NATAP'S NATIONAL AIDS TREATMENT ADVOCACY PROJECT

POSITIVE + INFORMATION

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Summary of the 2002 Retrovirus Conference

IN THIS ISSUE:

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

The information reported in this newsletter is a summary of the comprehensive coverage of the 2002 9th Annual Retrovirus Conference available on the NATAP website, (www.natap.org).

New Drugs: Excitement, Hope and Optimism

The highlight of this meeting was the presentations on new classes of drugs for HIV. For the first time in a number of years the majority of presentations in the new drugs session at the Conference focused on genuinely new drugs for HIV. Although these developments are in early stages, there was a general feeling of hope and optimism surrounding these presentations. As well, several new drugs from currently available classes of drugs are in more advanced stages of development.

The development of HIV entry inhibitors is very exciting. There are several steps involved in the process by which HIV enters the CD4 cell. HIV entry inhibitors act to prevent HIV from entering the CD4 cell, while the current classes of drugs act to prevent HIV from reproducing itself while in the CD4 cell. The process by which HIV enters the CD4 cell includes binding of HIV to the cell and then fusion into the cell. SCH-C is an entry inhibitor that blocks one of the steps for binding. The drug is in the early stages of being tested in HIV-infected individuals. It has favorable characteristics including potency, but there is a potential safety concern that is being examined. SCH-D is a sister drug that Schering Plough has as a backup.

BMS 806 is a model entry inhibitor that represents the promising entry inhibitor development program at Bristol Myer Squibb. Testing is expected to begin in healthy volunteers.

As discussed below, T-20 is a fusion inhibitor in the late stages of development in HIV-infected individuals. The large phase III study is ongoing so results are not yet available, but results from earlier studies suggest that this drug will be important for patients with extensive treatment experience.

Several promising NNRTIs and protease inhibitors for patients with resistance to these classes of drugs are in early stages of development; two intergrase inhibitors are also in early stages of development, both are discussed below.

Perhaps, in several years we will have enough HIV entry inhibitors to compose an entire regimen consisting of just these drugs, or several entry inhibitors to combine with an integrase inhibitor.

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Several important Epidemiological Trends were reported on at Retrovirus -

The rates of traditional opportunistic infections are decreasing due to HAART improving the immune system with increased CD4 counts and lower viral load. But, patients are experiencing increased rates of death due to liver disease, kidney disease, Non-Hodgkins Lymphoma (cancer), and pancreatitis. This is because patients are living longer. The rates of death due to liver disease were reportedly increased by 60% from 5% to 8%. This is due in part to hepatitis B and C. Similar increases in rates were reported for kidney disease and Non-Hodgkins Lymphoma. Rates for tuberculosis have decreased over 50%, PCP by 30%, toxoplasmosis by 30%. Although these rates have been reduced, patients are still getting these infections reflecting gaps in the care system.

- 25% of HIV positive persons in the USA may not know they have HIV.

- 33% of persons who know they have HIV are not receiving care.

- 27% of individuals with syphilis in a large study in Chicago have not been tested for HIV. One of the driving factors in the transmission of HIV is the presence of an STD. If a sex partner has an STD, the risk for transmission of HIV increases.

New Drugs: Resistance to Current Drugs

Tenofovir (PMPA, Viread)

This new nucleoTide was approved in October 2001, and is taken one pill once per day. It appears to be very effective for patients with resistance to currently available nukes. In a study of patients with extensive nuke resistance, Tenofovir was effective in reducing viral load by 0.6 log in most patients. In a few small studies this drug appeared to be as potent as a PI or NNRTI in patients who had never before taken therapy. The manufacturer is studying it in a firstline regimen as a substitute for a nuke. This drug has been studied for about 2 years. Although studies so far have not shown a safety problem, and it appears to be relatively free of tolerability concerns, it's suggested to monitor kidney related lab test (bloodwork). There is a suggestion that perhaps Tenofovir might have an effect on these lab tests. So far this has not been seen, but study data at 2 years suggested slight increases in these lab values. In animal studies using very high doses the animals developed bone problems. This has not yet been seen yet to be a problem in HIV-infected patients. A study is ongoing now to take a close look at the bone issue.

Tipranavir

This is a promising new protease inhibitor for patients with resistance to current protease inhibitors. This drug is uniquely made so as to be able to bind to the protease enzyme even if it has resistance mutations to other protease inhibitors. In preliminary studies, Tipranavir has shown to be potent for HIV-infected patients with extensive resistance to current protease inhibitors. It will have to be boosted with a low dose of ritonavir, as is Kaletra. Unfortunately, Tipranavir is in early stages in human testing and it appears that, if everything goes well, it will take about 1.5 to 2 years until it's available.

