I ANTI-HIV AGENTS

A. Changes to DHHS treatment guidelines—new recommendations for initial HIV therapy

In Canada and other high-income countries there are at least 24 anti-HIV drugs from which doctors can choose when writing a prescription. A combination of at least three of these drugs, chosen from different classes, is commonly called ART (the older name is HAART). This apparent abundance of choice masks an underlying reality—many of the drugs listed are older, are not as effective and are not as well tolerated as newer therapies.

To help guide doctors, nurses and patients when making decisions about the initial use of ART, the U.S. Department of Health and Human Services (DHHS) has been producing treatment guidelines for several decades. The DHHS guidelines are generally seen as the most comprehensive and detailed of all HIV treatment guidelines. Furthermore, the DHHS guidelines have been noted for their forward thinking and influence guidelines in other countries and regions.

In the latest update to the guidelines, medical and scientific advisors to the DHHS have greatly simplified the recommendations for the initial therapy of HIV. The guidelines now state that the initial regimen should be based on a backbone of either integrase inhibitors or a protease inhibitor. This has resulted in just five regimens being recommended.
DHHS recommendations

Integrase inhibitor–based regimens:
- dolutegravir (an integrase inhibitor sold under the brand name Tivicay) + Kivexa (abacavir + 3TC) or a single pill containing all three drugs taken once daily and sold as Triumeq
- dolutegravir + Truvada (a single pill containing tenofovir + FTC)
- Stribild – a fixed-dose combination of elvitegravir + cobicistat + Truvada. Elvitegravir is an integrase inhibitor. Cobicistat is a boosting agent that raises and maintains levels of elvitegravir in the blood so that once-daily dosing is possible.
- raltegravir (an integrase inhibitor sold under the brand name Isentress) + Truvada

A protease inhibitor–based regimen
- darunavir (a protease inhibitor sold under the brand name Prezista) + a small dose of ritonavir (Norvir) + Truvada

Although ritonavir is a protease inhibitor, when used in low doses it acts to boost and maintain levels of darunavir (or other drugs) so that once-daily dosing is possible.

Although not mentioned in the guidelines, a new fixed-dose formulation of darunavir + the booster cobicistat has become available in Canada and other high-income countries. This new formulation is called Prezcobix.

The updated recommendations from the DHHS have surprised some people because therapies that were once commonly favoured even a few years ago—efavirenz (Sustiva, Stocrin and in Atripla), Kaletra (lopinavir + ritonavir), atazanavir (Reyataz) + ritonavir, and rilpivirine (Edurant and in Complera and Eviplera)—have been left behind.

The recommendations for the regimens for first-line (initial) therapy use are largely based on the results of large, well-designed clinical trials.

REFERENCE:

II BONE HEALTH

A. Guidelines for assessing, preventing and treating low bone density in HIV

HIV-positive people are at increased risk for thinning bones or reduced bone density. Thinner bones are weaker and have difficulty supporting a person’s weight, therefore, they are prone to break or fracture.

The reasons for the elevated risk for bone issues in people with HIV may be related to at least the following factors:
- excess inflammation, a consequence of long-term viral infection
- poor nutrition
- being underweight
- tobacco use
- excess use of alcohol
- lower-than-ideal levels of vitamin D

Readers should note that other researchers have found thinner-than-normal bones in some young men at high risk for HIV before they acquired this infection.

Role of ART

Potent combination anti-HIV therapy (commonly called ART or HAART) has made a dramatic difference to the survival prospects of HIV-positive people. Research suggests the possibility that some young people who are diagnosed with HIV today and who initiate ART shortly thereafter will live into their 70s and 80s.

Despite this beneficial role of ART, some researchers, doctors and patients have raised questions about the impact that ART might have on bone health. Well-designed studies have found that once ART is initiated, bone density can diminish by an average of 2% to 6% for a year or two and then stabilize. Why this should occur during the first few years of using ART is not clear. One drug in particular, the nuke tenofovir (Viread and found in Truvada, Atripla, Complera and Stribild), has been associated with bone loss in some patients in some studies but not others. The reasons for this are not clear.
Developing recommendations

Faced with the bone-related issues mentioned here, a team of doctors and researchers from Australia, Europe, East Asia, Latin America and the U.S. collaborated to develop bone-focused guidelines to assist doctors and nurses caring for HIV-positive people. The team reviewed data from relevant studies that dealt with key common biomedical issues relating to bone health and arrived at agreement and recommendations. Before getting into the recommendations, we first discuss a term used.

A note on terms

Doctors sometimes use the term “fragility fractures.” This term refers to bones that have broken because of something as simple as falling from standing height, for example. Fragility fractures can be a concern for people with less-than-ideal bone density.

Major risk factors for fragility fractures include the following:

- a history of fragility fractures
- taking corticosteroids at doses of 5 mg/day or greater for more than three months
- a high risk for falling (perhaps because of difficulty with balance or vision)

Screening

The team made the following recommendations:

- all HIV-positive adults should be assessed for fragility fractures and low bone mineral density (BMD)
- patients who have fragility risk factors should undergo a bone density scan. Such scans are called DEXA (dual-energy X-ray absorptiometry) and use low-dose X-rays.

