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I ANTI-HIV AGENTS

A. Delaying therapy — the pendulum swings back

Since 1996 the availability of highly active antiretroviral therapy (HAART) in North America and Western Europe has helped reduced death rates from AIDS-related complications. Once the benefit of HAART became apparent, doctors were initially aggressive in prescribing it, even for their patients who had relatively high CD4+ T-cell counts. With the passage of time, however, it has become clear that HAART has limitations, including the following:

- issues of tolerability
- sometimes dangerous side effects
- the development of drug resistance
- complex adherence requirements
- therapy is not a cure

As a result, doctors and their patients are increasingly delaying therapy and treatment guidelines have been revised. Yet the important question “When is the best time to start therapy?” has not been answered and is something with which doctors and people with HIV/AIDS (PHAs) struggle. Recently, results from two large studies that can help decision-making when it comes to the issue of starting therapy have become available in the *Journal of the American Medical Association (JAMA)*. In these studies, researchers examined the effect of starting HAART in PHAs at different stages of HIV disease who had not previously used anti-HIV drugs. In the first study, conducted in Europe with about 3,000 subjects, researchers were trying to find out if PHAs with a high viral load were less likely to achieve a suppressed viral load (fewer than 500 copies) than PHAs who started therapy with relatively low viral loads. In analysing

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the data, the researchers found that having a high viral load or low CD4+ cell count were not barriers to a PHA's ability to achieve a suppressed viral load while taking HAART.

A second study, conducted in British Columbia, confirmed and extended the above findings. In this Canadian study, researchers collected data on more than 1,200 subjects who started taking HAART. Tracking the subjects over a two-year period, the researchers found that those who started therapy with 200 or more CD4+ cells had a relatively low risk of developing AIDS or dying compared to subjects who started therapy with fewer CD4+ cells. Based on the results of these two large studies, an editorial suggested the following general points:

- It would be reasonable to focus “primarily” on the CD4+ cell count (rather than on viral load) when trying to decide when to begin therapy.
- Having a CD4+ count of 200 cells marks a critical point in the course of HIV disease. According to the results from the BC study, it is probably best if HAART is started before the CD4+ count falls below this level.

Of course, these two points are general statements. Readers should note that in some PHAs the decline in CD4+ cell counts may be rapid. Frequent monitoring of these PHAs may help their doctors decide when to begin therapy before the CD4+ count falls below the 200 cell mark. Overall, the results of these two studies act as a guide for clinical decision-making.

In this issue of *TreatmentUpdate*, we review data from these two studies, focusing on the impact of therapy initiated at different stages of HIV disease. In particular, we will be looking at the data on survival.

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B. Response to HAART depends on T-cell count

Study details

Researchers in Western Europe analysed information collected from 3,226 HIV positive subjects, all of whom began therapy with at least three drugs taken in combination. These subjects were monitored for up to three years after they started therapy. Researchers were mainly interested in learning about the ability of therapy to suppress viral load in subjects with different CD4+ T-cell counts. The average profile of subjects at the start of the study was as follows:

- 27% female, 73% male
- 25% injection drug users
- 33% were heterosexual
- 43% were men who had sex with men
- 22% had AIDS
- the pre-study averaged viral loads and CD4+ cell counts for the entire group of 3,226 subjects were not available

Also at the start of the study, researchers divided subjects into three smaller groups based on their CD4+ cell count as follows:

- fewer than 200 cells
- between 200 and 349 cells
- 350 or more cells

Results — based on CD4+ cell counts

By the 8th month of the study, the proportion of subjects in each of the three CD4+ cell groups with a suppressed viral load (fewer than 500 copies) was as follows:

- fewer than 200 cells – 78%
- between 200 and 349 cells – 86%
- 350 or more cells – 83%

These differences between the three groups were not statistically significant.

Results — based on viral load

Another way researchers could group subjects was by their viral load at the start of the study. Those subjects who entered the study with relatively high viral loads — at least 100,000 copies — took significantly longer to achieve a suppressed viral load (fewer than 500 copies) than people who started the study with a relatively lower viral load — fewer than 100,000 copies. However, after four months of HAART, differences between the two groups began to grow smaller such that by the 8th month of the study the proportion of subjects in

each group who had fewer than 500 copies was similar.

Other factors

Other factors, such as the sex of the subjects or their having AIDS at the start of the study, had no significant impact on their ability to achieve a suppressed viral load.

