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I ANTI-HIV AGENTS

A. The 16th CROI

The Conference on Retroviruses and Opportunistic Infections (CROI) is the premier annual HIV scientific meeting. It allows for leading scientists and doctors to present the results of studies, debate controversial ideas and showcase new findings about the treatment and research of HIV/AIDS. In addition, CROI usually has a substantial body of work on co-infections and complications of HIV and its treatment. In recent years, data on the potential of anti-HIV agents to prevent the sexual transmission of HIV has increasingly been featured at the conference. This year's CROI, held on February 8 to 11 in Montreal, continued the conference's trend of providing exciting news on many HIV-related topics.

Last year, CROI featured emerging data on the side effects of highly active antiretroviral therapy (HAART), particularly heart attacks. While this sounds alarming, we urge our readers to bear in mind that heart attacks are not common in HAART users. Moreover, in some high-income regions, rates of heart attacks are falling among HAART users to levels seen in HIV negative people. This suggests that doctors are gaining experience in preventing this problem. In this issue of *TreatmentUpdate*, we present information that was highlighted at the 2009 CROI, including issues such as the following:

- when to start HAART?
- interesting combinations of anti-HIV drugs
- new drug boosters
- genetic therapy for HIV
- cardiovascular risk associated with some anti-HIV medicines
- keeping heart attacks at bay

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B. When is it best to start HAART?

Over the past 18 months, international treatment guidelines in high-income countries have suggested that HAART be started when CD4+ counts fall below the 350-cell mark. In these guidelines treatment can begin when the CD4+ count is higher, depending on special circumstances such as hepatitis co-infections, kidney disease, pregnancy and so on.

This is a major departure for the international guidelines, as for many years they had encouraged that treatment begin when the CD4+ count had fallen below the 200-cell mark. The reason for the change was that several studies had recently found an increased risk of death in people not taking HAART whose CD4+ counts were between 200 and 350 cells compared to people who were taking HAART (see *TreatmentUpdate* 170 and 171 for further details). Moreover, there are trends from large database-centered studies suggesting increased survival when HAART is started at even higher CD4+ cell counts.

However, these trends are not definitive and need to be confirmed in prospective randomized clinical trials. Until such trials have been completed, currently available guidelines are meant to be used as a guide because there is as yet no answer to the question: When is the best time to begin HAART?

Massive databases

Research teams in many high-income countries have assembled large databases containing health information on HIV positive people. These data sets can be used to analyse trends in health. One collection of these databases is called the ART-Cohort Collaboration and includes information from several countries and regions as follows:

- United States
- European Union
- Switzerland
- Alberta
- British Columbia

The collaboration has amassed and analysed information from 24,444 HIV positive people, of whom 808 have died. Researchers affiliated with this database wondered about the risk of death in people who began therapy at different CD4+ counts. To explore the issue of when it is best to begin HAART, they used their database to mimic a randomized clinical trial with 21,247 participants. For this theoretical exercise they did not include HIV positive people who were

injection drug users (IDUs) because, on average, there is an increased rate of death among HIV positive IDUs because of issues such as substance use, mental health and co-infections with liver-destroying viruses.

The study team found that people who began therapy when their CD4+ counts were less than 250 cells had the highest death rates. This was somewhat reduced when people began therapy at cell counts between 251 and 350 cells. The findings from this study suggest that starting HAART at CD4+ counts of 351 or higher is likely to reduce death rates.

These findings are based on an observational cohort study in selected people. Such studies cannot entirely rule out bias when interpreting their results, but they can serve as a guide to develop studies with a more robust study design. The findings from the ART-Cohort Collaboration confirm the recent decisions by treatment guideline committees to increase the threshold for initiating therapy to around the 350-cell mark. But the findings also raise the question about starting HAART at much higher counts.

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1. Sterne J and the When to Start consortium. When should HIV-1-infected persons initiate ART? Collaborative analysis of HIV cohort studies. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 72 LB.

C. Should HAART begin right after an HIV diagnosis?

Also exploring the issue of when is best to begin HAART is a group of researchers in Canada and the United States called the NA-ACCORD (the North American AIDS Cohort Collaboration on Research and Design). These researchers have joined 22 data sets to produce the NA-ACCORD, which contains health information collected from more than 9,000 HIV positive people.

Co-infections included

Like counterparts elsewhere, the NA-ACCORD team used its database to create a *virtual* clinical trial, hoping to assess the effect of either immediately initiating treatment after diagnosis or deferring treatment in people with CD4+ counts greater than 500 cells until their counts fell below the 500-cell threshold. In total, 2,616 people were assigned to immediately begin HAART and 6,539 people were assigned to delay starting HAART.

