I ANTI-HIV AGENTS

A. Introduction

At the annual Conference on Retroviruses and Opportunistic Infections (CROI), North America’s premier HIV/AIDS scientific conference, cutting-edge research findings are usually presented and controversial treatment and prevention issues debated. The 15th annual CROI, held in Boston February 3-6, 2008, was no stranger to controversy, as the results of a large database analysis called DAD raised questions about the safety of the commonly used nucleoside analogue abacavir (Ziagen).

In this issue of Treatment Update we tackle the DAD analysis, exploring its design and findings, with the assistance of several of Canada’s leading HIV/AIDS researchers.

Also in this issue are findings from trials of anti-HIV drugs in development.

In the next Treatment Update we will have further information from CROI, focusing on co-infections such as hepatitis C and complications such as thinning bones, cardiovascular disease, blood sugar issues and hormonal changes in women with HIV.

B. Controversial findings on abacavir and heart attacks

Abacavir (Ziagen) is a commonly used anti-HIV drug that belongs to a family of medicines called nucleoside analogues, or nukes. Abacavir is found in the following combinations:

- Kivexa (abacavir + 3TC [lamivudine])
- Trizivir (abacavir + 3TC + AZT [Retrovir, zidovudine])
A drawback of some nukes is that they can cause lipoatrophy—a process in which the fatty layer just under the skin (subcutaneous fat) wastes away. Abacavir alone or in combination with 3TC (Kivexa) is not associated with fat wasting. Indeed, abacavir users may even develop increased fat in their limbs.

In several clinical trials, abacavir has been found to be an effective part of combination therapy, lowering viral loads and raising CD4+ counts.

The use of abacavir is associated with the possibility of a hypersensitivity reaction in up to 8% of people who took the drug. However, in many high-income countries today, a simple blood test is available that can predict the likelihood of such a reaction. Potential abacavir users can have this test performed before they start using the drug. Armed with this screening tool, doctors can now prescribe abacavir to patients who have a negative test result, knowing that the chance of a hypersensitivity reaction occurring during abacavir therapy is very, very low.

Digging deeper
DAD is the name of a large database project centred in Copenhagen, Denmark, that collects information from 212 HIV clinics, mostly in Europe but also from some clinics in Australia and the United States. Health-related information from more than 33,000 patients is stored in DAD’s database. From time to time, DAD scientists query the database in an effort to answer research questions.

Drugs such as d4T (Zerit, stavudine) and AZT are called thymidine analogues (the T in both drugs stands for thymidine). Unfortunately, the use of d4T is associated with nerve damage, lipoatrophy and increased levels of cholesterol and triglycerides in the blood. AZT to a lesser extent can sometimes cause fat wasting. So the DAD team decided to investigate if there was any link between the use of thymidine analogues (AZT and d4T) and cardiovascular disease. When they did not find a link, they decided to look at other nukes, namely abacavir, ddI (Videx EC, didanosine) and 3TC. It is important to note that DAD did not have enough patients on tenofovir (Viread) to analyze the possibility of a link between this drug and heart disease.

Unexpected results
At the 15th Conference on Retroviruses and Opportunistic Infections (CROI) in February, researchers from Copenhagen presented findings from an analysis of DAD. They unexpectedly found that the recent use of abacavir (in the past six months), and to a lesser extent ddI, was linked to an increased risk of heart attacks.

Because of abacavir’s good safety record, many researchers were puzzled by these findings. Initially, so was the DAD study team, so they reviewed their findings just to be sure.

Focus on heart attacks
Out of 33,347 HIV positive people, heart attacks occurred in 517 as of February 2008. The distribution of heart attacks among people using certain medications was as follows:

- 124 people were either using ddI or had recently stopped using ddI (within the past six months) when a heart attack occurred.
- 192 people were either using abacavir or had recently stopped using abacavir when a heart attack occurred.
- 237 people had been using HAART, but not abacavir or ddI, and also had a heart attack.

Bear in mind that the overall proportion of people with heart attack was relatively low—1.6%.

At risk for heart attacks
HIV positive people who had recently used abacavir were likely to fit the following profile:

- males 45 years and older
- females 55 years and older
- diabetic
- higher-than-normal blood pressure
- higher-than-normal levels of lipids—cholesterol and triglycerides—in the blood

This profile is striking and worthy of further attention because the DAD team declared that “patients with a high underlying cardiovascular risk” seemed to be more likely to have a heart attack. Other key points from the study are as follows:

- Exposure to abacavir was not linked to the development of other forms of cardiovascular disease, such as stroke.
- The risk of a heart attack in recent abacavir users was double what would normally be expected.
- Discontinuing abacavir or ddI reduced the risk of developing a heart attack.
- There was no link between CD4+ counts, viral load and heart attacks.
The findings from the DAD study are startling and now require additional investigation to confirm, understand and explain the results. Researchers are puzzled by the findings because abacavir has been in use in high-income countries for over a decade yet it has never been associated with heart attacks.

What’s next?
The DAD study is an observational study. These types of studies are useful for finding associations but cannot prove cause and effect. Observational studies, because they are not randomized, cannot entirely rule out the possibility of bias when interpreting their findings. For example, abacavir was approved later than all of the other nukes to which it was compared, suggesting that abacavir users may have differed in ways that were not captured by the DAD study.

Moreover, the DAD study was unable to take into account every bit of data that might have been useful in making a link between abacavir, ddi and heart attacks. Also, as previously noted, tenofovir was not included in the analysis, so we do not know if it is associated with an increased risk of heart disease in the DAD cohort. For these and perhaps other reasons, the results from DAD are controversial.

Now that the DAD analysis has been released, it should incite the following courses of action:

- Regulatory agencies need to review their databases, checking for reports of abacavir- and ddi-related side effects, particularly looking at heart attacks and related issues.
- Other databases held by hospitals and research agencies, such as the large Veterans Administration (VA) database in the United States, need to be queried about heart attacks among HIV positive people and whether there was any link with abacavir or ddi. The VA database is one of the largest in the world, containing health information on more than 40,000 HIV positive people.

