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## I SIDE EFFECTS AND COMPLICATIONS

### A. Inflammation and HIV

In high-income countries and regions, such as Australia, Canada, Western Europe and the United States, highly active antiretroviral therapy (HAART) is widely available because of subsidized access. As a result, AIDS-related infections and deaths have greatly decreased. This effect of HAART is so immense that researchers expect that some HIV-positive people who can adhere to therapy and who have minimal co-existing complications can live near-normal life spans.

### Viral infections and inflammation

A consequence of many viral infections is that the immune system is activated. This is a normal procedure that enables the immune system to go into a heightened state of alert and mobilize its forces against invading germs. Once an infection has been brought under control and the invading germs wiped out, the immune system then dampens down activation to a more normal state.

HIV infection activates the immune system very early in the course of infection. This activation appears to cause dysfunction within the immune system, also very early in the course of infection. Some researchers theorize that prolonged activation of the immune system due to HIV infection leads to increasingly dysfunctional behaviour by the immune system and, eventually, if treatment is not started, to the development of AIDS.

Although HAART is very good at suppressing HIV in the blood, infected cells continue to produce low levels of HIV in the body. And although the immune system continues to experience activation, albeit at a reduced level

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555 Richmond Street West, Suite 505  
Toronto, Ontario M5V 3B1 Canada  
phone: 416.203.7122  
toll-free: 1.800.263.1638  
fax: 416.203.8284  
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because of HAART, this continued activation over many years may gradually degrade organ-systems such as the heart and blood vessels, kidneys, bones, and so on.

Experiments conducted on monkeys infected with the AIDS-causing virus SIV and those in people taking HAART over the long-term confirm the presence of low-level activation. Because of the potential for continuous activation of the immune system to accelerate the ageing process, research teams in high-income countries are beginning to focus on this aspect of HIV infection. Their efforts are aimed at gaining a better understanding of why this activation occurs in the presence of HAART and developing ways to safely lessen it.

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## B. French study unexpectedly uncovers role of substance use in heart attacks

Several years ago researchers working with a large observational database called DAD (with more than 33,000 HIV-positive people) announced that they had found a link between the use of the anti-HIV drug abacavir (Ziagen and in Kivexa, Epzicom and Trizivir) and an increased risk for heart attack. They also announced that they found a link between the use of the anti-HIV drug ddI (Videx EC, didanosine) and an increased risk for heart attack. Several other studies have not found this link with abacavir (and none have found a link with ddI), and so the initial findings from DAD

have become deeply controversial for at least these and other reasons, as follows:

- Observational studies such as DAD are very good at finding associations but cannot by their design prove cause (taking a particular drug) and a resulting effect (heart attack).
- Abacavir has had a good overall track record of safety, so researchers were surprised by its association with heart attack.
- Cardiovascular events—heart attacks and strokes—can sometimes have related underlying causes, yet DAD found only an increased risk of heart attack but not stroke.
- It is possible that there were events or data in DAD that may have been overlooked which could, in theory, have biased researchers' interpretation of its analyses. For instance, DAD researchers announced last February that about 20% of people who had a heart attack while using abacavir had had a heart attack in the past. This finding might make it difficult to draw firm conclusions about the role of abacavir in heart attacks in these people.
- DAD researchers are unable to fully take into account factors such as preexisting kidney disease in all participants. This may affect their conclusions. What's more, DAD has not yet released findings on substance use by its participants, particularly substances that can stress the heart, such as cocaine, crystal meth and other stimulants. So it is possible that these factors could have biased the researchers' analyses. On the other hand, sometimes patients may be embarrassed or uncomfortable about disclosing the use of substances to their doctors, so it may not be possible to get this information.

Finally, at least two large databases, the French Hospital Database (with more than 77,000 HIV-positive people) and the Veterans Administration (almost 20,000 HIV-positive people), have not found an association between the use of abacavir and the development of heart attack or stroke. A recent analysis of Kaiser Permanente, a large database in northern California with records on more than 35,000 HIV-positive people, has found that the risk of heart attack and stroke has significantly decreased over time (1996 to 2008), falling to levels seen in HIV-negative people.

### About the French Hospital Database

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 278 cases of heart attack, all of which were confirmed by a research cardiologist. These 278 cases occurred among more than 77,000 people, about 80% of whom were using HAART (*personal communication*, Dominique Costagliola, PhD).