None of the participants had previously used anti-HIV drugs. What makes the analysis from the NA-ACCORD interesting is that unlike ART-Cohort Collaboration, the North American researchers included people who were co-infected with hepatitis C virus (HCV).

The average profile of this study's participants who began therapy immediately was as follows:

- 82% male, 18% female
- age – 40 years
- CD4+ count – 674 cells
- viral load – 5,000 copies
- hepatitis C virus co-infection – 25%

The major difference between this group and the people who delayed therapy was that the second group did not begin therapy until their CD4+ count was about 390 cells. This assumption takes into account that in many high-income countries today most HIV positive people appear to delay therapy.

Results—deaths

There were 196 deaths in people who began therapy immediately vs. nearly twice as many deaths (410) in people who delayed therapy until their CD4+ counts fell below the 500-cell mark. Other findings from this study were as follows:

- Overall, the risk of death was reduced by 60% when people began therapy at CD4+ counts of 501 or higher.
- For each decade of increased age, the risk of death rose by 60%. This is due to a number of reasons, perhaps chiefly because the immune system tends to degrade with age, regardless of HIV infection.
- The risk of death remained the same whether or not HCV co-infection was taken into account or not.

The causes of death whether people started therapy immediately or delayed initiation were mostly as follows:

- cardiovascular disease (heart attack and stroke)
- liver related (mostly due to complications of hepatitis caused by HCV infection)

The results of this study support the initiation of HAART at earlier time points in the course of HIV infection—when CD4+ counts are relatively high, perhaps even shortly after HIV infection has been diagnosed. However, these results are based on data from an observational study, and such studies

cannot entirely eliminate the possibility of bias when interpreting their results. Although this and other studies make a strong case for the more immediate use of HAART, they do not take into account the psychological effect of an HIV diagnosis or the news that treatment should begin shortly after such a diagnosis and the possible impact these might have on a person's mental health and ability to initiate and be highly adherent to HAART.

When to start?

Perhaps further clarity as to the ideal time to start HAART will emerge from an international clinical trial that is being planned. START—Strategic Timing of Antiretroviral Treatment—is sponsored by the American National Institutes of Allergy and Infectious Diseases (NIAID) and will be a randomized clinical trial. START is expected to begin recruiting potential participants later in 2009. Participants will have a CD4+ count of at least 501 cells and will be randomly assigned to one of the two following groups:

- immediate HAART
- delayed HAART until the CD4+ count falls below 350 cells

The study is expected to last for up to six years and researchers mainly will be assessing so-called hard endpoints, such as the development of AIDS-related and non-AIDS-related complications and/or death.

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1. Kitahata M, Gange S, Moore R, et al. Initiating rather than deferring HAART at a CD4+ Count >500 Cells/mm³ is associated with improved survival. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 71.

D. Atazanavir and raltegravir— an interesting combination

In general, the protease inhibitor atazanavir (Reyataz) is used at a dose of 300 mg with a small dose (100 mg) of another protease inhibitor, ritonavir (Norvir), both drugs taken once daily. In this combination, atazanavir has anti-HIV activity and works by interfering with a viral enzyme called protease. The purpose of the small dose of ritonavir in this combination is to enhance levels of atazanavir. Ritonavir has this effect by increasing the absorption of atazanavir in the intestine and by delaying the breakdown of atazanavir in the liver. The net effect is that atazanavir levels in the blood are increased

for prolonged periods, allowing once-daily dosing. Drugs such as ritonavir, when used in this way, are called pharmacokinetic boosters or enhancers. A drawback of ritonavir is that it can raise levels of cholesterol and triglycerides in the blood, potentially increasing the risk of cardiovascular disease. Also, some people who use ritonavir can get nausea or diarrhea. Atazanavir is made by Bristol-Myers Squibb (BMS) and ritonavir is manufactured by Abbott Laboratories.

Enter raltegravir

Raltegravir is a new drug that belongs to the class of drugs called integrase inhibitors. It works by interfering with an enzyme—integrase—needed by HIV. Raltegravir is made by Merck and Company, Inc. This drug also has the effect of boosting levels of atazanavir in the blood. Scientists at both BMS and Merck have cooperated and conducted a trial of twice-daily atazanavir and raltegravir in HIV negative people. Their findings suggest that both drugs can be used safely on such a schedule. Further studies assessing the anti-HIV effects of atazanavir-raltegravir as part of HAART are underway.

Study details

Researchers recruited 22 healthy HIV negative participants for their study, the design of which was as follows for all participants:

- days 1 to 5: raltegravir 400 mg taken twice daily
- days 6 to 12: atazanavir 300 mg taken twice daily instead of raltegravir
- days 13 to 26: both atazanavir and raltegravir at the doses listed above

After day 26, participants stopped taking the study medicines and were monitored for up to 14 additional days.