Querying databases such as the VA and others takes on additional importance in light of the DAD findings. This is because conducting a randomized controlled trial to try to investigate the issue of abacavir, ddi and heart attacks would require about 20,000 HIV positive volunteers at high risk for cardiovascular disease and take at least three years to complete. Such a trial would be expensive and complex and may therefore be difficult to conduct.

- GlaxoSmithKline (GSK), the manufacturer of abacavir, has begun checking its own databases of abacavir-related adverse effects. Preliminary results from a review of 15,000 patient records in the GSK database have not found any link between abacavir and heart attacks (Tjark Reblin GSK, personal communication).
- Research-cardiologists need to be made part of the investigating team to try to resolve the issue of abacavir, ddi and heart attacks.
- HIV infection appears to increase inflammation, both directly and indirectly. Proteins produced by HIV-infected cells appear to damage heart muscles and HIV itself can infect blood vessels. Also, inflammation associated with many other diseases unrelated to HIV increases the risk of heart attacks. These all complicate the mystery of abacavir’s potential role in heart attacks as reported by DAD.

Unanswered questions
Clinics that have sent data to DAD need to review cases of heart attacks among abacavir and ddi users to try to better understand how these or other drugs might have played a role in the DAD results. In reviewing medical records, some issues that are worth noting or pursuing include the following:

- Were any abacavir or ddi users who had heart attacks also taking statins (drugs to lower cholesterol)? These drugs also have anti-inflammatory activity and their use can reduce the risk of a heart attack.
- What proportion of the people using abacavir who experienced heart attacks had undergone abacavir hypersensitivity screening? This question is important because, as we mentioned earlier, abacavir can cause hypersensitivity reactions in a small proportion of people.

Hypersensitivity reactions can occur with many drugs. In the case of some anti-cancer drugs, the severe inflammation associated with a hypersensitivity reaction can lead to a heart attack. Speculation: It is plausible that inflammation triggered by exposure to abacavir in an HIV positive person at high risk for cardiovascular disease might have led to a heart attack. So it may be worth investigating clinic records to find out if abacavir hypersensitivity screening was done for patients who experienced a heart attack in the DAD study.
• The short-term use of abacavir was linked to an increased risk of heart attack in the DAD study. Clinics need to review their data to find out why some patients were given abacavir. Were these patients at high risk for heart attacks before they received abacavir?

• Abacavir is widely prescribed by doctors in high-income countries, and, in general, heart attacks remain rare among people with HIV/AIDS.

**Options**

For the average healthy HIV positive person taking abacavir who has minimal risk factors for cardiovascular disease, there is probably little risk in continuing to take abacavir. However, HIV positive people who take abacavir should speak to their doctor if they have one or more of the following characteristics:

- smoke tobacco
- are male and 45 years or older
- are female and 55 years or older
- have higher-than-normal blood pressure
- have higher-than-normal levels of lipids in their blood
- have cardiovascular disease
- have a close family member who has a history of heart attacks or cardiovascular disease
- have diabetes

Depending on the outcome of this discussion and their doctor’s approval, it might be useful for some HIV positive people taking abacavir to lower their risk for cardiovascular disease. This can begin in a number of ways, including the following:

- seeking help, support and instructions for quitting smoking (this point is noteworthy because smoking is perhaps the greatest risk factor for a heart attack)
- getting therapy to lower high lipid levels and blood pressure
- receiving treatment for diabetes
- obtaining dietary advice
- beginning an exercise program

For people at high risk for cardiovascular disease, in addition to the steps mentioned above, and after discussion and agreement with their physician, discontinuing abacavir and replacing it with another medication is also an option. But bear in mind that if abacavir is discontinued the other nuke or nucleotide analogue that might be used as a substitute can also have side effects. Here are just a few:

- d4T – This nuke can cause lipoatrophy, nerve damage and increased lipid levels. So the use of d4T does not seem to be appropriate for HIV positive people at high risk for cardiovascular disease.
- tenofovir (Viread, and in Truvada and in Atripla) – This nucleotide analogue is generally effective and safe in patients beginning anti-HIV therapy. However, in people at high risk for cardiovascular disease, some of whom have high blood pressure, the kidneys will not likely be functioning normally. Since tenofovir is processed by the kidneys and can cause kidney dysfunction, it may not be the most appropriate choice for some patients at high risk for cardiovascular disease. For all we know, it may be as bad as or worse than abacavir, as we have no information on tenofovir from DAD.

The DAD findings on abacavir and ddI suggest that better guidelines are needed to ensure that HIV is appropriately treated and that cardiovascular risk is identified and reduced where possible. Later this year, a team of Canadian researchers will unveil such guidelines.

**Acknowledgements**

We would like to thank the following researchers for their helpful discussion and, in some cases, review:

- Julian Falutz, MD – McGill University, Montreal
- Marianne Harris, MD – St. Paul’s Hospital, Vancouver
- Richard Lalonde, MD – Montreal Chest Institute, Montreal
- Julio Montaner, MD – St. Paul’s Hospital, Vancouver
- Marek Smejia, MD, PhD – McMaster University Hospital, Hamilton

**REFERENCES:**


8. Kuller L and the SMART study group. Elevated Levels of Interleukin-6 and D-dimer are Associated with an Increased Risk of Death in Patients with HIV. Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections, 3–6 February 2008, Boston, MA. Abstract 139.


