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## Contents

### I ANTI-HIV AGENTS

- A. Maturation inhibitor reappears 1
- B. Raltegravir (Isentress) 3
- C. Raltegravir—results after two years 3
- D. Raltegravir as initial therapy 4
- E. Darunavir—favourable results after two years 5

### II CANCER

- A. Concern about cancer risk with raltegravir 6
- B. Predicting who is at high risk for lymphoma 7

## I ANTI-HIV AGENTS

### A. Maturation inhibitor reappears

In order to create new copies of itself, HIV infects cells of the immune system called CD4+ T-cells. Once inside these cells, HIV can take control and transform the cells into mini virus factories.

Anti-HIV drugs work by interfering with vital viral replication processes (steps in the creation of new viruses). Specifically, most of these drugs interfere with viral enzymes. Although there are more than 20 approved therapies for HIV, many are chemically related to each other and can generally be placed into the following main groups:

- reverse transcriptase inhibitors
- protease inhibitors
- co-receptor blockers
- integrase inhibitors
- fusion inhibitors

Because many of these drugs are in the same chemical families, if HIV becomes resistant to one drug in a family, or class, it may have varying degrees of resistance to other drugs in the same family. This is called cross-resistance and it can limit future treatment options. Cross-resistance highlights the need for new effective therapies.

### First bevirimat

Researchers in the United States have developed a novel anti-HIV compound called PA-457, also known as bevirimat dimeglumine. This drug belongs to an emerging group of anti-HIV medicines called maturation inhibitors. Bevirimat is the first drug in this class.

This drug has had a chequered history. It was initially developed by Panacos Pharmaceuticals Inc.

produced by



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with promising preliminary data reported. However, further development of bevirimat then stalled for several years as Panacos encountered problems. The main issue was that in a significant proportion of HIV positive volunteers HIV unexpectedly appeared to be resistant to bevirimat. This is odd because HIV maturation inhibitors have never been used in clinical trials before, so researchers were mystified about this finding. A possible explanation for this unexpected viral resistance is that in some people HIV has naturally developed mutations that can render maturation inhibitors ineffective from the start.

### Myriad takes control

Panacos then sold the drug to another company, Myriad Pharmaceuticals Inc., based in Salt Lake City, Utah. Myriad renamed bevirimat MPC-4326 and also is developing HIV maturation inhibitors of its own, which are code-named MPC-9055 and MPC-461359. Of these three drugs, MPC-4326 (bevirimat dimeglumine) is the furthest along in clinical development.

MPC-4326 was originally developed in a liquid formulation. However, a tablet formulation is now used in clinical trials.

To move forward with MPC-4326, Myriad has to find a way to predict which HIV positive people have preexisting resistance to this drug. Information in the public domain suggests that Myriad is developing a relationship with the Belgian diagnostics company Virco BVBA to develop a test for maturation inhibitor resistance. Virco appears to have developed a genotypic resistance test that can detect resistance to MPC-4326. Using this assay, a reanalysis of a limited number of blood samples from previous clinical trials suggests that in some people who are not resistant to MPC-4326 significant decreases in viral load (about 1.26 log) are possible.

In the coming months, hopefully the ability of researchers to interpret the results of this assay will improve. A phase 2b clinical trial of MPC-4326 is planned for North America later this year in treatment-experienced HIV positive people.

Results from previous clinical trials of MPC-4326 suggest that the drug is generally well tolerated. Headache is the most common side effect and even this was mild in severity.

Many anti-HIV drugs are broken down in the liver or kidneys by different enzymes. An advantage of MPC-4326 is that it is not processed by the more common pathways in the liver that often lead to significant drug-drug interactions. MPC-4326 is processed in the liver by the same class of enzymes (called UGTs) that metabolize some other anti-HIV drugs such as raltegravir (Isentress). Very little of MPC-4326 is processed by the kidneys. This means there are few other HIV drugs that will change the way MPC-4326 is processed in the body. Additionally, laboratory studies suggest that MPC-4326 does not inhibit the liver enzyme cytochrome P450 3A4 which processes many anti-HIV drugs. Therefore there is a low likelihood for MPC-4326 to affect the processing of other anti-HIV drugs and consequently have little impact on the levels of other anti-HIV drugs in the body.