The average profile of participants was as follows:

- 27% female, 73% male
- age – 32 years

Results

In general, the amount of atazanavir absorbed fell between 10% and 20% during the period when it was taken with raltegravir compared with the period when it was taken without raltegravir. However, atazanavir levels remained 10-fold greater than the levels needed to suppress HIV.

On the whole, the amount of raltegravir absorbed increased between 40% and 55% when it was taken with atazanavir. However, in some people raltegravir levels did not significantly increase.

Safety

Side effects reported during the study were generally “mild-to-moderate” in intensity, according to the research team. Common side effects seen when both drugs were taken were as follows:

- jaundice (yellowing of the skin and whites of the eyes)
- headache

Three participants quit the study because of side effects that occurred when both drugs were taken, including the following:

- abnormal heart beats (one person)
- mild rash (two people)

The manufacturer of atazanavir, Bristol-Myers Squibb, is conducting another study of atazanavir and raltegravir taken twice daily in HIV positive participants to assess any potential side effects on the heart. If the combination proves safe and effective, it may form a future treatment option for some HIV positive people.

REFERENCE:

1. Zhu L, Mahnke L, Butteron J, et al. Pharmacokinetics and safety of twice-daily atazanavir (300 mg) and raltegravir (400 mg) in healthy subjects. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 696.

E. Are new drug boosters coming?

Protease inhibitors used in high-income countries mostly include the following:

- atazanavir (Reyataz)
- darunavir (Prezista)
- fosamprenavir (Telzir)
- lopinavir (in Kaletra)
- saquinavir (Invirase)
- tipranavir (Aptivus)

All of these drugs are taken together with a small dose of ritonavir, another protease inhibitor (PI). The purpose of ritonavir is to increase absorption and slow down the breakdown of the other protease inhibitor in the body. The net effect of taking ritonavir with any of these other PIs is that

their levels in the blood remain high for prolonged periods, allowing for once- or twice-daily dosing. Drugs such as ritonavir, when used in this way, are called pharmacokinetic (PK) enhancers or boosters.

Ritonavir is also mixed with lopinavir and put into a tablet formulation and sold as Kaletra. These medicines are made by Abbott Laboratories. So far, Abbott is the only company to put an enhancer and PI into one pill—a co-formulation. But other pharmaceutical companies, like Gilead Sciences, are beginning to develop their own boosters to co-formulate with their medicines. Gilead makes several commonly used HIV medicines, such as the following:

- tenofovir (Viread)
- FTC (emtricitabine, Emtriva)
- Truvada (tenofovir + FTC) in one pill
- Atripla (tenofovir + FTC + efavirenz/Sustiva) in one pill

Gilead also has other HIV medicines that it is testing, such as the integrase inhibitor elvitegravir (GS 9137). Elvitegravir needs to be taken with a pharmacokinetic booster in order for it to be taken once daily. Now Gilead has developed its own booster called GS 9530. Gilead hopes to put all of the following drugs into one small pill so they can be taken just once daily:

- tenofovir
- FTC
- elvitegravir
- GS 9530

Unlike ritonavir, GS 9530 has no anti-HIV activity. At a dose of 150 mg, GS 9530 has about the same boosting effect as 100 mg of ritonavir.

Safety

Tested at doses ranging between 50 mg and 200 mg, GS 9350 seems to be well tolerated. This PK enhancer, now entering further stages of clinical testing, does not appear to increase lipid levels in the blood.

Much work remains to be done to understand all of the potential interactions that GS 9350 might have, not just with other anti-HIV agents but also the many medicines that HIV positive people use for the following conditions:

- anxiety
- cardiovascular disease
- depression

- diabetes
- bacterial and fungal infections

In the works

Gilead plans to compare the effects of its new four-drug co-formulation—its so-called quad pill—against Atripla in 2009. Another study using GS 9350 with atazanavir is also being planned.

Yet another booster

A small corporation, Sequoia Pharmaceuticals Inc., has developed a PK enhancer called SPI-452. They have tested it with the protease inhibitors atazanavir, saquinavir and darunavir. In all cases, SPI-452 was an effective booster and it does not seem to significantly raise levels of bad cholesterols (LDL) or triglycerides in the blood. Side effects reported were generally mild in intensity. In 45 people exposed to SPI-452, side effects included the following:

- headache
- nausea
- upset stomach
- diarrhea

SPI-452 is currently a liquid formulation. Historically, liquid formulations of HIV medicines are not pleasant tasting and have been generally shunned by HIV positive adults. So, to be taken seriously, the company would have to develop a pill formulation of this drug.