Survival

The number of deaths that occurred during the study by CD4+ count grouping was as follows:

- fewer than 200 cells – 104 deaths
- between 200 and 349 cells – 20 deaths
- 350 or more cells – 13 deaths

Adjusting for the number of people in the study and the length of time they were monitored, the researchers calculated that the risk of death for subjects who started therapy when their CD4+ count was below the 200 cell mark was three times greater than for subjects who started therapy with between 200 and 349 CD4+ cells.

AIDS or death

Another way researchers analysed the data was to note the numbers of subjects who developed AIDS-related diseases or who died during the study in the following manner:

- fewer than 200 cells – 267 subjects developed AIDS or died
- between 200 and 349 cells – 44 subjects developed AIDS or died
- 350 or more cells – 32 subjects developed AIDS or died

According to their calculations, the researchers found that subjects who started therapy when their CD4+ count was below the 200 cell mark were at least five times more likely to develop AIDS-related diseases or die compared to subjects who started therapy when their counts were 350 cells or greater. This difference between the two groups was statistically significant; that is, not likely due to chance alone.

Key points

Consensus is emerging that PHAs should start HAART before CD4+ counts fall below the 200 cell mark. The study researchers note that “how close to this value the CD4+ cell count should be permitted to [fall]” before therapy is initiated is something over which there is no consensus. Indeed, the timing of therapy for an individual PHA may depend on “the degree of CD4

depletion [doctors and PHAs are] willing to tolerate.”

1. In this large study, researchers did not find that viral load responses to HAART were worse in PHAs who had between 200 and 349 CD4+ cells compared with PHAs who had higher cell counts in “either the short-term or long-term.”

2. Researchers did not find that viral load responses to HAART were worse in PHAs whose pre-treatment viral load ranged between 10,000 to 100,000 copies and those who had fewer than 10,000 copies.

Among subjects who entered this study with a viral load greater than 100,000 copies, it took longer for their viral load to fall below the 500 copy mark once they began therapy than it did for subjects who had pre-HAART viral loads below the 10,000 copy mark. Nonetheless, by the 8th month of therapy the proportion of subjects with suppressed viral loads was similar regardless of whether pre-study viral loads were high (100,000 copies) or low (fewer than 10,000 copies). As well, similar proportions of subjects experienced virologic failure.

3. Other issues to consider, and not explored in this study, include the following:

- younger people may have a faster increase in CD4+ cell counts than older people when first given HAART
- the point in HIV disease below which immune recovery with HAART cannot be maximized

Hopefully other studies will investigate these and other issues related to the timing of therapy.

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C. Starting HAART and its effect on survival

Summary

Researchers in the province of British Columbia (BC) reviewed information in their database on more than 1,200 PHAs. The data was collected between August 1996 and September 1999. The research team was examining data to find the effect of HAART on survival. In analysing their data the researchers took into account the following factors which might have had an impact on survival:

- a diagnosis of AIDS
- protease inhibitor (PI) use
- age
- gender
- CD4+ cell count
- viral load

According to their calculations, which analysed these factors together, the CD4+ count at which subjects started therapy was the only significant factor linked to their subsequent survival.

Study details

Researchers enrolled 1,219 subjects who had never used anti-HIV therapy and who had the following profile at the start of this study:

- 15% female, 85% male
- average age – 37 years
- average CD4+ count – 280 cells
- average viral load – 120,000 copies
- 13% had AIDS

On average, subjects were monitored for about 2.3 years. The most commonly prescribed combinations of anti-HIV drugs were as follows:

- d4T (Zerit, stavudine), 3TC (lamivudine, Efavir) and indinavir (Crixivan)
- AZT (Retrovir), 3TC and indinavir
- d4T, 3TC and nevirapine (Viramune)

Results – Survival

Over the course of the study, 104 subjects died. The proportion of these deaths that was due to HIV was about 79%.

Readers should note that the criteria for access to HAART were relaxed one year after the study started — in July 1997. In practical terms this meant that subjects who used HAART during the first year of the study had the following profile:

- high viral loads — averaging 170,000 copies
- nearly twice as likely to have AIDS compared to subjects who entered the study after July 1997
- very likely to have a protease inhibitor prescribed as part of their regimen

Survival and CD4+ cell counts

In focusing on survival, researchers divided subjects into the following three groups based on their CD4+ cell counts at the start of the study:

- fewer than 50 cells – 12% of subjects
- between 50 and 199 cells – 25% of subjects
- 200 or more cells – 64% of subjects

(Note: percentages do not total 100 because of rounding)

The proportion of subjects who died after one year in each group was as follows:

- fewer than 50 cells – 9% died
- between 50 and 199 cells – 6% died
- 200 or more cells – 1% died

These differences in death rates were statistically significant.

