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I ANTI-HIV AGENTS

A. Trizivir approved in Canada

On 17 October 2001, Health Canada approved the sale of Trizivir tablets in Canada. Trizivir contains the following three drugs:

- AZT (Retrovir) – 300 mg
- ABC (abacavir, Ziagen) – 150 mg
- 3TC (lamivudine, Epivir) – 300 mg

Trizivir was approved for the treatment of adults with HIV/AIDS, at a dose of one tablet twice daily, with or without food. Side effects that may occur from Trizivir include the following:

- nausea
- vomiting
- diarrhea
- difficulty falling asleep
- fatigue
- rash
- temporary, minor hair loss

Abacavir can cause a hypersensitivity reaction. People with HIV/AIDS who experience this reaction should never use abacavir or Trizivir again.

The cost of a month's supply of Trizivir is about \$945 CND, which is the cost of buying all three drugs separately.

A CATIE Fact Sheet on Trizivir is under development and will be available shortly.

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B. Caution with nelfinavir and some lipid-lowering drugs

Protease inhibitors (PIs) are often used as part of combination therapy for people with HIV/AIDS (PHAs). Examples of protease inhibitors include the following:

- amprenavir (Agenerase)
- indinavir (Crixivan)
- Kaletra (lopinavir/ritonavir)
- nelfinavir (Viracept)
- ritonavir (Norvir)
- saquinavir (Fortovase)

One of the side effects associated with this group of drugs is that they can increase levels of fatty substances in the blood, known as lipids, including cholesterol and triglycerides. Increased levels of these lipids raises the risk of heart disease.

To help reduce the risk of this complication, doctors often encourage their patients to exercise regularly, stop smoking and make changes to their diet. If these changes do not help, doctors then prescribe lipid-lowering drugs, commonly called statins.

Because statins and PIs are often processed by the same enzymes in the gut and liver, these two groups of drugs can interact. Specifically, PIs have the potential to raise or lower levels of statins in the blood, and vice versa. This interaction can increase the risk of new side effects or make pre-existing side effects worse. It is also possible that the effectiveness of PIs can be reduced because of drug interaction(s). To find out about possible drug interactions between PIs and statins, researchers in the U.S. conducted small, short studies on 32 healthy, HIV negative subjects (16 female, 16 male) who were given one of the following statins for one month:

- atorvastatin (Lipitor) – 10 mg/day
- simvastatin (Zocor) – 20 mg/day

After taking one of these drugs for two weeks, subjects also received nelfinavir 1,250 mg twice daily for 14 days. All drugs were taken with food.

Results – Statins

The researchers found that there were indeed interactions between nelfinavir and the statins. In the case of Lipitor, the amount of this drug that was absorbed nearly doubled when it was taken with nelfinavir. When Zocor was taken with nelfinavir, levels of this statin in the blood were

six times greater than when it was not taken with nelfinavir. Levels of these drugs in the blood did not differ between females and males.

Results – Nelfinavir

Nelfinavir levels in the blood were not affected by the use of either statin. According to the researchers, the most commonly reported side effect of nelfinavir was diarrhea — 53% of subjects reported this problem.

What to do

Statins can cause a range of side effects including fatigue and, more seriously, a form of muscle damage called rhabdomyolysis. To reduce the risk of developing this painful complication, the manufacturer of nelfinavir suggests that Zocor not be used by people who are taking nelfinavir. They also suggest that if Lipitor is prescribed for nelfinavir-users, it should be used with caution, starting at the lowest dose — 10 mg/day.

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II SIDE EFFECTS

A. Lipodystrophy — introduction

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), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Fortovase), lopinavir/ritonavir (Kaletra)

PHAs who are also 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. 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
- 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 Q₁₀

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.

In this section of *TreatmentUpdate* 123, we present highlights from the **3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV**, 23-26 October 2001. We will be focusing on the following issues:

- blood sugar problems
- fat redistribution
- specific drug toxicities

In the following issue of *TreatmentUpdate*, further reports from this conference will appear, covering such aspects as:

- liver damage
- hormonal problems

Unless otherwise noted, all references are from the lipodystrophy workshop.

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B. Glucose — from food to blood sugar

The food we eat can be divided into three basic groups:

- proteins
- fats
- carbohydrates – starch and sugar

In different parts of the intestine these groups of food get broken down or digested. Sugar or glucose is absorbed from the intestine into blood. The blood carries glucose around the body to cells. Using specialized proteins called glucose transporters, cells can then pull in glucose from the blood. Once inside the cell, glucose can be “burnt” to release energy.