C. Lopinavir and ritonavir (Kaletra) tablets get tested

Putting more than one medication in one pill is a process called co-formulation. Having more than one medication in a pill reduces the overall number of pills that a patient needs to take every day; therefore, co-formulation should result in improved adherence. Co-formulation will become increasingly common in high-income countries as pharmaceutical manufacturers realize that people prefer to take as few pills as possible. The combination of two drugs, lopinavir and ritonavir (Norvir), in one capsule or tablet is called Kaletra. The newer formulation of lopinavir and ritonavir is called the Kaletra tablet, and it has several advantages over the capsule formulation, such as the following:

- it does not require refrigeration
- it can be taken with or without food
- it has a reduced number of pills per day

Researchers in Canada, Spain and the United States conducted a clinical trial called MOS-730. This study enrolled more than 600 people with HIV/AIDS to compare the safety and effectiveness of lopinavir tablets taken once or twice daily to that of the capsules (both formulations taken as part of highly active antiretroviral therapy, or HAART).

The results showed that the tablet formulation was as effective as the capsule formulation. There were no apparent differences in side effects between the capsule and tablet. When questioned, the majority of study participants preferred the tablet formulation. Further details appear below.

Study details

Researchers recruited 664 volunteers who had never previously taken anti-HIV therapy. They
randomly assigned the volunteers to one of the following four regimens:

• lopinavir tablets – taken once daily
• lopinavir capsules – taken once daily
• lopinavir tablets – taken twice daily
• lopinavir capsules – taken twice daily

All participants also received the co-formulation of two other anti-HIV medicines, tenofovir (Viread) and FTC (emtricitabine, Emtriva), in one pill called Truvada.

At the start of the study, the average profile of participants was as follows:

• 20% female, 80% male
• age – 39 years
• viral load – 100,000 copies
• CD4+ cell count – 215 cells

Results—one year later
In clinical trials, a proportion of participants leave for many reasons. In this study, about 15% of participants dropped out of the trial. About 5% of participants left the once-daily group because of side effects compared to 3% in the twice-daily group. However, this difference was not statistically significant.

Results—effectiveness
After 48 weeks the proportion of participants with viral loads below the 50-copy mark was as follows:

• once-daily regimen – 77%
• twice-daily regimen – 76%

This difference was not statistically significant. The results suggest that a once-daily regimen of lopinavir tablets or capsules is not worse than a twice-daily regimen of the same drug.

In general, HIV positive people with high viral loads (more than 100,000 copies) may not always respond as well to therapy as people with lower viral loads. However, in the present study, both once- and twice-daily regimens were effective in volunteers with high viral loads.

Side effects
Historically, lopinavir capsules are associated with an increased risk of diarrhea. There were hopes that the newer tablet formulation would decrease that risk, however, researchers only collected data on diarrhea during the first eight weeks of the present study and during that time no significant difference in diarrhea was noted between the tablet and capsule formulation. As well, neither once- nor twice-daily dosing seemed to have any significant difference on this side effect.

There were no significant differences among any of the study groups on the following blood tests:

• liver enzymes levels greater than five times above the upper limit of normal
• cholesterol greater than 300 mg/dL
• triglycerides greater than 750 mg/dL
• changes in kidney health

Focus on lipids
Levels of total cholesterol, triglycerides and LDL-cholesterol (so-called “bad” cholesterol) did not increase as much in participants taking twice-daily regimens as it did in those taking the drug once daily.

Overall, once-daily lopinavir tablets was not less effective than twice-daily lopinavir. The tablet formulation appears to be similar to the capsule formulation in terms of safety and effectiveness.

REFERENCE:

D. A note about clinical trials
For the past several years, the co-formulation of lopinavir and ritonavir, called Kaletra, has been the leading anti-HIV agent, at least when it comes to protease inhibitors. Manufacturers of other anti-HIV drugs conduct clinical trials of their drugs vs. lopinavir/ritonavir to try to show that the competing drug is as good as or perhaps even better.

In theory, a clinical trial to demonstrate that one drug has the same effectiveness as another (an equivalence trial) would need to show that both drugs have identical outcomes. However, in practice, such a study may be very difficult to conduct, as there are always some difference(s) in the results of comparative clinical trials.
As a result, pharmaceutical companies have been conducting what are called “non-inferiority” trials where they seek to show that one drug is not worse than its competition and likely has similar effects. In this issue of Treatment Update, we present results from several non-inferiority studies.

E. The Castle study: lopinavir vs. atazanavir

Drug companies are constantly trying to devise interesting names for clinical trials, and now we present one such study, called Castle, that compared effects of lopinavir/ritonavir to atazanavir (Reyataz)/ritonavir.

Dr. Jean-Michel Molina from Paris, France, presented interim results from a two-year study that enrolled 883 participants who were randomly assigned to one of two regimens:

- atazanavir/r (300/100 mg) + tenofovir 300 mg + FTC 200 mg (440 volunteers)
- lopinavir/r (400/100 mg) + tenofovir 300 mg + FTC 200 mg (443 volunteers)

Note that volunteers taking the first regimen only had to take their pills once daily, while volunteers on the second regimen had to take the lopinavir/r portion of their regimen twice daily.

Also, the co-formulation of tenofovir and FTC was used (Truvada). This was taken once daily. During the first year of the study, participants assigned to the lopinavir/r group used the capsule formulation of that drug. In the second year they received the tablet formulation.

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

- 31% female, 69% male
- age – 35 years
- viral load – 100,000 copies
- CD4+ cell count – 200 cells
- 13% of participants were co-infected with hepatitis B or C viruses

The goal of this study was to demonstrate that atazanavir/r is not worse than lopinavir/r.

Results

Results from the first year of the study were presented at CROI. The proportion of participants in each group who had their viral load suppressed (below the 50-copy mark) after one year was as follows:

- atazanavir/r – 78%
- lopinavir/r – 76%

This difference was not statistically significant. It also demonstrates that atazanavir/r is not worse than lopinavir/r.