Survival and viral load

The researchers also divided subjects into the following groups based on their viral load at the start of the study:

- fewer than 100,000 copies
- 100,000 copies or greater

The rates of death for subjects in each of these two groups were as follows:

- fewer than 100,000 copies – 2%
- 100,000 copies or greater – 4%

These differences in death rates were statistically significant.

The big question

Which factor was most associated with survival? In an initial analysis researchers found that those PHAs who had one of the following factors before they started therapy had an increased risk of death:

- using a protease inhibitor
- previous diagnosis of AIDS

When researchers re-analysed the data (called a multivariate analysis), taking into account several factors — CD4+ cell count, viral load, use of PIs — they found that only one factor remained statistically significant:

- CD4+ count at the start of the study

The risk of death

Using this analysis that accounted for several factors the researchers calculated the risk of death as follows:

- Subjects who started therapy when they had fewer than 50 CD4+ cells were nearly seven times more likely to die than subjects who had at least 200 CD4+ cells.
-

- Subjects who began therapy with a CD4+ count between 50 and 199 cells were three times more likely to die than subjects who started therapy when they had at least 200 CD4+ cells.

These differences were statistically significant.

The risk of developing AIDS or dying

By the end of the study, the following events had occurred:

- 25 subjects developed AIDS
- 57 subjects died

The researchers calculated the risk of subjects developing AIDS or dying from the time they began to use HAART and came up with the following results:

- Subjects who began therapy when they had fewer than 50 CD4+ cells were about eight times more likely to develop AIDS or die than subjects who started therapy when they had at least 200 cells.
- Subjects who began therapy when their CD4+ count ranged between 50 and 199 cells were five times more likely to develop AIDS or die compared to subjects who started therapy when they had at least 200 cells.

Important issues

1. In this study, most deaths occurred in PHAs who had fewer than 200 CD4+ cells. At first there appeared to be a higher number of deaths among people who used a PI. This occurred because PHAs who initially received PIs were considered to be in poor health and at high risk for developing AIDS or dying by their doctors. But when researchers recalculated the risks, taking into account several factors such as CD4+ cell counts, age, sex, viral load and PI use, only the CD4+ cell count at the start of therapy was associated with subsequent survival.

2. While this study does not reveal the best time to begin therapy, it provides other important information, namely:

- If therapy is started below a “critical threshold” — a CD4+ cell count of 200 cells — then the benefit(s) of HAART are reduced.
- Delaying therapy when there are less than 200 CD4+ cells greatly increases the risk of developing AIDS or dying.

Data from another large American study in which subjects were also monitored found the following:

- 85% of men who had fewer than 200 CD4+ cells and viral loads greater than 110,000 copies who did not use anti-HIV drugs would develop a life-threatening infection or die within 2.3 years.

This point is noteworthy because in the BC study, of those subjects with a similar profile who received treatment, only 22% developed AIDS or died.

Points to consider

1. The research team notes that when monitoring PHAs who have not yet started HAART, the emphasis should be on CD4+ cell counts.

2. If PHAs are going to start therapy it should be initiated before their CD4+ cell count falls below the 200 cell mark.

3. Although the best point in the course of HIV disease to start therapy is still not clear, this study does provide valuable information about the risks of delaying therapy, particularly at low CD4+ cell counts. This information should be useful for those who counsel PHAs about the timing of therapy.

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II SELECTED HIGHLIGHTS FROM ICAAC

The 41st annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) was held in Chicago, 16-19 December 2001. ICAAC can be summarized as a meeting that focuses on “bugs and drugs.” We now present selected highlights from posters and presentations from the 41st ICAAC that deal with HIV and the treatment of PHAs. Unless otherwise noted, all references are from this meeting.

