduce fat accumulation in the belly. It has also been shown that it may reduce fat in the face, although water accumulation in the face can occur leading people to believe they are regaining fat in their face. HGH is not FDA approved to be used for lipodystrophy, although a study is planned to look at this use. Mulligan reported improved lipid profiles but worsening glucose under both fasting and hyperinsulinemic conditions. She said these results suggest that treatment with HGH is associated with hepatic, as well as peripheral insulin resistance that might lead to elevated sugar. She suggested testing for glucose tolerance before using HGH and that diabetics should not use HGH. Further testing of HGH will be done with lower doses (perhaps 1 mg/day) and less frequent dosing to see if this improves safety while retaining effectiveness. Additional side effects are also associated with use of HGH at the currently used doses. Guillermo Santos from the Betances Health Center in NYC reported on data collected from case reports of 94 patients who used HGH at his center. Patients were started on high doses (4-6 mg/day), but the dose was reduced in patients experiencing clinical symptoms. Dose reduction occurred within an average of 4-5 months after starting HGH. Adverse events occurred in 85% of patients: joint pain or water accumulation (31%); fatigue (15%); 8% hypoglycemia (abnormally low sugar in blood). A similar side effect profile has been seen in patients taking 3 mg/day dosing.

It was discussed at the Lipodystrophy Workshop how insulin resistance can occur in muscle, liver, and the periphery (arms, legs, etc.).

One study at the Workshop found that nephrolithiasis (kidney stones) from indinavir may be more likely to occur in females, but this study was conducted in Thailand.

Heart disease appears to loom as a potential problem in the future due to risk related to increased cholesterol, triglycerides, and insulin resistance in patients receiving HIV therapy. It was suggested at recent conferences that risk factors such as smoking, diet, exercise, cholesterol may be more of a concern than HAART itself.

When to Begin Therapy

There is a good deal of controversy about when to begin therapy. Several research papers have reported that patients who start therapy when CD4s are between 200-350 can respond to therapy in terms of achieving undetectable HIV as well as patients who start when CD4s are about 500. However, there are several studies suggesting this may not necessarily be the case. Results from these several studies suggest that patients starting therapy when CD4s are higher (>350) are more likely to achieve undetectable viral load and sustain this. Still, there is general agreement that starting therapy after CD4s decline to below 200 is risky. Everyone generally agrees that the sooner you begin therapy the more likely you may be to develop side effects: lipodystrophy (body changes), elevated sugar and lipids (cholesterol, triglycerides).

The ability to maintain adherence over a long period of time is difficult. Quality of life is affected once a patient starts therapy because side effects can occur and the strict schedule for taking the medications has little flexibility. Some patients who start therapy earlier may be more likely to have problems with adhering to the strict schedules for taking therapy. However, it's also important to be aware that some regimens are more convenient to take and are less likely to cause side effects/toxicities. These regimens may be easier to adhere to and may have less negative effect on quality of life. These are issues to discuss in depth with your doctor, and to consider closely in making your decision. If a patient misses doses because of the difficulties discussed above, they are at risk for developing resistance to HIV drugs.

In consideration of all these difficulties facing patients after starting therapy, the US Dept. of Health and Human Services HIV Treatment Guidelines for Adults were changed to recommend deferring the start of therapy. Previously, if CD4 count was 500 or viral load was about 20,000 copies, the Guidelines suggested to consider therapy. The revised Guidelines recommend considering therapy when CD4s are 350 and viral load 55,000 (using PCR viral load test) and 35,000 bDNAviral load test. Of course, these are general guidelines and everyone has a different personal situation. The decision on when to begin therapy is a personal one and the patient should make a decision based on what is important to them, after considering all these factors. Your personal situation may require a different approach on when to begin therapy. And of course the Guidelines also recommend that if a patient has any HIV-related illness, such as PCP pneumonia or thrush, they should consider starting therapy regardless of CD4 count or viral load.