### REFERENCES:

1. Beelen A, Otto J, Fidler M, et al. Phase I, single ascending oral dose study of the safety, tolerability, and pharmacokinetics of a novel HIV-1 maturation inhibitor in HIV-negative, healthy volunteers. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 570.
2. Van Baelen K, Salzwedel K, Rondelez E, et al. Susceptibility of human immunodeficiency virus type 1 to the maturation inhibitor bevirimat is modulated by baseline polymorphisms in Gag spacer peptide 1. *Antimicrobial Agents and Chemotherapy*. 2009 May;53(5):2185-8.
3. Adamson CS, Waki K, Ablan SD, et al. Impact of human immunodeficiency virus type 1 resistance to protease inhibitors on evolution of resistance to the maturation inhibitor bevirimat (PA-457). *Journal of Virology*. 2009 May;83(10):4884-94.
4. Malet I, Wirlden M, Derache A, et al. Primary genotypic resistance of HIV-1 to the maturation inhibitor PA-457 in protease inhibitor-experienced patients. *AIDS*. 2007 Apr 23; 21(7):871-3.
5. Connor A, Evans P, Doto J, et al. An oral human drug absorption study to assess the impact of site of delivery on the bioavailability of bevirimat. *Journal of Clinical Pharmacology*. 2009 May;49(5):606-12.
6. Smith PF, Ogundele A, Forrest A, et al. Phase I and II study of the safety, virologic effect, and pharmacokinetics/pharmacodynamics of single-dose 3-o-(3',3'-dimethylsuccinyl) betulinic acid (bevirimat) against human immunodeficiency virus infection. *Antimicrobial Agents and Chemotherapy*. 2007 Oct;51(10):3574-81.
7. Yebra G, Holguín A. The maturation inhibitor bevirimat (PA-457) can be active in patients carrying HIV type-1 non-B subtypes and recombinants. *Antiviral Therapy*. 2008;13(8):1083-5.
8. Martin DE, Galbraith H, Schettler J, et al. Pharmacokinetic properties and tolerability of bevirimat and atazanavir in healthy volunteers: an open-label, parallel-group study. *Clinical Therapeutics*. 2008 Oct;30(10):1794-805.

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9. Martin DE, Smith P, Wild C, et al. In vitro and in vivo disposition of PA-457, a novel inhibitor of HIV-1 maturation. In: *Program and abstracts of the 15th International Conference on AIDS*, 11–16 July 2004, Bangkok, Thailand. Abstract WePeA5644.

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## **B. Raltegravir (Isentress)**

Raltegravir works by interfering with a viral enzyme called integrase. It is the first integrase inhibitor available for the treatment of HIV infection. Initially developed for use by treatment-experienced patients, once raltegravir had shown that it was a very effective part of combination therapy in this group, it was also developed for use as first-line therapy in people who have never used anti-HIV drugs. Raltegravir is taken twice daily with or without food.

In this issue of *TreatmentUpdate*, we review results from clinical trials in which raltegravir has been used as follows:

- results after two years of using raltegravir
  - interim results from a trial of raltegravir in first-line therapy
  - a review of cases of cancer seen in trials of raltegravir
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## **C. Raltegravir—results after two years**

The initial clinical trials of raltegravir were of a relatively short duration. Since raltegravir represents an entirely new class of anti-HIV drugs, it is important that people who use it are monitored for possible side effects. So regulatory authorities in the European Union and United States have asked the developer of raltegravir, Merck, to continue to monitor the health of people who use the drug for five years. In this report we combine the latest results from participants in two clinical trials of raltegravir—Benchmark 1 and Benchmark 2.

