TreatmentUpdate 189

Vol. 24, No. 3
May 2012

Available online at
www.catie.ca/en/treatmentupdate

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I BONE HEALTH

A. Reduced bone density and HIV

Many studies have found that some HIV-positive people tend to have bones that are not as thick or dense as they ought to be. Such bones have reduced bone mineral density, as minerals such as calcium have been removed, rendering the bones more porous and weak.

Osteopenia is a relatively mild form of reduced bone mineral density and osteoporosis is the more severe form. People with osteopenia or osteoporosis are at heightened risk for breaking bones when they have accidents or fall. Osteopenia and osteoporosis can even lead to damage in the absence of accidents as the spine and hips slowly degrade under the burden of bearing the body's weight.

There are many risk factors for developing reduced bone mineral density among HIV-negative people and these same factors are at play among HIV-positive people. While some of these factors can be changed, some cannot, as the following lists show:

Risk factors that *cannot* be changed:

- history of fractures among parents, brothers or sisters
- personal history of fractures
- being a woman – bone density decreases during the transition to menopause
- being elderly

Risk factors that *can* be changed:

- use of corticosteroids
- excess intake of alcohol
- smoking tobacco

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- use of street drugs such as crystal meth, heroin and related substances
- deficiency of the hormone estrogen in women
- insufficient exercise
- less-than-ideal body weight
- insufficient intake of calcium

Some HIV-positive people may have additional risk factors, including:

- deficiency of vitamin D (needed to absorb calcium and other minerals used for bone building)
- being depressed
- deficiency of the hormone testosterone in men
- chronic inflammation
- co-infection with hepatitis C virus (HCV)

Chronic inflammation is a consequence of HIV infection. Although use of potent combination anti-HIV therapy (commonly called ART or HAART) can greatly reduce inflammation, because ART does not cure HIV infection some residual inflammation remains.

Impact of ART

In general, after a person begins to take ART bone density may continue to decrease by 1% to 4% for several years, then stabilize and even increase.

Tenofovir and bones

Several studies have found that the use of the drug tenofovir (Viread, and in Truvada, Atripla and Complera) as part of ART may *temporarily* accelerate bone thinning in a minority of HIV-positive people. However, in such studies the loss of bone mineral density associated with the use of this drug tends to stabilize over time in most people. Moreover, results from randomized clinical trials comparing different treatments have **not** found an increased risk for fractures among people who use tenofovir or tenofovir-containing drugs.

Reports have emerged from studies of a different design, specifically observational or cohort studies, of an increased risk of either kidney dysfunction or an increased risk for fractures among some participants who used tenofovir. A future issue of *TreatmentUpdate* will review and explain those findings.

Tenofovir may cause kidney dysfunction in a small proportion of participants in randomized clinical trials, and this dysfunction may affect the kidneys' ability to regulate calcium or phosphorus levels. These minerals are used to maintain bone mineral density. In most cases when kidney dysfunction has occurred in tenofovir users in randomized clinical trials it was usually temporary.

Tenofovir has been widely used for the past decade in high-income countries. For the vast majority of tenofovir users, the drug is safe and effective when used as directed.

Concern about efavirenz

Use of efavirenz (Sustiva, Stocrin and in Atripla) is associated with having lower-than-normal levels of vitamin D in the blood of some HIV-positive people. This vitamin helps to absorb calcium and phosphorus from food, and reduced levels of vitamin D may affect the ability to maintain bone mineral density.

Other drugs

Drugs that have the potential to affect kidney health, impact the functioning of bone cells or interfere with the body's processing of vitamin D, if taken over the long term or frequently, may also have the potential to affect bone mineral density. Such drugs can include the following:

- antibiotics – Bactrim/Septra (trimethoprim-sulfamethoxazole)
- antiviral agents – acyclovir (Zovirax) and valacyclovir (Valtrex), foscarnet (Foscavir), cidofovir (Vistide)
- antifungal agents – amphotericin B
- antiseizure drugs – phenytoin, carbamazepine, valproic acid
- antidepressants – lithium
- anti-inflammatory drugs – ibuprofen (Advil, Motrin), naproxen (Naprosyn), acetaminophen (Tylenol), indomethacin (Indocid)
- opiates – codeine, morphine, methadone and related substances

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B. Building better bones

There are several nutrients and activities that can help improve bone health and bone mineral density. In this issue of *TreatmentUpdate*, we underscore some of these.

Calcium

In general, adults need between 1,000 and 1,200 mg per day of calcium. To find out more about getting calcium from your diet, see the following CATIE resources:

CATIE's *Practical Guide to Nutrition* (see the chapter called "Managing the Effects of HIV and Meds on the Body")

CATIE's *Positive Side* magazine has these two informative articles:

- Good to the Bone (http://www.catie.ca/en/positiveside/fallwinter-2001/good-bone)
- Boning up on Bone Health (http://www.catie.ca/en/positiveside/summer-2011/boning-bone-health)

Vitamin D

Many studies have found that HIV-positive people have either a deficiency or less-than-ideal levels of this vitamin in their blood. Factors such as liver and kidney disease can also play a role in depleting vitamin D. Some medicines and herbs used by HIV-positive people can also reduce vitamin D levels, including the following:

- antibiotics – rifampin (rifampicin) and isoniazid, commonly used to treat TB. Vitamin D levels can sometimes fall after as little as two weeks' exposure to these drugs.
- anti-seizure drugs – phenobarbital, carbamazepine, phenytoin, valproic acid
- anti-cancer drugs – Taxol and related compounds
- antifungal agents – clotrimazole and ketoconazole
- anti-inflammatory drugs – corticosteroids
- anti-HIV drugs – emerging research suggests that the drugs efavirenz (Sustiva, Stocrin and in Atripla) and AZT (Retrovir, zidovudine and in Combivir and Trizivir) may reduce vitamin D levels in some people. In contrast, exposure to darunavir (Prezista) appears to raise vitamin D levels. Researchers continue to study the possible effects of different medications on vitamin D levels, so expect more news about this in the years ahead.
- herbs – St. John's wort or its extracts (hypericin, hyperforin)

A deficiency of vitamin D causes the body to produce excessive levels of parathyroid hormone (PHT), which may over the long-term cause bone thinning.