A. Atazanavir overview

Atazanavir (BMS-232632) is a new protease inhibitor that is being developed by Bristol-Myers Squibb. Most currently licensed protease inhibitors (PIs) usually cause increased levels of lipids — cholesterol and triglycerides — in PHAs who use them. Atazanavir offers several advantages over currently licensed PIs, including the following:

- once-daily dosing
- does not significantly increase lipid levels

Atazanavir has potential to be used as a booster — much in the same way that the PI ritonavir (Norvir) is often used to boost levels of other PIs such as:

- amprenavir (Agenerase)
- indinavir (Crixivan)
- lopinavir (in Kaletra)
- saquinavir (Fortovase, Invirase)

One possible drawback to atazanavir is that users can develop higher-than-normal levels of the waste product bilirubin in their blood. The long-term effect of this is not yet clear.

B. Atazanavir vs. nelfinavir

Dr. Ian Sanne, of South Africa, presented data from a large study using 464 HIV positive subjects to compare the effect of the following two protease inhibitors (PIs) :

- atazanavir – 400 mg or 600 mg once daily
- nelfinavir (Viracept) – 1,250 mg twice daily

Both drugs were taken along with regular doses of the following nukes:

- 3TC (lamivudine, Epivir)
- d4T (stavudine, Zerit)

All subjects enrolled in this study (called Trial 008) had never been previously exposed to anti-HIV drugs. At the start of the study, subjects had the following profile:

- average CD4+ count – about 270 cells
- average viral load – about 50,000 copies

Results

After one year, in one analysis, the proportion of subjects with viral loads below the 400 copy mark was as follows:

- atazanavir 400 mg – 64%
- atazanavir 600 mg – 67%
- nelfinavir – 53%

On average, the increase in CD4+ counts — about 200 cells — was similar in each group. The average increase in cholesterol (compared to pre-study levels) in all subjects on atazanavir and nelfinavir was as follows:

- atazanavir – 5%
- nelfinavir – 25%

The average increase in triglyceride levels compared to pre-study levels was as follows:

- atazanavir – 5%
- nelfinavir – 17%

Side effects

After one year, higher-than-normal levels of bilirubin developed in the following proportion of subjects:

- atazanavir – 17%
- nelfinavir – fewer than 1%

The proportion of subjects with diarrhea was as follows:

- atazanavir – 17%
- nelfinavir – 56%

Readers should bear in mind that subjects in this study had not previously used anti-HIV drugs. Results may therefore be different in PHAs who have been exposed to such drugs and who then proceed to use atazanavir. This drug is currently being tested in clinical trials in Canada, the countries of the European Union and South Africa.

REFERENCE

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C. Atazanavir boosts saquinavir

In people with HIV/AIDS (PHAs) whose initial protease inhibitor-containing regimen no longer works, doctors may prescribe dual protease inhibitor (PI) regimens where one PI boosts the level of the other PI used in the combination. This has the advantage of increasing levels of the boosted PI in the blood (to prolong its anti-HIV activity) and reducing the number of times that pills need to be taken daily. In one study, researchers in Buenos Aires examined the effect

of taking atazanavir in order to boost saquinavir levels in PHAs whose previous PI-based regimen no longer worked.

Study details

Researchers recruited 85 adults and randomly assigned them to receive the following PI combinations along with two nukes:

- atazanavir 400 mg or 600 mg and saquinavir 1,200 mg, both drugs taken once daily
- ritonavir 400 mg and saquinavir 400 mg, both drugs taken twice daily

Subjects had a viral load ranging between 1,000 and 100,000 copies and at least 100 CD4+ cells.

Results

On average, viral load decreases were slightly greater among subjects receiving ritonavir-saquinavir than those receiving atazanavir-saquinavir. Increases in CD4+ cell counts were also greater in subjects receiving ritonavir-saquinavir. However, on average, levels of triglycerides and cholesterol declined in atazanavir users, while increasing in ritonavir users. PHAs who use atazanavir may have a lower risk of developing cardiovascular disease than those who use ritonavir and possibly other protease inhibitors.

REFERENCE

Has D, Zala C, Schrader S, et al. Once-daily atazanavir plus saquinavir favourable affects total cholesterol (TC) and fasting triglyceride (TG) profiles in patients failing prior PI therapy (Trial A1424-009), Wk 24). Late-breaking abstract 16.

D. Tenofovir

Tenofovir (Viread) is a new drug recently licensed in the United States. Tenofovir belongs to a new class of drugs called **nucleotide** analogues and may be particularly useful for people with HIV/AIDS (PHAs) whose virus is resistant to the **nucleoside** analogues (nukes) AZT or d4T.