### **Study details**

Raltegravir was used by people who had HIV that was resistant to drugs from commonly used classes of anti-HIV medicines. All participants were given what the researchers called optimal background therapy (OBT)—an individualized combination of anti-HIV drugs that researchers prescribed by taking into account each participant’s treatment history and resistance profile.

Clinical trial volunteers were randomly assigned in a 2 to 1 ratio to one of the following study groups:

- raltegravir 400 mg twice daily and an optimal background therapy (OBT) – 466 volunteers
- fake raltegravir (placebo) and an OBT – 237 volunteers

The average profile of participants at the time they entered the study was as follows:

- 12% female, 88% male
- 46 years old
- CD4+ count – 120 cells
- viral load – 50,000 copies

### **Results—after 96 weeks**

Overall, the proportion of clinical trial participants in each group whose viral load was less than 50 copies was as follows:

- raltegravir + OBT – 57%
- placebo + OBT – 26%

This difference was statistically significant; that is, not likely due to chance alone.

### **A closer look at combinations**

In this clinical trial of treatment-experienced patients, those who had not previously used powerful new anti-HIV drugs—such as T-20 (Fuzeon) or darunavir (Prezista)—and who received them as part of their OBT regimen were able to suppress their viral load below 50 copies as follows:

- raltegravir + OBT (containing T-20 and darunavir) – 79%
- placebo + OBT (containing T-20 and darunavir) – 63%

With darunavir as the only powerful new drug in the OBT, the results were as follows:

- raltegravir + OBT (containing darunavir) – 71%
- placebo + OBT (containing darunavir) – 40%

And if there were no powerful new drugs in the OBT, the virologic results were like this:

- raltegravir + OBT – 57%
- placebo + OBT – 19%

These results demonstrate that raltegravir has powerful anti-HIV activity and when it’s used with other active drugs, the results are even better.

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Bear in mind that the participants in this trial were treatment-experienced and had few treatment options. Because of their relatively low CD4+ counts (an average of 120 cells at the start of the study), they were at risk for a range of health complications. Not surprisingly, some deaths from AIDS-related complications occurred. However, people who received raltegravir were less likely to have the following events happen:

- recurrent AIDS-related infections
- new AIDS-related infections
- deaths

On average, the CD4+ cell count of raltegravir recipients increased by 123 after 96 weeks in the study, compared to an increase of 49 for participants who received placebo. This difference was statistically significant.

### Side effects—overall

As participants were generally in poor health when they entered the study, they may have been more susceptible to drug side effects. Perhaps because their health did not significantly improve, serious side effects were more common among people who received placebo.

### Side effects—symptoms

The following side effects were more common among people who received placebo:

- diarrhea
- nausea
- headache
- vomiting

However, fatigue was more common among raltegravir users.

### Side effects—lab tests

In this study, seriously abnormal laboratory test results were uncommon. Based on the data supplied by Merck, it is difficult to assess which abnormal laboratory results were due to exposure to raltegravir. For instance, higher-than-normal levels of cholesterol were seen in some raltegravir users (10%) compared to people on placebo (6%). However, raltegravir has not caused this problem in other clinical trials and changes in cholesterol may have been due to the complex regimens in the OBT, many of which probably contained ritonavir (Norvir). Moreover, the difference was not statistically significant.

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## Summary

Raltegravir, as part of combination therapy, proved to be of potent and durable benefit in this study. In participants who received an OBT regimen of active anti-HIV drugs, up to 79% of those taking raltegravir had viral loads below the 50-copy mark after two years of use. Raltegravir was generally well tolerated.

### REFERENCE:

1. Steigbigel R, Cooper D, Eron J, et al. 96-week results from BENCHMRK 1 and 2, Phase III studies of raltegravir in patients failing ART with triple-class-resistant HIV. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 571b.

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## D. Raltegravir as initial therapy

Raltegravir has shown that it can be a useful part of combination therapy for treatment-experienced people. And when tested as part of combination therapy for first-line treatment against a regimen containing efavirenz (Sustiva), it was found to be as effective.