Medically guided supplementation of vitamin D is necessary to raise levels in the blood to at least 75 nmol/litre (30 ng/ml). This may mean that some people, particularly those with severe vitamin D deficiency, may require daily doses prescribed by their physician that range between 2,000 and 5,000 IU (international units) of vitamin D_3. For further information about vitamin D dosing and safety issues, see *TreatmentUpdate 185.*

http://www.catie.ca/en/treatmentupdate/treatmentupdate-185/nutrition/overview-vitamin-sources-dosing-drug-interactions-toxi

Exercise

Athletes generally tend to have greater bone mineral density than non-athletes. This suggests that physical exercise is useful for building bone density. Indeed, this is the case in adolescents whose skeletons are still growing. In adults, physical exercise helps to prevent further bone loss and among some HIV-negative people may even increase bone density by 1% or 2%. Before starting

an exercise program, speak to your doctor to find out what kind of exercise is right for you.

Note that exercise (aerobic and resistance training), extra calcium and vitamin D are not enough to significantly reverse osteoporosis in HIV-positive people. There are drugs that are specifically designed to strengthen bone density and reverse osteoporosis. The most commonly used drugs to help people with osteoporosis are called bisphosphonates and we discuss these later in this issue.

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C. Bone growth and shrinkage

As children grow, so do their bones, as new bone tissue is placed on top of existing bones, particularly in the legs and backbones. This process of lengthening bones is called modeling. During the teenage years, sex hormone (estrogen and testosterone) levels rise, helping to strengthen bones, which become thickest in early adulthood.

In adults, an activity called bone remodeling is what chiefly affects bone strength and density. Bone remodeling repairs microdamage within the skeleton. It also helps to release calcium stored in bone so that the amount of calcium in the blood remains within an ideal range.

Remodeling can be triggered by microdamage on bones that are heavily used or that have accumulated stress from wear and tear. Insufficient calcium in the diet forces the body to absorb calcium from bone. Prolonged poor dietary intake of calcium causes the body to leech calcium from bones, and this leaves them thinner and weak.

Parathyroid hormone

When the body does not obtain enough calcium from food the parathyroid glands (located in the neck) release higher-than-normal levels of parathyroid hormone (PTH). Prolonged elevated levels of PTH cause the body to absorb calcium from the skeleton and the kidneys to resorb calcium from the urine. PTH also helps the body convert vitamin D_2 to its active form, vitamin D_3. All of these steps increase the amount of calcium absorbed from the intestine and available for use by tissues. However, no amount of PTH or vitamin D is going to make up for missing calcium over the long term.

Hit by hormones

Remodeling of bone is also affected by many hormones or hormone-like compounds, including the following:

- estrogen
- testosterone
- vitamin D
- parathyroid hormone
- interleukins
- tumour necrosis factor (TNF)

In HIV infection, the immune system undergoes excessive activation and inflammation and produces many chemical signals or cytokines (interleukins, TNF and so on). Studies in men at high risk for HIV or who have recently become HIV positive have found unexpectedly high rates of osteopenia and osteoporosis compared to HIV-negative men of similar age.

HIV infection appears to be associated with premature menopause in some women.

All of this information suggests that HIV-positive people are at increased risk for thinning bones.

Although many studies have reported small changes in bone density in HIV-positive people, surprisingly, such small changes can have a big impact on the ability of bones to carry the body's weight. For instance, among HIV-negative people small changes in bone density affects the architecture of bones, making them more porous and weaker.

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D. Changes in bone density among HIV-negative men, some of whom used tenofovir

A placebo-controlled clinical trial called iPrEX was conducted to assess the safety and effectiveness of daily Truvada (a fixed-dose combination of two drugs in one pill: tenofovir + FTC) in reducing the risk of HIV transmission among gay and bisexual men and transgender women. Overall, Truvada, as part of a comprehensive prevention package (which included regular testing and treatment of sexually transmitted infections, HIV prevention counseling and so on), reduced the risk of becoming HIV positive by about 44%. For further details about iPrEX, see the following CATIE resources:

- Truvada for HIV prevention - some good news but caution is still needed http://www.catie.ca/en/catienews/2010-11-25/ truvada-hiv-prevention-some-good-news-caution-still-needed
- Pre-exposure prophylaxis (PrEP) Fact Sheet http://www.catie.ca/en/fact-sheets/prevention/pre-exposure-prophylaxis-prep

Tenofovir is one of the drugs in Truvada, and over the past decade there have been reports of less-than-normal bone mineral density (BMD) in some HIV-positive tenofovir users. So researchers involved with the iPrEX study in San Francisco, California, conducted analyses of bone mineral density among a subset of iPrEX participants before and after their exposure to tenofovir. All participants in the subset were men who have sex with men (MSM). The study team noted that about 10% of participants had thinner-than-normal bones. Low bone mineral density was associated with substance use *before* participants began to take Truvada. Once in the study, about 13% of tenofovir users and 6% of placebo users had their bone mineral density decrease by more than 5%.

Study details

Bone density is primarily assessed using low-dose X-ray scans called DEXA (dual energy X-ray absorptiometry). DEXAs were done at the start of the study and 12 and 24 months later.

Also, study staff interviewed participants so that other health-related information could be gathered. In total, data from 210 MSM were used.

Understanding DEXA results

Based on the results of DEXA scans, bone density results are given T or Z scores. T scores compare a person's bone mineral density to those in a young population of similar gender and race/ethnicity. Z scores compare a person's bone mineral density to those of other people of similar age, weight, race and gender.

Scores (or BMD) with a minus sign in front of them have less-than-ideal bone density. For instance, a score between -1 and -2.5 indicates osteopenia, and a score below -2.5 indicates osteoporosis.

Results – Baseline

Researchers were surprised to find that about 10% of participants (20 men) had serious loss of bone mineral density, mostly in the spine but also some in the hip and thigh, even before they had been exposed to Truvada.

The study team had expected to find that about 5 out of 210 men (2%) had a serious degree of bone loss.