The next step would be further clinical trials. Whether other pharmaceutical companies would be interested in testing Sequoia's PK booster is not yet clear. But what seems likely is that ritonavir's position as the *only* PK enhancer for use with HIV medicines seems limited. It will take several years for clinical trials with the PK enhancers mentioned in this report to be completed.

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2. Guttendorf R. Preclinical and early clinical evaluation of SPI-452, a New pharmacokinetic enhancer. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 41.

F. Gene therapy

In high-income countries, HAART became available in 1996. HAART has greatly reduced deaths from AIDS-related infections. As a result, HIV positive people who do not have serious co-existing health conditions and who are engaged in their care and treatment are likely to have near-normal life spans.

HAART has enabled people to live longer lives. However, HAART is not the ideal solution for HIV treatment for the following reasons:

- This therapy has to be taken every day, once or twice daily, for the rest of a person's life. Taking HAART every day as directed is a behaviour called adherence. No one knows how long the high levels of adherence needed for HAART's success can be sustained.
- HAART causes side effects, both long- and short-term.
- HIV can develop resistance to HAART, reducing future treatment options.

All of these points generate interest in developing simpler, safer HIV therapy and even a cure.

Harnessing the immune system

Since the beginning of the AIDS pandemic, scientists have dreamt of ways to make the immune system more easily resist HIV. In the past 15 years research teams in high-income countries have been conducting experiments involving gene therapy in their labs and, in some cases, in HIV positive volunteers.

The code for life

Cells contain genes, which in turn contain DNA—the code for life. DNA contains instructions that tell cells how to work: to make proteins and enzymes, perform repairs, build new cells and so on. Genes can be turned off and on as needed.

Gene therapy is currently being tested to try to correct such conditions as hemophilia, cardiovascular disease, Parkinson's disease and HIV infection.

How it works

Genes can't simply be injected into cells; they have to be delivered by a vector (a carrier). The most commonly used vector is a virus. This is because viruses are very good at getting into cells and inserting the viral genes into the cell's DNA. For gene therapy experiments, scientists take viruses, sometimes mouse viruses, and weaken them,

removing their capacity to cause disease. Once this is done, technicians then insert the genes that they want to be transferred to people into the virus or vector. Further details about the transfer of genes appear in our next story.

Caution

Gene therapy can carry risks. For instance, sometimes the new genes carried by the weakened virus may get inserted into a cell's DNA near genes that can help trigger the growth and development of tumours. If the new genes get turned on, cancer-causing genes already present in human cells may also become active. However, there have been many clinical trials of gene therapy for several disorders and the number of deaths has been very low. Moreover, in clinical trials with HIV positive volunteers, nobody has died because of the transfer of genes.

Next we have a report on the latest trial of gene therapy for HIV infection.

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7. Kohn DB, Candotti F. Gene therapy: fulfilling its promise. *New England Journal of Medicine*. 2009 Jan 29;360(5):518-21.

G. A clinical trial of gene therapy for HIV

Researchers in California and Australia have developed a gene therapy called OZ1. This therapy works by making CD4+ T-cells resistant to HIV infection. Results from previous and current clinical trials suggest that OZ1 is safe and has modest effectiveness. However, OZ1 is important in other ways, which we explain later in our report.

About OZ1

Researchers began their project by finding a virus to carry the genes they chose for therapy. The virus they selected was one that caused leukemia in mice. However, they removed the cancer-causing genes and inserted genes that did the following:

- cause CD4+ cells to make an enzyme that cuts up a specific part of HIV's genetic material; as a result, in cells treated with OZ1, HIV is unable to cause infection.

Study details

Researchers recruited 74 participants whose average profile at the start of the study was as follows:

- 92% male, 8% female
- age – 37 years
- CD4+ count – 700 cells
- viral load – less than 400 copies
- all participants were taking HAART

Researchers randomly assigned participants to one of two groups, as follows:

- OZ1 – 38 volunteers
- placebo – 36 volunteers

Researchers removed blood from the study volunteers and filtered out some bone marrow stem cells, identified as CD34+. They then infused the filtered blood back into participants. CD34+ bone marrow stem cells can develop into any one of a wide range of cells used by the immune system, including CD4+ cells.

The stem cells were collected and cultured and then infected with the weakened mouse virus that carried genes to help make them resist HIV infection. After they were infected, the stem cells were stimulated to produce more CD34+ cells for several days.

These cells were then infused back into participants based on their weight—5 million cells per kg of body weight. For instance, a person who weighed 70 kg would have received 350 million CD34+ cells. Each person received a single infusion of cells. On average, about 54% of the cells infused contained OZ1 genes.

Participants in the placebo group also received CD34+ cell infusions but without protective OZ1 genes.

Participants were highly motivated and able to undertake the 45 visits to study clinics over two years—a requirement of the study. HAART was interrupted during the study to assess the impact of uncontrolled HIV infection on the gene-enhanced cells.

