I ANTI-HIV AGENTS

A. Maraviroc approved in Canada

On September 21, 2007, Health Canada approved the use of the novel anti-HIV drug maraviroc. To be sold under the brand name Celsentri, maraviroc is meant for treatment-experienced people who have HIV-1 that is resistant to other medications. Maraviroc will be marketed by Pfizer Canada.

In clinical trials lasting one year, maraviroc was found to significantly reduce production of new HIV and raise the level of important T-cells in the blood. These changes led to improved health for people with HIV/AIDS (PHAs). In these trials, maraviroc was found to be generally safe.

Why maraviroc is different

Maraviroc is the first approved oral medication in a new class of anti-HIV drugs called entry inhibitors. Currently, there are four other classes of approved medications for the treatment of HIV infection, as follows:

- nucleoside analogues (nukes)
- non-nukes (NNRTIs)
- protease inhibitors
- fusion inhibitor

When used in combination, these drugs are usually effective. However, HIV can develop mutations that help it resist the effect of these drugs. This is why the ongoing discovery and development of new anti-HIV agents is important. Maraviroc has antiviral activity against strains of HIV that are resistant to currently licensed medications.

Most approved therapies for the treatment of HIV infection work by interfering with HIV after...
it has infected a cell. Maraviroc is different because it works by covering a molecule called CCR5, which is found on the surface of cells of the immune system. HIV needs to attach itself to CCR5 in order to enter and infect a cell. Maraviroc blocks access to CCR5 so HIV cannot get in, hence it is called an entry inhibitor.

Know your co-receptors
HIV needs a number of different receptors to help it enter and infect a cell. The first of those receptors is called CD4. This receptor is found on many cells of the immune system, including T-cells and macrophages.

But HIV also needs at least one of two co-receptors—CXCR4 (X4) or CCR5 (R5)—to help it get into a cell. HIV that prefers R5 receptors is called R5 tropic and HIV that prefers X4 receptors is called X4 tropic. Some forms of HIV can attach to either receptor; these viruses are called dual or mixed tropic.

To help assess which kind of virus predominates in PHAs, the company Monogram Biosciences developed a test called Trofile. Using this test, a sample of blood can be analysed to find out the tropism of HIV.

Before using maraviroc, a Trofile test must be performed on a patient’s blood sample to help physicians decide if the drug is going to work.

More about Trofile
In order to profile the co-receptor tropism, potential maraviroc users will have their blood assessed with Trofile prior to starting therapy with this drug. This will help doctors determine who might benefit from maraviroc. This is an important step because maraviroc only works against HIV that prefers to use R5, and some people have HIV that prefers to use X4 or both X4 and R5.

Trofile results can be as follows:

- **R5 tropic** – this means that a person’s HIV prefers the CCR5 co-receptor; maraviroc will work
- **X4 tropic** – this means that a person’s HIV prefers the X4 co-receptor; maraviroc will not work
- **dual/mixed tropism** – this means that a person’s HIV can attach to both X4 and R5 co-receptors; maraviroc will not have a significant benefit

Trofile is an expensive test, costing hundreds of dollars. However, because the use of maraviroc depends on knowing a person’s HIV co-receptor preference, Pfizer is paying for the cost of Trofile in Canada. Trofile is expected to be available in major treating centres across Canada and is currently used in the maraviroc expanded access program (EAP).

Cost
Maraviroc will be available for sale in Canada in mid-October 2007. The wholesale price is about $33 per day for either 150 mg or 300 mg, taken twice daily. The drug will be supplied in bottles containing 60 film-coated tablets.

In the United States, the wholesale cost of maraviroc is about $29 per day. In that country, the brand name of maraviroc is Selzentry.

In the European Union, as in Canada, maraviroc will be sold under the brand name Celsentri.

The long and winding road
Once Health Canada approves a drug, physicians can prescribe it but patients must pay for the drug unless their private insurance plan provides coverage. HIV/AIDS is a catastrophic disease that affects people’s ability to work and requires expensive care. In Canada, the cost of HIV medications is subsidized by provincial and territorial ministries of health. Each ministry has a listing of drugs for which it is prepared to pay. These listings are called formularies.

After federal approval, each HIV medicine must undergo another review process called Common Drug Review (CDR). As part of this review, recommendations are made as to whether the drug in question should be:

- listed on formularies
- listed on formularies with conditions, in which case its use is restricted
- not listed at all

The CDR may even result in no decision being made for the time being as additional information is gathered. With the exception of Quebec, all provinces and territories, the Departments of National Defense and Veterans Affairs and the Non-Insured Health Benefits plan participate in CDR.