Among participants who entered the study with a viral load greater than 100,000 copies, the proportion that had their viral load fall below the 50-copy mark after one year in each of the two groups was as follows:

- atazanavir/r – 74%
- lopinavir/r – 72%

Again, this difference was not statistically significant and nor was the difference between the following increases in CD4+ counts:

- atazanavir/r – 203 extra CD4+ cells
- lopinavir/r – 219 extra CD4+ cells

Results—side effects

The proportion of participants who developed side effects of a moderate to life-threatening intensity was as follows:

Jaundice
- atazanavir/r – 4%
- lopinavir/r – 0%

Nausea
- atazanavir/r – 4%
- lopinavir/r – 8%

Diarrhea
- atazanavir/r – 2%
- lopinavir/r – 11%

Rash
- atazanavir/r – 3%
- lopinavir/r – 2%

The sponsor of the study, Bristol-Myers Squibb (BMS), is also the manufacturer of atazanavir. At CROI, BMS only released information on what it termed “selected” side effects. Hopefully, in the future, the complete details on this study will become publicly available.
F. Is PF-232798 a possible successor to maraviroc?

Maraviroc (Celsentri) is the first of a new family or class of anti-HIV medicines called entry inhibitors. Maraviroc works by blocking an important receptor, called CCR5, found on the surface of cells. By blocking or covering up this receptor, maraviroc prevents HIV from entering and infecting the cell.

When taken as part of HAART, maraviroc can suppress viral loads and raise CD4+ cell counts. The drug is taken twice daily.

Scientists working for the pharmaceutical company Pfizer have developed a new CCR5 receptor blocker. For now, the compound only has a strange designation—PF-232798.

In lab experiments, the new entry inhibitor stops HIV from entering cells. It may have potential anti-HIV activity against strains of HIV resistant to maraviroc.

So far, limited studies have been conducted with this compound and they suggest in the short-term the following:

- PF-232798 is well absorbed
- a dose of 250 mg once daily results in high and sustained anti-HIV levels in the blood
- the drug is well tolerated at the 250 mg dose

A more detailed study to assess the effectiveness of PF-232798 has been conducted in Germany with symptom-free HIV positive people. However, Pfizer is analyzing the results, which are not yet publicly available.

If the news on PF-232798 is promising, further trials of this drug will be forthcoming.

REFERENCE:

G. Receptor blocker (SCH 532706) enters clinical trials

Another compound that can block the CCR5 receptor is called SCH 532706. Made by Schering Plough, this drug has been tested at a dose of 60 mg twice daily and when taken with the booster ritonavir (Norvir) it may have
potential for once-daily dosing. This is because ritonavir raises levels of SCH 532706 in the blood for prolonged periods.

At CROI, researchers presented data from a small clinical trial where 12 HIV positive volunteers were given a combination of SCH 532706 with 100 mg of ritonavir twice daily for 10 consecutive days. For two weeks after this they did not receive any medications.

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

- all were male
- age – 36 years
- CD4+ cell count – 327 cells
- viral load – about 40,000 copies
- 1/3 of participants had never previously used anti-HIV drugs
- 2/3 of participants had interrupted HAART for about 8 months before entering the present study

Results
During the first 10 days of the study, viral load fell by an average of 1.3 logs. After day 10 of the study, when participants stopped taking both SCH 532706 and ritonavir, viral load continued to fall for four more days, down to 1.6 logs below pre-study levels. This suggests that SCH 532706 persists in the blood for several days after a person stops taking it.

On the 20th day of the study, when participants were not taking any drugs, viral load had risen but was still one log below pre-study values.

During the study, the use of SCH 532706/ritonavir was not able to fully suppress viral loads below the 50-copy mark. But this was not unreasonable as participants were taking what is essentially SCH 532706 monotherapy.

By the 10th day of the study, CD4+ and CD8+ cell counts rose by 59 and 114 cells respectively. However, these gains were not sustained after that day.

Most side effects reported in this trial were mild, according to the study doctors. When they did occur, side effects included the following:

- diarrhea
- stomach pain
- nausea
- frequent bowel movements

About 25% of participants had higher-than-normal levels of the liver enzyme ALT in their blood while exposed to the study medications.

It is likely that further testing of SCH 532706/ritonavir will occur in the future.

REFERENCE:

H. Vicriviroc
Another entry inhibitor also made by Schering Plough is called vicriviroc. This drug remains in clinical trials but results from a one-year study in HIV positive volunteers were presented at CROI.

Study details
In the clinical trial Victor-E1, researchers from 12 countries recruited 116 participants, all of whom used the three common groups of anti-HIV medications:

- nucleoside analogues (nukes)
- non-nucleoside analogues (NNRTIs or non-nukes)
- protease inhibitors

Due to exposure to these drugs, all participants had HIV that had a degree of resistance to these three types of medications.

Before entering the study, all volunteers had blood samples screened for the type of HIV that was present. Only those who had HIV that used the CCR5 receptor were allowed to participate in the trial.

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

- 20% female, 80% male
- age – 45 years
- CD4+ cell count – 200 cells
- viral load – 32,000 copies
- note that about 30% of participants had a viral load greater than 100,000 copies

Based on the results of resistance testing, medical history and so on, researchers assigned all participants to receive HAART, or what they called an optimized background regimen (OBT).
Changes in CD4+ counts were as follows:

- placebo – an increase of 65 cells
- vicriviroc 20 mg – an increase of 134 cells
- vicriviroc 30 mg – an increase of 102 cells

There were no significant differences among the three arms when it came to side effects. Nausea and diarrhea were common in all study participants. No deaths or cancers occurred during the study. After one year, all participants were allowed to continue to receive vicriviroc if they wished; this was called the open-label phase of the study. During this time one participant developed cancer—non-Hodgkin’s lymphoma.

Further and longer-term studies of vicriviroc are important, as there have been previous reports of an apparent increase in the risk of cancer in volunteers exposed to this drug.

REFERENCES:

II PREVENTION

A. The elusive AIDS vaccine

In the 25 years since HIV was discovered, researchers have made many strides in the fight against AIDS. One notable advance was the development of combination therapy for HIV. This has led to prolonged survival for HIV positive people who have access to and who can adhere to these medications.