FRAX

The team stated that certain patients might not need DEXA scans, as follows:

- patients without major risk factors for fragility fractures
- men aged 40 to 49 years
- women who have not entered menopause and who are at least 40 years old

In such cases, the team recommended that doctors use the Fracture Risk Assessment Tool (FRAX). This is an online calculator that can provide predictions about the risk of a person developing a major fracture over the next 10 years of his/her life. Specifically, FRAX estimates the risk of a fracture occurring in the backbone (spine), forearm, shoulders and hips.

FRAX calculators have been developed by the World Health Organization (WHO) and optimized for many countries, including Canada.

The team recommends that FRAX be repeated “every two to three years or when a new clinical risk factor develops.”

FRAX takes into account at least the following risk factors:

- age
- race
- country
- gender
- height and weight
- parental history of fracture

A link to a FRAX calculator appears in the section on bone resources in this issue of Treatment Update.

DEXA

The team stated that it is “reasonable” to assess bone density with DEXA scans in the following groups of HIV-positive people whose likelihood of developing a major fracture in the next decade of their life (as predicted by FRAX) is at least 10%:

- men aged 40 to 49 years
- women aged 40 to 49 years who have not begun the transition to menopause

The team also recommended the use of DEXA scans in the following populations:

- all post-menopausal women
- all men 50 years of age and older
- adults “with a major fragility risk factor regardless of age”

The team stated that “routine DEXA screening of all HIV-[positive] patients on ART is not recommended.”
Spine fractures

The doctors stated that initially painless fractures in the backbone are “common” among HIV-positive people, with such problems occurring in up to 25% of this population. Furthermore, the team noted that the presence of these fractures is “a strong risk factor for future fractures.”

The team recommends that the height of patients should be measured every one to two years in adults who are aged 50 years and older. The loss of 2 cm or more in height in such a period is suggestive of osteoporosis and possibly a fracture in the spine.

To screen for these subclinical (initially painless) fractures, the team recommends that X-rays of the spine or a DEXA-based fracture assessment be done, particularly in women aged 70 years and older and men aged 80 years and older. Readers should note that a recent report (appearing later in this issue of TreatmentUpdate) suggests that these subclinical fractures have been found to occur in HIV-positive people who are much younger than these thresholds suggested by the researchers.

Lab tests

The team stated that blood tests should not be used to “determine fracture risk or low bone density.” Although such tests exist, their findings are not always definitive and their use is largely restricted to research settings.

ART

The team stated, “As the benefits of ART far outweigh the potential negative long-term effects on [bone density and bone] metabolism and fracture risk, local or national guidelines for initiation and choice of ART regimen should be followed.”

In patients with low bone density or who have osteoporosis, the team recommends that certain anti-HIV medicines be avoided, including the following:

- tenofovir (Viread and found in Truvada, Atripla, Complera and Stribild)
- boosted protease inhibitors

Today most protease inhibitors are used with a small dose of the protease inhibitor ritonavir (Norvir). The purpose of a low dose of ritonavir is to raise and maintain, or boost, levels of the other protease inhibitor being used so that once-daily dosing is possible. Over the past five years, commonly prescribed combinations of boosted protease inhibitors have included the following:

- darunavir (prezista) + ritonavir
- atazanavir (Reyataz) + ritonavir
- lopinavir + ritonavir (co-formulated in one pill called Kaletra)

In 2015, the U.S. Department of Health and Human Services (DHHS) recommended that for the initial treatment of HIV infection doctors prescribe combinations of ART containing an integrase inhibitor or the combination of darunavir + ritonavir.

The reasoning behind the recommendation by the team to avoid tenofovir-containing medicines or boosted protease inhibitors other than darunavir + ritonavir is as follows:

“…these regimens have been associated with greater decreases in bone density compared with other [nucleoside analogues] and raltegravir [Isentress].”

The team stated that the combination of dolutegravir (Tivicay) and Kivexa (abacavir + 3TC) is a regimen that they recommend. Dolutegravir is an integrase inhibitor. However, they caution that only limited information on the impact of dolutegravir-containing regimens on bone health is available.

Soft bones

Osteomalacia (soft bones) generally occurs when bones do not get enough of the minerals calcium and/or phosphorus. This can cause bone pain, weak muscles, low bone density and fragility fractures.

There are some reports of osteomalacia occurring in HIV-positive people who were using tenofovir or efavirenz (in Sustiva, Stocrin and Atripla).

The team advised doctors that osteomalacia should be suspected in patients with low bone density and the following:

- higher-than-normal levels of phosphorus (or phosphate) in the urine
• low levels of phosphate in the blood
• elevated levels of parathyroid hormones in the blood
• severe vitamin D deficiency – less than 25 nmol/L (or less than 10 ng/mL) in the blood

In cases of osteomalacia, the team recommended that the use of efavirenz and/or tenofovir should be avoided.

Fragility fractures and healthier habits
The team recommends that all HIV-positive people who are at high risk for fragility fractures be counselled about healthier living strategies. Counselling should include at least the following topics:

• smoking cessation (where appropriate)
• avoid excessive intake of alcohol
• engage in regular weight-bearing and muscle-strengthening exercises
• take steps to prevent falls

Calcium
The team encourages doctors to remind their patients to eat foods containing a sufficient amount of calcium every day (referral to a dietician may be necessary).

The team recommends that, ideally, the first approach to attaining daily calcium requirements is to increase the intake of calcium from food. However, the team noted that “calcium supplements may be appropriate if dietary calcium intake is insufficient.”