Maraviroc will undergo the CDR process later this year and the results will be available sometime in 2008.
In Quebec, which operates outside of the CDR, formulary authorities will hopefully list the drug by mid-2008.

**Expanded access program for Canada**
In the meantime, Canadian physicians who have patients who may benefit from maraviroc can consider enrolling them in the maraviroc expanded access program. For more information about this EAP, physicians can call the following telephone numbers:

- 1.514.693.4101
- 1.800.267.2553 ext. 4101

The maraviroc EAP is expected to operate until the CDR recommendation.

**REFERENCES:**

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**B. One year clinical trial results with maraviroc**

In a study called Motivate 1, researchers enrolled participants who had experienced treatment failure with their previous regimens. The study team randomly assigned them to one of the following groups, or arms:

- placebo and an optimized background therapy (OBT) based on their treatment history and the results of resistance testing
- OBT and maraviroc 300 mg once daily
- OBT and maraviroc 300 mg twice daily

The dose of maraviroc was reduced to 150 mg (either once or twice daily) if participants also used protease inhibitors (except tipranavir [Aptivus]) or delavirdine (Rescriptor).

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

- 10% female, 90% male
- age – 46 years old
- CD4+ count – 160 cells
- viral load – 71,000 copies

The protease inhibitor darunavir (Prezista) was not used in this study and only about 10% of participants in each arm had access to T-20 (enfuvirtide, Fuzeon).

**Results—Changes in viral load**
On average, the decrease in viral load in each arm was as follows:

- placebo and OBT – minus 0.8 logs
- maraviroc once daily and OBT – minus 1.66 logs
- maraviroc twice daily and OBT – minus 1.82 logs

These differences between maraviroc users and people who received placebo were statistically significant; that is, not likely due to chance alone.

Another way to assess the strength of maraviroc is to examine the proportion of volunteers in each arm whose viral load fell below the 50-copy mark. The results are as follows:

- placebo – 16%
- maraviroc once daily – 42%
- maraviroc twice daily – 47%

These differences between either maraviroc dose and the placebo group were statistically significant.

Here are the proportion of people who entered the study with a high viral load (more than 100,000 copies) and who later had this fall below the 50-copy mark:

- placebo – 7%
- maraviroc once daily – 31%
- maraviroc twice daily – 32%

And here are the proportion of people who entered the study with a viral load below 100,000 copies and who later had this fall below the 50-copy mark:

- placebo – 27%
- maraviroc once daily – 55%
- maraviroc twice daily – 60%
Dropouts and safety
When comparing the placebo arm of the study to the maraviroc arms, maraviroc appeared to be generally safe. Moreover, there were no significant differences between both arms of the study when it came to assessing serious or life-threatening effects. One way to infer the tolerability of a drug is to compare the number of participants in each arm who left the study, as follows:

- placebo – 6%
- maraviroc once daily – 6%
- maraviroc twice daily – 5%

AIDS and death
The proportion of volunteers who developed AIDS-related infection during the study was relatively small and similar in each group, as follows:

- placebo – 5%
- maraviroc once daily – 5%
- maraviroc twice daily – 5%

The proportion of deaths in each study arm was small and not significantly different:

- placebo – 1%
- maraviroc once daily – 1%
- maraviroc twice daily – 2%

No deaths were caused by maraviroc.

Focusing on infections and cancers
Between 10% and 15% of volunteers exposed to maraviroc were likely to develop the following symptoms:

- pneumonia
- cough
- fever
- dizziness

Fortunately, only one case of the AIDS-related pneumonia (PCP or Pneumocystis jiroveci pneumonia) occurred. The other causes of pneumonia were not disclosed. Researchers are not sure why lung infections were more common in some maraviroc users.

There were a few cases of oral/throat yeast infections in maraviroc users—seven in all vs. none in placebo recipients.

There were also seven cases of herpes that occurred in the maraviroc groups compared to two cases in the placebo group.

All of these differences in infections between groups were small and puzzling.

PHAs are at increased risk for cancer of the lymphatic system—lymphoma. In this study, there were two cases of lymphoma in the maraviroc arms and two cases in the placebo group.

Looking at the liver
Regular monitoring of liver enzymes and the waste product bilirubin in the blood is an important part of care, as increased levels of these suggest the possibility of liver damage and related issues.