Although the AIDS crisis is generally considered a problem affecting low- and middle-income countries, particularly in sub-Saharan Africa, HIV continues to spread in the high-income regions of North America and Western Europe. As with many infectious diseases, a vaccine that could
Recognizing this, even in the early days of the HIV epidemic, scientists have pursued vaccine research. Yet, despite many clinical trials with at least 30 different potential HIV vaccines, all have failed. Years of effort and work are put into the design, creation and testing of a potential vaccine, so to have such a large number of failures is disheartening.

Challenged by complexity
One reason that it is so difficult to find an effective HIV vaccine is that this virus is like no other; it attacks and disables the body’s defenses against germs—the immune system. Moreover, what we call the immune system is really a complex network of organs, tissues and cells scattered throughout the body. How this network functions is not fully understood. Throw HIV into this mix, and you have the makings of a giant puzzle.

The string of failures that litter the AIDS vaccine landscape should serve as a starting point where immunologists might review, reflect upon and reconsider past and current vaccine strategies. Perhaps the time has come to review research that may have been forgotten, overlooked or avoided in the race to an AIDS vaccine. In such an exercise, clues about successful immunity against HIV might emerge and this could incite new research on HIV vaccines.

Below is a quick review of some of the challenges faced by HIV vaccine designers, followed by areas of research that may be useful for a potential vaccine.

With T cells, timing is everything
In cases of SIV (simian immunodeficiency virus) or HIV infection, the immune system’s premier infection-fighting cells—CD8+ T cells—are able to attack virus-producing cells and reduce the amount of virus in the blood. However, these cells are unable to stop the spread of HIV (or SIV) from the mucosa to the lymph nodes and tissues lining the gut, where most T cells reside.

Still, vaccine designers have focused on stimulating CD8+ cells to respond to viral invasion. However, several research teams have found that the immune system takes too long, perhaps two to three weeks, to respond with large numbers of CD8+ cells that can contain HIV infection. Moreover, the few cells that are readily available to fight HIV have a limited capacity to do so. So, vaccines that depend on CD8+ cells to prevent HIV infection may not work, as suggested by experiments in monkeys and in the lab. Other teams of researchers have focused on trying to get HIV vaccines to stimulate antibodies that can attack or neutralize HIV.

Antibodies—too little, too late?
Experiments on monkeys deliberately infected with SIV suggest that any vaccine based on antibody stimulation would need to trigger a massive output of antibodies from the immune system. Such production would have to occur quickly, within six hours of exposure to SIV, to be effective. Also, the vaccine must be able to maintain high levels of neutralizing antibodies for SIV or HIV infection to be controlled.

The production of antibodies or CD8+ cells that can attack a specific germ, such as HIV, relies on one part of the immune system called adaptive immunity. This type of immunity takes time to reach sufficient levels that can control an infection. So, antibody-based HIV vaccines are unlikely to be able to quickly staunch HIV.

What is to be done?
The ideal type of immune response to HIV would be one that could be invoked within seconds or minutes after exposure to this virus. The immune system is capable of responding quickly, as happens in some people who have rapid allergic reactions to certain foods or insect venom. Harnessing such a response for an HIV vaccine might be useful. However, to date, vaccine designers have not concentrated on such approaches.

An ancient defense system
Part of the immune system that evolved many millions of years ago is called innate immunity. These defenses rely on recognizing patterns in the cells of germs that make them appear different from the body’s cells. The immune system can then quickly respond to the invading germs. It is beyond the scope of this report to delve into the complexities of innate immunity. However, this type of immunity in part relies on cells such as natural killer cells, macrophages and dendritic cells. So far, most HIV research has focused on B cells and T cells. Clearly, a different research focus is needed if innate immunity is to be exploited.
Slippery when wet
HIV’s first contact with the immune system is usually in the wet tissues of the mucosa—the anus, penis and vagina—and the mucosal immune system has developed to protect these sites. The immune system in the mucosa behaves somewhat differently from the immune system in the rest of the body, so research to understand how the mucosal immune system interacts with HIV is vital. Unfortunately, no one likes to have samples of mucosal tissue removed for study, and progress uncovering the mysteries of this part of the body has been slow.

Exposed yet seronegative
Scientists in laboratories in Winnipeg, Nairobi, Milan, Toronto and Stockholm have found that a very small number of people who have been sexually exposed to HIV have managed to remain HIV negative. Yet their immune systems, particularly in the mucosa, show traces of having encountered HIV. Research into why they have managed to fight off HIV might come in handy when designing a vaccine.

Not Invented Here
The American National Institutes of Health (NIH) in Bethesda, Maryland, is the largest biomedical funding and research body in the world. The NIH spends about $600 million dollars every year on HIV vaccine research. Nearly one-third of this goes toward developing and testing potential vaccines.

At the recent American Conference on Retroviruses and Opportunistic Infections (CROI), held February 3 to 6, 2008, in Boston, HIV vaccine research came under scrutiny. Dr. Ron Desrosiers, head of the New England Primate Research Center, highlighted the problems with the current approach toward an HIV vaccine fostered by the NIH. He stated that “no [HIV vaccine] now under development has any reasonable hope of being effective.”

Dr. Desrosiers was not the only prominent researcher to challenge the NIH. Virus expert Dr. Neal Nathason, a former head of the NIH’s office of AIDS research, voiced similar concerns at CROI. Both scientists suggest that rather than continue to test potential vaccines that are unlikely to work more studies need to be done to understand the immune system and how it interacts with HIV. Indeed, readers should note that no research team has any idea as to what is the ideal immune response needed to protect the body from HIV infection.

Meeting in March
In January 2008, Dr. Desrosiers and 13 other researchers wrote a letter to Dr. Anthony Fauci, the head of the National Institutes of Allergy and Infectious Diseases (NIAID, an arm of the NIH). Their letter articulated their concerns regarding the NIH’s research priorities when it comes to HIV vaccine research. As a result, the NIH held a daylong meeting on March 25, 2008, in Bethesda to consider the scope and balance of its research activities regarding HIV vaccines.