Recommended calcium intakes by the team are as follows:

• men (50 to 70 years) – 1,000 mg of calcium daily
• men (71 and older) – 1,200 mg of calcium daily
• women (51 and older) – 1,200 mg of calcium daily

Vitamin D
Multiple studies have found that HIV-positive people tend to have lower-than-ideal levels of vitamin D in their blood. The team encourages doctors to have laboratories assess the amount of vitamin D in the blood of their patients who have low bone density or who have a history of fractures. In addition, the team noted that doctors should consider testing vitamin D levels in people with the following factors associated with low vitamin D:

• dark skin
• avoiding sun exposure
• malabsorption of nutrients
• a diet poor in vitamin D
• obesity
• chronic kidney disease
• past or current use of efavirenz

Recommendations about vitamin D dosage
The team recommends that supplementary vitamin D be given to HIV-positive people whose levels in the blood are graded as follows:

• insufficient – less than 50 nmol/L (20 ng/mL)
• deficient – less than 25 nmol/L (10 ng/mL)

The goal of vitamin D supplementation, the team stated, is to raise levels in the blood to “approximately 75 nmol/L (30 ng/mL).” Once this is achieved, the next goal should be maintenance of this level and that dosing should be driven by blood test results.

The importance of vitamin D
Vitamin D helps people absorb calcium from their diet and has an important impact on bone and muscle health. Furthermore, many medicines used to treat osteoporosis work best when vitamin D levels in the blood are at least 75 nmol/L. The team stated that it is important for patients to achieve the target level of vitamin D (in their blood) before therapy for low bone density is prescribed.

Vitamin D dosing
When a patient’s blood concentration of vitamin D is greater than 75 nmol/L, the team says that 1,000 IU/day of vitamin D₃ should be sufficient to maintain this concentration.

For patients whose blood levels are between 50 and 70 nmol/L, the team says that 2,000 IU/day of vitamin D₃ should help to raise these levels to the target of approximately 75 nmol/L. However, the
team notes that doctors may need to “consider a more aggressive replacement strategy” if patients have any of the following conditions or features:

- hyperparathyroidism
- osteomalacia
- malabsorption
- obesity
- taking medicines that affect the production of vitamin D

Higher doses of vitamin D need to be considered because patients with any of these conditions may take longer to reach the target concentration of 75 nmol/L of vitamin D in their blood.

For patients whose blood levels are between 37.5 and 50 nmol/L, the team recommends higher doses, such as the following:

- 50,000 IU/week of vitamin D$_2$ or D$_3$ for between eight and 12 consecutive weeks (or “the equivalent of 6,000 IU/day of vitamin D$_3$”).

Again, the team cautions that doctors may need to “consider a more aggressive replacement strategy” if patients have any of the previously listed conditions or features.

A checklist
Prior to initiating therapy for low bone density, the team encourages doctors to screen their patients for potential causes of low bone density, including the following:

- low levels of vitamin D in the blood
- elevated levels of parathyroid hormone in the blood
- higher-than-normal levels of thyroid hormone in the blood
- lower-than-normal levels of testosterone in both men and women
- Cushing syndrome (a disorder where the body produces too much of the hormone cortisol)
- kidney disorders
- some cancers
- some gastrointestinal disorders

For more information about vitamin D, its forms, sources and recommendations by specialists, see this link:


A future issue of TreatmentUpdate will have more information on vitamin D.

Additionally, the team asks doctors to avoid prescribing certain medicines that are associated with thinning bones, such as the following, “if appropriate alternatives are available”:

- anti-seizure drugs
- proton pump inhibitors (used to reduce stomach acidity)
- certain antidiabetic drugs called glitazones
- corticosteroids

Specific therapy for low bone density
The team recommends one of the following medicines for treating low bone density:

- alendronate (Fosamax, Fosavance) – 70 mg once weekly by mouth, accompanied by calcium carbonate 1,000 mg/day and vitamin D$_3$ 400 IU/day
- zoledronic acid (Aclasta, Zometa) – 5 mg administered intravenously once yearly

The team states that treatment with these drugs needs to be individualized; that is, treatment should be reviewed after the first three to five years of administration. The reasons for this period of reassessment are to assess changes in bone density and fracture risk and to screen for the possibility of rare side effects such as osteonecrosis of the jaw and fracture of the thigh bone. For more information about these potential side effects, see this previous issue of TreatmentUpdate:


There are other medicines that could be used for the therapy of osteopenia or osteoporosis; however, the team did not provide detailed recommendations about them.
Effectiveness

The team mentions several ways to assess whether therapy has been successful (these assessments have been validated with thousands of HIV-negative people):

- lack of new fractures or signs/symptoms of new fractures
- maintaining height (less than a 1-cm decrease)
- either no decrease or an increase in bone density in the hip and spine when assessed by DEXA scans
- reduction in the level of proteins in the blood or urine that are associated with thinning bones (these may only be available from research laboratories)

If the recommended therapies do not work, the team suggests that doctors refer patients to a specialist.

REFERENCES:


B. Investigating fracture risk in women with and without HIV

To better understand health issues among women at high risk for or who have HIV, researchers at clinics in key cities in the U.S. have collaborated on a study called WIHS (Women's Interagency HIV Study, pronounced “wise”). This study is important because it has enrolled women who are from the same general community with a similar socioeconomic profile. Its findings are highly relevant to the HIV epidemic among women in the U.S. and perhaps some other high-income countries as well. A recent analysis from WIHS sought to understand health-related information collected with a particular focus on fractures. Over an average of 10 years of monitoring, the researchers found that HIV-positive women were more likely to develop fractures than HIV-negative women. Possible factors associated with an increased risk for fractures were also analysed.