Results

Four weeks after infusion, technicians detected HIV-resistant cells from blood cells in 94% of people in the OZ1 group. One year after the infusion, this figure fell to 12% and two years after the infusion it fell to 7%.

OZ1 recipients tended to have higher CD4+ and CD8+ counts than people who received placebo, but this difference did not reach statistical significance.

Eight weeks after participants underwent a treatment interruption, viral load was generally lower in the OZ1 group compared to placebo. Again, this difference was not statistically significant.

Results—safety

None of the participants assigned to receive OZ1 died or had severe heart, kidney or liver toxicity. Three serious complications did occur in the study but all in the placebo group.

The study protocol included an interruption of therapy. During this time, new outbreaks of the flu, herpes and oral yeast infections occurred in both groups.

In perspective

This study of OZ1 was the largest randomized controlled trial of gene therapy in HIV to have reached the phase II stage of development. The improvements in CD4+ counts and viral load were at best modest. Still, the results underscore a promising trend in those measures. Future gene

therapy experiments need to find ways to do the following:

- get more CD34+ stem cells to take hold in the bone marrow
- prolong the life of CD4+ cells containing gene therapy
- demonstrate significant anti-HIV activity
- consider enrolling HIV positive people who have not yet started HAART

Further experiments with this and other forms of gene therapy for HIV are being planned in the United States.

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II COMPLICATIONS AND SIDE EFFECTS

A. Falling rates of heart attacks

Concern about cardiovascular disease—particularly heart attacks and strokes—arose several years after HAART was introduced in high-income countries. This concern was based on increased cholesterol concentrations that are detected in the blood shortly after therapy begins.

However, in 1998 the level of this concern rose after reports of chest pain in two HAART users appeared in a journal. Chest X-rays and other tests revealed that these men had partially blocked arteries. The men were relatively young (27 and 37 years old) and had been using HAART for seven months before they developed symptoms. Both had major risk factors for cardiovascular disease (CVD), as follows:

- 27 year old – tobacco and cocaine use
- 37 year old – diabetes and a family history of CVD

Following this, other doctors reported similar cases. These reports spurred research into CVD and HIV. As a result, emerging research suggests

that HIV infection increases the risk of CVD in a number of different ways, such as these:

- Over the long term, HIV infection appears to be linked to a narrowing of blood vessels. This could increase blood pressure and the chances that unnecessary blood clots may form. Such clots, if large enough, could block the flow of blood, causing tissue damage and heart attacks.
- Chronic viral infections—such as HIV—can cause inflammation, damaging the lining of blood vessels. This damage increases the risk of CVD.
- Added to this are the increased lipid levels often seen in HAART users.

All of these factors increase the risk of CVD.

To track trends in heart attack and stroke in people who use their services, the large health maintenance organization Kaiser Permanente in California reviewed its giant database focusing on health information captured between 1996 and 2008. The database contained information on more than six million people, about 35,000 of whom are HIV positive. The findings suggest a large and significant decrease in rates of heart attack among HIV positive people.

Details

The study team specifically reviewed information collected on heart attacks and stroke and who sought hospital care for these issues. The profile of HIV positive people in their database was as follows:

- 10% female, 90% male
- age – 41 years

Results—heart attacks

In the years 1998 to 1999, rates of heart attacks had risen and become more common in HIV positive people. After this time, heart attack rates began to decline and by 2008 had fallen to almost the same level as in HIV negative people. Indeed the difference in heart attack rates between HIV positive and HIV negative people was not statistically significant in 2008.

Results—stroke

Rates of stroke were greatest among HIV positive people in the years 1996 to 1997; by 2008, rates of stroke had declined to a point just a bit higher than in HIV negative people. As with heart attack rates, the difference in rate of stroke between HIV negative and HIV positive people was not statistically significant in 2008.

Key points

1. Between 1998 and 2003, the rates of heart attacks and stroke were greater among HIV positive than HIV negative people. However, by 2006, rates of CVD incidents (heart attacks and stroke) began to decline among HIV positive people so that by 2008 the difference in heart attacks was no longer statistically significant.

Rates of strokes were similar in both groups by 2008, in part due to an increased rate of stroke in HIV negative people.

2. According to the study team, the decline in heart attacks and stroke among HIV positive people is probably linked to three things, as follows:
- use of more lipid-friendly medicines such as tenofovir (Viread and in Truvada and Atripla) and atazanavir (Reyataz)
 - increased use of lipid-lowering agents such as statins
 - reducing traditional risk factors for heart attacks, such as smoking, insufficient exercise, obesity, poor diet and so on

These findings provide hope for HIV positive people and their care providers that heart attacks are not inevitable and the risk for this complication can be greatly reduced.