They conducted additional analyses in blood samples of 16 of these 20 men with unexpectedly low bone mineral density and found that two men had extremely low vitamin D levels and another two men had very low levels of testosterone. Both of these are factors in osteopenia and osteoporosis. However, these analyses don't explain the findings in the majority of men, so the research team conducted statistical analyses of behaviour and reduced bone mineral density. They found that men with the following behaviours were highly likely to have thinner-than-normal bones:

- use of amphetamines (speed, crystal meth)
- inhaling poppers (amyl nitrate) or glue

In contrast, men who reported that they took supplemental vitamin D and calcium were significantly less likely to have low bone mineral density.

Results – Tenofovir

Overall, participants who used tenofovir developed a statistically significant decrease in bone mineral density, averaging about 1%, at the hip or spine.

However, among some participants a greater degree of bone loss occurred, as follows:

- 36% of men taking tenofovir and 20% taking placebo lost more than 3% of BMD where the thigh bones meet the pelvic bones
- 14% of men taking tenofovir and 3% taking placebo lost more than 3% of BMD in their hips

These differences were statistically significant; that is, not likely due to chance alone.

Results – Fractures

As reduced bone density is associated with an increased risk for fractures, researchers investigated cases of broken bones, distributed as follows:

- Truvada users – six people had eight fractures
- placebo users – four people had four fractures

In all cases, fractures were due to trauma (accidents or violence) and not to tenofovir.

The iPrEX bone study

In this analysis of bone health, about 10% of HIV-negative MSM in the study had reduced bone mineral density *before* they were exposed to Truvada. This is about five times greater than would be expected. This finding calls for further study of HIV-negative MSM to better understand factors associated with reduced bone mineral density.

Overall, tenofovir's effect on bone mineral density was small and not linked to a statistically increased risk for fractures. However, it is noteworthy that in a substantial subset of men who received tenofovir, decreases of more than 3% in bone mineral density were detected over the course of the study.

The findings from iPrEX suggest that reduced bone mineral density may be an unrecognized problem among other men who are at high risk for HIV. A recent Dutch study may have suggested something similar.

The Dutch bone study

In that study, researchers in Amsterdam assessed a group of 33 MSM in whom HIV was detected very early, as part of a study. All the men were HIV negative six months prior to their most recent HIV test. DEXA scans done between 21 and 45 days after these men became HIV positive found high rates of osteopenia (45%) and osteoporosis (6%). Blood tests did not find elevated levels of proteins (or markers) associated with inflammation, so it is unlikely that HIV-related inflammation was responsible for such a large decrease in bone density occurring in such a short time after HIV infection. Certainly the high viral loads seen in early HIV infection may have played a role in bone thinning. However, it is also possible that some of these men had decreased bone mineral density prior to HIV infection. Some of them had less-than-ideal body weight, a factor associated with reduced bone density.

Further studies are needed in men at high risk for HIV infection to understand why the incidence of low bone mineral density is greater than expected. Similar studies need to be done for women.

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E. HIV and menopause

Several years ago a team of researchers at the Albert Einstein College of Medicine in The Bronx, New York, who specialized in women's health issues investigated menopause in HIV-positive women. As part of this investigation they reviewed relevant studies on the subject.

Age at onset of menopause

Among healthy HIV-negative women, menopause usually occurs around the age of 50. However, reports have emerged of premature menopause in some HIV-positive women. Some observational and cross-sectional studies have found early onset of menopause linked to the following factors among HIV-positive women:

- low CD4+ cell counts (less than 200 cells)
- low levels of physical activity
- use of street drugs (opiates can lower estrogen levels)
- smoking tobacco (long-term use of tobacco can also lower estrogen levels)
- having a low income

Some studies have found that Black women are more likely to have earlier onset of menopause than White women, while some studies have not found this.

Due to issues of study design, specifically the observational nature of many studies involving women and menopause, it is difficult to be certain about which factor (substance use or low income) plays a leading role in premature onset of menopause. Moreover, the Bronx researchers note that substance use and having a low income are relatively common among women with HIV infection, particularly in North America and Western Europe.

Symptoms that occur in menopause

Women transitioning into menopause can experience one or more of the following symptoms:

- breasts become tender
- hot flashes and night sweats
- difficulty falling asleep
- difficulty thinking clearly
- forgetfulness
- severe headaches
- changes in mood
- vaginal dryness
- sexual dysfunction

In some studies, HIV-positive women have reported more symptoms associated with menopause than HIV-negative women. The reasons for such differences are not clear but some researchers think they may be related to age and educational levels. For instance, in one study of HIV-negative women, those who were 45 years or older were more likely than younger women to link vaginal dryness and hot flashes to menopause. Also, HIV-negative women who graduated from high school were more likely to make the same links than women who had not also graduated from high school. Similar analyses concerning age and education and menopause have not been widely done among HIV-positive women.

One study has found that HIV-positive women were less likely to report symptoms associated with menopause to their doctors because they were not sure if menopause was responsible or if there were

other ongoing health issues. This finding underscores the need for HIV-positive women to report their symptoms to their doctor so they can be investigated.

Hormonal changes

As the ovaries begin to transition to menopause, their output of hormones changes and levels of FSH (follicle-stimulating hormone) rise. A sustained increase in FSH indicates reproductive aging. Levels of another hormone, LH (lutenizing hormone), also rise while levels of estrogen fall in menopause.

In one study, researchers compared data from 82 HIV-positive women and 15 HIV-negative women. They found that HIV did not affect levels of the following hormones:

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

Another study found that antiretroviral therapy did not affect levels of estrogen and prolactin.

Unfortunately, most studies on hormone levels in HIV-positive women did not take into account factors such as stress and substance use, which could also have affected their levels.

Bone health

In general, studies have found that HIV-positive women tend to have a greater degree of bone thinning at the hips and spine compared to HIV-negative women. Among HIV-negative women, such changes can even occur before menopause. Moreover, studies of HIV-positive women in high-income countries have found that low levels of vitamin D in the blood are common.

Most studies have found that anti-HIV therapy (ART) generally does not accelerate bone loss over a period of several years.

Cardiovascular disease

Research suggests that HIV infection is linked to an increased risk for cardiovascular disease (CVD) among men and women. In part, this increased risk may arise because of ongoing inflammation triggered by a chronic viral infection. As high levels of estrogen appear to have some degree of anti-inflammatory activity, it is possible that the cardiovascular system of postmenopausal women, regardless of HIV status, are more susceptible to the subtle effects of inflammation.