Study details

Researchers analysed data collected between 2002 and 2013. This information was obtained from twice-yearly interviews, medical examinations, blood tests and other assessments. In total, data from 1,713 HIV-positive and 662 HIV-negative women were analysed. Our report focuses on the HIV-positive women.

Recruitment for the study occurred at clinics in the following cities:

- The Bronx/Manhattan
- Brooklyn
- Chicago
- Los Angeles
- San Francisco
- Washington, DC

Upon entering the study, the average profile of HIV-positive participants was as follows:

- age – 40 years
- body mass index (BMI) – 29
- current smoker – 45%
- underwent or undergoing menopause – 19%
- history of injecting street drugs – 28%
- history of fracture(s) – 4%
- a moderate or worse degree of kidney disease – 8%
- CD4+ count – 480 cells/mm³
- history of AIDS-related illness – 40%
- taking potent combination anti-HIV therapy (ART) – 63%
- active hepatitis C virus infection – 24%

Results—New fractures

During the study a total of 360 women (16%) developed fractures, distributed as follows:

- HIV-positive women – 18%
- HIV-negative women – 14%

This difference was statistically significant; that is, not likely due to chance alone.
Fragility fractures—fractures that can occur because of falls from standing height (as opposed to major trauma such as car accidents)—occurred in 4% of all women and were distributed as follows:

- HIV-positive women – 5%
- HIV-negative women – 4%

This difference was not statistically significant.

Here is some additional information about the women at the time new fractures occurred:

Average age
- HIV-positive women – 42 years
- HIV-negative women – 40 years

Proportion who had completed the transition through menopause
- HIV-positive women – 57%
- HIV-negative women – 47%

None of these differences was statistically significant.

Compared to HIV-negative women, HIV-positive women were more likely to have fractures in the hips.

Also, HIV-positive women were more likely to have fragility fractures in parts of the body not commonly associated with these fractures, such as the following:

- foot
- toe
- hand
- finger
- ankle
- knee

**Linked to fractures**

Taking all the data they collected into account, the researchers found that the presence of HIV infection raised the risk of developing a fracture by 45%.

Other factors linked to an increased risk for fractures were as follows:

- older age
- being white
- history of fracture(s) prior to entering the study
- history of substance use
- history of using cocaine

**Strengths and weaknesses**

This analysis of data captured over a decade was particularly useful because, unlike some other studies, WIHS enrolled HIV-positive and HIV-negative women from the same communities. This is important because many studies tend to compare HIV-positive people from an idealized average HIV-negative person, not necessarily from the same geographic and socio-economic group.

Furthermore, although there have been many studies of bone density in HIV-positive people, such studies have enrolled mostly men. Despite this, WIHS found that rates of fracture in HIV-positive women were similar to those found in a study among Danish HIV-positive men.

There are limitations to WIHS. A major one was that researchers were unable to distinguish the impact on bone health of co-infection with hepatitis C virus from that of substance use. Another limitation was that reports of fractures by participants were not confirmed with additional X-rays or verified in medical records.

**What to expect**

Based on the WIHS results, doctors associated with the study stated that they expect fracture rates “will increase over time in [HIV-positive] women as they age. In particular, rates may increase among women [who are not black] and in women with a history of substance use.”

The results from WIHS confirm findings from other studies about an increased fracture risk among women with HIV, even among women who are merely middle-aged.

The WIHS findings underscore the importance of efforts by doctors and nurses to screen and treat HIV-positive women for low bone density.

**REFERENCE:**

Sharma A, Shi Q, Hoover DR, et al. Increased fracture incidence in middle-aged HIV-infected and uninfected women: updated results from the Women’s Interagency HIV
C. Menopause, race/ethnicity and changes in bone density

As people age, bones tend to become thinner and more prone to fractures. Researchers have found that HIV-positive people are generally at an increased risk for thinning bones and fractures. Among women who have transitioned through menopause, major shifts in the production of hormones—estrogen and progesterone—have occurred. While these shifts affect fertility, they also affect bones.

Scientists in New York City have been conducting research called the Menopause Study (MS). Just over a decade ago they enrolled women, about half of whom were HIV-positive, and have been monitoring changes to their hormones and health. Participants underwent twice-yearly interviews, physical examinations, blood tests and other assessments. A subset of women had low-dose X-ray scans called DEXA (dual-energy X-ray absorptiometry), which are used to assess bone density. The latest analysis from MS focused on the complex relationship between race/ethnicity, stages of menopause and bone density.

Study details

Researchers analysed data from 219 HIV-negative and 246 HIV-positive women who began to enter the study in 2001. All of these women had two DEXA scans while in the study—one at the beginning of the study and the other at least 18 months later. This allowed researchers to assess changes in bone density over time.

The average profile of HIV-positive participants upon entering the study was as follows:

- age – 47 years
- body mass index (BMI) – 28
- CD4+ count – 486 cells/mm³
- HIV viral load – 141 copies/mL
- taking anti-HIV therapy – 70%
- history of AIDS – 31%
- current smoker – 61%
- ever used opioids – 31%

At study entry, almost 20% of all women had transitioned through menopause; that is, they were postmenopausal. Over the course of the study, an additional 10% of HIV-positive women and 6% of HIV-negative women became postmenopausal.