Not giving up
Much work remains to be done in understanding the immune system and how to protect it from HIV. Given the complexity of the task, this effort will take many years. Unless there is a breakthrough, an effective AIDS vaccine is not likely to appear for at least a decade, and perhaps much longer. Dr. Anthony Fauci put it this way in a recent report in the *New England Journal of Medicine*:

“To be brutally honest with ourselves we have to leave open the possibility that we might not ever get a vaccine for HIV. People are afraid to say that because it would then indicate that maybe we are giving up. We are not giving up. We are going to push this agenda as aggressively and energetically as we always have. But there is a possibility—a clear and finite possibility—that that’s the case.”

In Canada
The Canadian government, together with the Bill and Melinda Gates Foundation, has formed a partnership to strengthen Canada’s contribution to the search for an AIDS vaccine. The partnership is called Canadian HIV Vaccine Initiative (CHVI). It brings together important ministries and agencies—such as the Public Health Agency of Canada, Health Canada, Canadian International Development Agency and Industry Canada—with Canada’s outstanding research agency, the Canadian Institutes of Health Research (CIHR). To find out more about CHVI, visit its website at:

http://www.chvi-icv.gc.ca/index-eng.html
In the meantime...

As a vaccine is unlikely in the foreseeable future, the HIV pandemic will continue, and so HIV prevention research needs to be strengthened. In high-income countries, a portfolio of HIV prevention activities needs to be explored, enhanced and field-tested, including the following issues:

- safer-sex messages
- addiction prevention and treatment
- increased public recognition, acceptance and treatment of mental health conditions
- harm reduction
- more widespread HIV testing
- post-exposure prophylaxis
- pre-exposure prophylaxis
- microbicide development and testing
- education on the prevention of sexually transmitted infections
- community engagement and capacity building

REFERENCES:


B. Swiss guidelines take a troubling turn

In February 2008, the Swiss National AIDS Commission published an article about safer-sex practices. Specifically, the Commission stated that HIV positive people are not at risk for transmitting HIV to their partners if they meet all of the following requirements:

- they are adherent to highly active antiretroviral therapy (HAART)
- their viral load in the blood is consistently below the lower level of detection (usually 50 copies in Canada and 40 copies in Switzerland)
- they are in a “stable relationship”
- they do not have any sexually transmitted infections (STIs)

Readers should note that the Swiss Commission’s statements about unprotected sex are based on opinion and not fact. We urge all sexually active people to continue to practice safer sex and take other precautions so as not to acquire or pass on HIV to their partners and to protect themselves from other STIs, many of which can be symptom-free.

In response to the Swiss Commission’s opinion, the following agencies have recently reinforced...
the importance of safer sex in preventing HIV infection:

• the Public Health Agency of Canada (PHAC)
• the American Centers for Disease Control and Prevention (CDC)
• the French Ministry of Health
• the World Health Organization (WHO)
• UNAIDS (the United Nations program on AIDS)

That the Swiss have issued guidelines that appear to weaken prevention messages against HIV transmission is disheartening, particularly at a time when HIV infections are on the rise in the high-income regions of North America and Western Europe.

What’s up?
There are many problems with the opinion of the Swiss Commission. Perhaps most disturbing is that it is based on an apparent belief and not robust scientific data. Moreover, some of the references cited by the Swiss do not appear to support their opinion. The assumptions made by the Swiss Commission are weak, as they appear to have overlooked, forgotten or misunderstood important research.

A key assumption made by the Swiss commission is that a suppressed viral load in the blood results in a suppressed viral load in other parts of the body, particularly in the genital tract. In this article we summarize evidence showing that this is not the case. We also address other weaknesses that significantly undermine the foundations of the Swiss Commission’s opinion.

The limits of therapy
Introduced in high-income countries in 1996, highly active antiretroviral therapy, or HAART, which consists of potent combinations of anti-HIV drugs, has helped save and extend the lives of many HIV positive people. The drugs work by impairing HIV’s ability to infect cells and produce new viruses. This gives the immune system a chance to begin to repair the damage caused by HIV.

However, after many years of HAART and good adherence in HIV positive people, researchers have not been able to cure HIV infection. Attempts at a cure have consisted of intensifying therapy, adding unusual medications to regimens and, later, the cessation of HAART. But once HIV positive people stop taking HAART, virus levels surge, damaging the immune system and increasing the risk of death.

It is important to bear in mind that HAART can also cause unpleasant and dangerous side effects. Although much progress has been made in the past 25 years against AIDS, HIV remains an incurable and deadly infection.

Viral load—undetectable may be misleading
To ensure that anti-HIV therapy is working, doctors regularly have blood samples from their patients assessed for viral load, as one of the goals of HAART is to suppress viral load in the blood as low as possible. Commercially available technology can usually assess viral loads as low as 50 copies. When a viral load result returns with an “undetectable” reading—below the 50-copy mark—it does not mean that HIV is not replicating. New copies of HIV could be produced and new infections could be occurring in the body, but the test cannot accurately assess viral loads below the 50-copy mark. Tests that can count viral load below the 50-copy mark are restricted to research laboratories and not used for routine care.

Viral load—focus on 2%
It is also worth remembering that only 2% of the body’s immune cells are carried in the blood at any given time. The vast majority (98%) of the immune cells, including CD4+ cells, spend most of their time in the lymph nodes and lymph tissues lining the gastrointestinal tract. Since so little HIV is actually produced in the blood, we cannot be sure that routine viral load testing accurately reflects the amount of HIV present in other parts of the body. Thus an undetectable viral load in the blood does not necessarily indicate a low or a high level of HIV replication in other parts of the body.