T-20

T-20 is a fusion inhibitor, which is a type of entry inhibitor. Because this is a new class of HIV drugs, patients with resistance to currently available HIV drugs are not expected to have resistance to T-20. This drug is being studied primarily for patients with extensive treatment-experience, but was potent in studies of patients with no treatment experience. T-20 is in the final testing stages in humans, and is expected to receive FDAapproval within a year. This drug is administered by subcutaneous injections twice daily, similar to insulin for diabetes. The most common side effect appears to be injection site reactions. Preliminary studies have been conducted to identify dosing for kids. The manufacturer has a sister drug called T-1249, which appears to be more potent than T-20 and effective against HIV with T-20 resistance.

Integrase Inhibitors

Integrase is the enzyme that integrates HIV-DNA into the patient's DNAin the cell nucleus. Researchers have been trying to develop integrase inhibitors for years without success. S-1360 is a promising integrase inhibitor in early development. GlaxoSmithKline is starting phase I and II studies in humans. Merck is also in the very early stages of trying to develop an integrase inhibitor, but no new information was reported at the conference.

Atazanavir

This is a new protease inhibitor entering final phase III human study before the FDA reviews it for approval. The unique aspects of this drug are that it is the first once-per-day PI, and so far it does not appear to raise triglycerides and cholesterol. It will not be boosted by low dose ritonavir when used for initial therapy. In early studies this PI looked about equivalent to Viracept. One of the interests for this drug is to see its effect on body changes, since it does not appear to increase cholesterol or triglycerides. This drug will have some effectiveness for patients with a little PI resistance, but it does not appear to be effective for patients with extensive PI resistance. Tipranavir appears to be more promising for highly resistant patients.

Atazanavir Expanded Access Program
Drug companies make their HIV drugs available to needy patients before the drug is approved. Usually, drug is available in this manner only to patients with limited treatment options who cannot wait until approval. Your doctor will have to contact the drug manufacturer and fill out forms to request the drug. Drugs offered in expanded access are still experimental; they have not yet been FDA approved. Atazanavir is expected to be available in your pharmacy in 2003. Currently, this program is just collecting names, but is expected to be distributing the drug in the near future. Call for information: 1-877-726-7327.

NNRTIs for Resistance

TMC-125 is a new NNRTI which appears in preliminary short-term study in HIV-infected patients to be very potent and shows promise to be effective for patients with resistance to the current NNRTIs (efavirenz, nevirapine, delavirdine). The manufacturer of the drug reports that it appears to have a unique capacity in animals to achieve better penetration and achieve higher levels in HIV reservoirs than currently available drugs. DPC-083 and its backup sister drugs are a group

of NNRTIs also in early stages of development that appear to be potent against HIV with extensive NNRTI resistance and promises to be a once per day drug. It appears to have similar but hopefully lessened side effects than efavirenz.

STIs and Therapy Interruptions or "drug holidays"

The original idea behind structured therapy interruptions (STIs) was that if you stopped and started therapy several times in a structured way the immune system would be exposed to HIV and naturally develop a response which could control HIV without HAART. In patients who have been newly infected with HIV within the past 1-2 months, several studies have found evidence that STIs may stimulate such an immune response. This benefit may occur because the virus has not yet had enough time to destroy the immune system. Further studies are ongoing to explore the safety and confirm the effectiveness of this still experimental concept in newly infected patients.

In patients with chronic HIV (infected with HIV for longer than several months) study results do not show any such benefit for most patients. A small percentage (6%) appear to control HIV, but this benefit may be just coincidental. Still, the overwhelming majority of patients did not benefit and patients were unable to control HIV during interruptions. However, researchers are looking at the possibility that "therapeutic" vaccines may be able to stimulate an immune response for the patient on HAART, enough to control HIV after interrupting HAART. Several vaccines are being developed and researched to see if this is possible. So far the research process is in the early stages and there is still little evidence that this approach will be successful. But it is too soon to make a judgement, and this concept may prove to be successful. In previous attempts to develop vaccines for similar situations it has been difficult to be successful.

Immediately below we discuss the risks of interrupting therapy. There appear to be a number of risks but researchers continue to explore ways to interrupt therapy safely. One hope is that interrupting therapy may result in reduced cholesterol, triglycerides, and sugar and perhaps slowing fat redistribution without taking too many risks. The NIH is studying serial interruptions of seven days on therapy and seven days off therapy.

What are the risks of interrupting therapy? Patients sometimes stop taking their HAART due to concerns about side effects and toxicities including body changes. Patients also get tired of adherence. It's understandable that it can become difficult to persist in taking HAART for years. But interrupting therapy is a risky choice to make. After stopping therapy CD4 counts can decline and viral load can increase. Patients can get opportunistic infections and perhaps develop cognitive impairment.