### Study details

Researchers in North and South America, Europe and the Asia-Pacific region enrolled 562 HIV positive people who had not previously used anti-HIV drugs and randomly assigned them to one of the following groups:

- raltegravir group: raltegravir with a fixed-dose combination of tenofovir and FTC (Truvada) – 281 volunteers
- efavirenz group: efavirenz with a fixed-dose combination of tenofovir and FTC – 282 volunteers

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

- 19% female, 81% male
- age – 37 years
- CD4+ count – 208 cells
- viral load – 100,000 copies
- 7% had hepatitis B or C
- 15% had a history of AIDS

### Results

After one year, the proportion of participants in each group who had a viral load below the 50-copy mark was as follows:

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- raltegravir group – 86%
- efavirenz group – 82%

Changes in CD4+ counts after one year were as follows in each group:

- raltegravir group – 189 additional cells
- efavirenz group – 163 additional cells

Based on the design of this study (a non-inferiority design) and the results, it is clear that combination therapy containing raltegravir is “no worse than” combination therapy containing efavirenz. This result suggests that both drugs have near-equal effectiveness.

It is noteworthy that the raltegravir-containing regimen had fewer overall drug-related side effects. As well, researchers also pointed out the following about raltegravir:

- It had significantly fewer side effects that affected the central nervous system (brain and spinal cord).
- It was safe in people co-infected with hepatitis B or C viruses.
- It was effective against strains of HIV that are commonly found outside of high-income countries.

As raltegravir is tested in more people for first-line therapy in the coming years, it will likely be approved for this use in HIV positive people.

#### REFERENCE:

1. Lennox J, Dejesus E, Lazzarin A, et al. Subgroup analyses from STARTMRK, a Phase III study of raltegravir-based vs. efavirenz-based combination therapy in treatment-naïve HIV-infected patients. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 573.

## E. Darunavir—favourable results after two years

Darunavir (Prezista) is a powerful anti-HIV drug. When used as part of combination therapy and taken twice daily, darunavir can help raise CD4+ counts and decrease viral load in most treatment-experienced people who have taken this drug in clinical trials.

Results from clinical trials suggest that once-daily darunavir (800 mg) together with a small once-daily dose of ritonavir (100) can be an effective part of highly active antiretroviral therapy (HAART) for people starting their first drug

regimen. The manufacturer of darunavir, Tibotec, is conducting a long-term clinical trial called Artemis, expected to last up to four years. In this study, 689 HIV positive people who had never been exposed to anti-HIV drugs were recruited and randomly assigned to one of the following combinations:

- darunavir (800 mg) and ritonavir (100 mg), both taken once daily
- lopinavir (800 mg) + ritonavir (200 mg) co-formulated into tablet formulation (Kaletra), taken either once or twice daily; in practice, most people took Kaletra twice daily

All participants also received a fixed-dose combination called Truvada, which contains these two anti-HIV drugs:

- tenofovir (Viread)
- FTC (emtricitabine, Emtriva)

The average profile of people at the time they enrolled in Artemis was as follows:

- 30% female, 70% male
- age – 35 years
- CD4+ count – 225 cells
- viral load – 67,000 copies

Adherence in this study was assessed by means of questionnaires that participants completed from time to time.

### Results—overall

After two years the proportion of participants whose viral load was below the 50-copy mark was as follows:

- darunavir-ritonavir – 79%
- lopinavir-ritonavir – 71%

This difference between treatments was statistically significant; that is, not likely due to chance alone. Statistical analysis suggests that the combination of darunavir-ritonavir is superior to lopinavir-ritonavir in this study.

### Results—adherence

When researchers assess the results among participants with excellent adherence, there were no significant differences in the ability of either regimen to suppress HIV. However, among participants who had what the research team called “sub-optimal” adherence, better suppression of

viral load occurred in volunteers taking darunavir-ritonavir as indicated below:

- darunavir-ritonavir – 76%
- lopinavir-ritonavir – 53%

### Results—CD4+ cell counts

After two years, participants on the study regimens had increased CD4+ cell counts as follows:

- darunavir-ritonavir – 171 extra cells
- lopinavir-ritonavir – 188 extra cells

This difference was not statistically significant.

