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I ANTI-HIV AGENTS

A. Expanded access to tenofovir

Tenofovir, also known as Viread, is a type of anti-HIV drug called a nucleotide reverse transcriptase inhibitor. Tenofovir is not a major breakthrough — it is not as potent as, say, the protease inhibitor indinavir (Crixivan). However, advantages with tenofovir include once-daily dosing and it may be useful against HIV that is resistant to 3TC (Epivir, lamivudine). Tenofovir will likely be approved for use only in people who have previously used anti-HIV medications.

Until then, the manufacturer, Gilead Sciences, is making tenofovir available at no cost for physicians to give to some people with HIV/AIDS (PHAs) in the following countries:

- Canada
- United States
- France
- Germany
- Italy
- Spain
- United Kingdom

Gilead will consider requests for tenofovir from physicians in Canada for their patients with the following profile:

- 18 years or older
- viral load – at least 10,000 copies (Amplicor), or about 5,000 copies of bDNA (Chiron)
- CD4+ count – 100 or fewer cells OR between 101 and 200 cells if any opportunistic infections have occurred in the past 90 days
- failure of at least two protease inhibitors (PI) or a PI and a non-nuke

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For more information about the tenofovir expanded access program or to register patients in Canada and the United States, physicians can phone: 1.877.226.8802. Physicians in Europe can call this number: 33.1.44.90.34.46

A CATIE Fact Sheet about tenofovir is in development and will be available shortly on the CATIE website at www.catie.ca.

B. New formulation of ddI approved in Canada — Videx EC

On October 4, 2001, Health Canada approved a new capsule formulation of the anti-HIV drug ddI (didanosine, Videx). The new formulation is called Videx EC and consists of a capsule filled with tiny beads of ddI. These beads are covered with a coating designed to protect them from the damaging effects of stomach acid. Videx EC is available in white capsules containing the following doses of ddI:

- 400 mg
- 250 mg
- 200 mg
- 125 mg

This nucleoside analogue is approved for use by HIV positive adults in combination with other anti-HIV drugs. The recommended dose of Videx EC is 400 mg once daily for people who weigh more than 60 kg (roughly 132 pounds), and 250 mg for those who weigh less than 60 kg. The drug should be taken on an empty stomach, 30 minutes before a meal or two hours after a meal.

Previous formulations of ddI were taken together with an antacid (buffer) to protect the drug from stomach acid. Indeed, 95% of a ddI tablet consists of buffer. Because of the large amount of buffer, users of ddI tablets often experienced symptoms such as nausea, bloating, diarrhea and gas when they took the tablets. In a recent study comparing ddI tablets to Videx EC, subjects who switched to the capsules had significantly fewer of these side effects.

Another advantage to Videx EC is that, because it has no buffer, it does not interact with drugs such as indinavir (Crixivan), Cipro and with the "azole" group of antifungal drugs — fluconazole (Diflucan, Triflucan), ketoconazole (Nizoral) or itraconazole (Sporanox).

Earlier concerns that Videx EC may not be as effective as the tablet formulation have proven unfounded and regulatory authorities in the European Union and the United States have also approved Videx EC for once-daily use.

Videx EC should be available for sale in Canada by mid-January 2002. In the meantime, there will be no expanded access to this drug.

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II ANTI-CANCER AGENTS

A. AIDS and lymphoma

Like HIV, certain other viruses — such as HPV (human papilloma virus) and HHV-8 (human herpes virus-8) — are also sexually transmitted. Therefore, it should come as no surprise that some HIV positive people who also test positive for these other viruses can develop certain cancers caused by HPV (cervical and anal cancer) and HHV-8 (Kaposi's sarcoma).

The cause of another AIDS-related cancer, non-Hodgkin's lymphoma, is more puzzling. In people whose immune systems have been attacked by HIV, the risk of developing lymphoma is about 100 times greater than that of HIV negative people. It is not clear why HIV positive people have an increased risk for lymphoma but not any number of other strange cancers. One theory is that certain immune cells called B-cells are overstimulated by HIV and a common virus called EBV (Epstein-Barr virus). Eventually some of the overstimulated B-cells in lymph nodes and tissues turn into tumours.

