I ANTI-HIV AGENTS

A. New drugs, new hope, old lessons

The annual Conference on Retroviruses and Opportunistic Infections (CROI) is North America’s premier scientific meeting on HIV/AIDS. This year the conference took place from February 25–28 in Los Angeles. The meeting deals mostly with research and treatment of HIV/AIDS. But many other related issues—such as vaccine development, treating complications of HIV infection, managing co-infections, how HIV gradually disables the immune system and transmission of HIV—are all topics that were addressed this year. Coverage of treatment and HIV transmission issues in low-income countries has gained increased attention at CROI in the past several years.

Advances in the treatment of HIV infection have always been an important aspect of CROI. In the mid-1990s, word about the powerful and life-prolonging effect of protease inhibitor–based therapy first appeared at CROI. In 2007, attendees’ expectations were largely met because of sessions in which results of emerging therapies were presented. These therapies include the following new classes of anti-HIV medications:

- maraviroc – This drug works by blocking a receptor called CCR5 found on the surface of cells. HIV needs this receptor in order to get inside and infect a cell. Drugs such as maraviroc are called entry inhibitors.
- integrase inhibitors – These drugs work by interfering with an enzyme used by HIV called integrase. One integrase inhibitor is called raltegravir (MK-0518) and is being developed by the pharmaceutical company Merck & Co. Gilead Sciences is developing another integrase inhibitor called elvitegravir (GS 9137).
When either maraviroc or raltegravir is used as part of combination therapy, both drugs have strong anti-HIV activity, resulting in increased CD4+ cell counts, decreased viral load and, consequently, improved health. While there are many new anti-HIV therapies under development, maraviroc and raltegravir are most likely to become available in expanded access programs soonest. Before these expanded access programs are approved, both drugs can be requested by physicians through Health Canada’s Special Access Program.

New drugs: Proceed with caution
Maraviroc and raltegravir have been tested for a relatively short period of time—less than one year in publicly released data. So far, these drugs do not appear to cause serious side effects in large numbers of people, a promising development. However, as more people with HIV/AIDS (PHAs) use these drugs for longer periods, unexpected side effects may emerge. Therefore, while there is certainly an urgent need for these medicines, particularly among treatment-experienced PHAs, some caution should be taken as their long-term effects are not known.

The lesson of lipoatrophy
A good example of what might happen over the long term with medications is the emergence of lipoatrophy—loss of subcutaneous fat. This is the fatty layer that lies just under the skin. When this occurs, fat is lost in the face, arms and legs, resulting in a disfiguring appearance. In the mid-to-late 1990s when this problem appeared in an increasing number of PHAs, researchers were not sure why it occurred. Because protease inhibitors had been released during this period, it seemed natural to link their use to lipoatrophy. However, several years of research revealed that exposure to certain medications called thymidine analogues—d4T (stavudine, Zerit) and AZT (zidovudine, Retrovir)—were the chief culprits behind the loss of fat. Recently, both American and British treatment guidelines have been amended so that the use of d4T is discouraged, at least for the initial therapy of HIV infection.

Concern about efavirenz
At the 14th CROI, researchers became concerned that another medication, the non-nuke efavirenz (Sustiva, Stocrin), may have the potential to cause lipoatrophy. Several years ago, clinical trials found that efavirenz, when taken as part of combination therapy, had strong anti-HIV activity. Efavirenz was then listed in several treatment guidelines as being equivalent in potency to a protease inhibitor when used as part of combination therapy. But, meanwhile, researchers in France who were trying to understand lipoatrophy were conducting test-tube experiments on human fat cells with efavirenz. They found that this drug appears to affect the health, growth and development of fat cells. Also, over time, the concentration of efavirenz in fat cells becomes many times greater than it is in the blood. The massive accumulation of efavirenz in fat cells may cause these cells to malfunction and eventually die. At the 14th CROI, two studies comparing the effects of efavirenz to the effects of protease inhibitors were presented. Both found that the use of efavirenz was linked to an increased risk for the development of fat wasting in PHAs. This development has occurred several years after efavirenz was licensed and should stand as a cautionary note.