Lead researcher Dominique Costagliola recently reanalyzed the FHDB's large dataset to find any links between the occurrence of a heart attack and any of the following anti-HIV drugs commonly called nukes:

- ABC (abacavir)
- AZT (zidovudine/Retrovir, and in Combivir and Trizivir)
- ddC (zalcitabine, Hivid)
- ddI (Videx EC, didanosine)
- d4T (stavudine, Zerit)
- 3TC (lamivudine, and in Combivir, Kivexa and Trizivir)
- tenofovir

Overall, there was **no** statistically significant connection between the use of any of these nukes—including abacavir—and a heart attack.

It is important to note that French researchers made sure to take into account other conditions that are known to cause heart attacks and which could have biased their results and caused them to draw false conclusions, including these:

- higher-than-normal blood pressure
- smoking tobacco or having quit in the past three years
- family history of premature cardiovascular disease
- abnormal cholesterol levels
- diabetes
- use of cocaine or other illicit substances
- viral load
- CD4+ and CD8+ cell counts

The French researchers also took into account the use of the following anti-HIV medicines, in case they might have played a role in heart attacks observed in abacavir users:

- atazanavir (Reyataz)
- ritonavir (Norvir and in Kaletra)
- tipranvir (Aptivus)
- FTC (emtricitabine, Emtriva)

Researchers found that the use of these particular medicines had no significant effect.

### **A lot of cardio risk factors**

The French researchers found that out of 278 abacavir users who had a heart attack, only five had no risk factors for cardiovascular disease (CVD). This means that 98% of abacavir users who had a heart attack had at least one risk factor for cardiovascular disease. Indeed, a large proportion (nearly 40%) of the 278 people had three or more risk factors for CVD.

### **The role of HIV**

Other studies have found that having HIV infection appears to be a risk factor for CVD. Among the 278 abacavir users who developed a heart attack, 56% had a detectable viral load. This could have played a role in the development of heart attack.

### **Cocaine**

Going beyond previous analyses, French researchers specifically checked for the use of cocaine and other substances or behaviours, such as injecting drug use, in abacavir users who had a heart attack. Cocaine, which can be snorted or injected, is a stimulant and can stress the heart. Because injection drug use is one of the means by which HIV is transmitted, it is not surprising that some HIV-positive people use cocaine and other illicit drugs.

To find out if these drugs played a role in some of the heart attacks seen in some abacavir users, the FHDB did another analysis. When the researchers took into account the use of cocaine or other illicit substances among people who were prescribed abacavir, again they found **no** link between the use of abacavir and heart attacks. Furthermore, the researchers found that many of the people who used cocaine and other illicit drugs also had traditional CVD risk factors. Perhaps their use of cocaine in the setting of other CVD risk factors might have greatly increased their risk for having a heart attack.

In conclusion, Dr. Costagliola noted that traditional risk factors (high cholesterol, blood pressure and so on) in concert with cocaine and injection drug use are “very strong risk factors for [heart attack] in HIV-1 infected patients.”

Therefore, based on the most recent analysis of the large French Hospital Database, particularly taking into account the use of cocaine and other illicit substances, it seems that exposure to abacavir is

not statistically linked to the development of a heart attack.

However, doctors caring for HIV positive patients who use cocaine or stimulants or inject illicit substances may wish to avoid the use of abacavir in this population.

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## C. VA study fingers kidney disease as a major predisposing factor for heart attacks

Researchers with the Veterans Administration (VA) system in the U.S. have amassed a large dataset collected from nearly 20,000 HIV-positive people who sought care and treatment. These researchers note that rates of heart attack appear to be declining recently among HAART users in the U.S., particularly those from northern California, so they are puzzled by the reports of an increased heart attack risk in people who have used abacavir.

VA researchers decided to analyse their database for any possible link between the use of abacavir and the development of a heart attack or stroke. They noted that in addition to traditional CVD risk factors, conditions such as chronic kidney disease and, in some studies, hepatitis C virus (HCV) infection also increase the risk for heart attack or stroke. What's more, VA researchers underscored the following: Because the anti-HIV drug tenofovir can cause kidney toxicity, the presence of pre-existing chronic kidney disease in some people might have caused doctors to prescribe abacavir instead of tenofovir. This may have resulted in a large proportion of abacavir users having an increased risk for heart attack because of a pre-existing condition—chronic kidney disease. To explore these and other issues, VA researchers conducted a study.