Know your lymphoma

Although there are several types of lymphoma, in PHAs lymphoma can be placed into two groups:

- systemic lymphoma – this type of lymphoma has spread to several places in the body, usually the lymph nodes, bone marrow, intestines and liver
 - primary central nervous system lymphoma – this type of lymphoma occurs in the brain/spinal cord
-

There isn't any specific sign or symptom that indicates a person has lymphoma. Symptoms can vary depending on the location and number of the tumour(s). In some people, there may be as few symptoms as fatigue and swollen lymph nodes. In others there may be headache or seizures, fever, night sweats and unintentional weight loss. To help diagnose lymphoma, magnetic (NMR) and X-ray (CAT) scans can be useful, as are analyses of spinal fluid and tumour samples.

Lymphoma then and now

In the time before protease inhibitors (PIs), prospects for survival after a diagnosis of lymphoma in PHAs were not encouraging. On average, PHAs survived about six months after a diagnosis of this cancer. The use of combination anti-HIV therapy that includes a PI or non-nuke appears to have greatly increased the chance of survival for PHAs who have lymphoma. This is because PIs increase CD4+ counts and decrease the risk of developing AIDS-related infections. Such an effect is important because before HAART was available PHAs with lymphoma often died from infections brought about because of chemotherapy's impact on their bone marrow and immune system.

However, despite the decreased risk of AIDS-related infections in users of highly active antiretroviral therapy (HAART), most studies have not found a significant decrease in the risk of developing lymphoma among HAART-users. A recently published study from France may be an exception and we report their findings next.

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B. Encouraging news on lymphoma from France

Study details

French researchers analysed data from medical records contained in a database on over 80,000 HIV positive subjects collected since 1989 from 69 hospitals. They also reviewed medical records on AIDS-related lymphoma from three major AIDS treatment centres in Paris — Hôpital Rothschild, CHU Pitié Salpêtrière and Hôpital de l'Institut Pasteur.

Results from the database

The researchers compared data from a period before HAART was available (1993-1994) against that from a period when HAART was in use (1997-1998). On the whole they found that the proportion of PHAs developing systemic lymphoma fell by 50% in the more recent era. When the researchers looked specifically at the data on brain lymphoma, they found that this condition was three times less common in the more recent era.

Looking at the CD4+ cell counts

Despite these apparently favourable changes the researchers also found that the risk of developing both types of lymphoma among people with similar CD4+ counts had **not** changed in the more recent period. For instance, in the pre-HAART years, people who had 350 or more CD4+ cells had almost the same risk of developing lymphoma as people with similar cell counts in the more recent time. There was a similar trend for other CD4+ count ranges (for example, between 100 and 200 cells). Not surprisingly, in both periods, the proportion of PHAs with lymphoma increased as the CD4+ cell count fell.

Results from subjects in the three Parisian hospitals were similar to those seen from the large database. The researchers found that the proportion of PHAs with lymphoma in the brain in the more recent period decreased compared to the earlier time.

The changing profile of lymphoma

In general, the research team found that subjects in the more recent time tended to have higher CD4+ counts than subjects in the time before HAART. Since lymphoma is most common in people with very low CD4+ counts — fewer than 50 cells — and most people in the recent era had higher CD4+ cell counts, the proportion of people with lymphoma was decreased compared to the pre-HAART era. Indeed, lymphoma rates among people with fewer than 200 CD4+ cells fell from about 50% in the pre-HAART era to 24% in the years HAART was available.