New hopes: Fat burning
Other abnormalities with fat can occur in people who use highly active antiretroviral therapy (HAART). One of them is lipohypertrophy—fat accumulation in the belly. In this condition, fat gets deposited deep in the belly, wrapped around vital organs. This type of fat, called visceral fat, is not easily removed, so news that a new compound called TH9507 can help PHAs lose belly fat was encouraging. TH9507, also called tesamorelin, is being developed by the Canadian company Theratechnologies. The drug works by stimulating the brain to release growth hormone (GH). In HIV infection, levels of GH are less than normal. This hormone is important for maintaining muscles and strength and for burning fat. In a six-month placebo-controlled trial in PHAs, TH9507 helped to reduce belly fat. A downside is that the drug had to be injected under the skin daily. A second study has started recruiting participants in the United States and is about to start recruiting participants across Canada.

Living longer
Now that more anti-HIV agents will gradually become available in high-income countries, there may be a justified sense of relief, particularly among treatment-experienced PHAs who urgently need additional therapies. Readers should note that while two new classes of medications are emerging—entry inhibitors and integrase inhibitors—as well as two promising non-nukes—TMC125 (etravirine) and TMC278 (rilpivirine)—this is likely all that will become widely available for the next three years. Both PHAs and their doctors will have to use these medications cautiously, crafting regimens to maximize the
effectiveness of the new drugs and minimize the development of resistance.

In *TreatmentUpdate 160*, we present selected highlights from the 14th CROI. In our next issue we will continue our coverage from this conference, including topics such as additional experimental HIV treatments, Canadian research on treating fat accumulation and monotherapy with protease inhibitors.

REFERENCE:

B. Leading to lipodystrophy

In high-income countries, many anti-HIV therapies are available for sale. These can be divided into four classes as follows:

**Nukes (nucleoside analogues):**
- 3TC – lamivudine (Epivir)
- ABC – abacavir (Ziagen)
- AZT – zidovudine (Retrovir)
- ddI – didanosine (Videx)
- d4T – stavudine (Zerit)
- FTC – emtricitabine (Emtriva)

Nucleotide analogue:
- tenofovir (Viread)

Although tenofovir is a nucleotide analogue, it is usually regarded as another nuke.

Nukes are often co-formulated into combinations that are together in one pill, such as the following:
- AZT + 3TC – Combivir
- 3TC + ABC – Kivexa
- AZT + 3TC + ABC – Trizivir
- FTC + tenofovir – Truvada

**Non-nukes:**
- efavirenz (Stocrin, Sustiva)
- nevirapine (Viramune)

Under development are the following non-nukes:
- TMC125 (etravirine)
- TMC278 (rilpivirine)

**Protease inhibitors:**

These days, most protease inhibitors are taken together with a small dose of another protease inhibitor, ritonavir (Norvir). The reason for this is that ritonavir helps delay the breakdown of the other protease inhibitor (PI), leading to high and prolonged levels of this other drug in the blood. In practice, this means that most PIs can be taken once or twice daily. The following PIs are generally available in high-income countries:
- fosamprenavir (Telzir)
- atazanavir (Reyataz)
- darunavir (Prezista)
- indinavir (Crixivan)
- lopinavir + ritonavir (Kaletra, Aluvia)
- nelfinavir (Viracept)
- ritonavir (Norvir)
- saquinavir (Invirase)
- tipranavir (Aptivus)

**Fusion inhibitor:**

So far only one fusion inhibitor is available and it is injected twice daily.
- T-20 – enfuvirtide (Fuzeon)

**From AZT to HAART**

The first anti-HIV drug, AZT, was introduced in the late 1980s. In the early to mid-1990s, several other nukes were released, including ddI, d4T and 3TC. In that time, these drugs were used either on their own, as monotherapy, or together with another nuke. Compared to the combinations used today, monotherapy with a nuke was mildly useful for a short period of time. Indeed, before HAART became available, survival with AIDS was relatively short and deaths from life-threatening infections were common.