Results—Comparisons by HIV status

After an average of five years in the study, DEXA scans revealed that in general HIV-positive women had reduced bone density in their hips and thighs compared to HIV-negative women.

A note on terms

Researchers who study menopause have divided this process/event into several stages as follows:

- premenopause – menopause has not yet began
- perimenopause – the early stage of menopause, when periods become irregular and may become shorter or longer. Some women also experience symptoms such as problems sleeping, hot flashes and vaginal dryness. Perimenopause usually occurs when women are in their 40s.
- menopause – eventually periods stop and when a woman has not had her period for 12 consecutive months, menopause has occurred. Symptoms such as hot flashes, sleeping problems, decreased energy and, in some women, feelings of anxiety and sadness can occur. Other issues associated with menopause can include dry skin, thinner hair and weight gain. The transition through the stages of menopause can last several years.
- postmenopause – menopause is finished

Results—Stage of menopause and bone loss

When researchers examined the overall impact of changes in bone density and menopausal stage they found the following:

- Women who entered the study while in perimenopause and then became postmenopausal had the greatest decrease in bone density, averaging about 1.7% per year.
Women who were postmenopausal throughout the study had their bone density decrease by an average of 1% per year.

Women who were premenopausal when they entered the study and who became perimenopausal and remained in perimenopause throughout the study had their bone density decrease by 0.64%.

Women who were perimenopausal when they entered the study and remained in perimenopause throughout the study had their bone density decrease by about 0.60%.

A look at race/ethnicity and HIV

Overall, the researchers found that HIV did not accelerate bone thinning among women who were black.

However, among women who were white or Latina, HIV infection was associated with a 0.6% decreased bone density per year in the hips.

Black women and changes in bone density during the menopause transition

All black women in the study, regardless of HIV status, experienced greater loss of bone density in the hips during the menopause transition than women of other ethno-racial groups. Among all black women, here are some changes in bone density depending on the stage of menopause with which they entered and ended the study:

- perimenopause to postmenopause – a decrease of 1.9% in bone density occurred
- postmenopausal throughout the study – a decrease of 1.3% occurred
- premenopause to perimenopause – a decrease of 1% occurred
- perimenopausal throughout the study – a decrease of 0.76% occurred

ART

Starting anti-HIV therapy (commonly referred to as ART or HAART) was not linked to a decrease in bone density. However, the researchers found that interrupting ART and then restarting it was linked to decreased bone density at the thigh.

Use of the anti-HIV drug tenofovir (Viread and found in Truvada, Atripla, Complera and Stribild) was not directly linked to the loss of bone density. However, when participants stopped taking tenofovir, the density of their bones at the thigh and spine increased.

We caution readers that this study was observational in nature so firm conclusions about the impact of tenofovir on bone health cannot be drawn. Furthermore, the reasons for the discontinuation of tenofovir were not reported; these could have affected the interpretation of the data.

Bear in mind

These findings about the stage of menopause and different ethno-racial groups shed new light on bone thinning in women. According to the researchers, the results of the MS study can help doctors and nurses caring for HIV-positive women. By taking factors such as HIV infection into account for non-black women and the stage of menopause for black women, doctors may be able to identify women at the greatest risk for bone thinning (and therefore fracture risk) and prioritize patients for discussions about the initiation of screening and the offer of treatment for low bone density.

REFERENCE:


D. Backbone fractures and HIV

Breaks (fractures) in the bones that make up the spine are relatively common in people with osteoporosis. According to doctors in Milan, Italy, affected people may not initially notice such fractures. This lack of recognition tends to occur because at first such fractures may be minor and symptom free. However, even a person with an initially symptom-free spine fracture is at increased risk for future fractures, both in the spine and hips. Furthermore, a growing number of fractures in the spine can cause pain, severe difficulty with movement and posture and, eventually, an increased risk of death.
To explore the presence of backbone fractures in HIV-positive people, doctors in Milan analysed health-related information collected from a fracture-screening program at their clinic. Among 194 participants who underwent assessments of bone density and had X-ray scans of their spine, doctors found that 12% had fractures in their backbone and 9% had deformities arising because of fractures in the spine. People aged 51 and older were significantly more likely to have backbone fractures than younger participants. Unexpectedly, most fractures (70%) were diagnosed in people who did not have osteoporosis.

While most studies of fracture risk in populations deal with the issue of the density of bones, the Milan (and other) researchers also raise the issue of the micro architecture of bone. Another study in HIV-positive people has also raised this issue, and bone micro architecture is likely an issue that requires further research in people with HIV.

Study details
Doctors in the infectious disease clinic at the University of Milan conducted an extensive screening program for bone thinning and fracture among HIV-positive people. In addition to undergoing low-dose X-ray scans called DEXA (dual-energy X-ray absorptiometry), used for assessing bone density, participants had X-ray scans of their spine and extensive blood tests.

People who had a history of backbone fractures and/or were using medicines to increase bone density were not enrolled.

