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## I SIDE EFFECTS

### A. Damage to the power plant

The use of highly active antiretroviral therapy (HAART) has helped to reduce complications from AIDS in North America and Western Europe. Unfortunately, however, HAART-users can experience a range of side effects, including the following — which collectively is called the lipodystrophy syndrome:

- changes in body shape
- varying degrees of diabetes
- thinning bones
- increased risk of heart disease

Hampering efforts to understand why these side effects occur is the fact that people with HIV/AIDS (PHAs) are often taking combination therapy made up of treatments from at least two of the following groups of drugs:

- nukes (nucleoside analogues) — AZT (Retrovir), ddC (Hivid), ddI (Videx), d4T (Zerit), 3TC (Epivir, lamivudine), abacavir (ABC, Ziagen)
- non-nukes — delavirdine (Rescriptor), efavirenz (Sustiva, Stocrin), nevirapine (Viramune)
- protease inhibitors — amprenavir (Agenerase), indinavir (Crixivan), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Fortovase)

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PHAs who are co-infected with hepatitis C virus (HCV) may also be using interferon-alpha and the anti-HCV nuke ribavirin (Virazole).

Even though treatment regimens can be complex, researchers around the world are beginning to develop ideas about some of the causes of drug side effects. Below are some brief explanations.

Nukes can damage the energy-producing parts — called mitochondria (Mt) — of a cell, including fat cells. Over time, with continued exposure to nukes, damaged Mt become dysfunctional and dwindle in number. The end result is that a cell has less energy with which to do its work. Cells experiencing this kind of energy shortage don't work properly and can die. Here are some examples of what can happen in cases of Mt damage:

- hearing loss
- depression
- painful nerves in the hands/feet (peripheral neuropathy)
- wasting of muscle tissue, including the heart
- weakness
- fat wasting
- malfunctioning kidneys
- type 2 diabetes
- thyroid hormone abnormalities
- lactic acidosis
- nausea
- vomiting
- abdominal pain

In the time before lipodystrophy became a common problem for PHAs, Mt damage also appeared in other, HIV negative people, particularly those with neurologic problems. In such cases, doctors used the following substances to treat Mt damage:

- L-carnitine
- B-complex vitamins
- co-enzyme Q<sub>10</sub>

Use of another group of anti-HIV drugs called protease inhibitors (PI) appears to increase the risk of type 2 diabetes and possibly heart disease by increasing levels of fatty substances in the blood. The role that non-nukes play in the HIV-lipodystrophy syndrome is not clear.

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3. Walker UA, Bickel M, Volksbeck SIL, et al. Evidence of nucleoside analogue reverse transcriptase inhibitor-associated genetic and structural defects of mitochondria in adipose tissue of HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes* 2002;29(2):117-121.

4. Lim SE and Copeland WC. Differential incorporation and removal of antiviral deoxynucleotides by human DNA polymerase. *Journal of Biological Chemistry* 2001;26:23616-23623.

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## B. Check-ups for the power plant?

Nucleoside analogues (nukes) were among the earliest class of drugs developed for treating HIV/AIDS. These drugs work by interfering with a viral enzyme needed by HIV to help make new viruses. To a much lesser extent, nukes also interfere with at least one enzyme needed by cells, which is probably responsible for some of their side effects.

Conducting studies on nuke-related toxicity in people usually requires that small pieces of muscle or liver be collected for analysis. But this is not practical for regular care of PHAs. Doctors can also order tests to check for the amount of lactic acid (lactate) in the blood — high levels suggest mitochondrial (Mt) toxicity. However, higher-than-normal levels of lactate don't tell doctors exactly when their patients are going to experience symptoms of Mt toxicity.