However, around 1996 a new class of drugs called protease inhibitors became available. When PIs and other anti-HIV drugs are used to treat HIV/AIDS (often a combination of at least three drugs), this is called highly active antiretroviral therapy (HAART). For the first time, prolonged recovery from previously hard-to-treat infections was possible.

**Enter lipodystrophy**

In the late 1990s, as more PHAs began to live longer, a strange collection of signs and symptoms called the lipodystrophy syndrome emerged. Features of this syndrome involve changes in body shape as well as changes to the biochemistry of
the blood. These changes can include the following:

- lipoatrophy – loss of subcutaneous fat (the fatty layer under the skin). Lipoatrophy causes a sunken appearance in the face, while the arms and legs also lose fat and can look thinner. Also, veins in the limbs appear to bulge because the subcutaneous fatty layer has disappeared.
- lipohypertrophy – fat gain. Lipohypertrophy can make women’s breasts larger and can cause both men and women to have bigger bellies.

Biochemical changes in the blood can also occur as a result of lipodystrophy, including the following:

- increased levels of sugar (glucose)
- increased levels of insulin

These changes suggest that the body is having difficulty keeping blood sugar within its normal range and that cells are beginning to resist the effects of insulin (insulin resistance). Left unchecked, these changes can lead to diabetes.

Other changes in blood include the following:

- increased levels of fatty substances, such as cholesterol and triglycerides
- increased levels of so-called “bad” cholesterol (LDL-c)
- decreased levels of so-called “good” cholesterol (HDL-c)

These changes in lipids increase the risk of cardiovascular disease.

Most distressing for many PHAs are the changes in appearance caused by lipoatrophy. At first, this was blamed on the use of protease inhibitors, as these drugs were introduced shortly before lipodystrophy in general and lipoatrophy in particular became noticeable. However, after much research, it became clear that fat wasting was linked to exposure to d4T and, to a much lesser extent, AZT. Both of these drugs are called thymidine analogues.

Treatment guidelines, first in the UK and then later in the US, now suggest that, at least for initial therapy, use of d4T be avoided so as to minimize the likelihood of lipoatrophy developing.

An unexpected result
At the 14th CROI, an unexpected development occurred. Results from two long-term clinical trials suggest that exposure to the non-nuke efavirenz can increase the risk of lipoatrophy.

The fact that two separate studies, one of which was relatively large, have found this result is disturbing and suggests that the relationship between efavirenz and fat wasting is not a statistical error or related to a fluke. Details about these studies as well as possible reasons that efavirenz might affect the health of fat cells appear later in this issue of TreatmentUpdate.

REFERENCES:

C. American study finds efavirenz linked to fat wasting
Since many potential therapies for HIV infection are available in high-income countries, it is important that different combinations get tested so that doctors and their patients can know more about their effectiveness, side effects and potential drug interactions. Having this knowledge should help simplify decision-making when choosing a treatment regimen.

Researchers with the American government-funded AIDS Clinical Trials Group (ACTG) conducted a study (ACTG 5142) using three different combinations of anti-HIV agents to try
to better assess their effectiveness and safety. The most commonly used medications for HIV infection fall into three groups—nukes, non-nukes and protease inhibitors. Each of the three regimens that the researchers tested excluded drugs from one of these categories. The reason for doing so was to help make it easier to find out which group of drugs caused particular side effects.

Here are the three combinations tested:

- a nuke-free regimen: lopinavir/r (Kaletra) + efavirenz
- a non-nuke-free regimen: lopinavir/r + 2 nukes
- a protease-inhibitor-free regimen: efavirenz + 2 nukes

The nukes used were as follows:

- AZT + 3TC
- d4T + 3TC
- tenofovir + 3TC

In this study, researchers used a conservative definition of lipodystrophy: Participants would be diagnosed with this syndrome if they lost at least 20% of the fat in their limbs.