Highs and lows of blood sugar

Because cells are very dependent on glucose for energy, the body tries to maintain blood sugar levels within a normal range using the hormone

insulin. When we don't eat enough food, the liver and kidneys try to maintain blood sugar levels by breaking down stored starch or protein and converting them into glucose.

After a meal, blood sugar levels usually rise and excess glucose gets deposited in fat and muscle cells. This storage is made possible because of the work of glucose transport proteins, activated by insulin.

Problems with insulin

Although insulin helps to activate glucose transporters to pull in blood sugar, this process can be impaired. When this happens, cells become less sensitive to the effects of insulin — a condition called insulin resistance. The development of insulin resistance is one of the earliest signs of the beginning of diabetes. In turn, having diabetes greatly increases the risk of developing cardiovascular disease.

C. Sugar blues and protease inhibitors

As previously mentioned, protease inhibitors (PIs) can increase the risk of type 2 diabetes. Here are some findings from several reasearch teams. Readers should note that although some of this work focuses on the PI indinavir, it is likely that all PIs have similar effects.

Just one dose

In one experiment, researchers in San Francisco gave a single dose of indinavir 1,200 mg or fake indinavir (placebo) to six healthy, HIV negative male subjects. The researchers found that indinavir significantly impaired the ability of insulin to help move glucose into cells, likely by reducing its effect on glucose transporters.

Impairing the work of glucose transporters may not be the only way that PIs cause sugar problems. German researchers have found that even when glucose is able to get inside a cell, HAART-users have difficulty breaking it down to release energy.

Reversing insulin resistance

Doctors are testing a number of drugs, singly and in combination, to help increase the body's sensitivity to insulin. Examples of these drugs include the anti-diabetic drugs metformin (Glucophage) and the glitazones — pioglitazone (Actos) and rosiglitazone (Avandia). The glitazones may also help to slow down or stop

the fat redistribution that can occur in PHAs with lipodystrophy.

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D. Metformin — long-term results

Results from a placebo-controlled study of metformin showed that this drug clearly helped insulin resistance and decreased weight and blood pressure in HIV positive subjects experiencing lipodystrophy.

After the initial three-month placebo-controlled part of the study, researchers offered subjects on placebo the option of receiving metformin. Those subjects who had received metformin from the start of the study could continue to do so provided that they had obtained benefit from the drug during the initial three-month phase.

A total of 19 subjects (2 female, 17 male) decided to enter this extension of the original three-month study. Their profile was as follows:

- average age – 45 years
- average viral load – between 1,100 to 1,700 copies
- average CD4+ count – about 480 cells

The dose of metformin used was 500 mg twice daily.

Results

Researchers monitored subjects for a total of nine months. During the initial three-month part of the study, insulin levels fell significantly only among those subjects who received metformin. This decrease was maintained for the rest of the study. In those subjects who initially received placebo, insulin levels fell significantly only after they received metformin in the second part of the study.

Those subjects who received metformin for a total of nine months had the greatest loss of excess weight, particularly of fat around the waist, compared to subjects who received the drug for only six months.

Side effects

According to the researchers, mild diarrhea occurred in 75% of subjects who received metformin but this problem cleared between three and six months after they started using the drug. No serious side effects were reported. Nor did anyone develop lactic acidosis — a side effect of metformin therapy.

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E. Focus on fat

In the lipodystrophy syndrome, strange changes in the distribution of fat occur. For instance, it is not uncommon for fat in the face, arms and legs to disappear while fat in the breast and stomach increase. As well, levels of fatty substances — cholesterol and triglycerides — tend to increase, particularly in PHAs who use HAART.

It is becoming increasingly clear that both protease inhibitors (PIs) and nukes play a role in the lipodystrophy syndrome. Nukes can affect the ability of fat cells to produce energy. These drugs can also cause fat cells to waste away. As previously mentioned, PIs can affect the ability of fat cells to absorb and burn glucose (sugar) to release energy. They also appear to affect the growth and development of fat cells. PIs can block the production of new fat cells and, over the long term, can cause mature fat cells to commit suicide, or apoptosis. The net effect of this is to cause fat, at least in some places, to disappear. Thus it is possible that nukes and PIs taken together have an even greater effect on the loss of fat than either group of drugs alone.