In the Motivate 1 study, researchers focused on finding cases of extremely high levels of liver enzymes (AST, ALT) and bilirubin in the blood. The reason for this is due to the reports of liver toxicity in studies of a now discontinued CCR5 inhibitor, aplaviroc. However, elevated liver enzymes were not common in the Motivate 1 study. For instance, the proportion of participants with extremely elevated levels of the liver enzyme AST (more than 10 times the upper limit of normal) was as follows:

- placebo – 1%
- maraviroc once daily – 1%
- maraviroc twice daily – 2%

Extremely elevated levels of bilirubin, another indicator of liver damage, were also uncommon.

Overall, these results suggest that maraviroc is a useful and generally safe part of combination therapy for treatment-experienced PHAs.

REFERENCE:

C. Maraviroc and resistance
An important issue faced by maraviroc users is the possibility of HIV developing resistance to this drug. This can be detected by rising viral load, suggesting treatment failure, or with more sophisticated testing with Trofile, revealing that HIV has shifted from R5 to X4 tropism.
To better understand this issue, participants in the Motivate 1 study had blood samples taken several times before the study began and at any time their viral load rose above the 500-copy mark. Some of these samples were to assess for viral tropism—whether their HIV preferred to use the R5 co-receptor, the X4 co-receptor, or both. These assessments are done with a test called Trofile.

The results from Trofile are given in the following way:

- **R5** – only CCR5 tropic virus was detected
- **X4** – only CXCR4 tropic virus was detected
- **dual/mixed** – both types of co-receptor-using viruses were detected

All potential study participants were screened to find out if they had R5 tropic virus, as maraviroc only works against this type of HIV. Of the 1,042 participants who had R5 virus at initial screening, about 8% apparently had a change in tropism between the time they were screened and the time when they were about to start taking study medications. This is an important point because it appears that Trofile, in a small proportion of cases, may not always correctly assess the tropism of HIV.

After the study was completed, researchers analysed the stored blood samples taken from participants. They focused on results from the 8% of participants whose tropism apparently changed. The study team found that at screening time, the viral load of this group was generally higher than that of the other 92% of PHAs in the trial. Also, the CD4+ counts of the 8% group were lower on average than the rest of the people in the study. These differences suggest that PHAs in the 8% group had immune systems that were degrading more quickly than those of the majority of participants.

On average, participants whose viral tropism shifted from R5 to X4 or dual/mixed were more likely to experience treatment failure earlier (within 70 days) than participants whose tropism did not change.

Once treatment failure occurred, participants stopped taking maraviroc. Within one month, their virus reverted from X4 to R5. What’s more, maraviroc users whose regimens failed with detectable X4 or dual/mixed virus had higher CD4+ cell counts than they did before they started taking maraviroc.

Overall, these results from the Motivate study support the safety of maraviroc.

**REFERENCE:**

### D. Using maraviroc in first-line therapy

Since maraviroc has shown to have good anti-HIV activity in treatment-experienced PHAs, it makes sense to test this drug in people about to start therapy for HIV infection for the first time. The Merit trial was designed to do just that, comparing the following regimens:

- **efavirenz (Sustiva, Stocrin) + Combivir (AZT and 3TC)—the efavirenz group**
- **maraviroc 300 mg twice daily + Combivir—the maraviroc group**

The average profile of the 721 volunteers enrolled in this study was as follows:

- 29% female, 71% male
- age – 37 years
- CD4+ count – 250 cells
- viral load – 74,000 copies

**Results—One year later**

Overall, the proportion of participants whose viral load fell below the 50-copy mark was as follows:

- efavirenz group – 69%
- maraviroc group – 64%

Changes in CD4+ counts were as follows:

- efavirenz group – an increase of 142 cells
- maraviroc group – an increase of 169 cells

While these are the overall results, bear in mind that the Merit study took place in both the Northern hemisphere (North America and the European Union) and the Southern hemisphere (South America, South Africa and Australia). There may be differences in these regions that could have affected the outcome of the study, such as:

- The type of HIV that is most common in high-income countries is usually different
from the type of HIV most common in low-income countries.
• Because of the lack of universal health care, people in low-income countries might have been sicker at the time they entered the study.

So the designers of the Merit study decided in advance to analyse the results based on geographic location. The proportion of participants from the Northern hemisphere whose viral load fell below the 50-copy mark was as follows:

• efavirenz group – 68%
• maraviroc group – 68%

The results from the Southern hemisphere were as follows:

• efavirenz group – 71%
• maraviroc group – 62%

This analysis by geographic region suggests that there may be differences in the populations in these regions. Hopefully Pfizer scientists can investigate the study data and explain why there were different outcomes in each region.