There is a trend in thinking that perhaps CD4 counts are better to use than viral load in deciding when to begin therapy. Several studies suggest that when viral load is <100,000 copies only the CD4 count is a useful tool to use in deciding when to begin therapy. These studies suggest that if viral load is >100,000 copies a patient should consider starting therapy, regardless of CD4 count. But, I think these are preliminary studies. I think both CD4 count and viral load are important to consider in deciding when to begin therapy. In addition, I am not convinced that it is safe to defer therapy until viral load is >100,000 copies. I believe that there are risks of harmfully depleting the immune system at viral loads lower than 100,000, such as perhaps at 40,000. We are unsure what level of viral load presents risks. We are unsure of the risks of depleting the immune system too much. Will this increase risk for premature cancers or opportunistic infections, or untoward general immune dysfunction? These are concerns, but we don't have clear answers. And we remain unsure what CD4 count to use in determining the cut-off for when to begin therapy. For now, the decision is a personal one between the patient and their doctor, using careful judgement. You must carefully consider the risks and benefits as you see them of starting earlier or deferring therapy. In the end, it depends on what the patient feels is most important to them, weighing the reduced quality of life that comes with taking therapy and potential health concerns in deferring therapy too long.

Preliminary research shows that in early HIV disease stage women have perhaps as much as 50% lower viral loads than men. After a number of years, perhaps 5, this difference appears to go away. This has led some doctors to say that in some situations perhaps the CD4 count may be a better indicator for when to begin therapy for a woman.

New Drugs

Atazanavir: A new once daily PI in development that may not cause elevations in cholesterol and triglycerides.

Atazanavir (TAZ) is a new protease inhibitor in phase III development that will be taken once daily (2 capsules) along with other drugs in a HAART regimen. In a recent study, TAZ was compared to nelfinavir in 467 previously untreated patients. All patients also received d4T+3TC with either PI. Both PI regimens appear to reduce viral load about the same. But the interesting development is that after 48 weeks, patients receiving TAZ had little or no increases in cholesterol, fasting LDL (bad cholesterol), and fasting triglycerides. The patients receiving atazanavir had increases in cholesterol, triglycerides and LDL cholesterol of 5-8% compared to increases for patients receiving nelfinavir of 25% for cholesterol, 23% for LDL cholesterol, and 50% for triglycerides. The most common side effect reported for the patients taking nelfinavir was diarrhea (56%). The rate of diarrhea was 15-20% in the atazanavir arm. Hyperbilirubinemia has been reported to occur with use of atazanavir. In this study it was reported as a serious adverse event in <1% of patients treated with the drug.

TAZ also has activity against HIV with limited PI resistance. Preliminary data suggests that HIV with extensive PI resistance (resistance to more than 3 PIs) may not respond to TAZ. Preliminary studies suggest that TAZ has a synergistic relationship with saquinavir.

At the recent ICAAC meeting in December in Chicago, a study was reported comparing TAZ + saquinavir to the double PI combination of 400mg ritonavir + 400mg saquinavir twice daily for patients with PI experience (88% of patients had prior PI experience). Saquinavir was also taken once per day at a dose of 1200 mg in combination with TAZ. Both regimens appeared to have equal effectiveness in reducing viral load in this study, although there was a slight edge to RTV/SQV (-1.50 log reduction vs -1.24). But more patients taking ritonavir+saquinavir discontinued from the study. This was a small initial study and TAZ ought to be compared to other PI regimens used for patients with PI resistance such as Kaletra.

In this study as well, TAZ showed favorable effects on triglycerides. Total cholesterol increased 10% from baseline to week 24 in the RTV/SQV arm. Total cholesterol stayed about the same in the 400mg dosed arm of TAZ, which is the dose being used for studies. Fasting triglycerides increased 90% in RTV/SQV arm (n=8) and decreased 23% in TAZ arms (n=28). 31% of patients receiving the TAZ 400mg regimen had diarrhea and 43% receiving ritonavir/saquinavir had diarrhea. 22% of patients receiving TAZ experienced abdominal pain. Jaundice (13%) was reported in the patients receiving 400mg of TAZ. Jaundice resolved upon discontinuation of TAZ and was not accompanied by increases in liver enzymes.

The NATAP website, **www.natap.org,** has comprehensive sections devoted to women, lipodystrophy, and hepatitis.