Newly reported information shows that there are perhaps additional risks associated with interruptions. Some patients who interrupted their therapy have developed drug resistance. The risk appears to be higher for patients taking an NNRTI. (A few patients taking 3TC developed 3TC resistance.) New information reported at Retrovirus showed that when you stop therapy HIV re-enters the brain and cerebral spinal fluid two weeks after it enters the blood. Viral load in the CSF and brain can go back to pre-HAART levels. We can presume that HIV also re-enters other viral reservoirs where HIV levels had been eliminated or reduced due to HAART. It is expected that once you re-start HAART virus levels will go down, but there is a risk you might have developed drug resistance and that you may not be able to reduce viral levels to the same levels they were while first on HAART. What is the long-term effect of a person repeatedly stopping and starting HAART? Researchers do not know if there are negative consequences or implications of continually repopulating reservoirs with HIV and emptying them. Will this tire out the tissues or immune system? We don't know.

The results of several studies suggest that increases in HIV viral load during therapy interruption may induce defects in the immune system. One study reported on at Retrovirus found that after interrupting therapy an important cell that fights HIV called the HIV-specific CD4 memory t-cell appears more likely to get reinfected with HIV. Although they were reinfected at a low rate, this raises some concerns that repeated therapy interruptions causing slow but relentless infection of these cells that respond to HIV might eventually erode the immune system. A second study found "HIV-specific proliferative" (responses that appear to fight HIV) responses were depressed when HIV was at increased levels.

A large European study (EuroSida) looking at 5000 patients reported at Retrovirus that 20% of patients took a therapy interruption of 3 months or longer. Patients lost about 30 cells on average over the first three months following the interruption. Viral load increased an average of 1 log during the first 3 months (for example, from 1000 to 10,000 or 10,000 to 100,000). The study found that perhaps being on HAART can help prevent HIV progression regardless of whether you have a lower CD4 count and detectable viral load. HAART may have a benefit independent of CD4 count.

Patients with CD4s < 200 after interruption tended to have quicker HIV progression and get sick. If patients had over 200 CD4s they tended not to have quicker HIV progression. This suggests that although there may be other risks from interrupting therapy such as resistance and repopulating virus reservoirs, if your CD4 counts are high enough you may not get an OI. However, this does not completely eliminate the risk for getting an OI. 23% of the patients on HARRT had HIV progression (clinical events) when CD4s were above 250 on HAART. The study authors listed events as deaths, esophageal candidiasis, NHL, and others. In this study, the rate (2.8%) of the occurrence of an OI or clinical event for patients with >200 CD4 who interrupted therapy was low (3 events in 109 patients). If you interrupt therapy and your CD4s are low you should talk to your doctor about starting prophylaxis medication to prevent an OI such as PCP. Try to be honest with your doctor if you want to stop therapy.

An ongoing French study is exploring the possibility of patients with extensive HIV drug resistance and advanced disease (CD4s of 27, viral load >100,000 and few if any treatment options) interrupting therapy for 8 weeks before re-starting a potent salvage regimen. A similar group of patients in this study did not take an 8-week interruption, but switched immediately from their current regimen to a potent salvage regimen. The interim 12-week results showed that patients who interrupted therapy for 8 weeks had a better viral load response. The hope is that resistant HIV might become more sensitive to the HIV drugs during the 8 weeks off therapy. Sensitive resistance tests show that drug resistance does not

disappear. It is felt by many resistance researchers that resistance is still there and will eventually re-surface. Perhaps virus is only re-sensitized to the drugs for a period of time. Further study results will be presented at the Barcelona International AIDS Conference in July. Additional research continues in therapy interruptions in the hopes of trying to make it effective for patients.

Women & HIV

A study reported that newly infected women with HIV who were on contraception were more likely to have mutated virus, lower CD4 counts, and higher HIV viral load. Although the study did not look at this, these results suggest these women may progress more quickly. The reduced CD4 count persisted as it was seen 5 years after HIV infection.

Women with higher viral load and lower CD4 counts may also have higher viral load in their genital secretions, and may present a higher risk for transmitting HIV. Women in this study with an STD were more likely to have a higher HIV viral load.

Several studies show that after HIV infection women tend to have about a 50% lower viral load than men do. Several studies suggest that 5 years later men and women tend to have similar viral loads. So, what are the implications of these gender viral load differences? Researchers are uncertain. More research is needed to understand this. But, since women may have a lower viral load than men some researchers think it may be more helpful to use a women's CD4 count in deciding when to begin HIV therapy rather than the viral load. Perhaps, women with higher viral load in early stage of HIV may progress more quickly. In a study reported on at Retrovirus women responded as well to HAART as men.

A study at Retrovirus found that HAART did not improve HPV in women. These findings are disappointing and are not consistent with the common belief that the incidence of cervical cancer is decreased among women on HAART. The study went for only 6 months; this may be too short to see a benefit from HAART. Further studies are needed to explore this association and determine the true prevalence of HPV associated cervical cancer among women with HIV.

Mother-To-Child Transmission Trends. As the use of HAART has increased to prevent HIV transmission from pregnant women to child, the rate of infection for newborns has decreased dramatically. An ACTG study (PACTG 367) looked at 2000 pregnancies at 67 hospital/clinic sites over 3 years. The maternal fetus transmission rate (MFT) decreased from 4.3% in 1998 to 1.6% in 2000.