Complications and side effects
The proportion of participants from each treatment group who reported side effects was similar, around 12%. The number of participants who developed AIDS-related complications was greater in the efavirenz group (12 PHAs) compared to the maraviroc group (6 PHAs).

The number of people who developed cancers in this study was slightly greater in the efavirenz group (16 PHAs) compared to the maraviroc group (10 PHAs).

There were two deaths in the efavirenz group and one in the maraviroc group.

The following side effects were more common among people who used maraviroc:

• unexpected tiredness or lack of energy
• runny nose or sore throat
• bronchitis

Among efavirenz users, the following side effects were more common:

• dizziness
• diarrhea
• vomiting

• lung infections
• strange dreams
• rash
• cough
• stomach pain

Lipid changes
In general, efavirenz users were more likely to develop increased levels of cholesterol and triglycerides in the blood than participants taking maraviroc.

Liver enzymes
Changes in liver enzymes were uncommon in this study, occurring in about 3% of participants in each group.

In summary
This trial was designed to show that maraviroc was not worse than efavirenz in first-line therapy. This type of trial is called a “non-inferiority” study. Overall, maraviroc was not able to suppress viral load below the 50-copy mark as well as efavirenz. Pfizer, the manufacturer of maraviroc, is trying to understand why this occurred.

REFERENCE:

E. Another receptor blocker— INCB9471

The Incyte corporation, based in the state of Delaware in the United States, has at least two anti-HIV compounds under development. Both of these experimental drugs work by interfering with HIV’s ability to attach to and use the CCR5 co-receptor. Incyte’s compounds can stop HIV from infecting cells and so they are called entry inhibitors. Both experimental agents only have code names at this time and the compound that is furthest ahead in clinical trials is called INCB9471.

In lab experiments with cells, INCB9471 has strong anti-HIV activity and seems to work in a slightly different way than maraviroc. The drug is well absorbed in people and needs to be taken only once daily.
In placebo-controlled experiments with 23 HIV positive people, researchers gave 19 volunteers different doses of INCB9471 while the remaining four volunteers received placebo. Results indicated that viral load fell by almost 2 logs after two weeks of exposure to INCB9471 at a daily dose of 200 mg. In these studies, INCB9471 was the only anti-HIV agent used by volunteers. After the 16th day, viral load began to rise, suggesting that HIV was developing resistance to INCB9471 when used as monotherapy.

Two out of 19 people who received the drug had the tropism of their HIV change from R5 to X4 and R5 (dual/mixed). After stopping the drug, both participants had their viral tropism revert to R5. This reversion to R5 suggests that participants' immune systems suffered no lasting damage.

Side effects
No serious side effects developed, but each of the following side effects (which were mild) occurred in a different participant:

- constipation
- diarrhea
- nausea
- headache
- hiccoughs
- rash

Another study by Incyte tested low doses of INCB9471 (12 or 25 mg once daily) with 100 mg of ritonavir (Norvir) taken twice daily. This latter drug helps boost and maintain levels of INCB9471 in the blood. When both drugs were taken in combination for 10 days, INCB9471 levels in the blood were just below levels seen when INCB9471 was taken by itself at a dose of 200 mg per day.

Future studies of INCB9471 are ongoing. Eventually the corporation hopes to test this receptor blocker in treatment-experienced PHAs.

REFERENCES:

F. PRO 140—a receptor antibody for HIV

PRO 140 is the name given to an antibody designed to interfere with HIV’s ability to attach itself to the CCR5 receptor. PRO 140 works in a slightly different manner than maraviroc. Importantly, the antibody does not affect the functioning of the CCR5 receptor. This may mean that PRO 140 does not have any effects on the health of the immune system and its ability to fight infections. Because PRO 140 achieves its anti-HIV effects in a manner different from maraviroc, it may have potential for use in people for whom maraviroc no longer works.

Initial enthusiasm for PRO 140 was guarded because the drug needed to be given intravenously every two weeks. In an era when most anti-HIV medications are taken orally, intravenous treatment would not be a preferred choice for patients or their doctors. However, the developer of PRO 140, Progenics Pharmaceuticals Inc., has created a new formulation of this drug that can be given by injection under the skin (subcutaneous injection). These injections would need to be done once every two weeks and could be done at home—a possibility that improves prospects for the drug.