Bear in mind that there are many factors that incite and propel CVD, many of which can be prevented or if present managed thereby lowering a woman's risk, including these:

- tobacco smoking
- substance use
- higher-than-normal blood pressure
- type 2 diabetes
- being overweight
- not getting enough exercise
- abnormal levels of cholesterol and triglycerides in the blood

Some studies have found an increased risk for CVD among HIV-positive women compared to HIV-positive men. The reasons for this are not clear but some doctors think that the presence of CVD risk factors may be greater in some HIV-positive women than men.

Menopause and the brain

Some women, regardless of HIV status, have reported that the transition to menopause is associated with neurocognitive changes such as difficulty thinking clearly, problems concentrating and being forgetful. Researchers have not presented a clear and robust rationale as to why reduced estrogen levels should be associated with these problems. A simple plausible explanation is that difficulty falling asleep is relatively common with the menopause transition. It is possible that women who do not get enough sleep on a regular basis do not feel refreshed and may thus have problems with memory and thinking clearly.

Some women, regardless of HIV status, may experience unexpected changes in mood—persistent sadness, anger and even depression. It is very important to alert doctors to any persistent or noticeable change in mood so that it can be assessed and, if necessary, treated.

As ART is widely available in Canada and other high-income countries, severe HIV-related cognitive problems are far less common today than before 1996. There is no evidence that HIV-positive women regardless of menopause status are more prone to cognitive problems compared to HIV-positive men.

Steps to better health

As women age, there are many simple steps they can take to stay healthy. The Bronx team of researchers encourages HIV-positive women to do the following:

- reduce alcohol and substance use
- improve their intake of healthy and nutritious food
- get support and treatment for co-existing health problems (such as co-infections, diabetes, depression)
- increase social contact by joining clubs or social groups
- increase the ability to cope with stress through activities such as regular exercise, yoga, meditation and other healthful events
- engage in activities that stimulate thinking

Much work remains to be done on women's health in general, and HIV-positive women's health in particular, including understanding their social, care and treatment needs as they age.

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F. Menopause and the risks and benefits of hormone therapy

As women age, their bodies undergo complex changes that affect many aspects of their health. Menopause is one such change, driven by altered hormonal levels.

The ovaries produce estrogens, estradiol and estrone, and around age 35 they begin to shrink. On average, the age of 50, production of estrogen has significantly decreased while production of other hormones, LH and FSH, is on the rise. As women approach menopause, changing hormone levels cause symptoms such as the following:

- hot flashes
- night sweats
- irregular periods with changes in bleeding
- vaginal dryness

Some women have reported these symptoms as they transition through menopause:

- mood swings
- depression
- difficulty concentrating
- poor memory
- sexual dysfunction

The intensity and duration of these symptoms associated with the body's entry to menopause can vary considerably.

Hormone therapy

One key part of the body affected by declining estrogen levels is the skeleton. The relatively high levels of estrogen in circulation during adolescence and early adulthood impair the body's ability to tear down bone.

Discussing the risks and benefits of hormone therapy with a doctor is vitally important because well-designed clinical trials of hormone therapy in HIV-negative women have found some unfavourable effects. For instance, data from large randomized clinical trials have found that supplemental estrogen can help relieve some symptoms of menopause. However, some doctors suggest that antidepressants, vitamin E or eating a diet rich in soy-based products may also provide some relief from these symptoms without the risks associated with the use of estrogen therapy.

In this report we explore data from clinical trials of hormone replacement in HIV-negative women. Unfortunately, data from large randomized clinical trials in HIV-positive women assessing hormone therapy are not available. However, the risks and benefits seen with hormone therapy in HIV-negative women likely apply to women with HIV as well.

Estrogen and bone mineral density

Clinical trials have found that estrogen can significantly and quickly increase bone mineral density at the hip and spine. These increases are sustained while hormone therapy continues. During this time, rates of fractures significantly decline.

An alternative to the use of estrogen is a class of drugs called bisphosphonates, examples of which include the following:

- alendronate (Fosamax, Fosavance)
- risedronate (Actonel)
- zoledronic acid (Aclasta, Zometa)

All of these drugs can increase bone density and significantly reduce the risk of fractures. Bisphosphonates work by impairing the body's ability to tear down bone.

Another possible product is parathyroid hormone (teriparatide), which can also increase bone density. Unlike other drugs, parathyroid hormone must be injected daily and stimulates new bone to grow. However, this drug must be used with caution and only for a limited time because of a possible increased risk for cancer. Once a person stops using periparatide, bone density quickly falls.

Generally, neither bisphosphonates nor synthetic parathyroid hormone affects the breasts or genital tract.

Estrogen risks – Endometrial cancer

Analyses of observational studies have found that the risk of endometrial cancer triples with short- or medium-term (between one and five years) estrogen-based hormone therapy. This risk of cancer increases considerably (about 10-fold) when estrogen is used for 10 or more years. Using a small dose of the hormone progesterone together with estrogen greatly reduces the risk of this cancer developing.

Estrogen risks – Breast cancer

An increased risk of breast cancer has been seen in observational studies of estrogen therapy; the longer the use the greater the risk. For instance, among women who used estrogen for less than five years the risk was very low. However, among women who used estrogen for five or more years the risk increased by 35%.

Unlike the case with endometrial cancer risk, combining estrogen with a progestin appeared to increase the risk for breast cancer.

Estrogen risks – Excessive blood clots

The ability of blood to clot is useful, as it helps staunch the loss of this vital fluid. However, unnecessary blood clots can block the flow of blood and cause serious complications such as stroke and heart attack. The risk for these problems increased about threefold among estrogen users.

Estrogen and cardiovascular disease

Results from observational studies done in the 1980s and 1990s suggested that estrogen-based hormone therapy could help reduce the risk of cardiovascular disease. However, note that observational studies can have their conclusions skewed by factors that were not accounted for in analyses. Indeed, robust clinical trials have found that women with pre-existing CVD did not significantly benefit from reduced risk for stroke and heart attack with estrogen supplements. In one trial of estrogen-progestin, a 50% increased risk of heart attack and stroke occurred in the first five years of the study. Other well-designed trials have also found an elevated risk for these complications with estrogen-progestin, a 24% increased risk for coronary heart disease and a 31% increased risk for stroke compared to placebo.

