TreatmentUpdate 167

Vol. 20, No. 3
April/May 2008
ISSN 11817187

Available on the World Wide Web at
http://www.catie.ca/tu.nsf

Contents

I NUTRITION

A. Chromium deficiency in HIV

The nutrient chromium can be found in the following foods:

- liver
- whole grains
- beans
- broccoli
- mushrooms
- spices such as cinnamon

Chromium is absorbed from the intestines and stored in the following locations:

- bone
- liver
- spleen
- muscle
- fatty tissue

Chromium can be stored in fat and muscle for about two weeks. The liver and spleen can store this nutrient for up to a year. The body appears to release most of its store of chromium in the urine.

According to the results of animal experiments, chromium appears to enhance the activity of the hormone insulin. This hormone is used to regulate blood sugar. When blood sugar levels are high, insulin, which is made by the pancreas gland, helps cells absorb sugar from the blood.

But other parts of the body also help to play a role in the regulation of blood sugar. For instance, the liver can help lower blood sugar by converting sugar into fat. Some of this fat can be stored in the liver, and some can be released into the blood in the form of triglycerides. So, while

produced by

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insulin is directly important for controlling sugar levels, it can indirectly affect fat levels.

Several research teams have noted that HIV positive people can develop changes in the effects of insulin and sugar levels. These studies suggest that there is a tendency for the following in HIV positive people:

- higher-than-normal levels of blood sugar
- higher-than-normal levels of insulin in the blood

In some HIV positive people, the effect of insulin seems to weaken over time—this is called insulin resistance. The pancreas gland makes insulin, and high blood sugar triggers an increased output of insulin as the body tries to regulate blood sugar. Eventually the gland becomes exhausted, leading to type 2 diabetes.

HIV and diabetes

Researchers at Toronto General Hospital have noted that there are similarities between the following three groups of people:

- HIV negative people with type 2 diabetes
- HIV negative people with chromium deficiency
- HIV positive people with altered sugar and fat metabolism

In experiments with these three groups of people, several research teams have found that supplementation with small amounts of chromium improved insulin sensitivity and other assessments of metabolism. So the Toronto researchers undertook to study chromium levels in HIV positive people to find out if there were any deficiencies and possible connection to blood sugar abnormalities.

Study details

The Toronto team recruited 104 participants from the following categories for this pilot study:

- 75 HIV positive people taking highly active antiretroviral therapy (HAART)
- 16 HIV positive people not taking HAART
- 13 HIV negative people (used for comparison)

Participants were mostly male and around 40 years old. Blood and urine samples were collected, as well as hair and nail clippings for chromium content.

Dieticians interviewed participants about their food intake to find out food sources of chromium.

The researchers assessed participants' body composition—proportion of muscle, fat, water and bone—by using BIA (bioelectrical impedance analysis).

Results

The study team found that HIV positive and HIV negative participants were receiving a similar amount of chromium from their food. However, levels of chromium in hair, nails and blood were lower in HIV positive people than in those without HIV.

The amount of chromium released into the urine was similar in HIV positive and HIV negative groups.

HIV positive participants who took HAART released significantly higher levels of chromium into their urine than HIV positive people not on HAART. Also, researchers found that the greater the amount of chromium detected in urine samples, the more likely the person had the HIV lipodystrophy syndrome.

What's next?

An important point about this study is its design. It was a cross-sectional study. These studies are like a snapshot of data at a particular time. They can only find associations, not prove cause and effect. Cross-sectional studies are useful for finding associations that might later be explored in studies with a different design.

These findings from the Toronto team suggest that there may be disturbances in chromium metabolism in some HIV positive people, particularly those on HAART. It also suggests the possibility that chromium may have a role to play in body shape changes seen in HIV/AIDS.

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B. Can chromium supplements help body shape?