Being in prenatal care can be very helpful in receiving proper care and preventing transmission to the newborn. 88% of the women in this study were in prenatal care starting in the 1st or 2nd trimester. 12% were not in care until the third trimester or until the time of delivery. 16% had an undetectable HIV viral load at entry into the study and 50% were undetectable at delivery. The average CD4 count was 392 and HIV viral load was 4,000 copies/ml.

The MFT rate was 20% in mothers not on HIV therapy. For patients receiving one HIV drug (AZT or NVP monotherapy) the rate was 5.3%. Use of multi-drug combinations reduced the rate further to 1.8%. The lower the HIV viral load the less chance for HIV transmission: 6% (HIV VL > 10,000), 2.5% (HIV VL 10,000 to 1,000), 0.9% (HIV VL < 1,000).

Are there safety concerns? Overall, the HIV Drug Pregnancy Registry (1-800-258-4263 or www.apregistry.org) shows a rate of 2.3% for adverse events or birth defects. This is not different than the rate for the general HIV negative population. The data on pre-term labor is conflicting. PACTG 367 did not show an increase of pre-term labor in over 1,000 pregnancies, whereas the European Collaborative and the Swiss-Mother-Child Cohort both did. HIV itself can cause pre-term labor so the jury is still out.

HIV nukes can harm cells; this is called mitochondrial toxicity. Such harm may prevent the cells from functioning properly. Elevated lactate levels reflect potential harm to the mitochondria. Of the 100 cases of lactic acidosis reported to the FDA, 83% were in women. 3 deaths have occurred in pregnant women on D4T/ddI: the women were on those 2 drugs for their entire pregnancies. Previous studies have not shown elevated lactate in infants not exposed to HAART in the first week after birth. A study reported at Retrovirus looked at 25 infants for the first 6 months of life who were exposed to HAART in utero and AZT during the neonatal period. Lactate was mildly elevated in 92% of the infants and highly elevated (>5 mmol/L) in 36% of the infants. The elevated lactate persisted for 6 months and then resolved. The average duration of HAART in utero was 17 weeks. The study authors recommend that all infants exposed to HAART in this manner be closely monitored for elevated lactate during the first 6 months of life.

Lipodystrophy

Rosiglitazone is an anti-diabetic drug that improves insulin resistance and improves fat loss (lipoatrophy) in HIV negative patients. It is thought that body changes in HIV may be related to insulin resistance, glucose intolerance, and diabetes. The hope was that that this drug and similar antidiabetic drugs might reverse body changes. But unfortunately, this study had negative results. It was a small pilot study that did not show that rosiglitazone had any benefit in reversing body changes: fat loss in subcutaneous fat in belly, or fat accumulation in belly.

Several studies were reported on at retrovirus of patients with fat loss whom were on d4T. Patients switched the d4T component of their regimen to abacavir. On average, fat loss slowly reversed or did not progress. There are a few qualifications about these findings. The studies were brief (6-12 months), and the improvement was the equivalent of only about 10%. A remaining question is if improvement will increase or slow or stop. Patients were unable to notice the improvement, but objective testing identified the improvements. The studies did not evaluate whether there was improvement in facial fat loss.

Risk for premature heart disease: Researchers have yet to conclusively prove a direct cause and effect between the elevated lipids seen associated with HIV drugs and the development of premature heart disease. However, a number of studies were reported at this year's Retrovirus Conference which show a potential risk. Although it hasn't been proven it does seem to make sense that when you have elevated cholesterol

and triglycerides you are at increased risk for developing heart disease. If heart disease is in your family history or if you have other risk factors (smoking cigarettes, bad diet, no exercise) this may increase your risk. Perhaps, if we have entire regimens of entry inhibitors in 4-5 years patients won't have highly elevated cholesterol, triglycerides and sugar.

A study showed that cholesterol and triglycerides can improve if you switch from a PI regimen to an abacavir-based triple NRTI regimen. But if you have pre-existing NRTI resistance (if you've previously used single or double NRTI therapy) you are less likely to be able to sustain viral load suppression after such a switch. That is because the NRTI resistance causes cross-resistance to abacavir and this can reduce the antiviral potency of abacavir. Switching from a PI to an NNRTI based regimen may reduce cholesterol and triglycerides.

Diabetes

Studies report that 1-6% of patients on a PI have diabetes. Results from previously reported studies in animals and HIV negative individuals found protease inhibitors may inhibit processing of sugar (perhaps more particularly with Crixivan). However, several studies reported on at Retrovirus found that other risk factors appear to play key roles in the potential for developing diabetes: family history, diet, exercise, persons with fat accumulation in belly, and persons with HCV or liver damage. Several studies have suggested that patients receiving nevirapine or abacavir triple NRTI-based regimens (Trizivir) may be less likely to develop diabetes. A large study conducted in California and reported at Retrovirus showed that HIV+ persons had double the rate of diabetes compared to HIV negative persons. Persons with HIV who were 25-54 years of age had even greater percentages with diabetes (5-7 times greater than HIV negative persons).