The average profile of participants was as follows:

- 73% male; 27% women
- age – 49 years
- body mass index (BMI) – 24
- CD4+ count – 460 cells/mm³
- taking ART – 71%
- co-infection with hepatitis B or C – 25%
- current smokers – 58%
- used corticosteroids – 15%
- used street drugs – 19%
- lower-than-ideal levels of vitamin D in their blood – 56%
- 33% of female participants had undergone menopause

Results—Bone density
DEXA scans revealed the following:

- 42% had normal bone density
- 43% had osteopenia (moderately thin bones)
- 15% had osteoporosis (severely thin bones)

Fractures
Analysis of the X-ray scans of the spine revealed that 12% of participants had fractures in their backbones. These fractures were distributed among different age ranges as follows:

- 39 years and younger – 2% had spine fractures
- 41 to 50 years – 12% had spine fractures
- 51 years and older – 24% had spine fractures

Fractures were distributed among people with different bone densities in the following ways:

- normal bone density – 10% had fractures (eight out of 81 participants)
- osteopenia – 11% had fractures (nine out of 84 participants)
- osteoporosis – 24% had fractures (seven out of 29 participants)

These differences were not statistically significant.

Risk factors for backbone fractures
Taking all of the health-related data they collected into account, researchers found that the following factors were statistically linked to an increased risk of backbone fractures:

- being older than 50 years of age
- having used corticosteroids

There were statistical trends that approached but did not reach significance, suggesting that perhaps a larger study might have found the following to also be risk factors:

- injection of street drugs
- excess alcohol drinking

However, in the present study these were not significantly linked to bone loss.
Bear in mind

The present study was done with data captured at one point in time. Such studies are cross-sectional in nature and can only provide a snapshot of what was happening at that time. Long-term observational studies of larger numbers of HIV-positive people may be needed to capture a more detailed picture of changes in bone health and the impact of drugs used to treat low bone density.

What is interesting about the Milan study was that many backbone fractures (70%) occurred in participants who did not have osteoporosis, suggesting that backbone fractures may be more common than expected among people with HIV.

A deeper look

The Milan study also suggests that, regardless of bone density, unfavourable changes are occurring deep within the bones (the microstructure or micro architecture) of some HIV-positive people. Such changes in micro architecture are only partially revealed by DEXA scans. More sophisticated assessments, such as high-resolution peripheral CT scans, would be needed to gain insight into the changes in the bones' micro architecture.

A Swiss study

Researchers in the Swiss city of Geneva using high-resolution CT scans have confirmed changes in the micro architecture of the bones of some HIV-positive men aged 60 and older. These researchers analysed data from 28 HIV-positive men and compared them to data from 112 HIV-negative men of similar age. In this study the following factors were statistically linked to unfavourable changes in bone micro architecture:

- low levels of physical activity
- lower-than-normal levels of estrogen
- higher-than-normal levels of proteins in the blood linked to bone thinning

There was no connection between poor bone micro architecture and the following:

- the use of the anti-HIV drug tenofovir (Viread and found in Truvada, Atripla, Complera and Striibild)
- testosterone levels in the blood
- vitamin D levels in the blood

Furthermore, none of the HIV-positive men were taking treatment for low bone density.

The Swiss study was small but innovative in its use of high-resolution CT scans.

The combined results of the studies from Italy and Switzerland should pave the way for further investigation into the underlying reasons for the unfavourable changes to bone micro architecture.

REFERENCES:


E. A clinical trial of zoledronate for increasing bone density

The drug zoledronate (also known as zoledronic acid and sold under several brand names including Aclasta, Zometa and Reclast) is one of the drugs that doctors can prescribe to help maintain or increase bone density. This drug belongs to a class of medicines called bisphosphonates and works by interfering with cells that break down bones. By impairing the activity of such cells (called osteoclasts), bone density can be maintained or increased. Zoledronate is given at a dose of 5 mg intravenously once a year.

Researchers in Barcelona, Spain, conducted a clinical trial of zoledronate by randomly assigning participants to receive one of the following interventions:

- one dose of zoledronate + dietary counselling
- dietary counselling alone

After about one year, participants who had received zoledronate were again randomized to one of the following interventions:

- a second dose of zoledronate
- continued dietary counselling
Over the course of this two-year study, bone density in the spine of participants who received counselling alone decreased by about 2%. Among participants who received zoledronate for one year, bone density of the spine increased by 5%. Among participants who received the drug for two years, bone density increased by 8%.

These changes in bone density may seem small but clinical trial data from thousands of HIV-negative people suggest that such increases are associated with a reduced risk for fractures.

**Study details**

Researchers enrolled 31 participants who were mostly male (only a handful were women) and who had been on a stable anti-HIV regimen for at least six months. At the start of the study, participants were randomly assigned to receive one of the following interventions in a 2:1 ratio:

- zoledronate + dietary counselling – 21 participants
- dietary counselling – 10 participants

Zoledronate was administered intravenously at a dose of 5 mg over 15 to 30 minutes.

Dietary counselling was given every four months to educate participants and remind them to eat sufficient calcium from food. Participants also received 800 IU/day of vitamin D₃. This dose of vitamin D helps the absorption of calcium from the intestine but is unlikely to have a significant impact on bone density.

After 48 weeks, zoledronate users were further randomized to receive either a second dose of the drug or no additional dose.