### Study details

The VA team analysed health-related information collected between 1996 and 2004. They divided participants into several groups based on their treatment as follows:

- HAART containing abacavir
- HAART without abacavir
- taking only one or two anti-HIV drugs (usually these would be nukes)
- not taking any anti-HIV treatment

This last group of people not taking medicines was used as control, or comparison, group.

Researchers analysed medical records of 19,424 HIV-positive people whose average age was 46 years and who had been monitored for at least four years.

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## Results

The VA team found that 80% of people in its database used anti-HIV drugs and the following events occurred during the study period:

- heart attacks – 278 cases
- stroke – 868 cases

The VA team found that people with heart attacks, compared to people who did not have a heart attack, were more likely to fit the following profile:

- be older (51 years vs. 46 years)
- have diabetes
- have high blood pressure
- have abnormal cholesterol levels
- have chronic kidney disease; that is, an eGFR (estimate-glomerular filtration rate) of 60 or less. [For more information about the kidneys and how doctors assess kidney health using eGFR, see *TreatmentUpdate 174* at [www.catie.ca/tu.nsf](http://www.catie.ca/tu.nsf).]

## Heart attack and treatment

The VA team noted that rates of heart attack remained relatively stable over the study period. When they examined the data, looking at the possible impact of treatment on heart attack, here's what they found:

- HAART containing abacavir – no significantly increased risk of heart attack
- HAART without abacavir – no significantly increased risk of heart attack
- taking only one or two nukes – a 44% increased risk of heart attack

## Heart attack and chronic kidney disease

- People who had an eGFR below 60 had a 400% increased risk of heart attack.
- People who had an eGFR between 60 and 89 were just beyond the threshold of statistical significance for an increased risk of heart attack.
- People who had a normal eGFR (90 or greater) did not have an increased risk for heart attack.

## Stroke and treatment

When they examined the data, looking at the possible impact of treatment on stroke, here's what the VA researchers found:

- HAART containing abacavir – no significantly increased risk of stroke
- HAART without abacavir – no significantly increased risk of stroke
- taking only one or two nukes – no significantly increased risk of stroke

## Did pre-existing conditions affect prescription?

Researchers found a highly statistically significant link between the presence of chronic kidney disease and the nuke that doctors prescribed patients. For example, patients given abacavir were statistically more likely to have chronic kidney disease than patients given tenofovir. Because chronic kidney disease places people at increased risk of heart attack, the relative excess prescriptions of abacavir to people with kidney disease may have led to the false conclusion that the use of abacavir caused heart attacks.

The VA study is not perfect—it is a retrospective study, which looks back at events that already happened. But the VA collected data on heart attacks between 1996 and 2004, while the DAD study only started collecting data on heart attacks in 1999.

The VA researchers suggest that in some other studies, such as DAD, the role of chronic kidney disease in abacavir users has not been fully assessed and this might have led the study teams to conclude that the use of abacavir was somehow linked to the development of a heart attack.

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## D. BICOMBO study looks at the safety of abacavir

The BICOMBO study was a Spanish study that randomly assigned treatment-experienced participants to change the nuke portion of their regimen to one of the following:

- abacavir + 3TC – 167 patients
- tenofovir + FTC – 168 patients

The BICOMBO study team looked at a subgroup of participants from its study to assess the impact of nukes on the following:

- inflammation of the lining (endothelium) of blood vessels

- an imbalance between factors affecting blood flowing or clotting, favouring an excessive formation of blood clots
- insulin resistance (occurs in pre-diabetes and diabetes)

The BICOMBO researchers noted that factors such as cardiovascular disease, diabetes, uncontrolled HIV infection or other health conditions might affect the risk of developing a heart attack. Not taking these factors into account could have inadvertently led to biases when interpreting the results of several studies in which abacavir was linked to an increased risk for heart attack. So the BICOMBO team proposed to do a sub-study in a smaller group of patients, examining factors that can increase CVD risk, and therefore heart attacks, before and after its study.

### Study details

The BICOMBO sub-study focused on 46 participants who received abacavir + 3TC and 34 others who received tenofovir + FTC.

Some of the proteins they assessed in the blood included the following:

- high-sensitivity C-reactive protein (hsCRP)
- interleukins-6 and -10
- TNF-alpha
- adiponectin
- D-dimer
- insulin

Levels of these and other proteins were similar between participants at the start of the study.