Now researchers in Vancouver, British Columbia, may have a possible solution. Dr. Hélène Côté and Dr. Julio Montaner and other scientists have developed a novel test for measuring the amount of Mt DNA in blood samples. This is important because levels of Mt DNA decrease over time as mitochondria become damaged, such as when people are taking nukes. Dr. Côté's test relies on PCR technology — something that's commonly used in many tests, including the viral load test. If commercially developed, the new PCR-based test could be used for regular assessment of Mt toxicity in PHAs. In the following report, we describe recent research in this area done by Dr. Côté and colleagues.

#### REFERENCE

Côté HCF, Brumme ZL, Craib KJP et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *New England Journal of Medicine* 2002;346:811-820.

## C. Assessing nuke toxicity

### Study details

Doctors at St. Paul's hospital in Vancouver, British Columbia, recruited three groups of people for their study:

- 24 healthy HIV negative subjects
- 47 symptom-free HIV positive subjects who had never used anti-HIV therapy
- 8 HIV positive subjects who had symptoms of higher-than-normal levels of lactic acid (hyperlactatemia — moderate-to-severe fatigue and rapid, unintentional weight loss)

The eight subjects were all taking combination anti-HIV therapy that included the nuke d4T (Zerit, stavudine). Technicians analysed blood samples from all subjects to measure levels of DNA in Mt as well as in cells. Lactic acid levels (lactate) measurements were also performed.

### Results

The researchers found that HIV negative subjects had the highest level of Mt DNA. The second highest level was found in HIV positive subjects who had never been exposed to anti-HIV therapy; they had about half the amount of Mt DNA that HIV negative people had. The lowest level of Mt DNA was found in HIV positive subjects with symptoms of hyperlactatemia who were taking anti-HIV therapy. Indeed, their level of Mt DNA was about 22% of normal. These differences were statistically significant.

The good news is that the researchers had enough data on seven of the eight subjects with symptoms to make some important observations. They found that when seven subjects stopped taking their therapy because of severe side effects, Mt DNA levels gradually rose, reaching levels detected in HIV positive subjects who had never used combination therapy. This point is important as it shows that PHAs can recover from Mt damage. On average, it took between one and four months for Mt DNA to recover sufficiently so that PHAs could resume taking combination therapy.

There was no link between having symptoms of high levels of lactic acid and the following:

- CD4+ cell counts
- white blood cell counts
- liver enzyme levels

### Key points

1. Levels of Mt DNA were very low in PHAs who were taking anti-HIV therapy and who had symptoms of Mt toxicity.
2. The decrease in Mt DNA occurred before lactic acid levels rose — confirming a link between Mt toxicity and lactic acid.
3. Levels of Mt DNA rose when PHAs stopped taking therapy to a level near those seen in PHAs who had never used HAART. However, this level was, on average, about 40% below that of healthy HIV negative subjects. This point is important because it is likely that Mt DNA levels may not be able to rise to normal. This is possibly because HIV produces proteins that damage mitochondria. These findings may, in part, explain the fatigue that is one of the hallmarks of HIV/AIDS.
4. All eight subjects who developed hyperlactatemia were using d4T as part of their combination regimen. It is possible that d4T may be more toxic to Mt than other nukes, but this needs to be confirmed in other studies.

### More on nukes

In another study at the U.S. National Institutes of Health (NIH), researchers conducted laboratory experiments with cells and nukes. They found that **all** currently licensed nukes affected an important cellular enzyme. These researchers noted that most studies have focused on the ability of nukes to affect the activity of a cellular enzyme to some degree. However, more research needs to be done on what happens when nukes are taken up by, or incorporated into, Mt DNA. Once incorporation happens, then Mt toxicity may persist because the Mt is not quickly able to cleanse itself of the nuke, particularly if exposure to nukes continues. In light of these findings, perhaps it is not surprising that supervised drug holidays were necessary in order for subjects to recover from hyperlactatemia.