Other evidence for the immunologic impact of HAART is the change in length of survival after a diagnosis of lymphoma. In the time before HAART, survival after lymphoma diagnosis averaged about six months. Since HAART became available, the average survival has increased nearly three times to about 20 months. Because the treatment of lymphoma has not greatly changed in the past decade this increase in survival is likely due to the effects of HAART. So as long as PHAs can continue to maintain high CD4+ counts, lymphoma rates should continue to fall. However, PHAs' risk of developing this cancer will not go away because HAART is only able to partially repair the damage wrought by years of HIV infection. More research on better, less toxic anti-cancer therapies, immune boosters and tests to predict which PHAs are at high risk of developing lymphoma are urgently needed.

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C. Chemo and HAART extend survival with lymphoma

Many studies suggest that the use of HAART can reduce the risk of developing AIDS-related infections. In those PHAs who develop the AIDS-related cancer called non-Hodgkin's lymphoma, the use of HAART combined with chemotherapy appears to prolong survival compared to the time when HAART was not available.

Although this news is promising, much work remains to be done in the field of AIDS-related cancer treatment. For instance, protease inhibitors are notorious for raising or lowering levels of other drugs in the blood. Little research has been done on how this class of drugs affects commonly used chemotherapy (or how chemo affects protease inhibitor levels). To begin to address some of these issues, research teams across the United States conducted a study on which we now report.

Study details

Researchers enrolled 63 HIV positive adults whose profile at the start of the study was as follows:

- 8% female, 92% male
- average age – 41 years

- all had newly diagnosed systemic lymphoma
- none had brain lymphoma
- none had previously received treatment for lymphoma
- average CD4+ cell count – 138 cells
- average viral load – 29,000 copies

Chemotherapy was given in 21-day cycles, that is, subjects received intravenous chemotherapy on the first day of every cycle and then a “rest” for the remaining 20 days, after which another cycle began. The length of the cycles varied depending on the response to treatment.

Low dose

The first 41 subjects received reduced or modified doses of intravenous chemotherapy called mCHOP as follows:

- cyclophosphamide (Cytosan, Procytox) – 375 mg per square metre of skin
- doxorubicin (Adriamycin) – 25 mg/m²
- vincristine (Navelbine, Oncovin) – 1.4 mg/m²

For the first five days of each cycle, subjects also received tablets of the anti-inflammatory drug prednisone 100 mg/day. To protect their bone marrow from the toxicity of chemotherapy, subjects received the bone marrow stimulant G-CSF (Filgrastim) on days 4 through 13 of each cycle.

High dose

The remaining 26 subjects received a standard CHOP regimen:

- cyclophosphamide (Cytosan, Procytox) – 750 mg/m²
- doxorubicin (Adriamycin) – 50 mg/m²
- vincristine (Navelbine, Oncovin) – 1.4 mg/m²

They also received prednisone and G-CSF in the dose and schedule as previously stated.

Subjects with tumours that spread to the brain/spinal cord also received cytarabine (Cytosar) 50 mg/week infused into their spinal cord during the first four weeks of the study to attack those tumours. All subjects received standard doses of the anti-HIV drugs indinavir (Crixivan), 3TC (EpiVir, lamivudine) and d4T (Zerit).

Results — Grading the response to chemo

Responses to chemotherapy can vary. Some people have a complete response and, for a time, all traces of the tumour disappear. We say “for a time” because cancer can recur. Others have what's called a “partial response” where some tumours

disappear while others remain. In some people the tumours don't shrink but they don't grow — this is called “stable disease.” In still other cases, the tumours continue to grow despite the use of chemotherapy. Cancer doctors call this “progression.” In some cases doctors are unable to assess the impact of chemotherapy because subjects develop other life-threatening complications and have to stop taking chemo; they may also leave the study or die.