A research team at Toronto General Hospital found a statistical link between low chromium levels in the blood and HIV infection, particularly in HAART users. The Toronto team also noted that some of the symptoms of chromium deficiency are similar to the metabolic problems—higher-than-normal levels of blood sugar and insulin and the weakened effects of insulin—in some HIV positive people. So the team later conducted a double-blind study with a modest dose of chromium vs. placebo in people with HIV infection. Their findings suggest that chromium supplementation may confer some benefit(s) in people with HIV/AIDS (PHAs) in the short-term.

Study details

Researchers recruited 59 HIV positive volunteers (4 females and 55 males) who had at least one of the following abnormalities:

- high blood sugar – greater than 6 nmol/l
- moderately elevated triglycerides – 2 mmol/l or greater
- elevated total cholesterol – 5.5 mmol/l or greater
- low levels of so-called good cholesterol (HDL-c) – less than 0.9 mmol/l
- abnormal body fat redistribution

Additionally, researchers assessed the volunteers' potential for having insulin resistance—a condition in which the body does not respond as effectively as it should to the effect of insulin. Out of the 59 volunteers, 50 who had insulin resistance were enrolled into the study and randomly assigned to one of the following arms, or groups:

- chromium, formulated as chromium nicotinate, 400 micrograms (mcg) per day
- fake chromium (placebo)

The trial lasted for four months and 25 participants in each group completed the study.

Participants who received placebo tended to be slightly older (average 50 years) compared to chromium recipients (47 years).

Results

During the study there were significant changes in the following assessments in participants who received chromium:

- decreased insulin levels in the blood
- decreased insulin resistance
- decreased triglycerides
- decreased body fat
- increased muscle mass

These differences between chromium and placebo groups were statistically significant; that is, not likely due to chance alone.

Other changes that occurred in the placebo group were also statistically significant:

- increased levels of so-called bad cholesterol (LDL-c)
- increased trunk fat

An increase in belly fat occurs in some HAART users. Among participants who had this problem before entering the study and who received chromium while in the study, belly fat decreased by 600 grams (or more than one pound). In people on placebo, belly fat increased by 1,500 grams (about 3.3 pounds) during the study. This difference in belly fat changes between the two groups was statistically significant.

This controlled study strongly suggests that modest doses of chromium supplementation (400 mcg/day) can help HIV positive people who have certain metabolic abnormalities over the short-term.

Another pilot study, conducted in the United States, found that a daily dose of 1,000 mcg of chromium (in the form of chromium picolinate) in eight HIV positive participants was able to significantly improve the body's sensitivity to insulin after two months. Two of the eight people developed abnormal liver enzyme levels and another developed excess levels of urea in the blood. The reasons for these changes are not clear.

Still, the results from the Canadian study using chromium nicotinate are promising but further research needs to do the following:

- confirm the Canadian study's results, hopefully with larger numbers of HIV positive volunteers, including women
- demonstrate that the benefits of chromium supplementation can last more than four months
- assess the safety and effectiveness of higher doses of chromium and possibly other formulations of chromium
- explore the impact of other nutrients, such as vanadium, that might also have a favourable impact on blood sugar and insulin levels.

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II HORMONES

A. Ovaries—hormone troubles in some HIV positive women

In high-income countries, the widespread availability of HAART has led to a dramatic decline in deaths due to AIDS-related infections. Researchers estimate that some PHAs in these countries who can adhere to and tolerate HAART may live out their natural life span.

Before HAART arrived, AIDS was seen as a fatal disease. And even though HAART most often prolongs survival in HIV positive people, it is hard to break the association between AIDS and death. Yet, as new and improved anti-HIV drugs become available and AIDS-related infections are no longer common, it is likely that PHAs and their doctors will make changes to how they view a diagnosis of HIV infection, at least in high-income countries. This may mean that plans and dreams that were postponed or shelved can now be realized by PHAs.

One such dream may include, for some HIV positive women, getting pregnant and having a baby. In order to conceive a child of their own, HIV positive women need to have healthy ovaries. A team of researchers from Strasbourg, France, has been studying hormones and ovaries in HIV positive women and their findings are troubling.