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B. France: a large hospital database looks at heart attacks

In 1989, doctors in France established the French Hospital Database (FHDB), which has collected health-related information on more than 77,000 HIV positive people. Researchers working in HIV sought to assess rates of heart attacks among HIV positive patients in France and looked at cases between the years 2000 and 2008. During this time they found 289 cases of heart attack, all of which were confirmed by a research cardiologist. These 289 cases of heart attack occurred among more than 77,000 people, about 80% of whom were using HAART (*personal communication*, Dominique Castagliola, PhD). To perform their analysis, researchers matched each case with at least one control patient. Each control was also HIV positive, had no history of cardiovascular disease, was of similar age and gender and went to the same clinic. The average profile of people with heart attacks (cases) was as follows:

- 10% female, 90% male
- age – 47 years
- CD4+ count – 427 cells
- viral load – 43% had a viral load below the 50-copy mark

Often, people who had experienced a heart attack (cases) had at least one risk factor for cardiovascular disease, as follows:

- smoking – 73%
- higher-than-normal levels of cholesterol – 52%
- higher-than-normal blood pressure – 21% of cases
- family history of CVD – 19%

Results—different anti-HIV agents

The research team assessed any relationship between the use of specific anti-HIV agents and the development of a heart attack. Here's what they found:

- Abacavir (Ziagen and in Kivexa and Trizivir) posed a heart attack risk only in some people who had used it for less than one year. The risk is very low, about 1%. There was no long-term heart attack risk with the use of abacavir. Also, there was no link between the use of abacavir, having a risk factor for CVD and the development of a heart attack. This last finding was deeply puzzling and suggests the possibility that abacavir use might trigger the development of a heart attack in an unexpected way. Note that 90% of people who were using abacavir had previously received d4T or tenofovir.

- Other nukes: There was a trend for an increased risk of heart attacks in people who had used AZT (zidovudine, Retrovir and in Combivir) and d4T (stavudine, Zerit). However, this trend did not become statistically significant and further investigation is needed to clarify it.
- Overall, the use of a protease inhibitor (PI) boosted with ritonavir was linked to a 16% increase in risk of heart attack for each year these drugs were used.
- Fosamprenavir (Telzir, Lexiva) was linked to a 52% increased risk of heart attack. Over a period of 10 years of continuous use, this risk would climb.
- Lopinavir-ritonavir (Kaletra) appeared to increase the risk of heart attack by 37% for each year used.

Bear in mind

1. The findings from France are interesting but not definitive. Because this was an observational study, the FHDB can find associations but cannot conclusively prove that exposure to a particular drug does indeed cause heart attacks.

That abacavir is somehow associated with the rare risk of a heart attack is unexpected, as until recently this drug had an excellent safety record. According to the FHDB, traditional risk factors for heart attacks were not linked to abacavir-associated heart attacks, which simply adds to the mystery.

2. An important point is that abacavir can cause inflammation—as seen in the hypersensitivity reaction that can occur in up to 8% of abacavir users who are not tested for their risk for this problem. In people who are tested for hypersensitivity before using abacavir, the risk of this problem (hypersensitivity) is rare.

In the FHDB, abacavir hypersensitivity testing results were not taken into account when looking at abacavir-related heart attacks. This is probably because hypersensitivity testing has been available in Western Europe only for the past several years. This is an important point and here's why:

- In abacavir-related hypersensitivity reactions, inflammation occurs. In theory, such inflammation could play a role in cardiovascular-related events, such as the unnecessary formation of blood clots or even a heart attack.

- Abacavir hypersensitivity testing has only been introduced in Western Europe over the past several years. Armed with the results of this testing, physicians only prescribe abacavir to people who are unlikely to develop a hypersensitivity reaction. Yet the French database used data on people who used abacavir since 2000—a time when hypersensitivity testing was not available. It is possible that some of the people who used abacavir and who also developed a heart attack had this problem because they were susceptible to an abacavir hypersensitivity reaction—with its attendant inflammation—and, subsequently, a heart attack.
- Now that abacavir hypersensitivity testing is increasingly part of various blood tests that doctors request, only people at very low risk for abacavir hypersensitivity are prescribed abacavir. It is possible that, in theory, people screened for this hypersensitivity reaction could be at very low risk for an abacavir-related heart attack. Therefore, collecting information on people who were screened for this reaction and who also developed a heart attack is important in trying to understand how abacavir might play a role in heart attacks.

3. The FHDB has found that, in general, the use of a PI with ritonavir results in about a 16% increased risk of heart attack with each year this combination is taken.