Assessments of body fat were done with the use of low-dose X-rays called DEXA scans. These were performed before, during and after the study—up to two years after participants had entered this clinical trial.

A total of 753 HIV positive people who had never previously used anti-HIV medications were enrolled and their average profile at the start of the study was as follows:

- 20% female, 80% male
- age – 38 years
- CD4+ cell count – 191 cells
- viral load – 100,000 copies
- 13% had hepatitis C virus co-infection

Note that the following proportions of participants received the following drugs:

- AZT – 42%
- d4T – 24%
- tenofovir – 34%

**Results—Changes in body shape**

The ACTG team performed a detailed analysis of its results. No matter which way the combinations were assessed, it was clear that efavirenz was always associated with a greater degree of fat loss than lopinavir/r.

Lipoatrophy was defined by the study researchers as fat loss in the arms and legs of at least 20% compared to pre-study levels. The proportion of participants in each group who experienced lipoatrophy after two years was as follows:

- lopinavir/r + efavirenz – 9%
- lopinavir/r + 2 nukes – 17%
- efavirenz + 2 nukes – 32%

These differences between lopinavir/r and efavirenz were statistically significant.

**Lipoatrophy and nukes**

Because exposure to nukes is also associated with lipoatrophy, the study team assessed fat loss by use of each nuke. They found that d4T was associated with the most lipoatrophy, followed by the other drugs. The proportion of participants who used each nuke or nucleotide analogue and who experienced lipoatrophy was as follows:

- d4T – 42%
- AZT – 27%
- tenofovir – 9%

Then the ACTG team analysed lipoatrophy by assessing exposure to efavirenz or lopinavir/r and nukes. Again, use of efavirenz was always associated with a greater degree of lipoatrophy than use of lopinavir/r. Here is the proportion of participants who experienced lipoatrophy with each pairing of lopinavir/r and efavirenz:

- efavirenz + d4T: 51%
- lopinavir/r + d4T: 33%
- efavirenz + AZT: 40%
- lopinavir/r + AZT: 16%
- lopinavir/r + tenofovir: 6%
- efavirenz + tenofovir: 12%

Taking many factors into account, the risk of developing fat wasting in this study after two years with efavirenz was three times greater than with lopinavir/r.

In general, fat in the chest and belly increased between 12% and 16% over the course of this two-year study among all participants.
Results—Changes in lipids
All participants had increased cholesterol levels, which were greatest among those who received the combination of lopinavir/r + efavirenz. Increases in cholesterol were similar among participants who received efavirenz + 2 nukes or lopinavir/r + 2 nukes.

Another fatty substance, triglycerides, rose in all participants, reaching its highest level among those who used the combination of lopinavir/r + efavirenz. Increases in so-called “good” cholesterol (HDL-c) were greatest in the group that received the combination of lopinavir/r + efavirenz.

The findings from this study are unique to the drugs tested, and presenter Dr. Richard Haubrich cautioned that we should not draw conclusions about other protease inhibitors and non-nukes based on the results of this study.

Further information on efavirenz and lipoatrophy appears next.

REFERENCE:

D. A second study confirms fat loss issues with efavirenz
In the mid-1990s, long before the use of double protease inhibitors (PIs) was recommended, researchers at the Ottawa General Hospital were leaders in experimenting with the use of ritonavir-boosted PI combinations. So, it should come as no surprise that researchers at that hospital are once again conducting studies with boosted PIs.

Because HAART often involves taking many pills and has both short-term and long-term side effects, researchers are trying to find ways to minimize the burden of pill-taking and reduce side effects. A strategy that might be tested is to first suppress HIV replication as low as possible, and then to switch PHAs to a less intensive regimen. This is called induction-maintenance.