Unlike nukes, tenofovir appears to be only mildly toxic to the energy-producing parts (called mitochondria) of a cell. Tenofovir is therefore unlikely to cause damage to the nerves, liver or pancreas gland. Another advantage of this drug is that it is taken as a single tablet once daily. Tenofovir is being tested in PHAs who have previously used anti-HIV drugs.

Study details

In a randomized, placebo-controlled study, researchers added either tenofovir or fake tenofovir (placebo) to the existing treatment regimens of 552 subjects for at least six months. At the start of the study, the profile of subjects was as follows:

- 14% female, 86% male
- average age – 41 years
- average viral load – 4,500 copies
- average CD4+ count – 420 cells
- subjects had previously used anti-HIV drugs for about 5 years

Results

By the 6th month of the study, viral load had not decreased in subjects who received placebo. Among subjects who received tenofovir, viral load fell, on average, to about 1,000 copies. The proportion of subjects who achieved a viral load of fewer than 400 copies in each group was as follows:

- placebo – 13%
- tenofovir – 42%

On average, subjects using placebo had a decrease of about 11 CD4+ cells. In subjects using tenofovir, the CD4+ count increased by about 13 cells.

General side effects

Toxicity from tenofovir was uncommon, with fewer than 1% of subjects developing the following symptoms:

- diarrhea
- nausea
- damage to nerves in the hands and/or feet (peripheral neuropathy)

Kidney dysfunction

A few more subjects who used tenofovir (2%) developed minor kidney damage compared to subjects who used placebo (1%). Kidney damage was detected by higher-than-normal levels of the protein creatinine in blood and urine samples. As well, decreased levels of the mineral phosphorus were detected in about 6% of subjects on tenofovir compared to 5% of subjects on placebo. Long-term monitoring is needed to find out if these changes in a small proportion of tenofovir users are important and have any impact on the long-term health of kidneys and bones (where the body stores phosphorus).

Tenofovir is available through an expanded access programme for selected PHAs in Canada. For more information, see the CATIE Fact Sheet on tenofovir available at www.catie.ca/facts.nsf.

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3. Squires K, Pierone G, Berger D, et al. Tenofovir DF: a 24-week interim analysis from a Phase III double-blind, placebo-controlled study in antiretroviral experienced patients. Abstract I-666.

E. Saquinavir vs. Sustiva once daily

In an effort to simplify therapy, researchers are testing different combinations and schedules of drugs. One combination being studied is the protease inhibitor (PI) saquinavir (Fortovase, Invirase) with the PI ritonavir (Norvir). This is because ritonavir can boost levels of saquinavir in the blood for a prolonged period of time, extending its anti-HIV activity. This allows for a reduced number of pills that need to be taken daily. The downside of most ritonavir-saquinavir combinations is:

- it must be taken twice daily
- ritonavir can cause nausea and diarrhea in some PHAs

By reducing the dose of ritonavir and increasing the dose of saquinavir, researchers hope to develop a once-daily protease inhibitor regimen using currently licensed drugs. Once-daily regimens may be more convenient for people who have the following issues:

- hectic lifestyles
- are in methadone programmes
- are in prison
- require directly observed therapy

Study details

Dr. Julio Montaner and colleagues enrolled 161 HIV positive subjects who had not previously used anti-HIV drugs and who had the following profile:

- 30% female, 70% male
- average age – 37 years
- average viral load – 50,000 copies
- average CD4+ count – 350 cells

Researchers randomly assigned subjects to receive one of the following regimens together with two nukes once daily:

- saquinavir 1,600 mg and ritonavir 100 mg
- efavirenz (Sustiva) 600 mg

Results

The proportion of subjects in each of the following groups who achieved a viral load of fewer than 50 copies in each group was as follows:

- saquinavir-ritonavir – 60%
- efavirenz – 81%

This difference between the two groups was statistically significant; that is, not likely due to chance alone. The difference was probably caused by the greater number of subjects in the saquinavir-ritonavir group who left the study because of side effects.

On average, all subjects in the study had an increase of about 150 extra CD4+ cells. The increase was slightly higher for subjects who received saquinavir-ritonavir.