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## D. 9<sup>th</sup> Retrovirus Overview

The 9<sup>th</sup> annual Conference on Retroviruses and Opportunistic Infections was held in Seattle, Washington, February 24–28, 2002. While there were no major breakthroughs, there was some good news in the following areas:

### New drugs

Researchers are continuing to develop a variety of new drugs in the following classes: non-nukes (NNRTIs), protease inhibitors and chemokine receptor blockers. Some of these drugs should become more widely available in North America in 2003. Other new drugs continue to be studied.

### Simplifying treatment

While highly active antiretroviral therapy (HAART) is beneficial, users must often take a handful of pills several times daily. Now, new once-a-day formulations of drugs (such as Zerit XR) are being actively pursued. Doctors are also testing whether existing combination-therapy regimens can be safely and effectively taken once daily.

### Hepatitis C virus (HCV)

Long-term infection with HCV can cause liver damage. While treatment for HCV infection is available, it is unpleasant and does not work for a large proportion of people. In the time before HAART, liver transplants for PHAs who were co-infected with HCV were not encouraged. Now, because PHAs are living longer, researchers have found that liver transplants for some co-infected PHAs who have severe liver damage may be feasible.

### Reversing body shape changes

HAART-users often develop changes in body shape as fat gets redistributed around the body. For years researchers have been experimenting with changing PHAs' treatment regimens (called switching treatment) in an attempt to stop or reverse the changes in body shape. Several teams reported small but positive results in so-called "switch" studies.

In other areas the news was not as promising:

### Drug holidays

There has been a great deal of interest by PHAs in STIs (Strategic Treatment Interruptions) or drug holidays. Unfortunately, the results from studies on drug holidays have not been encouraging.

### Side effects

Warnings about new and strange side effects (such as severe muscle weakness) with commonly used AIDS drugs were reported. As well, warnings about existing side effects were strengthened by American regulatory authorities to remind doctors and their patients that AIDS drugs can cause severe side effects.

Although combination therapy has clearly saved many lives, more PHAs appear to be dying from complications related to liver and kidney damage. Whether or not this is a related side effect from treatment remains to be seen.

### Vaccines

The scale of two vaccine trials has been reduced due to disappointing preliminary results. However, this has not dampened enthusiasm for vaccine research, which continues to forge ahead.

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## E. Switching to abacavir to reduce fat wasting

At the 9<sup>th</sup> Retroviruses conference, there was a great deal of interest in creating regimens to avoid or reduce side effects. Although HAART has many benefits, its use is associated with side effects, including body shape changes. In such cases, fat that lies under the skin — called subcutaneous fat — disappears from the face, arms and legs. In some cases fat gets deposited in the breasts, abdomen and back of the neck (buffalo hump). Precisely why these strange changes occur is not clear, but a research team in Australia has a theory. According to the team, nucleoside analogues (nukes) can damage the energy-producing parts — called mitochondria — of fat cells. Unable to produce enough energy, fat cells malfunction and die. Certain nukes called "T" drugs (thymidine analogues) may have a closer link to fat wasting than other nukes. Examples of these "T" drugs are:

- d4T (Zerit, stavudine)
  - AZT (Retrovir)
-

To try to remedy HAART-related fat wasting, the Australian researchers conducted a study in which some HIV positive subjects who were using d4T or AZT as part of their combination therapy could replace (or switch) either of these “T” drugs with another nuke — abacavir (ABC, Ziagen). Researchers monitored subjects for six months to assess if there were any changes in body shape.

### **Study details**

Researchers enrolled 105 subjects with the following profile:

- all were male
- average age – 44 years
- average CD4+ count – 577 cells
- they had been using nukes for about 5½ years
- they had about three years’ exposure to AZT and another three years’ exposure to d4T
- 56% were using protease inhibitors
- they had moderate-to-severe fat wasting
- at least 80% of subjects had fat wasting in the face, arms, legs and buttocks
- no subject had previously used abacavir

The team randomly assigned 50 subjects to substitute their “T” nuke for abacavir and the remaining 55 subjects to continue taking their existing regimen.