High-dose vs. low-dose chemo

Responses to chemotherapy over the short-term by subjects receiving low-dose chemo (mCHOP) were as follows:

- complete response – 30%
- partial response – 30%
- progression – 25%
- unassessable – 15%
- stable disease – 0%

Responses to high-dose chemo (CHOP) over the short-term were as follows:

- complete response – 48%
- progression – 30%
- partial response – 9%
- unassessable – 9%
- stable disease – 4%

It is important to note that about 63% of subjects who received the low-dose chemo had lymphoma with widespread tumours as compared to 35% in the high-dose group. This difference in the distribution of people with severe lymphoma likely affected the response to therapy since the fewer the tumours, the better the response. Given this distribution, it is perhaps not surprising that cancer recurred in the following proportion of subjects who developed a complete response in the short term:

- mCHOP (low dose) – 33%
- CHOP (high dose) – 9%

On average, subjects who received mCHOP and had a complete response to chemo remained free from lymphoma for about nine months. The equivalent figure for subjects in the high-dose group has not been reached yet, but so far 80% of complete responders remain free from lymphoma one year after recovery.

Factors associated with recovery

The researchers examined possible reasons why some subjects developed a complete response. They looked at many factors including CD4+ count,

viral load, severity of lymphoma and age, among others. They found that the only significant factor enabling a complete response was the use of high-dose chemo.

Side effects

The following side effects were severe and occurred in the following proportion of subjects receiving low-dose chemo (mCHOP):

- higher-than-normal levels of liver enzymes – 48%
- very low levels of neutrophils (a type of white blood cell) – 25%
- constipation or abdominal pain – 18%
- higher-than-normal levels of the waste product bilirubin – 12%
- higher-than-normal levels of blood sugar – 10%
- nausea or vomiting – 3%

The following side effects were severe and occurred in the following proportion of subjects receiving high-dose chemo (CHOP):

- higher-than-normal levels of liver enzymes – 52%
- higher-than-normal levels of bilirubin – 17%
- constipation or abdominal pain – 17%
- very low levels of neutrophils – 13%
- nausea or vomiting – 9%
- higher-than-normal levels of blood sugar – 0%

Drug interactions

The results of measurement of drug levels in the blood suggested that levels of the following drugs were higher than normal during the study:

- cyclophosphamide
- doxorubicin

Despite this, increased bone marrow damage was uncommon, likely because subjects used G-CSF. Indinavir levels were not significantly affected by chemotherapy. Subjects in both high- and low-dose chemotherapy groups had increased levels of CD4+ cells during the study, probably because they were using HAART. Viral load also decreased in both groups for the same reason.

What is unusual about this study is that only one subject developed a life-threatening complication (caused by a fungus). In contrast, many previous studies of chemotherapy for AIDS-related lymphoma reported the occurrence of a variety of opportunistic infections.

This difference is probably because of the effect of HAART. All in all, results from this study point to a major change in the response to chemotherapy among HAART users who have lymphoma.

Doctors conducting future studies of HAART and chemotherapy may find it useful to monitor the level of anti-cancer drugs in the blood of subjects. This is because higher-than-normal levels of anti-cancer drugs can cause liver and bone marrow damage. Bone marrow damage was minimized in this study by the use of G-CSF.

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D. Can low-dose shark cartilage make Kaposi's sarcoma disappear?

Kaposi's sarcoma (KS) is a tumour that usually appears on the skin and most commonly affects HIV positive men who have sex with other men. Not surprisingly, therefore, KS is caused by a sexually transmitted virus — HHV-8 (human herpes virus-8). Although there is no cure for KS, sometimes the use of highly active antiretroviral therapy (HAART), with or without chemotherapy, can help shrink and control KS lesions.

Doctors at the University Hospitals of Cleveland, Ohio, reported details about their unusual and successful treatment of a KS lesion. According to their report, a 45-year-old man who developed a KS lesion on his foot sought medical care. Repeated blood tests revealed that he was HIV negative but was infected with HHV-8, the cause of KS. His CD4+, CD8+ and other blood counts were within the normal range. Laboratory analysis confirmed that his tumour was indeed KS. Doctors then prescribed oral ganciclovir, 1 gram three times daily for three months (because of its possible anti-HHV-8 activity), but this had no effect on his lesion.