In laboratory experiments with fat cells, French researchers have found that the anti-diabetic drugs known as the glitazones are able to reverse the negative effects that PIs can have on fat cells. Therefore, glitazones have the potential to stop or

even reverse some of the signs/symptoms of lipodystrophy — at least those signs/symptoms related to fat redistribution. This potential beneficial effect of glitazones needs to be tested in controlled clinical trials.

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F. Actos (pioglitazone)

For their study of the glitazone Actos (pioglitazone), researchers in Geneva recruited nine HIV positive subjects who were using HAART. That all subjects were taking anti-HIV drugs is important because Actos is processed in the liver by the same enzyme that helps break down protease inhibitors and non-nukes. This enzyme is called p450 3A4. Researchers gave Actos at a dose of 30 to 45 mg/day for six months.

Results

On average, subjects did not experience significant changes in weight. Levels of cholesterol remained stable while triglyceride levels showed a trend to decrease over time. Insulin resistance was normal at the start of the study and remained that way throughout the trial. X-ray scans did not detect any significant changes in fat redistribution over a period of six months.

Importantly, Actos did not appear to cause any detectable liver damage. Viral load levels remained stable in eight of nine subjects over the six months of the study.

Although controlled studies of Actos in HIV positive people are needed, the results of this small, short-term study suggest that Actos does not interfere with anti-HIV medication levels in the blood. Actos may also stop lipodystrophy from becoming worse, as four of nine subjects claimed that their fat redistribution improved while taking Actos.

Future studies of Actos in HIV positive people need to focus on the long-term impact of this drug on the following areas:

- liver health, particularly in people with hepatitis B and C
- the immune system
- detailed drug interaction experiments

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G. Rosiglitazone for lipodystrophy?

Another drug that is part of the glitazone group is rosiglitazone (Avandia). This drug also helps to make cells more sensitive to insulin and thus reduces high blood sugar levels. Doctors are prescribing this drug for their patients, hoping that Avandia will help prevent or reduce signs/symptoms of lipodystrophy.

A team of doctors in Houston, Texas, reviewed data from their clinic on PHAs who had been given Avandia. The doctors reported results on nine PHAs (2 female, 7 male) who had the following profile:

- average age – 52 years
- average CD4+ count – 500 cells
- average viral load – 1,243 copies

- five subjects were using protease inhibitor-containing combinations

Avandia was used at a dose ranging between 4 and 8 mg/day. After six months of using this drug, the medical team reported that four subjects experienced decreased fat wasting and/or fat redistribution. Controlled studies of Avandia are needed to find out about the long-term impact of this drug for the following reasons:

- to confirm and extend these findings
- to assess the safety of Avandia, particularly in PHAs co-infected with hepatitis C

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H. Toxicity profile of HAART

Because there is no combination of anti-HIV drugs that is best for everyone, therapy has to be tailored to the needs of each person. Decisions about choosing therapies are usually based on individual factors such as CD4+ cell count, viral load and the presence of symptoms of HIV/AIDS. Other factors, such as the ability to meet food, water and strict schedule requirements of certain regimens and the ability to endure certain side effects, likely play a role as well. Another point to bear in mind is that in the real world reports of side effects are usually greater than those that are received during clinical trials.

Doctors in Madrid, Spain, reviewed data on 499 subjects with HIV/AIDS who started taking HAART between the years 1996 and 2000. Their aim was to find out about drug-related side effects. These doctors collected data from PHAs attending an HIV/AIDS clinic.

Results

Overall, about 34% of subjects (172 subjects) developed drug-related side effects. In most of these cases (145 of 172 subjects, or 84%), subjects had to stop using the drug that caused the side effect. The following is a list of drugs and the proportion of users who experienced side effects as well as the most common side effects:

- protease inhibitors – 29% (kidney dysfunction, diarrhea)
- non-nukes – 23% (skin rash, dizziness, difficulty falling asleep, poor concentration)
- nukes – 7% (low levels of red blood cells, nausea, vomiting, diarrhea)

The drugs that caused the most side effects were as follows:

- indinavir (Crixivan)
- nevirapine (Viramune)
- efavirenz (Sustiva, Stocrin)

The researchers found that, on average, subjects had taken HAART for about a year before signs/symptoms of lipodystrophy appeared.