Some combinations have a higher-than-average risk of heart attack: lopinavir-ritonavir (Kaletra) is associated with a 37% increased risk and fosamprenavir-ritonavir (Telzir) is associated with a 52% increased risk of this event. Perhaps what is most shocking about the FHDB's findings is that the heart attack risk associated with a PI-ritonavir combination does **not** go away when this combination is stopped. Moreover, removing ritonavir from their calculations did not reduce the risk. Researchers are not sure why this is the case but this finding is disturbing.

4. Not enough data was available on people who used other PIs, such as darunavir (Prezista) or atazanavir (Reyataz), for the French researchers to make clear conclusions about their use and potential heart attack risk.

Clearly more research is needed in the area of heart attacks and HIV medicines.

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C. The DAD study: a large European database looks at heart attacks

A mostly European database called DAD (the Data collection on Adverse events of anti-HIV Drugs) has enrolled more than 33,000 HIV positive people in an attempt to try to find out more about uncommon side effects. The DAD study is currently ongoing.

Prior analyses of DAD have revealed that there appears to be an increased risk of cardiovascular disease (CVD) in some people who have used protease inhibitors. DAD has accumulated enough data and monitored the health of people long enough that it can report clear results about the use of the following drugs and their association with CVD:

- protease inhibitors – indinavir (Crixivan), lopinavir (in Kaletra), nelfinavir (Viracept) and saquinavir (Invirase)
- non-nukes – efavirenz (Sustiva) and nevirapine (Viramune)
- nukes – AZT (zidovudine, Retrovir), d4T (stavudine, Zerit), ddI (didanosine, Videx), ddC, 3TC (lamivudine), abacavir (Ziagen) and tenofovir (Viread)

For the current analysis, DAD monitored at least 33,308 HIV positive participants until February 2008 or until they developed their first heart attack. Of this total, here are the outcomes:

- no heart attack – 32,728 people
- heart attack – 580 people

Roughly 2% of people in the DAD study developed a heart attack. At the time of their heart attack, the average profile of the 580 people was as follows:

- 9% female, 91% male
- age – 49 years

- 75% had higher-than-normal levels of lipids in the blood
- 45% were currently smoking tobacco
- 30% were former smokers
- 17% had diabetes
- 14% had a family history of cardiovascular disease
- 36% used lipid-lowering therapy

Results

- Nukes – there was a trend toward an increased risk of heart attack the longer abacavir was used. Similar findings were seen with AZT. DAD researchers reported that exposure to ddI was linked to an increased risk of heart attack.
- Non-nukes – no association with a heart attack was detected
- Protease inhibitors – exposure to indinavir or lopinavir-ritonavir was associated with an increased risk of heart attack. Use of these drugs increased the risk by 13%.

Caution needed

Bear in mind that DAD is an observational study and such studies are best at finding associations but cannot prove cause and effect. Also, 20% of people who had a heart attack in the DAD study had had a previous heart attack. What this disclosure by the DAD researchers means for their conclusions is not yet clear. It is possible that the DAD researchers may have inadvertently biased their interpretation of the data by including people in their analysis who had more than one heart attack.

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D. Putting heart attack risk into perspective

In the 1980s, people in high-income countries who became HIV positive had about 10 years before succumbing to dreadful AIDS-related infections and eventual death. But in 1996, HAART became available and the spectre of many AIDS-related deaths gradually receded. Today, HIV positive people who have minimal co-existing health conditions and who are engaged in their care and treatment will likely have near-normal life spans. This benefit should not be overlooked in the race

to find the cause of heart attacks in some HIV positive people. Moreover, the numerous benefits of HAART continue to outweigh side effects.

This immense benefit of HAART sometimes gets tarnished by unwelcome news, such as reports of an increased *risk* of heart attacks if certain treatments are used. The news about heart attacks and the use of HAART is disturbing to both physicians and HIV positive people. However, it is important to bear in mind several points when reading about such news. These points may help place some perspective on the news and limit the development of anxiety.

Don't forget HIV

Emerging research suggests that HIV can infect the lining of blood vessels and that infection with this virus triggers inflammation. Also, research suggests that this inflammation may, in some cases, be linked to heart attack and stroke.

Heart attack numbers—DAD

While the increase in risk for heart attacks does sound large, depending on which study is examined, the actual number of people affected by this problem is relatively low. Indeed, in the DAD study, there were a total of 33,308 people, of whom 580 developed a heart attack while on HAART, about 2%. What's more, 20% of these 580 people had previously experienced a heart attack. That DAD did not take into account these prior heart attacks may have weakened its conclusions.

Heart attack numbers—French database

In the French Hospital Database (FHDB), there were 289 cases of confirmed heart attacks among at least 60,000 people taking HAART. This means that less than about 0.5% of people in this database developed a heart attack. This is very low and is reassuring about the overall safety of HAART when it comes to heart health.