After this failure, other options were considered, including the following:

- injecting the lesion with chemotherapy
- interferon
- cidofovir (Vistide)

- foscarnet (Foscavir)
- Panretin (alitretinoin)
- radiation therapy

None of these options were selected because the lesion was growing very slowly and the side effects of therapy were not “acceptable to the patient.” Instead the patient and his doctors chose an unconventional approach — low-dose oral shark cartilage.

Shark cartilage in the lab

In lab experiments with tumours and mice with cancer, shark cartilage and its extracts appear to block the growth of blood vessels that feed a tumour. KS tumours are often associated with a rich network of blood vessels, so perhaps its not surprising that the research team chose to study shark cartilage: therapies that have the potential to reduce blood vessel growth could help “starve” the KS tumour.

Researchers monitored the man as he took shark cartilage at a dose of 1,875 mg twice daily for the first three months. The dose was then changed to 1,500 mg three times daily for another 18 months.

After three months, the lesion began to shrink and its colour faded. By the sixth month it became thinner and it became almost impossible to notice. No side effects were reported during this time. The man continues to take shark cartilage (Dr. Scot Remick, personal communication).

Notes about the dose

Although shark cartilage has been tested in people with cancer, those subjects had received chemotherapy and also had “advanced” cancers of the breast, colon and lungs. Moreover, shark cartilage was given at a higher dose for only three months. In experiments where chemo is used to attack the blood vessel networks that nourish a tumour, the best results were obtained when researchers used low-dose chemo for longer periods of time.

It is possible that the KS tumour in this patient could have simply disappeared on its own — spontaneous regression. Until a controlled clinical trial takes place, we cannot be certain about the effectiveness of shark cartilage. Future research needs to examine issues relevant to PHAs, such as drug interactions and the additional effect of chemotherapy. Shark cartilage used in this man's treatment was distributed by Swanson Health Products and General Nutrition Center and cost between \$1.08 and \$1.32 US per day.

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E. Cidofovir for KS lesions

Treating the AIDS-related cancer Kaposi's sarcoma (KS) became easier with the introduction of HAART. Indeed, sometimes KS lesions would simply fade in HAART users without the need to resort to chemotherapy. As HIV develops resistance to HAART, the immune system again becomes weak, allowing previously controlled problems to flare up. Doctors in Verona and Rome, Italy, recently reported details about two HIV positive men who developed new KS lesions despite long-term use of HAART.

In both cases the men had been taking two nucleoside analogues and the protease inhibitor saquinavir. (We don't know if they were using the older version of the drug, Invirase, or the new, more potent formulation, Fortovase.) When the KS lesions appeared, both men had CD4+ counts greater than 300 and viral load levels below 100 copies. Doctors gave them chemotherapy — vincristine, vinblastine and interferon-alpha — but this had no effect on the KS.

The doctors then prescribed the antiviral drug cidofovir (Vistide) 5mg/kg of body weight, given intravenously once weekly for the first two weeks and later once every two weeks. One of the men received the drug for 10 months and the other for 12 months. After three months of cidofovir, in both men the KS lesions began to fade and eventually disappeared. When the men stopped using cidofovir they remained free from KS for a further six months and 15 months respectively.

The reason cidofovir worked is that it has antiviral activity against many viruses, including the virus that can cause KS — human herpes virus-8 (HHV-8). Normally the immune system keeps this virus

under control but HHV-8 levels rise as immunity weakens in people infected with this virus. For most of the time that the men received cidofovir, HHV-8 activity was suppressed. Unfortunately the drug is unable to cure this viral infection, so the lesions eventually returned. Perhaps if their anti-HIV regimen were changed, HHV-8 would again be brought under control. No side effects caused by cidofovir were reported.

In Canada, cidofovir is available to doctors who request the drug via Health Canada's Special Access program. In the U.S., the manufacturer, Gilead Sciences, supplies cidofovir. In many other countries cidofovir is distributed by the pharmaceutical company Pharmacia.