### **Results**

After six months, there was an increase in the fat content of the arms and legs of subjects taking abacavir compared to subjects who continued to take their pre-study therapy. This difference was statistically significant; that is, not likely due to chance alone. However, the rise in fat levels was only about 10% — an increase so small that the untrained eye would have difficulty noticing. Indeed, this increase in subcutaneous fat in the limbs was detected using X-ray scans called DEXA. The rise in fat in abacavir-users occurred regardless of the following factors:

- whether or not they used a protease inhibitor
- how long they had previously used nukes
- even if they had “profound” fat loss at the beginning of the study

Levels of abdominal fat in the abacavir group declined slightly. Levels of lactic acid in the blood — higher-than-normal levels suggest mitochondrial damage — declined slightly in the abacavir group, but did not decline in the other subjects. There were no significant changes in lipid levels — cholesterol and triglycerides — in the blood of subjects during the study.

On average, viral load remained suppressed in subjects who switched to abacavir.

### **Adverse events**

Two subjects in the non-abacavir group had heart attacks and 10% of subjects receiving abacavir developed a hypersensitivity syndrome associated with the use of that drug.

### **Key issues**

Readers ought to keep these results in perspective — the improvements in subcutaneous fat were small and needed to be confirmed with the use of X-rays. It is possible that it may take years, as the researchers theorize, for subcutaneous fat to reappear. The results from Australia were similar to those reported in other studies in which subjects were switched to abacavir to assess changes in fat wasting. This and other studies lay the groundwork for future research. For instance, should PHAs use combinations of nukes that avoid or minimize their exposure to “T”-containing ones such as AZT and d4T? Here are some possible combinations:

- abacavir and tenofovir (Viread)
- ddI (Videx) and 3TC (lamivudine, Epivir)
- ddI and tenofovir
- abacavir and ddI

The problem with this list is that there are only a few drugs from which to choose. Moreover, the listed drugs have other side effects. An alternative strategy may be to cycle the use of **all** nukes, using one combination for a fixed period of time, say six months to one year, and then switching to another combination for the next time period and so on. These are merely some possibilities of many that require investigation. Before rushing out to switch nukes, PHAs would be far better off to await the results of further studies that carefully weigh the risks (increased viral load, different side effects) and benefits (small, hard-to-notice increases in subcutaneous fat) of changing their regimens. Although nukes were among the first group of drugs to be approved for the treatment of HIV/AIDS, there is still a lot about them that needs to be understood.

### **REFERENCE**

Carr A, smith D, Workman C, et al. Switching stavudine or zidovudine to abacavir for HIV lipodystrophy: a randomized, controlled, open-label, multicentre, 24-week study. Abstract 32.

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## F. Using abacavir to avoid lipid problems

A common side effect of some HAART regimens, particularly those containing protease inhibitors, is the development of higher-than-normal levels of lipids — cholesterol and triglycerides — in the blood. Increased levels of lipids could raise the risk of developing cardiovascular disease as well as diabetes. To compare the effect of different HAART regimens on lipid levels and other side effects, researchers at GlaxoSmithKline and elsewhere conducted a study of the following regimens:

- AZT and 3TC (sold in one tablet called Combivir) and abacavir (ABC, Ziagen)
- Combivir and nelfinavir (Viracept)
- d4T (Zerit, stavudine), 3TC (Epivir, lamivudine) and nelfinavir

### Study details

Researchers enrolled 258 HIV positive subjects who did not have diabetes. Before entering the study none of the subjects had previously used anti-HIV drugs. Subjects had the following profile before they began to use the study drugs:

- 50% female, 50% male
- average CD4+ count — about 330 cells
- average viral load — about 25,000 copies

Subjects were monitored for about one year.

### Results — Viral load and CD4+ cell counts

Between 39% and 48% of subjects achieved viral loads below the 50 copy mark. The differences in viral load changes between the three study groups was not statistically significant. In general, subjects gained about 150 extra CD4+ cells during the study. Again, there were no significant differences in CD4+ cell increases between the three regimens.