What test should you use to screen yourself for diabetes? It appears the oral glucose tolerance test may be the most reliable test. Patients with insulin resistance may go on to develop diabetes. So it may be useful to test for insulin resistance. However, some doctors are raising concern that if insulin resistance is detected they are uncertain what should be done.

Bone Density and HIV Infection

Individuals infected with HIV have been observed to experience more loss of bone density than HIV-negative individuals. Some studies suggest bone mineral density (BMD) loss may be more common for patients on HAART, while other studies find equal rates of BMD loss for HIV+ persons with no treatment experience. However, the causes and significance of lower bone mineral density (BMD) in individuals with HIV remain unclear. Fortunately, despite the data from studies demonstrating lower bone densities in HIV-infected persons, severe osteoporosis and non-traumatic bone fractures in this population are rare. Osteopenia is mild to moderate loss of bone mineral density, and osteoporosis is severe loss of mineral density. Making it difficult to understand the causes of bone loss in HIV-infected individuals are the presence of a number of other risk factors for low bone density among many HIV-infected persons including corticosteroid use (from prior PCP treatment), low testosterone levels, alcohol abuse, weight loss and lack of exercise, among others. (The science of bone density has its own lingo. To learn more about bone density loss in HIV you can refer to: http://uwcme.org/courses/bonephys/index.html.)

"Osteopenia & HIV", written for NATAP by Andrew Carr, MD: www.natap.org/2000/lipo/osteopenia011501.htm

There wasn't much that was interesting at this Retrovirus Conference on bone problems in HIV. There was much more of interest at last year's Retrovirus Conference. Before reporting on the review of 2 studies from this year's conference, here is a summary review of bone loss in HIV from studies reported over the last 2 years.

Review of Bone Studies Prior to Retrovirus 2002

There have been numerous studies conducted and reported over the last 2 years finding various different potential explanations, potential causative factors, or associations related to bone mineral density loss in HIV including: prior corticosteroid use, nukes & elevated lactate (mitochondrial toxicity), lower weight prior to starting HAART, a greater rise in CD4 count on therapy, fat loss in leg, duration of HIV therapy, PI therapy, not associated with PI use, having lower body weight, older age, total body fat, lean body mass, and immune changes. It remains unclear what's causing bone loss in HIV. Other viral diseases can be associated with manifestations such as this; for example, liver disease is associated with bone loss and diabetes, and it is not understood why, or what the cause may be. The causes may be related to the change in the immune system that occurs from disease. In HIV, the changes in the immune system due to immune decline from HIV and partial immune restoration from HAART may be 2 of a number of things contributing to bone loss.

Actions that you can take that might help prevent bone loss include: weight-bearing exercise, better diet, vitamin supplementation (calcium), stop smoking & reduce excessive alcohol use.

1. Moyle reported at the Lipodystrophy Workshop in 2000 that HIV viral control with HAART may diminish risk of osteopenia. BMD was greater in the PI-treated than the NRTI-treated and in HIV+ patients who were never treated for HIV.

2. In a switch study where patients with osteopenia and on a PI were switched to a PI-sparing regimen, there was no apparent improvement; this could mean either the PI had nothing to do with causing osteopenia or the damage was irreversible. (ICAAC 2000)

3. McGowen at Gilead Sciences (study 903) reported 24% osteopenia among patients who never received HIV therapy, suggesting that HIV itself and other risk factors may be an important contributing factor causing bone loss (Retrovirus Conference 2001)

4. Knobel of Spain found osteopenia in 25% of patients who never received HIV therapy, in 40% of patients treated with protease inhibitors, in 33% of non-protease inhibitor treated, and in 16% of healthy adults. But these differences were not statistically significant (Retro 2001)

5. Chang of Korea reported on 100 Asians and found no difference in osteoporosis and osteopenia in a HAART-experienced group vs a HAART-naïve group of patients. In this study

of 100 Koreans, the rates of decreased bone mineral density in the lumbar spine (low back) were quite similar when comparing HIV negative patients, HIV-positive, HAART-naïve and HAART-experienced patients (18-24% range) (Retro 2001).

6. Lawal of St. Luke's-Roosevelt Hospital Center in New York City found HAART did not cause osteopenia but HIV did. He reported that the rate of osteopenia among HIV positive men in 1993 was similar to the rate among HIV positive men taking HAART in 1998. DEXA scanning was used. However, bone mineral density in both groups was significantly lower than in HIV negative patients. (Retro 2000)

7. Arpadi of Columbia University reported significant reductions in BMD among children with HIV, which increased with age but it was not associated with PI use. It could have been HIV, nukes, HIV therapy or all three (Retro 2001).