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F. Looking at soluble CD23 levels to predict lymphoma

Summary

As we noted in our first article on lymphoma, there isn't any quick and simple test to diagnose or predict which PHAs will develop this cancer. Nor are there any symptoms that specifically occur from having lymphoma. To try to remedy the situation, researchers in Italy have been monitoring levels of the a protein called soluble CD23 (sCD23) in the blood and fluid surrounding the brain — cerebrospinal fluid (CSF). They have found higher-than-normal levels of sCD23 in the CSF of PHAs who have brain lymphoma.

Study details

Researchers enrolled 36 HIV positive subjects who were diagnosed with non-Hodgkin's lymphoma. Samples of blood and CSF were collected for analysis. For comparison, similar fluids were collected from other PHAs who either had the brain infection toxo (toxoplasmosis), PML (progressive multifocal leukoencephalopathy) or dementia. Samples were also collected from symptom-free HIV positive people as well as from healthy HIV negative people. Measurement of sCD23 was done using a test kit supplied by Pharmingen.

Results — sCD23 in spinal fluid

The researchers found that those subjects who had high levels of sCD23 in their CSF were likely to have either brain lymphoma or lymphoma of the brain and elsewhere in their body. Moreover, levels of sCD23 in these subjects' spinal fluid were significantly higher than in samples from subjects with toxo or other brain problems. On average, sCD23 levels in the CSF were as follows:

- lymphoma in the brain and body – 47 ng/ml
- brain lymphoma – 20 ng/ml
- lymphoma in the body – 4 ng/ml
- toxo – 2 ng/ml
- PML – 1 ng/ml
- dementia – 0 ng/ml
- HIV negative – 0 ng/ml

Results — sCD23 levels in the blood

When technicians measured levels of sCD23 in the blood the results were somewhat different from those seen with the CSF measurements. The subjects with the highest sCD23 levels in the blood had lymphoma outside the brain. Average levels of sCD23 were as follows:

- lymphoma outside the brain – 38 ng/ml
- symptom-free HIV infection – 22 ng/ml
- HIV negative subjects – 22 ng/ml
- lymphoma in the brain – 13 ng/ml
- dementia – 11 ng/ml
- toxo – 10 ng/ml
- lymphoma in the brain and rest of the body – 8 ng/ml

The results from this study suggest that measuring levels of sCD23 in the CSF may be useful in helping to diagnose lymphoma of the brain. Measuring levels of this protein in the blood may not be as useful for confirming the presence of systemic lymphoma.

Why CD23?

Most of the lymphomas seen in HIV positive people were once B-cells. Because of HIV's constant stimulation of B-cells, along with weakened immunity, some B-cells in PHAs morph into tumours.

The protein CD23 is found on B-cells as well as on other immune cells such as macrophages. It is possible that overstimulated B-cells, particularly those that are pre-cancerous, produce the high levels of sCD23 that are seen in some PHAs who have lymphoma. Macrophages that are within the brain may also produce this protein when they are activated by the presence of tumours. These two

factors may account for the high levels of sCD23 in the CSF of PHAs with lymphoma.

Historically, the only other people who have high levels of sCD23 are those with a certain form of leukemia as well as those with allergies and asthma — other cases where B-cells may be overstimulated. Hopefully further research on sCD23 and lymphoma will be conducted in long-term studies. Results from such studies may help predict which PHAs are at risk of brain and other lymphomas.

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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.

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Describes several complementary therapies in accessible language and the role they may play in treating various AIDS-related complications and drug-related side effects.

Fact Sheets and Supplement Sheets

Cover conditions, symptoms, side effects, complementary therapies, vitamins, herbs, and other treatment issues.

HIV Treatment, Get the Facts, In-depth or Plain and Simple

Summarize the basics of HIV treatment in English and French and include a glossary.

HIV Viral Load Testing

Presents information about the viral load blood test in a straightforward question-and-answer format.

Managing Your Health, a Guide for People Living With HIV or AIDS, 1999 edition

Addresses social, legal, health-related and practical issues comprehensively and from a national perspective.

CATIE is a national, non-profit organization committed to providing free, current and confidential treatment information for all Canadians living with or affected by HIV/AIDS.

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