Side effects

Major side effects in the saquinavir-ritonavir group were as follows:

- nausea – 22% of subjects
- diarrhea – 6% of subjects

Changes in lipid levels were minor and similar among the two groups. The number of subjects who left the study because of side effects in each group is as follows:

- saquinavir-ritonavir – 8 subjects
- efavirenz – 1 subject

Issues to consider

Dr. Montaner suspects that some of the ingredients in Fortovase (the newer, soft-gel formulation of saquinavir) capsules may be responsible for the nausea and diarrhea reported in the study. He is conducting experiments with the original formulation of saquinavir — Invirase (hard-gel capsule). Preliminary results suggest that Invirase capsules have fewer side effects and are better tolerated when used at a dose of 1,600 mg together with ritonavir 100 mg, both drugs taken once daily. Dr. Montaner also reported that the combination of saquinavir-ritonavir had no significant effect on methadone levels in people using that drug.

REFERENCE

Montaner JSG, Saag M, Baryliski C, et al. FOCUS study: saquinavir QD regimen versus efavirenz QD regimen: 24 week analysis in HIV-infected patients. Abstract I-669.

F. Amprenavir and low-dose ritonavir

Amprenavir (Agenerase) is a protease inhibitor (PI) whose use in Canada is restricted to PHAs who have previously used anti-HIV drugs. Amprenavir is not as potent as first-line PIs, such as indinavir (Crixivan). In order to increase levels of amprenavir in the blood, and thus increase its anti-HIV activity, this drug is being tested in combination with the PI ritonavir. Researchers in the U.S. recently reported preliminary results from 104 subjects who were enrolled in a study testing two combinations of ritonavir-amprenavir.

Study details

A total of 115 subjects whose therapy was failing were enrolled in this study but data on only 104 subjects was presented. Subjects received one of two PI combinations together with the anti-HIV drugs abacavir (Ziagen) and either efavirenz (Sustiva) or tenofovir (Viread). The PI combinations tested were as follows:

- amprenavir 600 mg and ritonavir 100 mg, both twice daily
- amprenavir 900 mg and ritonavir 100 mg, both twice daily

At the start of the study, subjects had the following profile:

- average age – 43 years
- 16% female, 84% male
- average viral load – about 14,000 copies
- average CD4+ count – about 260 cells
- the most commonly used protease inhibitors before entering this study were indinavir (Crixivan) and nelfinavir (Viracept)
- on average, subjects had been taking anti-HIV therapy for about 5½ years
- testing of blood samples found that all 104 subjects had HIV that was sensitive to the anti-HIV effects of amprenavir

Results – viral load and CD4+ cell count

After six months, the proportion of subjects who achieved a viral load of fewer than 200 copies was as follows:

- amprenavir 600 mg – 69%
- amprenavir 900 mg – 73%

The average increase in CD4+ cell counts seen in the study were as follows:

- amprenavir 600 mg – 72 cells
- amprenavir 900 mg – 31 cells

The researchers are not sure why this difference occurred.

Side effects

The proportion of subjects in the amprenavir 600 mg group who experienced selected side effects was as follows:

- diarrhea – 50%
- nausea – 27%
- abdominal pain/discomfort – 20%
- vomiting – 17%

The figures for the amprenavir 900 mg group were as follows:

- diarrhea – 32%
- nausea – 71%
- abdominal pain/discomfort – 21%
- vomiting – 29%

Three subjects in each group left the study because of the following side effects:

- tiredness/lack of energy
- nausea
- diarrhea
- abdominal pain
- rash

Levels of amprenavir in the blood were similar in both the 600 mg and 900 mg groups. Tenofovir and efavirenz did not appear to reduce levels of amprenavir in the blood. Efavirenz's effect on amprenavir blood levels is being confirmed in another study. The study authors suggest that amprenavir 600 mg, boosted with ritonavir 100 mg, both drugs taken twice daily, may be a better regimen than higher doses of amprenavir (also boosted with ritonavir).

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Schooley R, Haubrich R, Sension M, et al. Efficacy, safety and amprenavir pharmacokinetic responses of twice-daily amprenavir and low-dose ritonavir regimens in HIV-1-infected, treatment-experienced adults for 24 weeks (ESS40006). Poster 1924.

G. Directly observed therapy (DOT)

Researchers in Vancouver, British Columbia, have found that the treatment of HIV positive substance users is challenging for the following reasons:

- co-infection with hepatitis C virus
 - interactions between anti-HIV medications and methadone
 - the complexity of some anti-HIV regimens
-

The research team, led by Dr. Stanley de Vlaming and colleagues, established a methadone-maintenance programme, in which subjects were given both methadone and highly active antiretroviral therapy (HAART) daily. PHAs in this programme were observed directly by a pharmacist as they took their medications.