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

- age – late 40s
- time since HIV diagnosis – 14 years
- at least 60% were taking a tenofovir-containing regimen
- CD4+ count – between 500 and 600 cells/mm³
- vitamin D levels – at least 15 ng/ml (about 38 nmol/L)
- body mass index (BMI) – 25

**Results—Week 48**

Percent changes in bone density in the spine were as follows:

- dietary counselling – minus 2%
- zoledronate + dietary counselling – plus 6%

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

Percent changes in bone density in the hips were as follows:

- dietary counselling – plus 0.9%
- zoledronate + dietary counselling – plus 3.5%

This difference was also statistically significant.

**Results—Week 96**

Percent changes in bone density of the spine were as follows:

- dietary counselling – minus 2%
- one dose of zoledronate + dietary counselling – plus 5%
- two doses of zoledronate + dietary counselling – plus 8%

These differences were statistically significant when comparing the effects of dietary counselling alone to one or two doses of zoledronate. However, there was no significant difference when assessing changes in bone density between the different doses of zoledronate.

Percent changes in bone density of the hips were as follows:

- dietary counselling – plus 2%
- one dose of zoledronate + dietary counselling – plus 4.5%
- two doses of zoledronate + dietary counselling – plus 5%

Although the increase in bone density in the hips among participants who only received dietary counselling might seem helpful, it was described by researchers as “modest” and they noted that there was no increase in the bone density of the spine among participants who received dietary counselling alone (without zoledronate).
A statistically significant difference in bone density was found when comparing the effects of dietary counselling to the use of two doses of zoledronate. However, there was no significant difference in bone density when either one or two doses of zoledronate were compared to each other.

**Bone turnover**

Although most people think of bones as hard and largely inactive, at the cellular level bones are very dynamic. Parts of bones are always being repaired, torn down and strengthened. This activity—whereby small parts of bones are torn down and repaired—is referred to as bone turnover by researchers.

Some proteins in the blood, called bone turnover markers, can be measured. These proteins can sometimes provide a rough idea of the balance taking place within the body between tearing down and building up bone. Assessment of these proteins is done as part of research studies and not part of routine care. Assessing changes in these proteins, in addition to X-rays, can give researchers an idea of what is happening in bones.

Overall, in the present study, the level of bone turnover markers fell significantly among participants who received zoledronate compared to those who did not get this drug. This suggested that among participants who received zoledronate bone density was more likely increasing rather than decreasing.

**Side effects and complications**

Three participants who received zoledronate had the following side effects that lasted for between one and two days after the drug was infused:

- lack of energy
- fever

**Bear in mind**

The results of this study suggest that one or two doses of zoledronate have broadly similar benefits on bone density and are better at increasing bone density than dietary counselling coupled with low-dose vitamin D₃. However, bear in mind that this study cannot provide firm results when it comes to comparing the effectiveness of the two zoledronate dose regimens. Although the study was randomized and had a control group (those who received dietary counselling), it enrolled a relatively small number of participants. The study results can serve as a guide to developing a longer and larger study to assess the impact of different doses and schedules of zoledronate in HIV-positive people.

**About zoledronic acid**

Studies with HIV-negative people who have thinning bones due to use of corticosteroids or menopause have found that zoledronate is more effective at maintaining or increasing bone density than other bisphosphonates such as risedronate (Actonel) and alendronate (Fosamax, Fosavance).

The improvement in bone density as a result of zoledronic acid in the Barcelona study is similar to that reported in small studies with HIV-positive people. The results of the Barcelona study confirm that a single dose of zoledronate can have activity that lasts up to two years.

Although rare cases of osteonecrosis of the jaw have been reported in some HIV-negative people who used zoledronate in other clinical trials, serious toxicity from zoledronate did not occur in the Barcelona study.

The Barcelona researchers stated: “Based on our results, doses [of zoledronate] could be spaced to prevent acute and long-term toxicity.” They added, “Both [a single dose and two consecutive yearly dosings] could facilitate adherence in patients who are already receiving a wide array of treatments.” They also noted that the intravenous administration of zoledronate bypasses the gastrointestinal problems that sometimes occur in users of oral bisphosphonate therapy. The researchers stated that zoledronate is processed by the kidneys and did not interact with anti-HIV drugs taken by participants (though the latter was not formally assessed in the present study).

**REFERENCE:**

F. A survey about preferences for bone therapy

Researchers have found that when people initiate potent combination anti-HIV therapy (commonly called ART or HAART) their bones can lose some of their density. Usually the loss is between 2% and 6%. However, by the second year of therapy this loss generally stabilizes.

Some researchers think that this period of initial bone thinning needs to be addressed rather than wait for bone density to fall to critical levels. Perhaps bone drugs could be used for a relatively short period of time after the initiation of ART to help stabilize bone density so that osteopenia and/or osteoporosis do not develop.

Toronto-based infectious disease specialist Darrell Tan, MD, and colleagues surveyed HIV-positive patients about their knowledge of bone issues and their willingness to take therapy to maintain or increase their bone density.

About half of the patients surveyed expressed a willingness to take short-term medicines to prevent bone thinning. The researchers also uncovered misperceptions about bone health that underscore the need for patient education about this topic.

Study details

Researchers developed a survey and recruited participants who attended a primary care clinic and a hospital-based clinic, both in downtown Toronto.

Participants were asked to complete a questionnaire concerning the following three themes:

- preferences regarding therapy to prevent and/or treat thinning bones
- knowledge about bone health
- knowledge about fracture risk

Participants were surveyed in the summer of 2013. A total of 112 participants completed the survey. Their average profile was as follows:

- 80% men, 20% women
- age – 43 years
- 25% had never taken ART
- 23% initiated ART in the past 12 months
- 52% had begun taking ART more than a year earlier

No participant was taking therapy to stabilize or increase bone density.