The FHDB found an increased *risk* for heart attack of 16% for each year a PI-ritonavir was used. But since the baseline risk of a heart attack for most people is low, this increased risk still remains low and that is why the number of people who developed a heart attack is low in the Cohort studies.

Lipid-lowering therapy

What is clear from the DAD study is that only 36% of 580 people who developed a heart attack received lipid-lowering therapy. Given that 75% of

the these 580 people had higher-than-normal levels of lipids in the blood, and that just over one-third of them received lipid-lowering medicines, this raises questions about the quality of care that European HIV positive patients receive. Lipid-lowering therapy, particularly the group of drugs called statins, has a number of protective benefits, including anti-inflammatory activity. In North America, physicians who are experienced in the care and treatment of HIV infection would have been much more likely to have prescribed a statin or other lipid-lowering medication in the same situation. It is possible that better management of cardiovascular risk factors in Europe might reduce the risk of heart attacks in HIV positive people. Certainly, data on decreasing rates of heart attacks in HIV positive people in California, reported earlier in this issue of *TreatmentUpdate*, support this possibility.

DAD vs. the French database

There are differences in the results of both of these databases and it is important to bear these differences in mind when considering their findings about heart attacks.

The DAD did not exclude people who already had a heart attack. This could have affected researchers' ability to reduce bias when interpreting their results.

On the other hand, the FHDB did exclude people who had previous heart attacks. This could strengthen the conclusions drawn by the FHDB.

Another difference between the two data sets is that people in France tend to be at lower cardiovascular risk than people in Northern Europe. This difference could have affected the outcomes of the French study.

The FHDB found an increased risk of heart attack with fosamprenavir. The DAD study is unable to reach conclusions about fosamprenavir at this time because it does not have enough people enrolled who are using this drug. The FHDB found no increased risk of heart attack in ddI users.

DAD vs. other data sets

Some analyses (at least four, including the DAD) have found that the use of abacavir is associated with an increased risk of heart attacks (though the actual proportion of people who experienced these heart attacks is very low). Most of these studies have had people who have been taking anti-HIV medicines for years. In contrast, there have been

at least three analyses that found no increased risk of heart attacks in abacavir users. These latter analyses have been done mostly in people who have been new to HAART. Thus, there may be a reasonable explanation for the different findings of various studies. This difference is worthy of further investigation.

Balancing risk

Since there are different findings depending on which data set is analysed, it is not likely that broad recommendations about which therapy to use (or not) can be made with high levels of confidence. So physicians and their patients will have to weigh the various risks of each anti-HIV drug before starting or switching therapy.

Observational studies such as DAD and the FHDB are good at finding associations but cannot conclusively prove cause and effect. But if the results from these observational studies are correct (and not based on incorrect analyses), then for a very small proportion of HIV positive people the use of abacavir can cause a heart attack. In such cases, it may be prudent for people at high risk for cardiovascular disease to not use abacavir. Some physicians, such as Dr. Peter Reiss, a member of DAD's steering committee, have suggested that even HIV positive people who have moderate cardiovascular disease risk factors should avoid abacavir. Unfortunately, there does not seem to be widespread international consensus or clarity about exactly what to do about abacavir and its potential for causing heart attacks.

Bear in mind that other anti-HIV drugs could also have side effects. For instance, tenofovir could be used to replace abacavir. Tenofovir can cause kidney dysfunction, which in turn reduces the ability of this organ to retain the body's calcium. Over the long term, reduced calcium could lead to thinning bones. This has been the case in another study presented at the 16th CROI.

The above example shows the complexity of decision-making that people with HIV and their physicians are grappling with now and in the future.

There are trends in DAD that suggest the possibility of finding of an increased risk of heart attack with other anti-HIV drugs in the future, if these trends continue. As DAD, the FHDB and other studies accumulate more participants over longer periods of time their conclusions will be closely watched in the years ahead.

Dangerous liaisons

Although researchers may disagree about the importance of findings from observational studies about HAART and heart attacks, what nearly every leading HIV researcher who studies cardiovascular disease in people with HIV agrees upon is this: Traditional risk factors for heart attacks and stroke play a huge role in causing these problems. So rather than rushing to dump HAART, a good first step would be to reduce or eliminate traditional risk factors for heart attack, at least the ones that can be changed, such as:

- smoking tobacco
- abnormal cholesterol levels – high concentrations of bad cholesterol (LDL) and low concentrations of good cholesterol (HDL)
- excess weight
- excessive levels of belly fat
- diabetes
- higher-than-normal blood pressure
- not enough exercise
- poor diet

As mentioned earlier in this issue of *TreatmentUpdate*, that researchers in California have found that heart attack rates can fall to near-normal levels in HIV positive people shows that the risk of heart attacks can be reduced despite the use of protease inhibitors.

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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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