Some researchers think that women who have minimal pre-existing risk for CVD may benefit from hormone therapy early in menopause. However, data are needed to support this.

Reanalyses of several hormone therapy clinical trials suggest that part of the reason for the increased risk for CVD may have been the relatively older age of the women and that they had pre-existing risk factors for CVD. Among women aged 50 to 59, estrogen seemed to reduce the risk for coronary artery disease. However, differences in risk between age groups were generally not statistically significant.

Researchers are not certain if different doses and formulations of hormone therapy will produce different cardiovascular risks.

Other conditions

Limited data suggests that hormone therapy appears to increase the risk for ovarian and lung cancers but appears to decrease the risk for type 2 diabetes.

What happens when hormone therapy stops?

In clinical trials, the elevated risk for heart attacks, stroke and excessive clotting associated with estrogen-progestin disappeared two years after this therapy ceased. Benefits associated with hormone therapy—suppression of hot flashes and increased bone density—also ended.

The risk for breast cancer was slightly elevated and there was a suggestion of elevated risks for lung cancer (and other cancers) and dying.

Bear in mind

Leading hormone experts caution: "Primary prevention of heart disease should not be viewed as an expected benefit of hormone therapy." They also add that "an increase in stroke and a small early increase in coronary artery disease risk should be considered [as possible adverse effects of hormone therapy].

Thus the risk and benefit of hormone therapy should always be carefully considered and discussed with health care providers.

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G. Higher rates of bone loss seen after menopause in HIV-positive women

Most research on changes in bone density in HIV-positive women has focused on women before they have entered menopause. Due to hormonal changes associated with menopause, women entering this phase of their life are at high risk for thinning bones.

A research team at Columbia University Medical Center in New York City has been studying bone density in both HIV-negative and HIV-positive women who have entered menopause. On average, HIV-positive women had double the annual rate of bone thinning compared to HIV-negative women. Such large decreases in bone mineral density places HIV-positive women at increased risk for osteopenia, osteoporosis and fractures as they age.

Study details

Researchers reported results from 55 HIV-negative and 73 HIV-positive women, all of whom were described as "postmenopausal" by the study team. The women had ceased to have periods and their level of estrogen was relatively low. None of the women were taking hormonal therapy or had a history of reduced bone mineral density prior to entering the study. This report focuses on the HIV-positive women.

The average profile of the HIV-positive women when they entered the study was as follows:

- age – 56 years
- time since onset of menopause – 10 years
- length of time HIV positive – 9 years
- history of AIDS – 47%
- lowest-ever CD4+ count – 195 cells
- current CD4+ count – 474 cells
- taking anti-HIV therapy (ART)– 78%
- vitamin D deficiency – 50%
- co-infected with HCV – 21%
- taking a calcium supplement – 23%

On average, women were in the study for about 18 months.

Results – Baseline

At the start of the study, HIV-positive women had thinner bones than HIV-negative women. Taking into account body mass index (BMI—a relative assessment of fatness that is derived from a formula for a person's weight and height), HIV-positive women had significantly thinner bones at these places:

- spine
- hip
- forearm

Results – Bone turnover

Bone tissue may feel thick and hard but, at the level of the cell, bones are very dynamic, as small parts of bones are always in the process of being absorbed so that they can be repaired. This process of tearing down and repair is called bone turnover.

In the present study, researchers analysed blood samples, assessing the levels of chemical signals associated with bone turnover. They found an imbalance in chemical signals favouring the

absorption of bone in HIV-positive women. This would suggest that HIV-positive women were at increased risk for osteoporosis and osteopenia.

Changes in bone over time

Researchers calculated that HIV-positive women lost about twofold more bone at the spine, hip and forearm than HIV-negative women.

Links to bone loss

Researchers took into account traditional risk factors linked to bone loss and found that factors such as race/ethnicity, age, weight and BMI were not associated with bone loss. However, HIV infection was significantly associated with thinning bones.

Among factors related to HIV, none of the following were linked to bone loss:

- lowest-ever CD4+ count
- CD4+ count at entry to the study
- having a history of AIDS

ART and bone loss

Overall, the use of ART was associated with reduced bone loss at the spine but not the hip or forearm. The reasons for this difference are not clear.

There was no difference in rates of bone loss between women taking ART based on protease inhibitors (28 women) or non-nukes (NNRTIs; 20 women).

The researchers reported that the rate of bone loss at the spine or forearm among the 12 women taking tenofovir-based regimens (tenofovir is sold as Viread and found in Truvada, Atripla, and Complera) was greater than among women who were not taking tenofovir by a factor of between two and four-fold. Even after taking into account factors such as BMI, age, race/ethnicity, CD4+ count, vitamin D levels, parathyroid hormone, phosphorus levels and so on, the rate of bone loss in the spines of tenofovir users was about twofold greater than in women who did not use tenofovir. This difference was statistically significant. However, caution must be used when interpreting this result and we will return to this finding later in our report.

Tenofovir use did not appear to affect the density of the hip bones.

Fractures

Overall, rates of fractures in women were not statistically different between HIV-positive (10%) and HIV-negative (8%) women.

When researchers assessed the severity of fractures, those fractures of moderate or severe intensity were more likely to occur among HIV-positive women (3%) than among HIV-negative women (0%). However, because of the relatively small proportion of fractures, this difference did not achieve statistical significance. Moreover, when researchers estimated the future 10-year risk of fractures among all women in the study, rates were slightly lower among HIV-positive women (5%) than among HIV-negative women (6%).

Findings in perspective

1. Overall, the research team found that postmenopausal HIV-positive women are at risk for what it called "excessive bone loss" at the spine and forearm compared to postmenopausal HIV-negative women.

2. HIV-positive women on ART did not lose as much bone mineral density as HIV-positive women who did not take ART. This suggests that, in general, ART has beneficial effects on bone density.

3. The accelerated loss of bone mineral density in the present study is probably due to the combined effects of lowered estrogen levels and HIV infection. Indeed, the HIV-positive women in this study had significantly less estrogen than the HIV-negative women, even though the HIV-positive women were about three years younger.

4. Most studies of changes in bone mineral density have focused on the spine and hip; the present study extends that to the forearm. That HIV-positive women were losing bone mineral density in the forearm suggests that this part of the body may be at increased risk for fractures.