Lopinavir/r (Kaletra) is a potent protease inhibitor that is commonly used as part of HAART. Recently, Canadian researchers as well as others in France, Spain, the UK and the US collaborated in a study to assess the effectiveness of one induction-maintenance strategy:

- Starting therapy with lopinavir/r + 2 nukes and then eventually switching some participants (those whose viral loads were below the 50-copy mark for three consecutive months) to a less intensive therapy for several years—lopinavir/r alone (Kaletra monotherapy). As a comparison, a group of similar PHAs would be kept on a regimen of efavirenz + 2 nukes also for two years.

Study details
Researchers recruited 106 participants—74 were assigned to receive lopinavir/r + 2 nukes and 32 were to receive efavirenz + 2 nukes. No PHAs in this study had previously used anti-HIV therapy.

The average profile of participants at the start of the study was as follows:
- 22% female, 78% male
- age – 38 years
- CD4+ count – 230 cells
- viral load – about 100,000 copies

Low-dose X-ray scans called DEXA, taken every six months, were used to assess changes in body fat.

After the third month of the study, participants who were receiving lopinavir/r + 2 nukes had their viral load assessed every month. Those participants whose viral load was below the 50-copy mark for three consecutive months then discontinued AZT and 3TC starting in the sixth month of the study and used only lopinavir/r (Kaletra monotherapy).

Results
In this report we will focus on the side effects related to the use of therapies in this study. In a separate report we will cover issues related to antiviral activity and resistance. In general, the antiviral effect of each regimen was found to be roughly equivalent.

Results—Changes in body shape
Initially, both groups experienced increased limb fat as the adverse changes to the body caused by HIV were reversed with treatment. However, after
the sixth month, limb fat levels in the efavirenz group began to decline. After one year, limb fat levels in the efavirenz group declined precipitously, falling well below their pre-study levels. Overall, the difference in limb fat between the lopinavir/r and efavirenz groups two years into the study was great—about 2 kilograms. Although low-dose X-ray scans were used to assess changes in body fat, it became obvious just by looking at participants exactly who was experiencing the loss of subcutaneous fat.

Researchers found that an increase in trunk fat (a gain of at least 20% from pre-study values) was linked to low CD4+ cell counts. Those participants with low CD4+ counts at the start of the study were more likely to experience increased fat deposits in the belly.

Changes in lipid levels were generally not significant between groups, although there was a trend for slightly higher triglycerides among lopinavir/r users.

REFERENCE:

E. Efavirenz and fat wasting—what might be happening?

Until very recently, fat wasting in HAART users was blamed on exposure to the drugs d4T and/or AZT, prolonged HIV infection or a combination of these. However, clinical trial results from the 14th CROI as well as test-tube studies conducted in France raise concerns about an additional drug—efavirenz—when it comes to the loss of subcutaneous fat.

According to laboratory experiments from France, efavirenz impacts the health of fat cells in a number of ways. This drug profoundly affects the ability of fat cells to produce some proteins that they need in order to grow and mature. Efavirenz does this by apparently suppressing the activity of key genes inside fat cells that produce these proteins.

In ACTG trial 5142 (reported earlier in this issue of Treatment Update) there were three regimens tested as follows:

- lopinavir/r + efavirenz
- lopinavir/r + 2 nukes
- efavirenz + 2 nukes

Severe fat loss after two years was found in the following proportion of participants:

- efavirenz + 2 nukes – 32%
- lopinavir/r + 2 nukes – 17%
- lopinavir/r + efavirenz – 9%

A question that immediately arises is: Why did the combination of lopinavir/r + efavirenz result in the lowest level of lipoatrophy? Part of the answer may be that no nukes, particularly thymidine analogues such as d4T or AZT, were present. Also, test-tube research done in Canada and France suggests that ritonavir may be able to stimulate the growth of fat cells and, perhaps, counter the effect of efavirenz. This requires further laboratory study with experiments on fat cells, comparing the effect of lopinavir, ritonavir and efavirenz.