In placebo-controlled studies with 39 symptom-free HIV positive people, infusions of PRO 140 at a dose of about 5 mg/kg of body weight have been able to suppress HIV production by at least 1.83 logs and, in some cases, as much as 2.5 logs. These differences may seem small but when it comes to suppressing the production of HIV, every bit counts.

Ten days after a PRO 140 infusion, HIV levels in the blood began to rise, suggesting that the antibody’s effect was waning when given as the sole anti-HIV agent.

PRO 140 was not associated with any serious side effects.

CD4+ cell counts increased by about 29%, or about 130 cells, in volunteers given the drug and remained elevated for up to three weeks after the injection.

Hopefully regulatory authorities will approve the testing of the new injectable formulation of PRO 140 for larger clinical trials in the months ahead.
G. Raltegravir (Isentress)—results after one year

Raltegravir, formerly MK-0518 and to be sold under the brand name Isentress, is a new drug for the treatment of HIV infection. Regulatory authorities in Canada will approve the sale of this drug in the fall of 2007.

Raltegravir represents an important development because it is the first of a new class of anti-HIV agents called integrase inhibitors. These drugs work by interfering with an enzyme essential for creating new viruses. By slowing down or stopping the activity of the integrase enzyme, raltegravir, as part of combination therapy, can significantly reduce viral load. As viral load goes down, CD4+ cell counts rise and health improves.

Raltegravir is active against HIV-1 that is resistant to the following classes of HIV medications:

- nukes (nucleoside analogues)
- non-nukes (NNRTIs)
- protease inhibitors
- fusion inhibitor

Raltegravir is also active against HIV that uses the co-receptors CCR5 or CXCR4.

After six months of treatment in a group of heavily pre-treated volunteers, raltegravir, as part of combination therapy, helped to suppress viral load below the 50-copy mark in as many as 67% of PHAs.

Recently, researchers presented the results of one year of raltegravir exposure in treatment-experienced PHAs during a study called Protocol 005.

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

- 10% female, 90% male
- age – 43 years
- CD4+ cell count – 240 cells

- viral load – 63,000 copies
- 10 years previous exposure to anti-HIV medications

All participants received an optimized background therapy (OBT) based on their treatment history and resistance testing. Participants who did not receive raltegravir received placebo. During the first six months of the study, the trial was placebo-controlled. After this, all participants received raltegravir (and OBT). Initially, raltegravir was given in different doses to different participants. However, after six months, the dose was standardized at 400 mg twice daily.

**Results—Viral load**

During the placebo-controlled part of the study, about 60% of participants who received raltegravir had their viral loads fall below the 50-copy mark. Among volunteers who received placebo and OBT, about 10% had their viral load fall below the 50-copy mark.

After one year, the proportion of raltegravir users with a viral load below the 50-copy mark was 50%.

**Results—CD4+ cell counts**

During the placebo-controlled phase of the study, CD4+ cell counts rose in raltegravir users by at least 100 cells. This was sustained through the next six months of the study. Among people who received placebo and OBT, during the first six months their CD4+ counts rose by about 25 cells. However, no further increase was noted after the sixth month.

**Focus on resistance**

Researchers found that 33 out of 133 participants (about 29%) who received raltegravir developed treatment failure during the first six months of the study. Most of these participants had detectable resistance mutations associated with raltegravir. Usually, resistance to raltegravir required the presence of at least two mutations.

In this study, factors associated with a reduced risk of developing raltegravir resistance were as follows:

- relatively low viral load (less than 100,000 copies) at the start of the study
- using T-20 (enfuvirtide, Fuzeon) as a new drug in the participant’s OBT
Complications and side effects
In this study, raltegravir was generally safe. Side effects that were seen in raltegravir users were also seen in participants who received placebo.

Three participants who received raltegravir had significantly increased levels of liver enzymes in the blood.

There were a total of four serious complications during the study:

- Higher-than-normal levels of lactic acid in the blood and kidney dysfunction occurred in one participant who took raltegravir at a dose of 600 mg twice daily. This person also developed blood poisoning from a bacterial infection and subsequently died.
- Severe inflammation of the pancreas gland (pancreatitis) occurred in one person receiving raltegravir at a dose of 200 mg twice daily. Researchers decided that this was due to the drugs in the OBT.
- A partially blocked artery was seen on a CAT scan in one person who received placebo.
- Accelerated loss of subcutaneous fat (lipoatrophy) occurred in a person who received placebo.

Cancers
During the first six months of the study, no new cancers were detected. However, after this time, when all participants received raltegravir, one participant’s lymphoma grew worse while another developed skin cancer.