5. Although the researchers found that use of tenofovir was associated with decreased bone mineral density, this finding must be interpreted cautiously because of the following reasons:

    - This was not a randomized clinical trial. Therefore, the interpretation of its findings

may be skewed by factors that the researchers did not take into account. For instance, we do not know why doctors prescribe tenofovir for some women but not others.
- The study was not specifically designed to assess the impact of tenofovir on changes in bone mineral density.
- The number of women taking tenofovir was relatively small.

However, the study's findings with regard to tenofovir are intriguing and suggest that tenofovir should be further studied among postmenopausal HIV-positive women in a clinical trial specifically designed for that purpose. Such a trial should be large and should last for several years.

6. The study was not designed to assess fracture risk, so firm conclusions about this issue cannot be drawn from the data.

Overall, the present study, while groundbreaking for its focus on postmenopausal HIV-positive women, clearly establishes the need for a larger and longer study with this population. Such a study takes on added importance because more women with HIV are aging, and researchers, doctors and women living with HIV need to know more about the intersection of HIV and aging.

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H. Long-term effect of zoledronate on bone health in HIV-positive men

A group of drugs called bisphosphonates has been used for the past two decades to improve bone density and reduce the risk of fractures. These drugs were initially designed for and tested largely in women.

One bisphosphonate is zoledronate. This drug can be given once a year via intravenous infusion over a period of 15 minutes. In clinical trials in HIV-negative people, zoledronate has been found to prevent hip and spine fractures in postmenopausal women who have osteoporosis. It can increase bone density in men and reduces the risk of subsequent death in people who have fractured their hips, a debilitating situation.

Zoledronate is meant to be taken once a year. However, emerging data suggests that less frequent dosing might be safe, effective and cheaper.

As HIV-positive people are at increased risk for thinning bones, bisphosphonates need to be tested in this population. So researchers in New Zealand conducted a study of zoledronate in men and found that two annual doses of this drug have prolonged and significant benefit on bone mineral density.

Study details

Researchers enrolled 43 HIV-positive men who were taking anti-HIV therapy (ART) and had reduced bone mineral density. The men were randomly assigned to one of the following interventions:

- 21 men – zoledronate 4 mg given as a 15-minute intravenous infusion once yearly for two consecutive years. The 4 mg dose of zoledronate was used because at the time of the study the now-standard 5 mg formulation was not available.
- 22 men – fake zoledronate (placebo) also given by intravenous infusion once yearly for two consecutive years

All participants received a daily supplement of 400 mg of calcium and 50,000 IU of vitamin D_3 once monthly.

DEXA scans were used to assess bone mineral density every six months for the first two years of the study. After the first two years, most participants entered an extension of the study, where they were monitored for up to six years and DEXA scans were less frequent.

No participant had any significant dysfunction of the following organs/glands (which could affect bone health):

- kidneys
- liver
- thyroid gland

Also, none of the men were using corticosteroids during the study, which can thin bones.

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

- age – 49 years
- weight – 75 kg (165 lbs)
- length of time HIV positive – 8 years
- CD4+ count – 550 cells
- proportion with a viral load less than 50 copies/ml – 80%
- duration of ART – 2 years
- total daily intake of calcium – 900 mg

Results – Turnover and density

Bone tissue may feel thick and hard but, at the level of the cell, bones are very dynamic, as small parts of bones are always in the process of being absorbed so that they can be repaired. This process of tearing down and repair is called bone turnover.

In the present study, researchers analysed blood samples, assessing the levels of chemical signals associated with bone turnover. They found an imbalance in chemical signals favouring the absorption of bone in all participants. However, among participants who received zoledronate, bone turnover rates fell significantly compared to placebo. This difference continued for six years.

The impact of zoledronate on bone mineral density was significant and also lasted for six years. For example, the bone density among zoledronate users was greater in the following locations compared to placebo:

- spine: +4%
- hip: +2%
- entire skeleton: +3%

Results – Vitamin D

At the start of the study, participants had less-than-ideal levels of vitamin D in their blood. Indeed, about 25% of them were severely deficient. Despite supplementation in all participants averaging 1,700 IU of vitamin D/day (50,000 IU/month), bone density among placebo users did not significantly increase during the study.

Fractures

Two participants who were taking placebo experienced fractures, one in the backbone and the other in the upper arm bone.

Exposure to tenofovir

Use of tenofovir (Viread, and in Truvada, Atripla and Complera) has been linked to decreased bone density in some studies. In the present study, seven people taking zoledronate and four taking placebo were also taking tenofovir-containing regimens. However, exposure to tenofovir did not affect the study's results.

Dropouts and deaths

The number of participants who were in the study for six years was as follows:

- zoledronate – 17 men
- placebo – 14 men

Overall, about 28% of participants prematurely left the study, mostly because they emigrated from New Zealand.

Two participants who received zoledronate died, one from lung cancer and the other's cause of death was not known (Mark Bolland, MD, *written communication*). These deaths were not related to the study drug.

Safety

Bisphosphonates given by intravenous infusion can sometimes cause temporary side effects—usually a flu-like syndrome that clears within two days but may last up to a week after the infusion. Two participants developed symptoms of a flu-like syndrome after zoledronate infusion, including high fever and muscle and bone pain, and as a result withdrew from the study.

Key points

1. Just two doses of zoledronate given once a year for two consecutive years were able to have a long-term, favourable and significant impact on bone mineral density compared to placebo among men taking ART.

2. The effect of zoledronate on bone mineral density in this study is of a similar degree as that seen in HIV-negative men and women who also used the following drugs:

   - alendronate 10 mg daily
   - alendronate 70 mg once weekly
   - zoledronate 5 mg once yearly for two consecutive years

The New Zealand researchers have also conducted a five-year study observing the impact of a single dose of zoledronate among HIV-negative women. In that study, favourable changes in bone density occurred and were similar to those seen in the present study of HIV-positive men.

3. As zoledronate has to be given just once a year, it may offer better adherence than drugs that have to be taken daily or weekly.