### Lipids

In general, lipid levels remained lowest among those subjects who used three nukes (NRTIs) — Combivir with abacavir — than in those who used protease-inhibitor-containing regimens. It is noteworthy that subjects who used d4T were significantly more likely to develop increased levels of lipids than subjects who did not use this nuke.

### Side effects

Nausea was more common among abacavir-users and diarrhea was more common among nelfinavir-users.

Throughout the study technicians analysed blood samples from subjects to measure levels of lactate (lactic acid). This is because higher-than-normal levels of lactate suggests damage to the energy-producing parts of cells called mitochondria. People with high lactate levels may develop the following:

- persistent fatigue
- nausea
- vomiting
- loss of appetite
- swollen, fatty liver

On average, lactate levels were highest in subjects using the nuke d4T than in those who did not use this drug.

The results of the study suggest that over a period of about one year, a combination of AZT, 3TC and abacavir is as beneficial as a protease-containing regimen in HIV positive people who have never previously used HAART. Moreover, the abacavir combination is significantly less likely to alter lipid levels than a PI-containing combination. Although the study used Combivir and abacavir, all three drugs are available in one tablet sold under the brand name Trizivir. The study is ongoing and further results may be available next year. GlaxoSmithKline and the researchers should be praised for recruiting such a large proportion of women in an HIV/AIDS study.

### REFERENCE

Kumar P, A Rodriguez-French, Thompson et al. Prospective study of hyperlipidemia in ART-naïve subjects taking Combivir/abacavir (COM/ABC), COM/nelfinavir (NFV), or stavudine (d4T)/lamivudine (3TC)/NFV (ESS40002). Abstract 33.

## G. Cause of serious illness among HAART-users not clear

HAART has dramatically decreased AIDS-related deaths in North America and Western Europe. Despite this benefit, some PHAs in these regions can still develop serious complications. It is therefore important that long-term monitoring of HAART-users be conducted to find out the following:

- the causes of serious illness in this population
- ways of predicting the onset of complications
- ways of preventing these problems

One team of researchers at the National Institutes of Health (NIH) and elsewhere in the United

States have begun this work and we report on their results.

### **Study details**

Researchers collected data from 3,227 HIV positive subjects who participated in several clinical trials between the years 1996 and 2001. They had the following profile:

- 16% female, 84% male
- average CD4+ count – 241 cells
- 37% had AIDS before entering the NIH study
- 46% had previously not used anti-HIV drugs
- at least 22% had hepatitis B and/or C viruses

On average, subjects were monitored for about 1½ years and they received HAART once they enrolled in a clinical trial.

### **Results — Defining the problem**

The NIH researchers analysed their data, in part, by collecting information on the number of “AIDS-related events” such as AIDS-related infections. They also collected data on serious or life-threatening complications (which they called “grade IV events”). These complications included such events as bone marrow damage, inflamed pancreas glands, liver-related problems and so on. In analysing their data, here is what the researchers found that occurred over the course of their study:

- number of AIDS-related events – 316
- number of grade IV events – 663

As a proportion of the study population, the figures can be expressed as follows:

- AIDS-related events – 14%
- grade IV events – 28%

Thus, grade IV events were twice as common as AIDS-related illnesses.

### **Survival**

After about 30 months, about 10% of subjects died. The risk of death from AIDS or a grade IV event was about equal. This attests to the severity of such complications. Although PHAs who had more than 200 CD4+ cells had a relatively low risk of developing AIDS (6%), their risk of developing a grade IV event was about four times greater (26%).