Entry Inhibitors for Adults & Children: T-20 and T-1249

The development of this new class of drugs is an important development for patients with resistance to the currently available HIV drugs. Patients with resistance to the current drugs are not expected to have resistance to these entry inhibitors, since they are a new class of drugs. T-20 and T-1249 are administered by subcutaneous injection. Large Phase III studies of T-20 in treatment-experienced patients are ongoing and FDA review for approval should take place within the year. With the availability of PMPA, using T-20 in combination should make an important difference for patients with severe resistance to currently available drugs. A short-term and relatively small expanded access program, due to a severe supply shortage, is available now by Roche and will offer drug only to 168 patients. Physicians can call 1-888-722-6321 to request information and register in the program. T-20 will be prioritized for patients with advanced disease: >10,000 copies/ml viral load, <50 CD4s, a recent OI.

T-20 monotherapy has been shown to reduce HIV viral load 1.50 log in short-term studies. In a Phase II study T-20 was given to 70 patients with extensive treatment experience. Regimens were individualized based on treatment history and genotype. Baseline CD4s were 90 and viral load 100,000 copies/ml. Patient had much ART experience: 97% PI experienced; 79% experience with all 3 drug classes; average number of previous drugs=9; on average, study patients were taking 5 ART drugs. There were no discontinuations attributed to T-20 related adverse events. 71% of the patients had mild to moderate injection site reactions. After 48 weeks 41 of the 70 patients completed the study; 33% of the study patients had <50 copies, between 50-400 copies/ml, or >1 log reduction in viral load but still had >400 copies/ml. 13% had <50 copies/ml. 10% had >50 but <400. And 10% had >1 log reduction in viral load from baseline but still had >400.

In a small preliminary study in children T-20 demonstrated effectiveness. The study included 13 treatment experienced children age 4-12 with average viral load of 29,000 copies/ml and CD4 count of 623. T-20 30 mg/m^2 or 60 mg/m^2 subcutaneously were added to stable but failing background therapy for 7 days then background ART was optimized. They reported that 60 mg/m^2 of T-20 appears to be an acceptable dose. T-20 was safe & well tolerated up to 8 weeks. 10 of 13 patients achieved a 0.7 log reduction in viral load by day 7. 9 of the 13 patients maintained response of > 1 log at 8 weeks with T-20 and optimized background.

T-1249 is a second generation entry inhibitor from Roche/Trimeris. From early research it appears to be more potent than T-20 and it has been reported to be effective against most HIV tested that were resistant to T-20. A 14-day study of subcutaneous injections of T-1249 monotherapy was conducted in 63 HIV+ adults received. Dose escalation was looked at in once or twice per day regimens: 6.25 mg once daily, 12.5 mg once daily, 25 mg once daily; or, 6.25 mg twice daily, 12.5 mg twice daily, 25 mg twice daily. Before starting the study, viral load was well over 100,000 copies/ml for the patients, and average CD4 count was 121. The patients in this study were very treatment-experienced. 98% had previ-

ous ART treatment; about 90% experienced with all 3 drug classes. On average the patients had used 10 ART drugs previously. And 52% of patients had mutations to all 3 classes of drugs. The best viral load response may not have been reached and higher doses will be explored. Using the highest dose of T-1249 (total daily dose of 50 mg/day), the average viral load reduction was about 1.3 log after 14 days. 40% of patients reported localized injection site reactions.

TMC-125

Tibotec-Virco is developing 2 protease inhibitors and an NNRTI for patients with resistance to drugs currently available in those classes of drugs. In preliminary testing in the test tube, TMC-125 had potent activity against HIV resistant to currently available NNRTIs. At the European ECCATHI meeting, investigators reported on a 7 day study conducted in Russia of patients receiving 900mg twice daily of TMC-125 monotherapy or a placebo. 19 treatment-naive men were enrolled with average CD4s of 650 and viral load of 57,000 copies/ml. The average reduction in viral load was a potent 2 log for the patients receiving TMC-125. TMC-125 was reportedly safe and tolerable in this small, brief study.