Nevirapine, the other licensed non-nuke, does not appear to cause any increased lipoatrophy, at least in one study.

Hopefully, investigations will begin looking into the effect of the experimental non-nukes TMC125 and TMC278 on fat wasting.

The fact that two clinical trials have found a significant loss of subcutaneous fat associated with the use of efavirenz is not a chance finding. The next step is unclear. Efavirenz is a potent and popular part of HAART, so the findings from ACTG 5142 may not be readily accepted by some physicians and their patients. Regulatory and research agencies could do the following:

- Convene an expert panel to assess the findings from ACTG 5142 and other studies on lipoatrophy and efavirenz.
- Initiate laboratory research to further study the underlying basis for the findings from ACTG 5142.
- Consider another clinical trial to confirm or refute ACTG 5142’s results.

REFERENCES:
for initial treatment of HIV-1 infection. Program and
abstracts of the 14th Conference on Retroviruses and
Angeles, USA. Abstract 35.

sparing of peripheral lipatrophy by HIV treatment with
LPV/r + ZDV/3TC induction followed by LPV/r
monotherapy compared with EFV + ZDV/3TC. Program
and abstracts of the 14th Conference on Retroviruses and
Opportunistic Infections, February 25–28, 2007, Los Angeles,
USA. Abstract 44LB.

suppression of the lipogenic pathway by the non-nucleoside
reverse transcriptase inhibitor efavirenz in 3T3 and human
preadipocytes or adipocytes. Journal of Biological Chemistry
2004 April 9;279(15):15130-15141.

the level of active ADD-1/SREBP-1 protein during

5. Dupin N, Buffet M, Marcelin AG, et al. HIV and
antiretroviral drug distribution in plasma and fat tissue of
HIV-infected patients with lipodystrophy. AIDS 2002; Dec
6;16(18):2419-24.

6. Nolan D. Do non-nucleoside reverse transcriptase
inhibitors contribute to lipodystrophy? Drug Safety

F. Integrase inhibitor raltegravir
makes its mark

For nearly 14 years, the pharmaceutical company
Merck has been inventing and testing a new group
of anti-HIV drugs called integrase inhibitors. As
their name suggests, these drugs work by
interfering with HIV’s ability to integrate itself into
and take over a target cell.

Along the long path of drug discovery and
development, several integrase inhibitors that have
performed well in the lab have failed in clinical
trials. So it is encouraging that the Merck drug
raltegravir (Isentress, MK-0518) has entered the
final stage of testing before approval for sale.

At the 14th CROI Dr. David Cooper from
Australia presented interim results from two
ongoing studies of raltegravir in heavily treatment-
experienced PHAs. A preliminary analysis of the
trials so far shows that raltegravir can be a very
effective part of combination therapy.

Study details
The code names for the studies are Benchmark 1
and Benchmark 2. These are two identical trials.
Benchmark 1 has enrolled volunteers from Europe,
the Asia/Pacific region and Peru. Benchmark 2
has enrolled volunteers from North and South
America.

Both studies are randomized and placebo-
controlled. Raltegravir is used at a dose of 400 mg
twice daily, together with the best combination of
anti-HIV agents as suggested by resistance testing.

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

- 13% female, 87% male
- age – 46 years
- CD4+ count – 150 cells
- viral load – 50,000 copies
- at least 90% of participants had AIDS
- many participants had been taking anti-HIV
  medications for about 11 years
- 21% of participants had not previously used
  T-20 (enfuvirtide, Fuzeon)

Results—Overall
Because the two studies have identical designs, the
results have been very similar. Raltegravir is clearly
superior to placebo. So far, only results from the
first four months of the studies have been released.

Results—CD4+ counts and viral load
On average, participants who received raltegravir
gained 80 extra CD4+ cells. Placebo recipients
gained only 30 additional cells.

On the other hand, changes in viral load were more
dramatic, with about 60% of raltegravir users
achieving a viral load below the 50-copy mark. In
contrast, about 30% of placebo recipients had their
viral load fall below this level.