### Results—side effects

More serious side effects, graded moderate to life threatening in intensity, were more likely to occur in people taking lopinavir-ritonavir (34%) compared to people taking darunavir-ritonavir (23%).

Diarrhea was significantly more common in users of lopinavir-ritonavir (11%) than in people taking darunavir-ritonavir (4%). This difference was statistically significant.

More people taking darunavir-ritonavir developed a rash (3%) than those taking lopinavir-ritonavir (1%). However, this difference was not statistically significant.

For the most part, neither regimen caused abnormal blood test results. However, more volunteers taking lopinavir-ritonavir developed higher-than-normal levels of cholesterol and triglycerides in their blood, also a statistically significant difference from darunavir-ritonavir users.

The use of darunavir-ritonavir as part of a once-daily regimen has recently been approved in Canada.

### REFERENCES:

1. Mills A, Nelson M, Jayaweera D, et al. Efficacy and safety of darunavir/ritonavir (800/100 mg) once-daily versus lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients at 96 weeks: Artemis (TMC114-C211). In: *Programs and abstracts of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy*, October, 25–28, 2008, Washington, DC, United States. Abstract H-1250c.
2. Nelson M, Yeni P, Sension M, et al. Factors affecting virologic response to darunavir/ritonavir and lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients in Artemis at 96 weeks. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 575.

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## II CANCER

### A. Concern about cancer risk with raltegravir

HIV infection can weaken the immune system, increasing the risk for life-threatening infections and certain cancers. In the early stages of clinical trials with raltegravir there were reports of an apparent increase in cancers seen in some raltegravir users. Concerned about this finding, researchers compared cancer cases seen in several raltegravir trials over time. Their findings suggest that there is no significantly increased risk of cancer due to raltegravir exposure. Possible reasons for the apparent increase in cancer cases are discussed later in this report.

### Study details

Researchers analysed data from five clinical trials that had these identifying names:

- P005
- Benchmrk 1
- Benchmrk 2
- P004
- Startmrk

The first three trials enrolled treatment-experienced people and the last two trials enrolled people who had never previously received anti-HIV therapy.

The average profile of treatment-experienced participants at the time they entered the study was as follows:

- 12% female, 88% male
- age – 45 years
- CD4+ count – 140 cells
- viral load – 56,000 copies
- 68% had symptoms of AIDS

The average profile of the people who were new to anti-HIV therapy was as follows:

- 19% female, 81% male
- age – 37 years
- CD4+ count – 233 cells
- viral load – 90,000 copies
- 20% had symptoms of AIDS

### A note on clinical trials

Before reading the results of the cancer analysis it is important to bear this note in mind: Large clinical trials do not recruit all of their participants

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all at once. Rather, recruitment can take weeks or even months as people gradually join the trial.

### Results—cancer in raltegravir users

In total, researchers examined health information from 1,039 people exposed to raltegravir and 605 who received placebo. Using a strict definition of cancer, here is what happened: Until the second month of the trials, cancer rates were similar in people who received raltegravir and those who received placebo or another agent. But after the second month of the study, cancers became more common in raltegravir users and the number of new cancers stabilized shortly after that time.

After about the third month of the study, cancer rates became essentially stable in raltegravir users, affecting about 1% of them over the next 20 months—the extent for which data was made available for this analysis.

### Results—cancer in people who received placebo

Until the second month of the trials, cancer rates were similar in people who received raltegravir and those who received placebo or another agent. After the third month of the study, cancer rates in people receiving placebo or another agent also rose such that by the fourth month of the study cancer rates were the same in both study groups.

After the sixth month of the study, cancer rates continued to climb in people receiving placebo or another drug and then stabilized around the 12th month. Overall, slightly more than 2% of people in this group developed cancer over the course of about 20 months.

These differences in rates of cancer between people receiving raltegravir and those who received placebo were not statistically significant.