8. "Avascular Necrosis" (bone death due to inadequate blood supply to the bones) Dr. J.C. Keruly of Johns Hopkins University reported 15 cases of "avascular hip necrosis" in their HIV Clinic Cohort. If required, the treatment is hipbone replacement with a metal "prosthesis" during surgery. The "incidence" rate in the current study was low but 47-fold higher than in the general HIV negative population. There was a significant trend in that the annual number of cases increased from 1995 through 2000 at their institution. Risk factors associated with this specific adverse event included steroid drug (prednisone, cortisone, others) use, low CD4 count (less than 200 cells) and a longer time with HIV, but not treatment for HIV. Nearly half of the cases had never taken a PI or NNRTI drug.

Similarly, Dr. D.M. Gaughan of Harvard School of Public Health reported 5 cases of "avascular necrosis" in HIV-infected children. The incidence rate was also much higher among HIV+ children than in the HIV negative general pediatric population. (Retro 2001).

9. At the Lipodystrophy Workshop in 2000, Andrew Carr looked at 221 HIV+ men and found 20% had osteopenia & 3% osteoporosis. Carr's opinion is that nukes contribute to bone loss. He reported that higher lactate and lower weight prior to commencing antiretroviral therapy were associated with bone loss. Lactate elevations are associated with NRTI use. There was no independent association with any other parameter, including type or duration of any antiretroviral drug or drug class, or with lipodystrophy at any site. Low spinal (but not low total) BMD was associated with both lactic acidemia and duration of nucleoside analogue therapy. Carr suggests that duration and magnitude of lactic acidemia are linked somehow to low BMD, especially in the spine. He hypothesized that the cause may be a direct effect of nucleoside analogs on osteoblast (bone-related cells) mitochondria. The other possibility is that hydroxyapatite (the principle bone salt that provides the compressional strength vertebrate bone) is being leached from bone to buffer the acid load of chronic lactic acidemia. Carr cautioned this study has limitations, as all these studies in bone loss & lipodystrophy do. The study did not look at women, children, various racial groups, or abacavir. Previously, several researchers including the group at Washington University reported an association between PI therapy and bone loss. I believe they have since recanted this proposition.

These studies suggest that there is no clear relationship between HAART and reduced bone mineral density. Also, there appears to be increasing information that HIV by itself might increase the risk of losing of bone mineral content. However, the cross-sectional design of many of these studies represents a major limitation. The preliminary results require therefore confirmation in longitudinal, prospective, well-controlled trials. Additionally, people with HIV appear to have increased incidence of traditional risk factors for osteopenia. Potential confounding cofactors that can contribute to developing osteopenia include being sedentary, cigarette smoking, nutrition (including inadequate calcium intake), current or past steroid hormones (prior exposure to steroid treatment for PCP, use of Megesterol acetate for appetite stimulation, postmenopausal hormone deficiency), excessive alcohol intake, genetics, elevated lipids, possibly lower body mass, diseases such as kidney failure & thyroid overactivity, and long-term treatment with cortisone (but not anabolic steroids, which if anything increase BMD).

Bone Studies at Retrovirus 2002

There were 2 studies of interest at the Retrovirus Conference this year. One study looked at 150 men on HAART and men who did not have HIV, all between 25 and 55 years of age. Using DEXAscans to evaluate bone loss, HIV-positive individuals had higher rates of osteopenia (45-55% vs 7-11%) and higher rates of osteoporosis (7-11% vs <2%) than HIV-negative persons. In this particular study, patients on HIV treatment may have been more likely to have bone loss than patients not on therapy, but as I stated above there have been studies showing that HIV+ patients who have never received HIV therapy may be just as likely to experience bone loss. There appeared to be little difference between patients receiving protease inhibitor or NNRTI therapy in terms of experiencing bone loss.

A second study followed 128 HIV+ persons, who were mostly white men taking HAART; and who received DEXA scans. These patients had a high rate (46%) of osteopenia (mild to moderately low BMD) or osteoporosis (severely low BMD). This could be because the study patients had additional risk factors for bone loss including being cigarette smokers, alcohol consumption of >2 drinks per day, history of significant weight loss or wasting, history of steroid use, low daily calcium intake by diet, and only 44% had moderate to high levels of physical exercise. After following patients for 72 weeks, they found no association of bone loss with any specific class of HIV antiretroviral drugs. Similar to diabetes, the authors concluded that the presence of traditional risk factors for bone loss, and factors associated with having HIV are important contributors to bone loss. Diet and calcium intake were monitored for the study patients. Interestingly, at the start of the study 61% of the patients were taking less than 1000 mg/d (RDA) of calcium and only 9% were taking calcium supplements at baseline but this rose to 35% by the end of the study (suggesting that when people find out about their bone densities they start downing the calcium and milk). By the end of the study there was a small increase in bone mineral density, suggesting that perhaps the increase in calcium intake helped (although the researchers did not evaluate this).

The presentation of these studies help move us in small steps toward a better understanding of the cause of bone demineralization among HIV-infected individuals. Research is now focused on factors other than direct antiretroviral toxicity. Patient factors, immune responses and drug effects may all act in concert. As we are learning with other metabolic complications, it is not a simple as it first seems.