Study details

Researchers reported findings from 72 HIV positive women who had the following average profile:

- age – 35 years
- history of pregnancy – 85%
- duration of HIV infection – 6 years
- proportion of women who had symptoms of AIDS in the past – 14%
- proportion of women using HAART – 63%
- proportion of women using HAART whose viral load was below the 50-copy mark – 62%
- CD4+ cell count – 437 cells

None of the women were pregnant at the time they were in the study, and none of them were taking hormone-replacement therapy or had been diagnosed with hormonal disorders.

Technicians took blood samples from participants between the second and fourth day of their menstrual cycle. The samples were analysed for many hormones and substances associated with fertility and ovarian health.

Also, during the study a gynecologist performed ultrasound scans of the ovaries.

Results

The team found that the following hormones were within their expected ranges:

- testosterone
- TSH (thyroid-stimulating hormone)
- estrogen
- prolactin

However, when researchers focused on lab tests or ultrasound measurements that dealt with ovarian

health, they found that 85% of participants had abnormal results, as follows:

- FSH (follicle-stimulating hormone)
- inhibin B
- AMH (anti-müllerian hormone)
- AFC (antral follicular count)

The study team found the following trends:

- In general, the older the woman was, the greater the chance that she had malfunctioning ovaries. This trend seemed to be accelerated in the women in this study.
- HAART users did not have abnormal inhibin B and AMH.
- CD4+ counts and viral load did not have any relationship to ovarian health.

Based on their results, the French researchers found a high rate of ovarian dysfunction among women. Altered levels of hormones and other changes were severe and occurred relatively early—the average age of women in this study was 35 years. These changes, if sustained, could ultimately lead to premature menopause.

The French doctors noted that HIV positive women who wish to have children should probably do so earlier in their life rather than later because of these findings.

The French study will hopefully prompt other researchers to conduct similar analyses of the ovarian health of HIV positive women.

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III CO-INFECTIONS

A. Hepatitis C virus—some background information

Hepatitis C virus (HCV) is spread by exposure to infected blood. The following behaviours, which can expose a person to infected blood, can help spread HCV:

- sharing unsterilized needles or other equipment used for injecting drugs
- sharing unsterilized tattooing needles
- sharing straws for snorting drugs
- sharing razors, toothbrushes and nail clippers

In general, HCV does not appear to be commonly transmitted between HIV negative men and women during sex. However, some HIV positive men are at high risk for acquiring HCV infection—specifically those who engage in the behaviours listed above and below:

- unprotected anal sex
- sharing unsterilized sex toys
- fisting and other traumatic practices
- having an enema

The risk of HCV transmission from an HIV negative mother to child is about 5%. However, in mothers who are co-infected with HCV and HIV, the risk is increased, perhaps doubled.

Estimating infection

In Canada, researchers estimate that about 1% of people are HCV positive. Another estimate is that about 20% of HIV positive people are co-infected with both viruses.

Exposure and infection

The majority of people exposed to HCV will not be able to clear the infection. Estimates by researchers suggest that between 60% and 85% of HIV negative people exposed to HCV will develop long-term (chronic) infection with this virus. For HIV positive people, researchers estimate that 90% exposed to HCV will develop chronic co-infection.

Symptoms

After HCV invades the body, it targets the liver. And it can take an average of seven weeks of infection before symptoms appear. Symptoms of HCV infection can include some of the following:

- loss of appetite
- nausea
- vomiting
- altered sense of taste and smell
- unexpected tiredness
- headache
- lack of energy
- muscle pain

- bone and joint pain
- heightened sensitivity to light

Other changes

The liver can become swollen and tender as a result of HCV infection and so can the spleen. In some cases, jaundice occurs as levels of the waste product bilirubin build up in the body, turning the skin and whites of the eyes yellow. However, for some people, HCV infection may not be associated with any symptoms.

Lab tests

Levels of liver enzymes—AST and ALT—usually rise during initial HCV infection. HCV viral load also becomes detectable.