A large trial comparing the effectiveness of raltegravir-containing combinations to efavirenz-containing combinations in first-line therapy is underway. The results from this study will be helpful for doctors and their patients when making decisions about starting HAART.

REFERENCE:

H. New drugs—hope and a degree of caution
Maraviroc and raltegravir both are available through expanded access programs in Canada and other high-income countries. These and the other medications featured in this issue of TreatmentUpdate are the result of excellent drug discovery and development programs. Both drugs, once they are approved, are poised to improve the health of thousands of PHAs.

While there is a great deal of anticipation about the approval and consequent easier availability of these drugs, we suggest that our readers may wish to exercise a degree of caution about these and any other newly licensed medication(s).

Maraviroc and raltegravir have only been tested for about a year in controlled clinical trials. At most, a couple thousand PHAs have been exposed to these medications in those studies. Doctors have some idea of what short-term side effects to expect, however, the long-term safety of these drugs is not known. So, it is possible that in the years to come, new and unexpected side effects may emerge. Note that most of the participants in studies with maraviroc or raltegravir were men. The full impact of these drugs in women is not yet known. Below are some more specific issues that have emerged when these and other drugs were studied in clinical trials.

Entry inhibitors—co-infections
CCR5 is a receptor used by cells of the immune system to send messages to each other. By covering up this receptor, it is possible in theory that drugs such as maraviroc and related compounds could interfere with the functioning of the immune system. So far, at least in clinical trials, this does not seem to have happened, perhaps because the immune system has other receptors that it can use instead of CCR5.

Still, recent research suggests the possibility that CCR5 receptors are particularly important for maintaining immunity against West Nile virus (WNV). This virus originated in Africa but over the past decade has spread across North America. By using entry inhibitors, it is theoretically possible that PHAs may become more susceptible to the effects of WNV infection, particularly in the brain. Long-term monitoring for this possibility may be needed in North America.

Entry inhibitors—liver damage
The development of an experimental CCR5 inhibitor, aplaviroc, was stopped because of increasing reports of liver damage. Work on another CCR5 receptor blocker, called MrkA, had its development halted because of liver
damage in animals. This damage was caused by the immune system attacking the liver. Researchers suspect that the immune system was tricked into this attack by the effects of the entry inhibitor. So it seems reasonable that some PHAs, particularly those co-infected with hepatitis-causing viruses and who use maraviroc and other entry inhibitors, have regular blood tests to monitor their liver health.

Entry inhibitors—cancers
Clinical trials of the experimental CCR5 receptor blocker vicriviroc (SCH 417690 or Schering D) are underway in PHAs. Results from a placebo-controlled study in 118 PHAs found that six cases of cancer occurred in participants randomly assigned to receive vicriviroc. Only two cases occurred in placebo users. One of the participants who initially received placebo later took vicriviroc and then developed cancer. Because HIV infection heightens the risk for cancer, the study team declared that “longer-term follow-up of patients exposed to CCR5 inhibitors is needed to determine the relationship, if any, to the development of [cancer].”

Integrase inhibitors—cancer risk no longer significant
Raltegravir is the first integrase inhibitor to be approved in the United States. It is expected to be approved in Canada later this fall. In clinical trials, few serious side effects have emerged with raltegravir. As part of the regulatory approval process, the American Food and Drug Administration (FDA) reviewed the dossier on raltegravir submitted by its manufacturer, Merck. The FDA noted that an imbalance of cancers was initially seen in raltegravir trials. Twenty cases of cancer were reported in 19 PHAs receiving raltegravir while none were reported in PHAs receiving placebo.

The types of cancers that occurred included the following:

- anal cancer
- cancer of the genitals
- lymphoma
- skin cancer
- Kaposi’s sarcoma
- Hodgkin’s lymphoma
- rectal cancer
- liver cancer

The FDA noted that PHAs who developed cancer were more likely to have a higher viral load (90,000 copies vs. 56,000 copies) and a lower CD4+ count (34 cells vs. 140 cells) than PHAs who did not develop cancer in the raltegravir trials.

The FDA pointed out that more recently the imbalance in cancer cases in raltegravir trials has shifted to this:

- raltegravir – 2.5% (19 PHAs) developed cancer
- placebo – 1.5% (5 PHAs) developed cancer

This difference is not statistically significant and the FDA sees no cause for alarm.

REFERENCES:
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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Credits
Writer
Sean Hosein
Editor
David McLay
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