Tenofovir (PMPA)

This is a new drug recently approved by the FDA for use in patients with HIV. Studies have been reported in patients with 4300 copies/ml of viral load and extensive prior HIV treatment experience with NRTIs, NNRTIs, and PIs. These studies show Tenofovir reduced viral load 0.60 log. Ongoing studies are looking at Tenofovir's performance in patients who are treatment-naive and have higher viral loads. PMPA appears to be an important and effective drug for patients with resistance to currently available drugs who are looking for another drug to add to a new regimen. Studies show that PMPA is effective for most patients with extensive NRTI resistance. Studies looking at safety go on about one year with use of PMPA and show it to be safe and tolerable. The longer-term safety has not been evaluated. The forerunner to PMPA was adefovir which was not FDA approved in part due to kidney toxicity which so far in a year of study has not been seen in patients receiving PMPA. At ICAAC, 100-week data showed slight increases in the number of patients experiencing grade 1/2 kidney related lab tests. It is unsure how significant this is.

Early studies using Tenofovir in animals at doses higher than humans receive showed bone abnormalities. This has not been seen so far in human studies. But studies of Tenofovir looking at this more closely are ongoing. A preliminary study reported at the recent ICAAC meeting found PMPA raised ddI blood levels by 40%, but it is unsure if this is really relevant. Drug levels for NRTIs in the blood may not reflect NRTI drug levels intracellularly where NRTIs are most active. Intracellular levels, not blood levels, are correlated with NRTI toxicities. In addition, a relatively short-term study did not show an increase in key ddI-related toxicities in patients. This question needs further attention. For patients coinfected with HCV and HIV, a small preliminary in vitro study found both interferon and ribavirin increased ddI levels. This has the potential to increase ddI exposure and toxicity, but this also needs further research attention, as it needs to be explored in humans receiving these therapies. The triple combination of interferon+ribavirin+ddI has potential use as an HIV therapy. Early short-term studies show interferon can reduce HIV viral load 0.25 to 0.50 log but the studies are short-term (3-6 months) and we have to see if the viral load reduction will be sustained for a longer period of time.

Tipranavir: New PI for Resistance

Tipranavir (TPV) is a new type of PI that will be combined with low doses of ritonavir to increase and enhance its blood levels, and has been shown in in vitro studies to be effective against HIV with extensive PI resistance. A small study of 21 patients was presented at the recent ICAAC meeting in Chicago. The problem with this study is that many patients did not have PI resistance although they had prior PI experience; 40%-50% of patients entering the study had no PI mutations. Also, PI resistance mutations for patients that had any were not reported. The potential appeal for TPV is in patients with extensive PI resistance, and this study did not look at these types of patients. However, as soon as a correct dose is identified, which should occur in 2002, extensive study of TPV will occur in patients with extensive PI resistance.

In this study, 2 twice-per-day TPV doses with NRTIs were explored: 500 mg with 100 mg ritonavir and 1250 mg TPV plus 100 mg ritonavir. These regimens were compared to ritonavir 400 mg + saquinavir 400 mg twice per day. Three twice daily doses of TPV will be explored in future studies: 500/100 (TPV/RTV), 500/200, and 750/200. In this study average patient viral load was 27,000 to 40,000 copies/ml for the patients receiving the 2 TPV regimens, and 16,000 for the patients receiving the RTV/SQV regimen, no real difference. The viral load reduction was about the same for all 3 regimens, about -1.40 log. About 55% in the 2 TPV regimens and 40% in the RTV/SQV regimen had >1 log reduction of viral load. 55% in the TPV 1250, 39% in the TPV 500 group, and 40% in the RTV/SQV group had <400 copies/ml. The percent of patients with <50 copies/ml was reported at 35% in TPV 1250, 22% in TPV 500, and 30% in SQV/RTV.

There were a total of 5 discontinuations in the TPV 500 arm (1 due to adverse event), 4 in 1250 TPV (2 due to adverse event), and 11 in RTV/SQV (5 due to adverse event). In sum, there were 3/42 (7%) AE-related discontinuations in the 2 TPV arms and 5/21 (24%) in the RTV/SQV arms. The most common drug related adverse events were gastrointestinal (GI): diarrhea, nausea, vomiting. The amount of GI side effects does appear to be related to the dose of TPV with higher dosing showing more GI side effects. Triglycerides increases (grade 3) occurred in 3 patients (14%) in TPV 500, 4 patients (19%) in TPV 1250, 1 patient (5%) in RTV/SQV.