A word about blips
In addition, many people on HAART experience “blips” in their viral loads. These are periods when the amount of HIV temporarily increases into the detectable range, generally anywhere from 51 to 500 copies. Usually the viral load drops back below detectable limits without a change in therapy. What causes these “blips,” how often they occur, and how long they last is not generally well understood. And the fact that blips are relatively common pokes yet another hole in the assumptions made by the Swiss Commission about the stability of viral load.
Timing of viral load tests
It usually takes a few weeks before viral load test results are sent to a doctor’s office. By the time a patient has returned to the doctor’s office for the results, several weeks or even a month may have passed since the test was done. During this time, viral load could rise depending on a number of factors. The viral load at the last test does not necessarily represent the viral load at another point in the future. One factor that can affect viral load is the ability to take medications every day, exactly as prescribed. This behaviour is called adherence.

Adherence and viral load
A recent American clinical trial documented how adherence can change over time, whether HAART is taken once or twice daily. As adherence degraded in the study, viral load rose above the 50-copy mark. When participants were told that their viral load had risen and they needed to submit another blood sample to confirm this result, their adherence improved and viral load fell below the 50-copy mark.

Adherence is a dynamic behaviour: It can go up or down and change yet again—and so can viral load. Therefore, relying on viral load measures to prevent HIV infection is fraught with risk.

Blood vs. semen
The genital tracts of men and women can have a different viral load from that of the blood. Men taking HAART may have a suppressed viral load in the blood, but viral load in the semen may not simultaneously be suppressed. Here is one reason for this:

• HAART may not fully penetrate and suppress HIV in the genital tract.

In one study at the University of Pittsburgh, researchers with experience finding HIV in different parts of the body monitored the health of eight men taking HAART for five years. During this time, viral load in their blood was below the 50-copy mark. However, the research team was able to find that HIV had been replicating, at low levels, in both blood and semen samples from the men over the five years of the study. This replication was not due to drug resistance but likely because drugs could not accumulate in all regions of the genitals. The team was also able to find a greater proportion of HIV-infected cells in semen samples than in blood, even though there are more cells to infect in the blood than in semen. This finding occurred throughout the study.

The source of HIV that occurs in semen is not clear. Some researchers have fingered the prostate gland as a possible reservoir of HIV. However, more recent research, focusing on men who do not have STIs, suggests that there may be other parts of the male genital tract that harbour HIV.

Other studies have also assessed HIV levels in semen samples from men whose viral load in the blood was less than 50 copies. Depending on the study, the proportion of these men with detectable HIV in their semen has been between 7% and 40%.

Overall, these studies highlight the risk of exposure to semen, even if viral load in the blood was less than 50 copies.

The Swiss Commission suggests that men with viral loads below the 50-copy mark may have HIV in their semen that might not be capable of causing infection. We argue against that. Researchers who have conducted long-term studies of HIV positive people on HAART have found HIV in cells from their blood and elsewhere that can replicate. The idea that HIV in semen may have special properties that render it non-infectious seems strange, given that sexual transmission is the most common way that HIV is spread.

Semen—more than HIV
Researchers have found that HIV is not the only virus that can be found in semen. Several teams have isolated the following viruses from human semen samples:

• cytomegalovirus
• hepatitis B virus
• hepatitis C virus
• herpes simplex virus
• human herpes virus-8
• human papilloma virus

Avoiding exposure to semen (and other fluids from the male genital tract) can reduce not only the risk of HIV infection but also other viral infections.

Women and viral load
Research on HIV in the female genital tract appears to be more limited than in men. However, results similar to those in men have generally been found. Specifically, HIV can be
detected in the genital secretions of women, whether or not they are taking HAART and regardless of the viral load level in their blood. Similar to the situation in men, not all anti-HIV medications can enter and reach high levels in the female genital tract.

And don’t forget the rectum
Researchers in Seattle, Washington, have assessed HIV not only in the blood but also in semen samples and rectal tissue from 64 men. Twenty-seven, or 42%, of these men were taking anti-HIV medications. The study team found that these medications reduced viral load in the blood and semen. But HIV could still be detected in the semen of these 27 men on medication. Furthermore, HIV could also be found in the rectums of the men, whether or not they took anti-HIV therapy.

Sneaky STIs
STIs in the genital tract can cause inflammation and activate latent HIV hiding inside cells. This activation stimulates HIV out of hiding and turns cells into virus factories. Increased HIV in the genital tract together with inflammation heightens the risk of transmitting HIV.

The Swiss Commission does suggest that HIV positive people be educated about the symptoms of STI infection. This approach to detecting possible STIs, while well intentioned, is at best problematic. Here is why:

A study by the San Francisco Department of Public Health of men who have sex with men found many cases where men were infected with STIs but were unaware of it because the infections were free of symptoms. Moreover, because the infections were at different places in the body, simply screening the urethra (the tube in the penis through which urine flows) for STIs would have missed detecting these infections elsewhere in the body. Here are some findings from their study:

- 85% of cases of rectal infections with either chlamydia or gonorrhea were symptom-free.
- 53% of chlamydia infections and 64% of gonorrhea were in either the throat or rectum
- 70% of chlamydia infections occurred in men who did not also have gonorrhea.

The San Francisco researchers say that these findings prompt the need for screening different parts of the body for these infections. They also underscore the fact that STIs can occur without causing symptoms.

Another study in Birmingham, Alabama, focusing on men, found that another STI—genital herpes—can occur in the absence of symptoms.

Overall, these findings confirm that self-checks for symptoms of STIs may not be the most reliable way to assess infection with these germs.

Misreading the data
One of the key studies upon which the Swiss Commission’s assumptions rest is an observational study from Spain. Observational studies are not the most reliable way to investigate a research question. These studies can find associations but are unable to link cause and effect.

In the Spanish study, researchers recruited heterosexual couples where one partner was HIV positive and the other partner presumed to be HIV negative. This was done between 1991 and 2003. Mostly the men were HIV positive. Researchers interviewed the other partner and collected blood for testing.