Among raltegravir users, viral load fell, on average,
100-fold (or 2 logs) below pre-study levels. In the
group who received placebo, decreases in viral load
were more modest, averaging about 1 log or 1⁄10 of
pre-study levels.

As is often the case in studies with treatment-
experienced PHAs, the more drugs in a regimen
that are active against HIV, the better the result.
In these studies, adding additional medications,
such as the following, enhanced raltegravir’s
effectiveness:

- T-20
- darunavir (Prezista)
Raltegravir appears to be slightly less effective when used at very low CD4+ counts (less than 50 cells) or high viral loads (more than 100,000 copies). Keep in mind that these are interim results and the final picture of raltegravir’s effectiveness awaits completion of the study.

**Resistance**

Analysis of samples of HIV taken from participants whose raltegravir-based regimens failed is ongoing. So far, analysis of samples from 32 out of 41 PHAs on such regimens suggests that mutations to raltegravir have developed. Specifically, two key mutation pathways have been identified:

- N155H
- Q148K/R/H

Much more work on exactly how HIV develops resistance to raltegravir must be done so that other key mutations can be identified. Eventually these will have to be added to the genotypic resistance tests commonly in use in high-income countries. Researchers are concerned that resistance to raltegravir may also result in resistance to the experimental integrase inhibitor elvitegravir (GS 9137). This possibility of cross-resistance among integrase inhibitors requires further study.

**Side effects**

Every drug has side effects. However, according to the data released by Merck, there does not seem to be any side effect specifically caused by raltegravir. Indeed, Dr. Cooper said that the medication was well tolerated. A small proportion of participants who received raltegravir reported fatigue. Further study of raltegravir will be needed to find out if this is indeed a side effect.

There have been a small number of deaths in Benchmark 1 and 2 to date. In a study population in which at least 90% of participants had AIDS, the “few deaths” that did occur, according to the presenter, were due to complications from life-threatening infections, liver cancer and lymphoma.

**REFERENCES:**


**G. Raltegravir—other issues**

The data from clinical trials so far suggest that raltegravir has strong anti-HIV activity, even in treatment-experienced PHAs. Several additional points arising from the clinical trials are worth considering:

1. **A low genetic barrier**
   Although raltegravir has strong anti-HIV activity, it needs to be taken with an effective combination of drugs for a number of reasons. First, raltegravir has what researchers call a weak genetic barrier. This means that it takes only a few mutations for HIV to develop resistance to this drug. A similar situation exists with non-nukes—efavirenz and nevirapine. Therefore, care is required when selecting other drugs in a raltegravir-containing combination.

2. **Safety**
   Amazingly, raltegravir appears to have few obvious side effects. This may be due to the integrase enzyme being essential for HIV but not human cells. However, one laboratory-based study independent of Merck has found that very high concentrations of integrase inhibitors have the potential to weaken the immune system’s capacity to make antibodies. But this only happened at concentrations 10 to 20 times above those that would normally be used in people. As long as raltegravir does not accumulate inside cells of the immune system at such high levels, such problems should not occur.

3. **Help from the immune system needed**
   In Benchmarks 1 and 2, there appeared to be a trend for raltegravir to be somewhat less effective in PHAs who had very low CD4+ counts (below 50 cells) or high viral loads (more than 100,000 copies). This is not surprising, as results from monkeys with an AIDS-causing virus suggest a similar effect. Overall, these findings highlight that a certain level of immunity is needed in order for raltegravir to be most useful.

4. **Access**
   Later this year, an expanded access program for treatment-experienced PHAs in Canada should become active. In the meantime, physicians with patients who urgently need this medication can
contact Health Canada’s Special Access Program (SAP) to request the drug. For general information about the SAP, including contact information and how the program works, please see the following link:


REFERENCES:


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

Treatment Update
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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
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Holistic health information and views for PHAs.

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