4. Another apparent advantage of zoledronate is that with just an annual dose for two consecutive years, bone mineral density increases significantly and is maintained for up to six years. When other drugs used to increase bone mineral density are discontinued, bones quickly become thinner, as is the case with the following drugs:

   - estrogen
   - denosumab
   - ondanacatib
   - teriparatide

5. The present New Zealand study was randomized and placebo controlled, and participants were monitored for up to six years, therefore its findings are robust. Disadvantages of the study were the relatively number of small participants and the dropout rate. As most dropouts were due to emigration, this appeared to be randomly and equally distributed between the study's two groups, so it was not likely to have a major impact on the results.

6. Participants in the New Zealand study had mildly thin bones—no osteoporosis—so the findings may not apply to other HIV-positive people with more severe bone loss.

7. Larger studies are needed to explore the long-term effect of one or two doses of zoledronate in HIV-positive men and women.

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I. A placebo-controlled study of alendronate in HIV-positive people

Researchers in France conducted a randomized, placebo-controlled study called ANRS 120-Fosivir in HIV-positive people with osteoporosis. The two-year study of alendronate revealed that the drug was safe and significantly improves bone mineral density.

Study details

Researchers screened more than 1,000 potential volunteers who had been HIV positive for at least five years to find participants with osteoporosis who did not have additional complications or conditions that could have had an impact on the study, such as the following:

- alcoholism
- difficulty swallowing medication
- stomach ulcers
- recent history of cancer
- vitamin D deficiency
- hormonal disorders (including those affecting thyroid and sex hormones)
- being underweight
- having previously received testosterone therapy
- serious heart, liver or kidney disease
- recent use of corticosteroids
- ongoing infections (apart from HIV)
- women who were breast-feeding or pregnant or planning to become pregnant
- received previous treatment for osteoporosis

After screening 1,079 people (842 men, 237 women), researchers randomly assigned 44 participants to one of the following interventions:

- alendronate (20 people) – 70 mg once weekly (taken orally)
- placebo (24 people) – once weekly (taken orally)

All participants also took 500 mg of calcium carbonate and 400 IU of vitamin D daily.

Low-dose X-ray scans (DEXA) were used to assess bone mineral density.

The average profile of the 44 participants at the start of the study was as follows:

- 42 males, 2 females
- age – 45 years
- 40% had a history of AIDS
- CD4+ cell count – 422 cells

- viral load – less than 50 copies
- all participants had osteoporosis
- 32% were taking tenofovir (evenly distributed between alendronate and placebo users)
- 40% were smokers

The study lasted for two years.

Results

At the end of the second year of the study, participants taking alendronate had significantly improved bone mineral density compared to participants who took placebo. Overall, bone mineral density increased at the spine or hip by 7% among alendronate users compared to placebo (1%). This difference was statistically significant.

Changes in bone mineral density at specific parts of the body were distributed as follows:

Spine
- alendronate: +7%
- placebo: +1%

Hip
- alendronate: +4%
- placebo: + 2%

The changes in bone mineral density of the hip were not statistically significant, likely because the changes were small; in order to detect a meaningful and statistically significant change, more participants would have been needed.

Adverse effects

Levels of liver enzymes in the blood were normal in all participants. There were no obvious differences in side effects between drug and placebo. This is not surprising, as alendronate is generally well tolerated when taken exactly as directed.

Fractures

Two fractures occurred among placebo users and none among alendronate users.

Gender imbalance

As with many HIV-related studies in high-income countries, the present study was imbalanced with respect to gender. Researchers explained this problem by noting that they did not recruit postmenopausal women because they wanted to "rule out an effect of osteoporosis risk factors [other] than HIV infection and its treatment." They also noted that osteoporosis seemed "less frequent in women than men in the HIV-infected population [in France]." The results in the study's two women were similar to that of men.

The present study has a robust design and produced clear results, confirming the beneficial effect of alendronate in HIV-positive men who have osteoporosis.

The long-term (between 10 and 15 years) use of alendronate has only been studied in elderly HIV-negative women. As alendronate and similar drugs are likely to be used in young and middle-aged HIV-positive people, long-term studies are needed to assess the drug's safety and effectiveness in this population, particularly in HIV-positive women.

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Rozenberg S, Lanoy E, Bentata M, et al. Effect of alendronate on HIV-associated osteoporosis: A randomized, double-blind, placebo-controlled, 96-week trial (ANRS 120). *AIDS Research & Human Retroviruses.* 2012; *in press.*

J. Understanding the risk/benefit of bone drugs

The most commonly prescribed drugs for increasing bone mineral density and reducing the risk of fractures is a class of drugs called bisphosphonates, which include the following:

- alendronate (Fosamax, Fosavance)
- risedronate (Actonel)
- zoledronic acid (Aclasta, Zometa)

These drugs resemble natural phosphate-containing compounds that are used to help the body regulate the buildup of minerals in the bone.

Bisphosphonates are very stable molecules and after a dose is taken they quickly attach themselves to bone. They work by impairing the body's ability to tear down or resorb bones.

In clinical trials these drugs have been found to reduce the risk of fractures, particularly at important places such as the spine and hip. When adherence rates are as good in the community as they are in clinical trials, the effectiveness of bisphosphonates is the same as in clinical trials.

Like all drugs, bisphosphonates can sometimes cause side effects. In this report we explore some possible adverse effects associated with these drugs, focusing on the parts of the body or the specific adverse effects.

Stomach and intestine

Some bisphosphonates can be taken intravenously and so the digestive tract is not affected. However, among oral formulations of these drugs, instructions for taking them must be adhered to, otherwise adverse events may occur that affect the stomach. Thus, upon waking in the morning and arising from bed, the following instructions are standard:

- The drug must be taken with a full glass of water (between 200 and 250 ml) and on an empty stomach.
- After taking the drug the person must remain upright for 30 minutes and not eat for between 30 and 60 minutes.

These steps allow water to carry the pill into the stomach and intestines, where it breaks down and is absorbed. If these instructions are not followed, the pill may lodge in the tube that connects the mouth to the stomach (the esophagus) or in the stomach itself, and then irritate these tissues. If that happens, the following symptoms can occur:

- difficulty swallowing
- sore throat
- burning sensation in the stomach

Such symptoms can appear regardless of whether the drug is taken daily, weekly or monthly.