Hepatitis

Hepatitis B

Adefovir is potent for HIV/HBV coinfected patients whether they have 3TC resistance or not, reducing HBV viral load by almost 5 logs. This was reported in a study at Retrovirus. Adefovir for HBV is being reviewed for approval by the FDA.

Tenofovir, a drug approved for HIV, was shown in a small preliminary study to also be very potent against HBV in coinfected patients with 3TC resistance. It reduced HBV viral load by 4.5 log.

FTC was studied in HBV monoinfected and found to be potent against HBV, and several additional new drugs are in early development for HBV.

Hepatitis C

After only 24 weeks of therapy with Pegasys+ribavirin, 44% had undetectable HCV viral load, in a study reported at Retrovirus. This compared to 15% who received standard interferon+ ribavirin. The full study is for 48 weeks of therapy with a 24-week follow-up period. Ribavirin was dose escalated, this may have effected results. Most study patients had genotype 1 and high HCV viral load.

Analysis of the results from this study suggested several important things:

(**1**) Although these results are preliminary, the response rate for the patients was not as good as seen for HCV monoinfected patients, suggesting that coinfected patients may not respond as well to HCV therapy as monoinfected patients.

(**2**) Researchers found that HIV may impair the response to HCV therapy.

(**3**) On a positive note, Pegasys+RBV was much more effective than standard interferon+RBV.

(**4**) The discontinuation rate was low in this study (14%).

IL-2: This immune modulator can increase CD4 cell counts and may be useful for patients on HAART who do not experience adequate CD4 increases. Small studies had previously suggested that IL-2 might be helpful against HCV, but a study was reported at Retrovirus showing it not to be effective against HCV.

Coinfected individuals should consider getting vaccinated against hepatitis A and B. Acute hepatitis A can be serious. A study from the federal government looked at 14,000 patients with HIV: only 14% of HCV infected patients received the hepatitis A vaccine. This may be due to the patient not wanting or tolerating them, the physician not prescribing them, or the patient not returning for the full course of the multiple injection therapy which requires multiple office visits over the course of months.

Transmission of HIV Drug Resistance

Transmission of HIV drug resistance is a growing and serious concern. Several studies have shown that an increasing number of individuals are acquiring HIV, either through sex or IVDU, that has resistance to current HIV drugs. Previously reported studies have suggested that newly infected persons with drug resistant virus may not respond as well to HAART. Safer sex and using new needles for drug use is always highly recommended.

At Retrovirus, investigators from the CDC presented study findings on drug resistance in a group of recently diagnosed and untreated HIV infected individuals as part of a 10 US city survey. They reported on 1078 individuals and showed that there is anl increase in the prevalence of resistance over the years of the study 1998-2000. They reported that resistance as measured by genotype increased from 5.5% in 1998 to 10.7% for any antiretroviral with increases in resistance for all drug classes. This rate of resistance is lower than that reported immediately below and from other reports because these study patients are chronically infected, not newly infected. As well the patients studied are a more diverse group in terms of how they were HIV infected and other factors that relate to treatment and access to care: 50% were African-American, 10% IVDUs, and 44% reporting only heterosexual exposure.

Researchers reported increasing rates of drug resistance in over 200 newly infected individuals studied in San Francisco. The overall prevalence in this selected group increased from 10.7% in 1996 to 27.6% in 2001. The increases were particularly striking for resistance to NNRTI's which increased from 0% to 17% while resistance to PI's over this time interval increased from 0% to 10%. In 270 treatment-experienced individuals, 39% were found to have NNRTI resistance, 38% PI resistance, and 60% NRTI resistance. The study authors suggested that NNRTI resistance is the easiest to transmit.

When To Begin HIV Therapy

Deferring therapy has risks

Lately we are seeing an increasing number of studies showing that a patient's ability to sustain undetectable viral load after starting HAART is reduced as CD4 counts go lower and as viral load goes higher.

On the other hand, due to the difficulties of taking HAART, including adherence and toxicities, doctors and patients have been delaying the time at which they initiate HAART. Recently, Guidelines were adjusted to suggest deferring the start of therapy from 500 CD4s to 350 and increasing the viral load threshold from 15-20,000 to 55,000. In recent years, several large studies have suggested that there is no risk to deferring therapy. At the same time there were several smaller studies suggesting there might be a risk associated with deferring therapy—reducing chance for achieving and sustaining undetectable viral load.

At the European AIDS Conference in November 2001 in Athens, a large study found that the ability to achieve and sustain undetectable viral load when starting HAART is reduced as CD4s decline and viral load increases. At this year's Retrovirus Conference two studies were reported finding that deferring therapy may have risks. Study findings suggest that patients who start therapy when CD4s are 200-350 may have increased risk for death than if they start therapy when CD4s are 350-500. The findings from these studies suggest your CD4 count and viral load when you start HAART may be key

to sustaining durable undetectable viral load. As CD4 counts go lower before starting HAART the ability to sustain viral suppression is reduced. The same appears true for viral load. As viral load is higher the ability to sustain undetectable viral load is reduced. One study found that if a person defers therapy it's important to use a potent regimen. Using a more potent regimen improved the chances for reaching and sustaining undetectable viral load even when therapy is deferred. If a patient delays therapy and is less adherent this will increase the risk for viral failure.