The researchers found that the partners of HIV positive people were more likely to be HIV negative if they joined the study in 1999 or after, compared to people who joined the study before this time. From this finding, the Swiss Commission inferred that using HAART reduced the risk of HIV transmission. However, there are several reasons why their inference may not be correct, as follows:

- only a small proportion (about 15%) of the HIV positive people in the study took HAART.
- viral loads were not included in the data analysis so we have no idea how many people were on suppressive HAART.
- importantly, the team performed a statistical analysis that took many factors into account (called a multivariate analysis). This revealed that use of HAART did not have an impact on HIV transmission.
- when asked about the use of condoms in the past six months, roughly half the participants noted that they were consistently practicing protected intercourse.

A factor significantly associated with HIV transmission in this study was having unprotected sex.
Toward the end of the report on their study, the Spanish team cautions that an increase in unsafe sex could “cancel or even reverse” any beneficial effect that HAART might have on transmission on HIV. In closing they make this point:

• “This is why it is important not to forget that the main preventive measure for HIV sexual transmission remains the avoidance of risky sexual practices.”

It is significant to note that the studies of sero-discordant couples used by the Swiss Commission in developing their guidelines investigated HIV transmission among heterosexual couples where the primary mode of transmission is vaginal intercourse. There is very little data on the impact of HAART on transmission through unprotected anal intercourse which is the most infectious mode of sexual transmission.

Reality check
There are many factors that can affect the risk of HIV transmission during sex, including type of sexual activity, the presence of sexually transmitted infections, use of condoms, and so on. Furthermore, these factors may change over time and from one situation to another. Because of these and perhaps other factors, calculating the precise risk of HIV transmission during sex is difficult.

Relying on the presence of a low viral load in the blood is not sufficient information to prevent infection, as HIV replication continues to take place in the body despite a low viral load in the blood. New copies of HIV can be produced in many parts of the body, such as the male and female genital tracts as well as the rectum.

STIs can cause infection without triggering symptoms. This means that self-checks for STIs are not a reliable way of assessing if these germs are present. And, even if the Swiss guidelines are restricted to people in stable relationships, in reality people have affairs and do not tell their spouse or partner.

Currently the scientific data do not support the claim that HIV positive people whose viral loads are undetectable cannot transmit HIV. More research is needed to find out the relationship between viral load, HAART and HIV transmission.

Practicing safer sex can help minimize the risk of transmitting and acquiring STIs, HIV and new drug-resistant strains of HIV.

Resources
The Canadian AIDS Society developed guidelines to help assess the risk of HIV transmission during sex. These are available from its website:

http://www.cdnaids.ca/web/repguide.nsf/pages/cas-rep-0307

The Public Health Agency of Canada recently issued a statement emphasizing the importance of safer sex to prevent the transmission of HIV. That statement is available at:


Acknowledgements
We thank the many doctors and infectious disease specialists across Canada who have given us their analysis of the Swiss Commission’s opinion. We particularly thank Tim Rogers, PhD, Paul MacPherson MD, PhD, Curtis Cooper MD and Jonathan Angel MD, for their assistance, helpful discussion, research and review in writing this article.

REFERENCES:


Hopkin M. HIV can never be cured: AIDS virus thwarts even the best drugs by hiding in gut. Nature 14 February, 2008. Available at:


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.
The Canadian AIDS Treatment Information Exchange (CATIE) in good faith provides information resources to help people living with HIV/AIDS who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.
We do not guarantee the accuracy or completeness of any information accessed through or published or provided by CATIE. Users relying on this information do so entirely at their own risk. Neither CATIE nor the Public Health Agency of Canada nor any of their employees, directors, officers or volunteers may be held liable for damages of any kind that may result from the use or misuse of any such information. The views expressed herein or in any article or publication accessed or published or provided by CATIE are solely those of the authors and do not reflect the policies or opinions of CATIE or the views of the Public Health Agency of Canada.

Permission to Reproduce
This document is copyrighted. It may be reprinted and distributed in its entirety for non-commercial purposes without prior permission, but permission must be obtained to edit its content. The following credit must appear on any reprint: This information was provided by the Canadian AIDS Treatment Information Exchange (CATIE). For more information, contact CATIE at 1.800.263.1638.

Credits
Writer
Sean Hosein
Editor
Ronnilyn Pustil
© CATIE, Vol. 20, No. 2
March 2008

What CATIE Does
The Canadian AIDS Treatment Information Exchange (CATIE) is committed to improving the health and quality of life of all people living with HIV/AIDS in Canada. CATIE serves people living with HIV/AIDS, and the people and organizations that support them, by providing accessible, accurate, unbiased and timely treatment information. CATIE provides such information through a comprehensive Web site, a bilingual toll-free phone service, electronic and print publications, a national reference library and workshops and exhibits at conferences across Canada.

CATIE Publications
TreatmentUpdate
CATIE’s flagship treatment digest on cutting-edge developments in HIV/AIDS research and treatment. Subscribe to TreatmentUpdate and automatically receive an email notifying you the moment a new issue is available on-line or contact us at 1.800.263.1638 to receive a print subscription.

A Practical Guide to HAART
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.
The Practical Guide series also includes:
• A Practical Guide to Nutrition
• A Practical Guide to Complementary Therapies
• A Practical Guide to Herbal Therapies

The Positive Side magazine
Holistic health information and views for PHAs.

Fact Sheets & Supplement Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

pre*fix
A harm reduction booklet for HIV+ drug users.

Contact CATIE
by e-mail: info@catie.ca
on the Web: http://www.catie.ca
by telephone: 416.203.7122
1.800.263.1638 (toll-free)
by fax: 416.203.8284
by post: 505-555 Richmond Street W
Box 1104
Toronto, Ontario
M5V 3B1
Canada

Production of this newsletter has been made possible through a financial contribution from the Public Health Agency of Canada.