Different types of HCV

There are at least six major varieties of HCV; these are called genotypes (for example, genotypes 1, 2, 3, 4, 5 and 6). These can be further divided into subtypes such as 1a, 2b and so on. Genotypes 2 and 3 respond well to therapy, but genotypes 1 and 4 generally do not respond as well. There is not enough experience with genotypes 5 and 6 to be certain about how they will respond to therapy. Genotype 3 is associated with an increased risk of liver damage (fibrosis) as well as fatty liver.

Early infection

Hepatitis C virus invades the liver but does not appear to directly cause any damage to that organ. However, the immune system detects HCV-infected liver cells and launches an attack, trying to get rid of the infection. As a result of this attack, the liver becomes inflamed and swollen. Sometimes, the immune system is able to rid the liver of HCV-infected cells and HCV. But in most cases this does not happen and the infection becomes chronic.

Long-term HCV infection—changes within the liver

During chronic infection, because the immune system tries to destroy HCV from spreading in the liver, HCV-infected cells and even uninfected liver cells are damaged and destroyed.

The liver attempts to repair and reduce the damage caused by ongoing inflammation and attacks by the immune system. But, unfortunately, the liver is unable to repair itself, as injured tissue is replaced by scar tissue containing collagen. This replacement is called fibrosis. Gradually fibrosis spreads to more liver tissue.

There are several ways to help grade or rank the degree of liver damage that occurs. Different scoring systems have different names and somewhat different ways of assessing liver damage. But, generally, what they have in common is this: the higher the score or grade, the worse the amount of liver damage that is present.

In severe cases of fibrosis, called cirrhosis, the blood supply within the liver is altered and liver cells have less access to fresh, oxygen-rich blood. In turn, this causes liver cells to become less efficient and to malfunction. As the blood supply within the liver changes and fewer liver cells receive fresh blood, blood pressure within the liver's blood vessels increases to try to compensate. Liver cells also release compounds that let the heart know that they are not receiving sufficient oxygen. So the heart pumps harder, trying to help oxygenated blood get to the liver.

Because the liver malfunctions, levels of estrogen in the blood increase.

As the body attempts to get more oxygenated blood to the liver, other organs may suffer. For instance, in chronic HCV infection, the kidneys receive less blood than they should. This causes them to malfunction, and water and salt build up in the body. Cirrhosis can result in the following symptoms:

- fluid build-up in the abdomen (ascites)
- swollen spleen
- white fingernails
- increased breast size in men
- loss of energy
- unintentional weight loss
- muscle wasting
- increased risk of type 2 diabetes

Cirrhosis and changes in lab tests

As a result of prolonged and worsening liver damage in cirrhosis, the following can occur:

- higher-than-normal levels of liver enzymes—AST, ALT, ALP, GGT
- increased bilirubin levels
- decreased levels of the protein albumin in the blood
- blood takes longer to clot
- less-than-normal levels of red blood cells, white blood cells and/or platelets (used to help blood clot)

Having cirrhosis also increases the risk of developing liver cancer.

Recovery

Reducing and, better yet, stopping alcohol intake can greatly help reduce the pace of liver damage in HCV infection. HCV positive people need to be seen by a specialist in HCV infection (either a liver specialist or an infectious disease specialist) so that the health of their liver can be assessed and the discussion about HCV treatment can begin. In high-income countries such as Canada, the standard treatment for HCV is a combination of a long-lasting form of interferon (called pegylated interferon) together with the antiviral drug ribavirin.