The average profile of people at the start of the BICOMBO study was as follows:

- 20% female, 80% male
- age – 43 years
- time spent on HAART – four years
- use of protease inhibitors – 8%

### Changes after one year

On the whole, people taking abacavir + 3TC did not have significant changes to levels of inflammatory proteins in their blood that were different from people taking tenofovir + FTC.

The researchers concluded that in otherwise-healthy participants the use of abacavir + 3TC compared to tenofovir + FTC did not result in

significant differences in blood tests used to assess the following:

- inflammation
- endothelial dysfunction
- insulin resistance
- increased risk for the formation of blood clots

The BICOMBO team added that “these results argue against the involvement of abacavir in any of these mechanisms and therefore do not explain the higher risk of [heart attacks] associated with recent abacavir use in some cohort studies.”

The strengths of the BICOMBO study are as follows:

- participants were randomly assigned to receive treatment
- a wide range of blood tests to assess CVD risk factors was conducted

A weakness of BICOMBO is that it was a relatively small study. Another randomized study called STEAL, with a similar number of participants, found an unexpected increase in the risk of cardiovascular complications, including heart attacks, in treatment-experienced people who received abacavir + 3TC compared to others who received tenofovir + FTC. Some people in STEAL had pre-existing cardiovascular disease before taking that study’s medication, particularly people who were assigned to receive abacavir.

Note: As we went to press, further details about the STEAL study as well as new developments from DAD are about to become available and we will write reports on these developments in upcoming issues of *TreatmentUpdate*.

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## E. Cardiovascular risk and HIV treatment

The findings from these recently presented studies raise questions about the findings from the DAD study. It will be interesting to see in the months ahead what these and other studies find as they continue their analyses.

Another finding from DAD was that in 2008 it announced that the use of ddI (Videx EC, didanosine) was linked to a nearly 50% increased risk for heart attack. Yet the next year, this apparent risk disappeared. This is very puzzling.

The findings from the French Hospital Database and the Veterans Administration studies are reassuring about the safety of abacavir. They draw attention to previously overlooked CVD risk factors in HIV-positive people, such as chronic kidney disease and the use of cocaine and other illicit substances. However, the results from the FHDB and the VA studies do not negate DAD's results. Rather, they should encourage researchers to try to explore and understand why DAD and a randomized but smaller study of treatment interruption called SMART both found that abacavir was linked to the development of a heart attack.

What's more, compared to DAD, FHDB and the VA, two relatively smaller but randomized studies—BICOMBO and STEAL—found conflicting results. And yet another randomized study about the same size as STEAL and BICOMBO, called ARIES, found that abacavir is **not** associated with heart attacks when used with or without ritonavir (Norvir)-boosted atazanavir (Reyataz). Overall, these conflicting findings and different study designs have led to some confusion among doctors and their patients as they try to make sense of this complexity.

If there is any relatively good news out of this complexity it is this: The proportion of people who have developed a heart attack in databases such as DAD and FHDB is relatively low—about less than 2%. This should be very reassuring to both doctors and their patients: Heart attacks in HIV-positive people taking HAART are **not** common.

### What to do?

At the 2009 Conference on Retroviruses and Opportunistic Infections (CROI), Dr. Peter Reiss, a member of the DAD steering committee, suggested that doctors should **not** prescribe abacavir to patients at **high** risk for cardiovascular disease. This course of action is prudent. Also,

based on the most recent analysis from the French Hospital Database, it seems that doctors may wish to consider not prescribing abacavir for patients who use cocaine or who inject illicit substances.

Additional suggestions may not be forthcoming until researchers can clear up the various results among different datasets and clinical trials and draw robust conclusions.

All of the researchers who participated in the different studies agree when it comes to the following point: Regardless of the anti-HIV treatment being used, an important step would be to greatly reduce or, when possible, eliminate **all** modifiable risk factors for cardiovascular disease—and to make the sustained commitment necessary to do so. HIV-positive people who have minimal co-existing complications have the potential to live near-normal life spans thanks to HAART. If this potential is to be realized, the risk factors for heart attacks, stroke and other complications of ageing need to be addressed.

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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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*Writer*  
*Editor*

Sean Hosein  
RonniLyn Pustil

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by post: 505-555 Richmond Street W  
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