Study details

Researchers enrolled 52 subjects who had the following profile at the start of the study:

- average viral load – 216,000 copies
- average CD4+ count – 202 cells
- all subjects were hepatitis C virus positive

Subjects were monitored for about 1½ years. They received either a once-daily or twice-daily combination of anti-HIV drugs. The following were the most commonly used combinations:

Once-daily regimens:

- nevirapine (Viramune), 3TC and ddI (Videx)
- ritonavir-saquinavir, 3TC and ddI

Twice-daily regimens:

- nevirapine and two nukes
- various protease inhibitors and two nukes

Results

During the study, 64% of subjects continued to use recreational drugs, including cocaine. Based on the type of regimen used, on average, CD4+ counts increased to the following levels:

- once-daily regimen – 390 cells
- twice-daily regimen – 357 cells

This difference between the two regimens was not statistically significant.

Subjects given nevirapine developed significantly higher CD4+ counts (an average of 483 cells) compared to those taking PI-based regimens (an average of 319 cells).

The proportion of subjects in each group who achieved a viral load of fewer than 400 copies was as follows:

- once-daily regimen – 66%
- twice-daily regimen – 74%

This difference was not statistically significant. Using the more sensitive viral load test that measures down to 50 copies, the proportion of

subjects in each group who achieved a viral load of fewer than 50 copies was as follows:

- once-daily regimen – 45%
- twice-daily regimen – 66%

Again, this difference between the two regimens was not statistically significant.

Although most subjects continued to use cocaine while in the study, 60% of cocaine users were able to achieve a viral load of fewer than 400 copies. Thirty-one subjects needed to have their methadone dosage adjusted during the study. No severe liver damage was detected, which is remarkable given that co-infection with hepatitis-causing viruses is common among substance users.

The results of this study show that directly observed therapy (DOT) may be useful for the combination of addiction and HIV treatment.

REFERENCE

Conway B, Prasad J, Smith N and de Vlaming S. Once-daily directly observed therapy (DOT) for management of HIV-infected individuals in a methadone program. Poster 1917.

III SIDE EFFECTS

In the previous issue of *TreatmentUpdate* (#123), we reported on key studies presented at the 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 23-26 October 2001. In this issue, we continue this report with a focus on hormonal problems seen in HAART users. Unless otherwise noted, all references are from the lipodystrophy workshop.

A. Thyroid troubles in France

The thyroid gland is located in the neck and produces hormones that affect almost every organ in the body. Thyroid hormones can have an impact on the following:

- energy levels
- muscle strength
- skin health
- cholesterol levels
- weight
- memory

A number of doctors have reported abnormal thyroid hormone levels in a small proportion of people with HIV/AIDS (PHAs) taking highly

active antiretroviral treatment (HAART), so hormone researchers in France decided to conduct a large study to find out more.

Study details

Researchers enrolled 221 HIV positive subjects with the following profile:

- 26% female, 74% male
- average age – 41 years

Results

Researchers found that the following proportion of subjects had thyroid hormone abnormalities:

- men – 8%
- women – 9%

Among healthy, HIV negative people, it is estimated that the proportion of those with abnormal levels of thyroid hormones is:

- females – 1.0 %
- males – 0.1%

In some subjects, researchers suspect that there may be a link between the length of time that protease inhibitors were used and levels of the thyroid hormone called “free T₄,” also known as “free thyroxine.” However, further study is needed to confirm and understand this possible connection.

REFERENCE

Esnault JL, Billaud E, Milpied B, et al. High prevalence of thyroid abnormalities in the era of highly active antiretroviral therapy. Abstract 16

B. Thyroid problems in Montréal

Researcher Maude Loignon and colleagues collected 18 months of data (and spent three long months in data analysis) on 80 HIV positive subjects from a Montreal HIV clinic. The purpose of their study was to try and find out if abnormal thyroid hormone levels were present in HAART users.