Assessing the liver

Keeping track of fibrosis is an important aspect of HCV care. Until recently, the chief way to assess liver fibrosis was to undergo a liver biopsy (a small sample of liver tissue is removed and examined under a microscope). But liver biopsies have drawbacks, so other, non-invasive ways of assessing liver health are under development. These other ways fall into two categories:

- scans or imaging, including ultrasound, CAT and MRI scans
- a combination of different blood tests

Blood tests (such as Fibrotest) can help to distinguish between little or no fibrosis and severe fibrosis. But note that they are not as precise in distinguishing between intermediate levels of fibrosis. And these tests may not be as useful in co-infected people because of pre-existing high levels of general inflammation due to HIV infection. Also the use of certain prescription medications by HIV positive people can affect these blood tests, potentially skewing fibrosis scoring systems that depend on this test. Here are some of those prescription medications:

- atazanavir (Reyataz) — this drug can increase levels of bilirubin in the blood
- non-nukes (NNRTIs) — these drugs can increase levels of the liver enzyme GGT
- protease inhibitors — these drugs often increase cholesterol levels

Therapy for HCV

The goal of therapy is to try to cure HCV infection. In some cases, as a result of successful HCV therapy, liver damage may be reversed. Psycho-social support is essential before, during and after HCV treatment. The best time to start HCV therapy will likely differ from one person to another depending on many factors, including the health of the liver, the person's overall health and the degree of immune system damage from HIV.

Who responds to therapy?

Therapy for HCV infection has many side effects and is expensive. So, finding out early if a person is on the road to recovery from this infection is essential. Patients who have an undetectable HCV viral load in their blood after four weeks of therapy have a high chance of recovery if they continue to take anti-HCV meds.

An international panel of HCV experts suggests that the following laboratory results indicate a very high chance of therapy failing:

- a decrease of less than 2 logs in HCV viral load after 12 weeks of therapy
- detectable HCV viral load after 24 weeks of therapy

The panel recommends that patients with these results should stop HCV therapy.

Ribavirin dosage

The antiviral drug ribavirin is a cornerstone of anti-HCV therapy. However, too high a dose of ribavirin can lead to anemia, while too low a dose reduces the chance of suppressing HCV. Several years ago, the most commonly used dose of ribavirin was about 800 mg/day. Based on results of clinical trials, an international panel of European and American experts recommends that people use the following doses of ribavirin, which are adjusted to a person's weight:

- people who weigh less than 75 kg – 1,000 mg/day
- people who weigh more than 75 kg – 1,200 mg/day

Early HCV infection

As is the case with many diseases, early treatment of HCV infection can increase the chances of recovery because serious liver damage has not set in. Generally, treatment for early HCV infection starts about 12 weeks after HCV infection has occurred. This is because there is a chance that spontaneous recovery from HCV, though uncommon, can occur without the use of medications within the first 12 weeks of infection.

Experts recommend 48 weeks of combination therapy for HCV (long-lasting interferon and ribavirin). Recovery rates are generally higher in people infected with genotypes 2 or 3 than in

those infected with genotypes 1 or 4. This is also the case in HIV co-infection.

HIV drug interactions

The following medications may intensify ribavirin-related side effects:

- AZT (zidovudine, Retrovir), also found in Combivir and Trizivir—its use should be avoided
- d4T (stavudine, Zerit) —its use should be avoided
- ddI (didanosine, Videx EC) —it should never be used with ribavirin

There are reports of a reduced response to HCV therapy in some people who have used the anti-HIV drug abacavir (Ziagen), also found in Kivexa and Trizivir. However, these reports have emerged from cohort studies. Such studies cannot entirely rule out bias when interpreting their results. So, at this time, definitive conclusions about the role of abacavir in co-infected people await the results from well-designed clinical trials.

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B. Liver damage occurs early in hepatitis C infection

Hepatitis C virus (HCV) appears to be an emerging co-infection among some HIV positive men who have sex with men (MSM). In HIV positive MSM, HCV is usually acquired after HIV infection. And, in these cases, it appears that HCV is spread through unprotected anal sex, or perhaps undisclosed injection drug use. Whatever the route of infection in MSM, further study is needed to better understand how HCV infection occurs.

Because HIV suppresses the immune system, some researchers are concerned that HCV co-infection can cause rapid liver damage. So a team in New York City conducted a study with HIV positive MSM who had recently been co-infected with HCV. This study involved interviews, liver biopsy, blood tests and other assessments. The results suggest that HCV prevention efforts need to be strengthened among MSM.