Results

Just over half (52%) of participants said that they would be interested in taking medicines to maintain bone density or prevent its loss. This result was the same regardless of whether or not participants were taking ART or had not yet started.

Participants presently taking a large number of pills were more willing to take medicines for bones should they need to in the future compared to participants taking relatively few pills.

Among participants who were willing to take bone medicines, most (80%) were willing to take them for “as long as needed.”

When offered a choice, a clear majority of participants preferred taking bone medicines once weekly (71%) to daily (13%).

Modest knowledge

Based on responses to the survey, researchers described participants’ knowledge of bone health as “modest.” Between 33% and 50% of participants were not aware that there were several important factors—such as HIV infection, some anti-HIV drugs, smoking and excessive use of alcohol—that could have an unfavourable impact on bone density and increase their risk for fractures. Furthermore, 83% of participants believed that osteoporosis was “something that only mattered for the elderly.”

Most participants (65%) stated that they had no risk factors for osteoporosis. In analysing the data collected, researchers were able to determine the following about the participants’ risk factors:

- major ethno-racial groups were distributed among participants as follows: white (42%), black (30%), Asian (12%)
- major HIV risk factors were as follows: 55% had condomless sex with another man; 35% had condomless sex with a heterosexual partner; 4% had received contaminated blood; 2% had shared needles
- fracture history – 21% had a previous fracture
- taking supplemental vitamin D₃ – 25%
• 24% had one risk factor for fractures
• 8% had two risk factors for fractures
• 4% had three risk factors for fractures

The researchers found the following risk factors present in participants:

• smoking
• past or present use of corticosteroids for prolonged periods (more than three months)
• parents who had a hip fracture
• excessive intake of alcohol
• rheumatoid arthritis
• liver disease
• premature menopause

Good for bones

A total of 55% of participants reported doing an activity that helps to strengthen bones—resistance exercises (weight lifting) once or more each week.

The survey shows that slightly more than half of the participants were willing to take therapy for low bone density. Furthermore, a clear preference for once-weekly therapy was expressed. The research team noted that this would make the once-weekly formulation of the drug alendronate (Fosavance) an “attractive option” for many patients.

Alendronate has been studied in large numbers of HIV-negative people at high risk for reduced bone density, including the following populations:

• postmenopausal women
• corticosteroid users
• men with prostate cancer who have taken prescribed therapy to reduce their production of testosterone

Alendronate has also been tested in small studies in HIV-positive people where it has significantly increased their bone density.

The researchers noted that other drugs, including zoledronate, could also be selected for future clinical trials in HIV-positive people.

The present Toronto study is a good and important step for assessing patient preferences for the prevention of low bone density among HIV-positive participants. A future study should assess a larger number of HIV-positive women about their preferences for bone therapy.

The Canadian HIV Trials Network is sponsoring a pilot study by Dr. Tan and colleagues. In this study, called CTNPT 021 or BATARI, researchers will test different interventions, including the following:

• immediate initiation of once-weekly alendronate (Fosavance) 70 mg with vitamin D$_3$
• delayed initiation of once-weekly alendronate 70 mg with vitamin D$_3$
• no alendronate or vitamin D$_3$

For more information about the BATARI study, visit this link at the CTN:

http://www.hivnet.ubc.ca/enrolling/ctnpt021/

REFERENCE:


G. Bone health resources

Osteoporosis Canada

This organization has many helpful resources about bone health; below are just a few:

Osteoporosis Canada
(http://www.osteoporosis.ca/osteoporosis-and-you/copn/)

Osteoporosis Canada’s guide to getting enough calcium in your diet
(http://www.osteoporosis.ca/osteoporosis-and-you/nutrition/calculate-my-calcium/)

Osteoporosis Canada’s guide to whether you need a calcium supplement
(http://www.osteoporosis.ca/osteoporosis-and-you/nutrition/supplements/)

Some medications that can affect your bones
(http://www.osteoporosis.ca/osteoporosis-and-you/secondary-osteoporosis/medications-that-can-cause-bone-loss-falls-and-or-fractures/)

FRAX (fracture risk assessment tool) for Canada
(http://www.shef.ac.uk/FRAX/tool.aspx?country=19)
CATIE Resources


**Canadian HIV Trials Network (CTN)**
Some trials investigating bone health:

A study on alendronate to help increase bone density (http://www.hivnet.ubc.ca/enrolling/ctnpt021/)

A study on fractures and bone micro architecture (http://www.hivnet.ubc.ca/clinical-studies/canadian-hiv-trials-database/ctnpt-001-fracture-case-control-study-in-hiv/)

A study on kidney and bone health in infants (http://www.hivnet.ubc.ca/clinical-studies/canadian-hiv-trials-database/ctnpt-003-2/)
Disclaimer

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

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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What CATIE Does

CATIE is Canada’s source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.

For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients’ needs.

CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

CATIE Publications

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CATIE News
CATIE’s bite-sized HIV and hepatitis C news bulletins.

HepCInfo Updates
CATIE’s bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

A Practical Guide to HIV Drug Treatment
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Positive Side magazine
Holistic health information and views written by and for people living with HIV.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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