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I. Hepatitis C treatment, HAART and side effects

Increasingly, doctors are using the new, long-lasting form of interferon alpha called peg-interferon (sold under the brand names Pegasys or Peg-Intron) and the drug ribavirin (Virazole) to treat hepatitis C virus (HCV) infection. Sometimes this therapy is given to PHAs who are also using HAART. It is important to note that most HAART regimens contain nukes — AZT, ddI, 3TC and similar drugs — and that the toxicity from nukes is thought to underlie many of the problems seen in the lipodystrophy syndrome. This point is noteworthy because a key part of HCV treatment is the use of the anti-HCV nuke ribavirin (Virazole, Virazid). Therefore, some doctors are concerned that use of ribavirin may intensify certain aspects of the lipodystrophy syndrome, such as fat wasting.

Study details and results

Researchers in France, concerned about this possibility, are studying the impact of HAART and anti-HCV treatment. They reported details on seven subjects who received the following therapy:

- 1 subject – peg-interferon and HAART
- 6 subjects – peg-interferon, ribavirin and HAART

Results

Within three months of starting their anti-HCV treatment, the following complications developed:

- all subjects lost weight
- three of the seven subjects developed fat wasting in their arms, legs and face
- four of the seven subjects had pre-existing fat wasting become worse

After three months the following complications developed:

- all subjects developed severe tiredness and nausea
- in three subjects the level of lactic acid in the blood rose to higher-than-normal levels

After the subjects stopped their anti-HCV therapy and switched their anti-HIV nuke component of HAART, high levels of lactic acid in the blood did not immediately decline.

High levels of lactic acid and fat wasting are not the only problems that some PHAs face when treated with HAART and anti-HCV drugs. Doctors in Madrid, Spain, reported on 35 subjects (32% female, 62% male) who received peg-interferon (50 micrograms/week) and ribavirin (800 mg/day); 31 of these subjects were also receiving anti-HIV therapy. Over a period of six months the following occurred:

- 37% had to reduce their dose of anti-HCV medication because of temporary bone marrow toxicity
- 9% had to stop anti-HCV therapy because of severe bone marrow toxicity

Not surprisingly, anemia was more frequent in subjects who were taking AZT as part of their HAART regimen than in subjects who used d4T instead.

A third group of researchers, also in Madrid, reported on the toxicity of anti-HCV treatment in combination with HAART in 43 co-infected subjects. After an average of nearly six months, three subjects developed signs/symptoms of higher-than-normal levels of lactic acid (hyperlactatemia) including the following:

- fatigue
- lack of appetite
- weight loss
- vomiting

Readers should note that higher-than-normal levels of lactic acid in the blood can occur without the presence of symptoms. According to the study team, high lactic acid levels occurred in twice as many subjects receiving ddI as compared with other nukes. One subject died as a result of complications from hyperlactatemia.

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J. Can delavirdine substitute for ritonavir?

The protease inhibitor (PI) ritonavir (Norvir) is often used together with another protease inhibitor such as amprenavir (Agenerase), indinavir (Crixivan) or saquinavir (Fortovase) because ritonavir can boost the level of these other PIs to a higher level than they would ever reach if they were taken without ritonavir. A ritonavir-boosted regimen often has the advantage of better anti-HIV activity than a single-PI regimen. Boosted regimens also allow PHAs to take their pills twice daily rather than three times daily. Another advantage of boosted regimens is that they often involve fewer pills than do unboosted regimens.

Unfortunately, a side effect of ritonavir and other PIs is that levels of certain lipids — cholesterol and triglycerides — usually rise above normal levels in people who use these drugs. Over time, if this increase continues, the risk of developing cardiovascular disease and diabetes increases. One possible way of dealing with this issue is to substitute the non-nuke delavirdine (Rescriptor) for ritonavir in PI-boosted regimens. This may be possible because delavirdine can also boost PI levels.

Study details

Doctors in Chicago, Illinois, reviewed medical records of eight male subjects who had initially used ritonavir either by itself or to boost levels of another PI — saquinavir, nelfinavir (Viracept) or indinavir. All subjects later switched their ritonavir for delavirdine-boosted regimens, using that non-nuke to raise levels of PIs.

Results

The doctors found that when subjects switched to a delavirdine-boosted regimen, their lipid levels fell, on average, by about 50%.

Caution and concerns

Although these findings are encouraging, before there's any rush to dump ritonavir, further study is needed to do the following:

- confirm that delavirdine can indeed boost PI levels
- confirm that the delavirdine-boosted PI levels reach as high as those levels seen with ritonavir

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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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