Study details and results

Researchers collected data on subjects who had the following profile:

- 19% female, 81% male

The research team found the following:

- 35% of subjects (20 males) had abnormal thyroid tests

- average age of subjects with these abnormalities – 45 years
- the 20 subjects had been taking anti-HIV drugs for about 8 years
- their average CD4+ count was 170 cells
- their average viral load was about 4,300 copies

Naming thyroid hormones

Here are the names of three thyroid hormones:

- TSH – thyroid-stimulating hormone or thyrotropin
- T₃ – triiodothyronine
- T₄ – thyroxine

Sometimes doctors may order the “free” form of the hormone to be measured. The “free” form of the hormone means the amount that is available in the blood for the body to use. The results of thyroid tests were as follows:

- antibodies that attacked the thyroid gland were detected in 20 subjects
- higher-than-normal levels of the hormone TSH (thyroid-stimulating hormone) were found in five subjects
- less-than-normal levels of the same hormone were found in four subjects
- less-than-normal levels of the thyroid hormone “free” T₃ were found in seven subjects
- less-than-normal levels of the thyroid hormone “free” T₄ were found in six subjects

In 19 of 20 subjects, technicians found higher-than-normal levels of triglycerides in the blood.

It is clear from this study that thyroid dysfunction is common in some PHAs who are taking HAART. However, it is not clear exactly why this problems occurs. Is it caused by protease inhibitors, non-nukes, nukes or a combination of all three groups of drugs? What role does HIV play in causing thyroid dysfunction? The work conducted by researchers in France and Canada is an important first step toward answering these questions.

REFERENCE

Loignon M, Martin M and Toma E. High rate of thyroid autoimmunity and dysfunction in HIV-infected adults receiving highly active antiretroviral therapy. Abstract 80.

C. Growth hormone: Does less equal more?

Growth hormone (GH) deficiency can occur in some PHAs with AIDS-related wasting. Injections of GH can help stop this complication. GH may also be useful for treating aspects of the HIV lipodystrophy syndrome. For instance, the fat redistribution and/or fat gain associated with the use of HAART has prompted some doctors to prescribe GH to some of their patients who can afford this expensive drug. The dose of GH that has commonly been used to treat wasting or fat redistribution is relatively high and, not surprisingly, side effects have been reported. To find out about GH-related side effects in PHAs, a research team performed a study.

Study details

The researchers reviewed medical records of 94 HIV positive subjects. The following side effects were reported by those using “high-dose” GH — between 4 mg and 6 mg daily:

- joint pain – 31%
- swelling due to fluid build-up – 31%
- tiredness/lack of energy – 15%
- back pain – 15%
- higher-than-normal levels of sugar in the blood – 8%

Because of these side effects, the research team suggests that lower doses of GH, similar to levels found in the body, should be studied in clinical trials with PHAs. Such a dose of GH would be around 1 mg/day.

REFERENCE

Santos G, Freund K, Sension F et al. Growth hormone dose-related side-effects in HIV/AIDS population; retrospective study. Abstract 111.

D. Testosterone troubles

Both male and female PHAs can develop less-than-normal levels of testosterone. Reduced levels of this hormone have been linked to the following complications:

- reduced energy
- depression
- reduced sex drive
- thinning bones (in males)

Dr. Peter Ford and colleagues in Kingston, Ontario, have been studying the impact of regular injections of testosterone injections (200 mg every three

weeks) in male PHAs. His research team has reported results on 40 PHAs, 17 of whom were using testosterone for about 1½ years.

Results

The team found that testosterone users were more likely to have fat located deep in the abdomen, around internal organs, than subjects not using testosterone. This fat build-up is likely due to age and use of HAART. Testosterone users had less fat under the skin (subcutaneous fat) than non-users. Perhaps more importantly, compared to non-users, PHAs who used testosterone had the following lipid profile:

- high levels of triglycerides
- lower levels of HDL (high density cholesterol – good cholesterol)
- higher levels of insulin in the blood

These differences between users and non-users of testosterone were statistically significant; that is, not likely due to chance alone. If these differences are maintained over the long-term, testosterone users may be at increased risk of cardiovascular illness.

Perhaps the development of testosterone creams and gels, which supply lower, more natural levels of this hormone, may be as useful and possibly safer than injections of high doses of testosterone. Clinical trials of low-dose testosterone in PHAs would be useful in dealing with this issue.

REFERENCE

Ford P, Tenzif S, Wobeser W, et al. Dyslipidemia and body composition effects of testosterone cypionate in a group of people living with HIV/AIDS in Ontario, Canada. Abstract 62.

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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