The Future: Once-A-Day Regimens For HIV

We are headed towards having a broad selection of once-per-day HIV regimens. Several studies have recently been conducted looking at various once-a-day regimens. PI regimens in research include the single PI called atazanavir, double PI combinations saquinavir+ritonavir (1600mg/100mg) and amprenavir (or the new formulation of amprenavir called "908") + ritonavir (1200mg/200mg or 300mg).

Preliminary research is looking at the possibility of d4T, nevirapine, abacavir, AZT and 3TC being used individually as once per day drugs. DDI is approved to be used once per day.

Julio Montaner, a researcher and physician in Canada, reported on a study looking at using a new formulation of d4T (d4T XR) once per day. This is an "extended release" formulation which was compared to the standard d4T formulation used twice per day in this study. Patients received either of the d4T formulations plus 3TC twice daily and efavirenz once per day. Patients were treatment-naive and about 75 patients were randomized to either d4T regimen. Before starting the study the average patient viral load was 49,000 copies/ml and CD4 was 350 in the d4T XR arm and 260 in the standard d4T arm. The effect on viral load and CD4 was about the same regardless of which d4T formulation the patients received. Interestingly, the study found patients receiving the d4T XR formulation experienced less neuropathy than the patients receiving the standard d4T (11% vs 1%). We will have to look at future studies to see if this is confirmed. The dose of d4T XR used was 100mg once a day for people weighing over 60kg (about 130 pounds) and 75mg once a day for those weighing less than 60kg. Larger more extensive studies are planned.

At the European HIV Conference (ECCATHI in Athens, October 2001) Jean-Michel Molina from Paris reported on a preliminary pilot study of a completely once-a-day regimen used in 40 treatment-naive patients. Patients received FTC (200 mg), Sustiva (600 mg), and ddI (400 mg if >60 kg; 250 mg if <60 kg) once per day. The new ddI EC formulation was used so that all of the drugs were taken at the same time, rather than having to take ddI separate from other drugs as was the case with the old formulation of ddI. Before starting the study the average patient viral load was 59,000 copies/ml and CD4 was 373. After 96 weeks, 85% (34/40) of patients had viral load <400 copies/ml and 80% had <50 copies/ml (ITT, non-completer=failure, strict analysis). The average CD4 increase was 272 cells at week 96. Molina reported that the most common treatment-related adverse events occurring during the first 24 weeks of the study were mild to moderate central nervous system symptoms (73% of patients), diarrhea (37% of patients), rashes (10%), and biochemical abnormalities. There were 4 serious adverse events possibly treatment related: (grade 3 hypertriglyceridemia in 2 and grade 3 transaminases in 2 [liver enzymes]). It was also reported that 8/9 patients with a baseline viral load >100,000 copies/ml had <400 copies/ml at week 96. FTC is very similar to 3TC in terms of safety and antiviral potency. It is in studies now and is taken once per day. If you have resistance to 3TC you will likely have resistance to FTC.

The Prevalence of Antiretroviral Drug Resistance in the US

Several smaller studies have shown similar findings as this study discussed below, that there appears to be a troublesome rate of resistance to HIV drugs in Europe and the US. Small studies have shown that newly-infected or diagnosed persons with HIV who have resistance to HIV drugs appear to respond less well to HIV therapy. At the recent ICAAC meeting, Doug Richman, a researcher and physician at the University of California at San Diego, reported on the first large study which tries to identify what percentage of patients with HIV under care in the US have drug resistance. The study looked at about 2000 patients being followed in another study. Richman said these patients are representative of the total number of patients in the US receiving care for HIV. He found that at least 50% of these patients had resistance to an HIV drug, and then suggested that this means that at least 50% of patients in the US have HIV drug resistance. He also reported that 63% of the patients, who were receiving care in his study, had detectable viral load (>500 copies/ml). Although several criteria used in this study suggested the researchers may have overestimated the 50% of drug resistance, previous studies have also suggested that about 50% of Americans receiving HIV treatment with HAART have HIV >500 copies/ml.