Study details

Researchers enrolled 11 HIV positive participants who initially did not have antibodies to HCV but these antibodies were detected during subsequent blood tests as participants sought medical care. Key lab results were as follows:

- levels of the liver enzyme ALT rose remarkably—reaching as high as 5 times the upper limit of normal
- HCV viral load was detectable
- no other hepatitis-causing viruses were detected

Routes of infection

When interviewed, participants disclosed that they had recently engaged in a variety of unsafe behaviours, including the following:

- unprotected anal receptive intercourse
- substance use with crystal meth (by injection)

- sharing needles for injection of other street drugs
- sharing equipment, such as straws, for snorting substances

Some other important information about participants is as follows:

- the men ranged in age from 31 to 56 years
- none of them had a sexually transmitted infection that could cause ulcers (and thus make it easier to become infected with HCV)
- CD4+ counts were between 170 and 842 cells

Most participants had a liver biopsy done within the first four months after HCV was detected in their blood.

Results

Analysis of the liver biopsies revealed inflammation and dead as well as dying portions of the liver. These findings would be unusual in early HCV mono-infection. They suggest that HCV-related liver damage is accelerated in the setting of HIV infection.

Most of the 11 men have begun treatment for HCV—pegylated interferon and ribavirin—but the results are not yet available.

The study team encourages doctors to conduct regular blood tests among their HIV positive MSM patients so that early HCV infection can be quickly detected and treated.

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C. Changes to fats and sugar in the blood because of hepatitis C

HCV infection of the liver is the trigger for inflammation and damage to that organ. But the effect of HCV on levels of lipids (cholesterol and triglycerides) and blood sugar is not well understood.

Researchers with the American AIDS Clinical Trials Group (ACTG) conduct clinical trials with HIV positive participants. In one study, ACTG 5095, researchers compared the anti-HIV effects of different combinations of medications. They also analysed blood samples from HCV positive study volunteers for changes in lipids and sugar. Their findings, from a study of about 1,000 participants, suggest that HCV infection appears to be linked to an increased risk of pre-diabetes and diabetes.

Study details

Researchers recruited 1,052 HIV positive participants whose average profile at the start of the study was as follows:

- 20% female, 80% male
- age – 38 years
- CD4+ count – 209 cells
- HIV viral load – 63,000 copies

In total, 108 participants (56% of whom disclosed that they injected street drugs) tested positive for antibodies to HCV and were presumed to be co-infected with this virus.

In ACTG 5095, participants were randomly assigned to receive one of the following three regimens:

- AZT (zidovudine, Retrovir) + 3TC (lamivudine) + abacavir (Ziagen)
- AZT + 3TC + efavirenz (Sustiva, Stocrin)
- AZT + 3TC + ABC + efavirenz

In this issue of *TreatmentUpdate*, we will focus on the metabolic results of this trial.

Results

Over a period of two years, researchers found the following changes in HCV positive co-infected people:

- levels of so-called bad cholesterol (LDL-c) remained relatively stable
- insulin resistance (suggestive of pre-diabetes) grew worse
- triglyceride levels fell

All of these changes were modest yet statistically significant.

At the start of the study, rates of diabetes were similar in people with HIV and those who had both HIV and HCV. However, by the second year of the study, rates of diabetes were three times greater among co-infected people. Exactly why this difference emerged is not clear but the difference was also statistically significant.

More research is needed to explore the link between HCV, diabetes and HIV treatment.

The results from ACTG 5095 underscore the case for testing for HCV and treating this infection early so as to minimize future complications.

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Shikuma C, Ribaudo H, Zheng E, et al. The effect of hepatitis C infection on metabolic parameters following initial therapy of HIV-infected subjects with nucleoside ± NNRTI regimens. Program and abstracts of the *15th Conference on Retroviruses and Opportunistic Infections.* 3–6 February 2008, Boston, MA. Abstract 931.

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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© CATIE, Vol. 20, No. 3
April/May 2008

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

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.

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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.

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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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