### Focus on cancers

In total, 46 participants developed 53 cases of cancer during the double-blind phase of the study. Commonly detected cancers included the following:

- Kaposi's sarcoma (KS)
- anal or rectal cancer
- cancer of the immune system – lymphoma

It is noteworthy that cancers were more common among treatment-experienced people. This is probably due to their weaker immunity as suggested

by their generally lower CD4+ counts upon entering the study. Tumours tend to take years to develop and it is possible that because treatment-experienced patients were sicker, their tumours were more advanced and could grow faster.

Even though highly active antiretroviral therapy (HAART) can quickly raise CD4+ cell counts in the blood—within days of initiating therapy—this increase in the first few weeks after starting HAART is merely a feature of redistribution as T-cells move from the lymph nodes to the blood. It takes several months before new and more functional T-cells and other parts of the immune system can regenerate and begin to help heal the damage wrought by HIV. Until the immune system gets repaired, there is still a risk for life-threatening infections and cancers during the first two to three months of anti-HIV therapy, particularly in people who initiate therapy at low CD4+ cell counts.

People taking raltegravir will continue to be monitored for the development of cancer. However, so far the data show that there is no increased risk of cancer in people due to exposure to raltegravir.

### REFERENCES:

1. Bonnet F, Chêne G. Evolving epidemiology of malignancies in HIV. *Current Opinion in Oncology*. 2008 Sep;20(5):534-40.
2. Bower M, Fisher M, Hill T, et al. CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. *Haematologica*. 2009; *in press*.
3. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008 Apr 23;22(7):841-8.
4. Engels EA. Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities. *AIDS*. 2009 May 15;23(8):875-85.
5. Cooper D, Steigbigel R, Lennox J, et al. Review of cancer incidence in raltegravir trials. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 859.

### B. Predicting who is at high risk for lymphoma

HIV infection weakens the immune system and increases the risk for life-threatening infections. HIV positive people are also at increased risk for the development of tumours. This risk arises because of a combination of weakened immunity

and co-infection with a number of sexually transmitted cancer-causing viruses, as follows:

- HPV (human papillomavirus) – this is linked to the development of cancers of the anus, penis and vagina
- HHV-8 (human herpes virus-8) – this is linked to the development of Kaposi's sarcoma (KS)
- EBV (Epstein-Barr virus) – this is linked to a cancer of the immune system called non-Hodgkin's lymphoma

Now that highly active antiretroviral therapy (HAART) is widely available in high-income countries, this therapy has helped to greatly reduce deaths from life-threatening infections. HAART works by suppressing production of HIV. In turn, this allows the immune system to begin to repair itself.

Regrettably, HAART does not cure HIV infection and the immune system is only partially repaired. This means that a degree of immune deficiency continues.

### **About the immune system**

Before delving into lymphoma, here is some important information about the immune system. This vast system consists of a network of vessels called the lymphatic system, which connects important organs such as the thymus and spleen as well lymph nodes and patches of lymph tissue throughout the body. Key cells that are part of the immune system and relevant to the formation of lymphoma are T-cells and B-cells.

### **More than an immune deficiency**

Initial theories about how HIV damages the immune system suggested that immunity was suppressed. This made sense because the infections seen in AIDS were those associated with immune suppression. But a closer and more sophisticated look at the immune systems of people with HIV/AIDS suggests a complex picture with part of the immune system—particularly B-cells—being overactive.

B-cells produce antibodies that can help control some infections. Over-stimulated B-cells—as seen in HIV infection—produce excessive levels of antibodies. This over-stimulation occurs because of HIV. And over-stimulation combined with viral co-infections such as EBV can lead to trouble. EBV can transform B-cells, channeling their growth away from a healthy member of the immune system to a cancerous cell that later forms a

tumour. These types of cancers are called lymphomas.

Although lymphomas can arise from both T-cells and B-cells in HIV/AIDS, malfunctioning B-cells are the main source of lymphoma.