Richman also reported that a good number of patients have high rates of resistance to protease inhibitors, NRTIs, and NNRTIs. He found that of all patients with >500 copies/ml viral load 78% had drug resistance. Of these patients, 70% had resistance to a NRTI (most commonly to 3TC), 42% to a PI, and 31% to a NNRTI; 51% had resistance to 2 or more classes of drugs, and 14% had resistance to 3 classes of drugs.

This study was conducted by looking at patients between 1996 (after the beginning of the availability of protease inhibitors) and 1999. It is likely that many of the patients with drug resistance had been on mono- and dual- NRTI therapy before starting a PI regimen. At that time, PIs were often not being used properly. Patients and doctors were often just adding a PI onto a failing NRTI regimen. So, a good deal of the resistance found in this study was due to these inappropriate uses of protease inhibitors.

Nonetheless, this concerning problem of drug resistance must be addressed, as we need the development of drugs effective against drug resistance. Not surprisingly, Richman also reported that patients with the most access to care were the most likely to have drug resistance in this study. He also cautioned about how he felt that switching therapies too often was a contributing factor to these high rates of drug resistance. Richman reported that patients seeing more knowledgeable and experienced HIV treating physicians were less likely to have drug resistance in this study. These high rates of drug resistance are of particular concern due to the risk of transmission of drug resistance to newly infected persons. Newly infected individuals who have resistant virus may not respond as well to HIV therapy.

Interestingly, drug resistance in Switzerland appears to be decreasing. It has been suggested that they have a better handle on treating their patients. This is due, in part to the smaller numbers of HIV-infected and the more geographic concentrations of the infected population.

In a perfect world where all doctors and labs performing and interpreting the tests understood how to interpret test results, you might assume use of drug resistance testing for patients who are newly diagnosed or treatment-naive could help address this problem. But, the problem is that many doctors do not understand how to interpret resistance test results. Often, they use the interpretation of the lab report given to them by the lab itself. However, labs are not in general proficient at proper interpretation and reporting of lab results. I think this may change in time as more standard ways to interpret test results are adopted but we don't have such uniform standards yet.

DDI and Food and Timing of Dose

Researchers at Bristol-Myers-Squibb reported on a study looking at the effect of food and the timing of a meal on the bioavailability of ddI EC in healthy volunteers. The study found that eating any food with ddI decreased blood levels. The study also found that food should be eaten at least 1.5 hours before taking ddI EC or 2 hours after taking ddI. The reduction in blood levels was modest and further research is needed to see if the modest reductions are clinically significant in HIV-infected patients, but the study concluded that ddI EC should be administered on an empty stomach.

NATAP has a special Women's Education Program, for more information call Gloria Searson at 1 888-26-NATAP

Abacavir Resistance

Previous studies have shown that if a patient has 3 or more AZT mutations they are likely not to receive much antiviral effect from abacavir. But findings from a new study reported at ICAAC called ZORRO, found that no matter how many AZT mutations a person had they could still respond well to abacavir unless 3TC resistance was also present. The study found that if a person had 3 or 4 AZT mutations and 3TC resistance, significant resistance to abacavir occurs. I think further study is needed to address the discrepancy in findings between previous studies and this new one.

How Low Does Your Viral Load Have to Be?

We know that several studies show that reducing viral load to <50 copies ml and maintaining it as opposed to just having viral load <400 results in more durable viral load suppression. But, many have asked: Is it beneficial to reduce and maintain viral load to a lower level, such as 20 or even 3 copies/ml? At the ICAAC meeting, Abbott researchers and Luc Perrin reported results from their study of this question with the use of Kaletra with d4T/3TC in treatment-naive patients. They found that reducing viral load to <3 copies/ml in the first 72 weeks of therapy did not make any difference. All patients maintained viral load <50 copies/ml for 72 weeks but some patients achieved <3 copies/ml once or multiple times. After 3 years of following these patients, the ability to maintain viral load <50 copies was the same whether or not patients achieved one or multiple test results below 3 copies. I see 2 potential limitations to the study. I would like to see longer follow-up than 3 years to confirm the findings. More important, since this study was conducted with Kaletra, do the results apply to other drugs? We don't know the answer to that, and perhaps these results may not apply to other drugs.