### **Which grade IV events occurred**

The most common grade IV event was complications from liver disease, related

to hepatitis virus infection. Other common problems included:

- bone marrow damage
- painfully swollen pancreas glands (pancreatitis)
- “psychiatric” difficulties
- cardiovascular complications
- kidney-related problems

Unfortunately, researchers were unable to find out the cause(s) of the grade IV events reported. Indeed, it is important to remember that many factors can play a role in the development of grade IV events, including the following:

- stage of HIV disease
- co-infections and other pre-existing problems
- drug interactions
- toxicity of anti-HIV drugs and other medications
- poor nutrition
- substance use (including alcohol and recreational drugs)
- a person’s genetic background

Researchers were also unable to make a link between specific HAART regimens and grade IV events.

This large American study points to the need for conducting more carefully designed long-term studies of anti-HIV therapies to help find out how different therapies affect survival and the development of serious complications (grade IV events). This would better clarify the risks and benefits of specific anti-HIV therapies.

### **REFERENCE**

Reisler R, Han C, Burman W, et al. Incidence of grade IV events, AIDS and mortality in a large multicenter cohort receiving HAART. Abstract 36.

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## **H. Protease inhibitors and lipid-lowering drugs — interactions**

### **Background and summary**

People with HIV/AIDS (PHAs) who use HAART can develop higher-than normal levels of lipids — cholesterol and triglycerides — in their blood. These changes can increase the risk of cardiovascular disease. To reduce this risk, doctors can prescribe lipid-lowering drugs, commonly called “statins,” examples of which include the following:

- Lipitor – atorvastatin
  - Mevacor – lovastatin
  - Pravachol – pravastatin
  - Zocor – simvastatin
-

Unfortunately, the enzymes in the intestine and liver that help absorb and break down these drugs also do the same to protease inhibitors. Thus, statins and protease inhibitors have the potential to interact as follows:

- raise or lower levels of one or both classes of drugs
- intensify pre-existing side effects
- induce new side effects
- reduce the effectiveness of anti-HIV therapy

To find out about these potential interactions, researchers in the U.S. conducted a study called ACTG A5047. According to their results:

- PHAs who use the protease inhibitor (PI) ritonavir (Norvir) together with the PI saquinavir (Fortovase) should avoid using Zocor.
- PHAs who take those PIs may need to adjust their dose of Pravachol.
- Users of the PI nelfinavir (Viracept) do not need to adjust their dose of Pravachol.

### **Study details**

Researchers recruited 56 HIV negative subjects (59% female, 41% male) and divided them into four groups where, at some point over the course of 18 days, they were given the following drugs:

- Group 1: Pravachol 40 mg/day, ritonavir-saquinavir
- Group 2: Zocor 40 mg/day, ritonavir-saquinavir
- Group 3: Lipitor 40 mg/day, ritonavir-saquinavir
- Group 4: Pravachol 40 mg/day, nelfinavir

Blood samples were collected throughout the study, which lasted for about 18 days.

### **Results**

In regard to the level of statins in the blood of subjects, researchers found that the following occurred:

- Group 1 — Pravachol levels fell by 50%
- Group 2 — Zocor levels rose by more than 3,000%
- Group 3 — Lipitor levels increased by almost 80%
- Group 4 — Pravachol levels were not significantly affected

Importantly, levels of all three protease inhibitors were not significantly affected by the use of statins. The doctors suggested the following courses of action for PHAs using ritonavir-saquinavir:

- Zocor and Mevacor (lovastatin), which is processed by the body in a similar manner, “should be avoided.”
- Lipitor “should be used with caution” and doctors may choose to prescribe a starting dose of 10 mg/day to a maximum of 40 mg/day.
- Pravachol appears to be safe to use with all three protease inhibitors.

Although the impact of statins on the relatively new PI lopinavir (in Kaletra) was not researched in the current study, the authors did draw attention to other experiments using lopinavir. There, researchers found that Lipitor levels were increased about five times greater than normal with the use of Kaletra.

Although statins are generally safe, the study authors note that they can cause muscle pain, weakness, and wasting in a small number of PHAs.

### **REFERENCE**

Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG study A5047. *AIDS* 2002; 16(4):569-577.

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### Disclaimer

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

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Summarize the basics of HIV treatment in English and French and include a glossary.

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