Another potential risk that has not been studied is the risk that the immune system might decline if therapy is started after CD4 counts decline. It has not been well studied but there is concern that deferring therapy until CD4s are low might encourage an increased risk for the development of cancers years later. At what level of CD4 count do you risk developing a cancer in the future if you defer therapy? Researchers and doctors do not know but a count of 300 CD4s has been suggested. Although the incidence of cancers may be increasing, we do not know if this is tied to starting therapy at a lower CD4 count.

Still, whenever you start HAART there are side effects and potential toxicities from the drugs, including the potential development of body changes and metabolic abnormalities (increases in cholesterol triglycerides, sugar). Some regimens can be selected which have less risk for developing these problems. Starting therapy does reduce your quality of life as you have to maintain strict adherence to taking medications in addition to the side effects/toxicities. So, in deciding when to begin therapy it is still important to weigh all these considerations – the benefits, difficulties, and risks.

Reinfection or SuperInfection

An important question for people with HIV — if I already have HIV, can I get a second virus if I have unprotected sex or share a needle? And if the second virus I get infected with is a more potent virus or one with drug resistance will that have a negative effect on me? A study presented at Retrovirus reported on one person who was newly infected with HIV and was infected with two different HIV strains of virus. The first virus, which took control, was multi-drug resistant. The second virus took over after 110 days after infection and was not drug resistant. I'm not sure researchers understand the implications of this.

The key question, which is controversial and I think relates to the above study, is – can a person with HIV get "reinfected" with a second HIV virus which is more potent or has multi-drug resistance? Although it's controversial, it appears to me and to some leading researchers I've spoken with about this that you can get reinfected with a second virus. This means that if you have unprotected sex with a person with HIV or share a needle with an HIV+ person you may get reinfected with a second virus. And if that virus is more potent or has drug resistance this may not be good for you.

Once-A-Day Therapy

D4T is now taken twice per day, every 12 hours. It is expected that a once-a-day d4T will be available in the Fall 2002.

A pilot study was reported at Retrovirus looking at Kaletra once per day. This study was conducted in treatment-naïve patients and showed that Kaletra once a day was effective, but not quite as effective as Kaletra taken twice a day. The once a day drug has not been studied in patients with protease inhibitor resistance. It will probably not be used for these patients because they will need more potent therapy. The use of Kaletra once per day still needs further study to confirm these preliminary findings. Saquinavir (1600 mg) boosted with low dose (100 mg) ritonavir taken once per day is in early research studies. Additional once a day PI therapy: amprenavir prodrug called 908 with low dose ritonavir is also in research studies. Amprenavir (1200 mg) + ritonavir (200 mg) was approved this year by the FDA for once per day therapy.

Several additional drugs are in research for once a day use. These include AZT, abacavir, 3TC, FTC, atazanavir, and nevirapine. DDI, Tenofovir, and efavirenz are already approved to be used once a day.

Pharmacogenetics: Abacavir Hypersensitivity

This is a new area of research in HIV. It is an attempt to understand a patient's genetic makeup to find out if their genes contribute to certain side effects or toxicities. If researchers can identify whether the presence of a specific type of gene can lead to experiencing certain side effects or toxicities doctors may be able to predict the occurrence of these side effects and decide not to use a specific drug for that patient. This type of research is in the early stages, but the first real and useful information was reported at Retrovirus on abacavir hypersensitivity. As you may know, about 3-5% of patients who start abacavir have to stop it due to hypersensitivity, which often is a constellation of side effects. This constellation of side effects usually include fever and may or may not include skin rash. Usually, once you start to experience the side effects of hypersensitivity they continue to worsen each day. The new research findings from two pilot studies show that by doing genetic testing of the patient there appears to be a good chance doctors may be able to predict who will experience hypersensitivity. Therefore, doctors can have a good basis to decide before taking abacavir if you will or will not experience this side effect. This research on abacavir is ongoing.

Older Folks and HIV

Untreated older folks have double the risk for reduced survival

There has been little research on HIV and treatment in older folks. A study reported at Retrovirus in over 700 individuals showed that older folks (>50 years of age) who were not treated with HAART had a lower chance for survival than younger folks who were not treated (31% vs 13% survival). But, if treated, both younger and older folks had the same survival. What does this suggest? Older folks may have a more impaired immune system and may not be able to delay therapy as long as younger folks. It also suggests that it is riskier for older folks not to be treated. Doctors or older folks themselves may not realize that they are at risk for having HIV since they do not fall into the standard risk categories. In retirement communities, people with HIV may not get properly tested.