Acute phase reactions (APR)

Temporary flu-like symptoms are more common among people who take intravenous formulations of these drugs; they rarely occur in people taking intermittent oral bisphosphonates. In one randomized, placebo-controlled study of zoledronate, after the first infusion 32% of participants who received this drug and 6% who received placebo experienced temporary symptoms such as the following:

- feeling feverish
- muscle pain
- bone and joint pain
- fatigue
- headache

However, after the second infusion, rates of these adverse effects among zoledronate users were around 7% (and 2% in placebo recipients). After the third infusion, rates were 3% for zoledronate users (and 1% for placebo recipients). All of these differences between zoledronate and placebo were statistically significant.

These symptoms usually occurred within a day after the infusion and cleared in about three days in most participants.

In another study, women who were deficient in vitamin D were more likely to experience these symptoms than other women. The greater the degree of vitamin D deficiency, the greater the risk of developing APR symptoms.

Doctors experienced in the use of intravenous bisphosphonates have prescribed standard doses of acetaminophen (Tylenol) at the time of the infusion and then for the next 72 hours as needed. This tends to minimize APR symptoms.

Cancer of the esophagus

In 2009, there were reports of 23 cases of esophageal cancer in the U.S. and 31 cases in Europe and Japan among people who had used bisphosphonates. However, these reports cannot prove that the drugs caused this particular form of cancer. Subsequently, observational studies in the U.S. and Europe did not find any link between these drugs and the development of cancer.

In the UK, researchers have amassed a large database—the General Practice Research Database (GPRD)—containing health-related information from about 42,000 people who have used bisphosphonates. Two studies have attempted to explore the issue of exposure to bisphosphonates and cancer using this database. One study gave the impression that bisphosphonates were not significantly associated with an increased risk for esophageal cancer, while the other study gave the opposite impression.

To resolve this apparent discordance, two scientists who engage in bone research reviewed the data from the two UK studies. They noted that there have been previous cases of studies into other drugs that have arrived at seemingly different conclusions when data from the GPRD has been analysed. However, when those previous studies with other drugs were carefully re-analysed, the reasons for differing conclusions became apparent.

In re-examining the two apparently conflicting bisphosphonate studies, the researchers found that important differences about the studies emerged:

- one study monitored people for 4.5 years
- the other study monitored people for up to 7.6 years

This difference in monitoring has the potential to have a huge impact on conclusions drawn by the study authors. By taking this difference in monitoring into account, the bone health experts were able to form useful conclusions about bisphosphonates. Here is what they suggested:

1. "For every 10,000 patients not exposed to bisphosphonates aged 60 to 79 years we can expect 10 cases of esophageal cancer over a five-year period." This information helps to place the studies' findings into perspective and the bone researchers encourage readers to make sense of so many (10,000) people by thinking of such a number being equivalent to a small town.

2. "There seems to be no increased risk [of cancer] in the first three years of treatment, although for every 10,000 patients treated with bisphosphonates, there may be anywhere between three fewer and seven additional esophageal cancers."

3. After three years of use, for every 10,000 patients treated with bisphosphonates, there are likely to be about five additional cases of esophageal of cancer, although it is possible that there will be between five fewer and 24 additional cases of esophageal cancer.

   Due to the observational nature of the studies, the bone researchers cannot provide firm estimates of cancer risk, and so there is some uncertainty about the actual number of people that could develop esophageal cancer.

4. Results from randomized clinical trials show that for every 10,000 postmenopausal women who receive bisphosphonates and who take them exactly as directed, about 1,000 fractures that might otherwise have occurred are prevented.

Unusual fractures

There have been isolated reports of unusual fractures (so-called atypical femur fractures) in some users of bisphosphonates. Mostly the bones that have broken are in the thigh. Some patients with this problem tend to experience thigh pain for weeks to months before a fracture spontaneously occurs. However, reviews of data from people who took bisphosphonates suggest that this problem is very rare and no clear link between the use of these drugs and atypical femur fractures has been proven.

Bone experts who have reviewed data on this problem suggest that among 10,000 patients using bisphosphonates there may be between "zero and two additional cases" of this problem per year. Thus the risk is very, very small.

Osteonecrosis of the jaw

Severe damage to the jawbones of some people who used bisphosphonates has been reported. However, it should be noted that the majority of such cases (95%) have almost always occurred among people who have received very high doses of bisphosphonates to prevent or treat bone disease arising from cancer. While most cases have occurred among people who received intravenous bisphosphonates, some cases have been reported among people who took oral formulations.

The quality of the data collected on cases of osteonecrosis of the jaw associated with exposure to bisphosphonates is mixed and so it is very difficult to draw robust conclusions. Therefore, the risk of developing osteonecrosis of the jaw among otherwise healthy users of bisophosphonates is not clear. If there is a risk, it is probably very, very low.

Eye problems

There have been reports about inflammation affecting the eye among people who received bisphosphonates. Much of this data comes from case reports or retrospective studies, which are not ideal for making robust conclusions about risks. In a controlled clinical trial with 7,765 women, the risk of eye inflammation or eye pain was 0.6% among participants who received zoledronate and 0.1% among people who received placebo. This difference was statistically significant. However, based on these figures, the risk of eye inflammation is still very, very small.

Abnormal heart rhythms

The heart is usually considered a large muscular pump that moves blood. This pumping action is enabled by changes in electrical activity within the heart. Atrial fibrillation (AF) is the most common type of disorder affecting the speed or rhythm of heartbeats. AF can cause chest discomfort, chest pain, stroke and heart attack.

Examining data from a large placebo-controlled trial found that AF occurred in 1.3% of participants who received zoledronate and 0.5% who received placebo. This difference was statistically significant. Note that there were no significant differences between drug and placebo in rates of stroke, stroke-related death, heart attack or death from cardiovascular causes.

A reanalysis of data from other studies with bisphosphonates—specifically alendronate, ibandronate and zoledronate—has generally not found an increased risk of AF, even in cases where high doses were used because of cancer.

It is possible that since bisphosphonate users are generally older people that they are at increased risk for AF and there is no real connection to exposure to these drugs. Therefore, there is probably either no increased risk for AF or if there is a risk, it is very, very small.

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© CATIE, Vol. 24, No. 3
May 2012

ISSN 1181-7186 (print)
ISSN 1927-8918 (online)
CATIE Ordering Centre Catalogue Number ATI-60197E
(*Aussi disponible en français, ATI-60197F*)

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

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