One way to reduce the risk of lymphoma is to use HAART and raise CD4+ counts. However, for reasons that are not clear, not all HIV positive people have high CD4+ counts as a result of using HAART, and the risk of cancer remains.

Researchers at the U.S. National Institutes of Health (NIH) have been monitoring the types of tests being explored in other cancers to assess who will develop, recover and relapse from cancers. One test, called FreeLite, assesses levels of fragments of antibodies in the blood. A recent study suggests that monitoring levels of antibody fragments may be useful in predicting the onset of AIDS-related lymphoma.

### **About antibodies**

Under the microscope, antibodies look a bit like the letter Y. They are made up of two basic parts, the bottom part of the Y is called the heavy chain and the two upper parts of the Y are called light chains.

To make antibodies, B-cells make both heavy and light chains and put them together. Sometimes B-cells make too many light chains and the excess is released into the blood. When light chains are unattached to heavy chains and are released into the blood, researchers refer to these light chains as free light chains. Cancer studies are underway in HIV negative people to assess changes in levels of free light chains and the development of cancer.

### **Study details**

Researchers at the NIH reviewed health information from three groups of people as follows:

- DCG (DC Gay Cohort) – this had 135 gay and bisexual men
- MCHC (Multicentre Hemophilia Cohort) – this had 1,700 hemophiliacs, some of whom had HIV
- ACC (Asia Cohort Consortium) – this had 2,800 people with AIDS

In these three groups there were a total of 66 HIV positive people who had confirmed diagnoses of non-Hodgkin's lymphoma (NHL). About 60% of lymphoma cases occurred before 1997.

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Researchers matched each of the 66 people with up to four other people—of the same ethno-racial group, age and CD4+ count—from the three cohorts that did not have NHL.

The study team obtained stored blood samples from the three groups and performed various laboratory tests, including assessing levels of free light chains.

## Results

Researchers found that between two and five years before the development of lymphoma, the 66 lymphoma patients had higher-than-normal levels of free light chains. Their levels of free light chains were higher than in HIV negative people and HIV positive people without lymphoma.

The NIH team concluded that assessments of free light chains were sensitive and could detect dysfunction in B-cells before lymphoma developed. They speculated that perhaps free light chain assessment could be used to monitor recovery and relapse in HIV-related lymphoma.

The findings from the NIH study are encouraging but a prospective study to explore assessments of free light chains in the present era is needed to confirm and explore this idea for HIV-related lymphoma and perhaps other cancers.

## REFERENCES:

1. Kosub DA, Durudas A, Lehrman G, et al. Gamma/Delta T cell mRNA levels decrease at mucosal sites and increase at lymphoid sites following an oral SIV infection of macaques. *Current HIV Research*. 2008 Nov;6(6):520-30.
2. Van der Vliet HJ, van Vonderen MG, Molling JW, et al. Cutting edge: Rapid recovery of NKT cells upon institution of highly active antiretroviral therapy for HIV-1 infection. *Journal of Immunology*. 2006 Nov 1;177(9):5775-8.
3. Bosch RJ, Wang R, Vaida F, et al. Changes in the slope of the CD4 cell count increase after initiation of potent antiretroviral treatment. *Journal of Acquired Immune Deficiency Syndromes*. 2006 Dec 1;43(4):433-5.
4. Engels EA. Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities. *AIDS*. 2009 May 15;23(8):875-85.
5. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. *Leukemia*. 2009 Feb;23(2):215-24.
6. Pratt G, Harding S, Holder R, et al. Abnormal serum free light chain ratios are associated with poor survival and may reflect biological subgroups in patients with chronic lymphocytic leukaemia. *British Journal of Haematology*. 2009 Jan;144(2):217-22.

7. Landgren O, Goedert J, Rabkin C, et al. Risk of AIDS non-Hodgkin's lymphoma is strongly predicted by elevated levels of circulating immunoglobulin-free light chains. In: *Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections*, February 8–11, 2009, Montreal, Canada. Abstract 29.
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### Disclaimer

Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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.

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### Credits

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### 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.

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