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Contents

I PREVENTION

A. HPTN 052: The trial that changed everything 1

B. Details and results of HTPN 052 1

C. Treatment and transmission issues arising from HTPN 052 3

II NUTRITION

A. Vitamin D – a busy little vitamin often caught in the wrong studies 5

B. Overview of vitamin D – sources, dosing, drug interactions, toxicity 5

C. Caution needed with vitamin D in certain conditions 11

D. Controversy in vitamin D dosing 11

E. Excessive immune activation and vitamin D – lessons from multiple sclerosis 13

F. Raising vitamin D levels in HIV-positive people 14

G. Possible roles for vitamin D in selected infections – TB, colds and flu, HIV, hepatitis C virus and bacterial vaginosis 16

H. Can vitamin D increase testosterone concentrations in men? 18

I. Statins and vitamin D – an unusual relationship 20

I PREVENTION

A. HPTN 052: The trial that changed everything

There are several memorable moments in the history of the HIV pandemic. The 1996 International AIDS Conference with its dramatic news about the lifesaving effects of highly active antiretroviral therapy (HAART) was one of those moments. The recent International AIDS Society's congress in Rome in the summer of 2011 will likely be looked back upon as another one of those moments, particularly for the field of HIV prevention. It was at the Rome conference that the results of trial HTPN 052 were released. That trial showed that in serodiscordant couples—where one partner is HIV-positive and the other negative—potent combination therapy for HIV (increasingly called ART instead of HAART nowadays) can significantly reduce the risk of HIV transmission between heterosexual couples. The results of trial 052 were beyond what its study team had anticipated. With no effective vaccine against HIV on the horizon, and the virus continuing to spread, the good news from trial 052 was embraced by attendees.

In this issue of *TreatmentUpdate*, we take an in-depth look at trial 052 and its results. Importantly, we also look beyond the trial results and assess what impact they might have on the real world, outside of a carefully controlled clinical trial.

B. Details and results of HTPN 052

Researchers with the HIV Prevention Trials Network (HTPN) enrolled HIV-1 serodiscordant couples from the following countries:

- Botswana
- Malawi

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- South Africa
- Zimbabwe
- Brazil
- India
- Thailand
- United States

The purpose of trial 052 was twofold:

- to assess the ability of ART to prevent transmission of HIV to the uninfected partner of a couple in a stable relationship
- to compare the effect of early vs. delayed ART in people with CD4+ cell counts between 350 and 550 cells

Researchers screened more than 10,000 volunteers in order to recruit 1,763 HIV serodiscordant couples for this study. This shows the vast amount of work that is necessary to undertake complex clinical trials.

HIV-positive participants were randomly assigned to one of the following two study groups as follows:

- early treatment with ART (886 couples)
- delayed treatment with ART (877 couples)

In the early intervention group, participants received ART immediately upon entry to the study. In the delayed treatment group, participants were monitored and received treatment when their CD4+ cell counts fell to 250 cells or less.

Upon enrollment, participants were screened and treated for sexually transmitted infections (STIs). For the first three months after enrollment, participants returned to the study clinic for monthly visits. Thereafter, visits were once every three months. Couples were encouraged to visit study clinics together to receive the following:

- counselling about the use of condoms for safer sex
- treatment of STIs if necessary
- receipt of sufficient ART until the next study visit

The HIV-negative partner was tested for HIV once every three months.

At each visit participants were regularly interviewed about their sexual behavior. The HIV-positive partner was questioned about adherence to ART and also received adherence counselling.

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

- 97% of couples were heterosexual and HIV infection was evenly distributed between men and women
- most participants were between the ages of 26 and 40 years
- at least 70% of couples reported sex in the past week and about 5% of such encounters were unprotected
- CD4+ cell count (of HIV-positive participants) – 430 cells
- viral load – 25,000 copies/ml
- about 5% of participants were diagnosed with STIs

Results—Transmissions

After about nearly two years, trial 052 was prematurely stopped because of striking differences in the number of HIV transmissions between the two study groups.

In total, 39 HIV transmissions occurred, distributed as follows:

- early therapy group – 4 transmissions
- delayed therapy group – 35 transmissions

However, researchers took blood samples from participants who became infected and from their partners and analysed the genetic material of HIV to see how closely the viruses were related between couples. Using this genetic analysis, the researchers could be reasonably certain that a total of 28 transmissions were linked to the partners in the study. According to the genetic analysis, the distribution of new HIV infections was as follows:

- early therapy group – 1 transmission
- delayed therapy group – 27 transmissions

This difference was statistically significant.

The remaining transmissions that occurred likely did so because the HIV-negative partner had sex with someone outside of the couple (who was not likely taking ART).

The single transmission that occurred in the early therapy group happened three months after the HIV-positive partner had initiated ART. In this case, transmission was from a woman to a man.

Having a relatively high viral load was linked to an increased risk of HIV transmission.

Participants who stated that they used condoms in 100% of sexual encounters were at reduced risk for HIV transmission.

Results—Treatment

Major clinical events—severe illness or death—were distributed as follows:

- early treatment group – 40 events
- delayed treatment group – 65 events

A factor that was highly predictive of such events was a person's viral load at the start of the study. The higher the viral load, the greater the risk of severe illness or death.

A common serious infection was tuberculosis (TB) outside the lungs, called extra-pulmonary TB, distributed as follows:

- early treatment group – 3 cases
- delayed treatment group – 17 cases

However, cases of pulmonary TB were more evenly distributed between the two study groups.

Deaths were distributed as follows:

- early treatment group – 10 deaths
- delayed treatment group – 13 deaths

This difference in the number of deaths was not statistically significant

Results—Side effects

It is important to note that because most trial participants were from low- or middle-income countries and regions, some of them used drugs that are no longer commonly used in high-income countries because of their side effects. Such drugs include:

- d4T (stavudine, Zerit)
- ddI (didanosine, Videx)

These drugs can increase the risk for a range of problems such as nerve damage, inflamed pancreas gland, liver damage and, particularly for d4T, unwanted changes to body shape and appearance of the face.

The most common adverse effects reported in the study fell into these categories:

- psychiatric and nervous system disorders
- disorders of metabolism and nutrition
- gastrointestinal disorders

Severe or life-threatening lab test results were distributed as follows:

- early treatment group – 27%
- delayed treatment group – 18%

Common abnormal lab tests included:

- less-than-normal levels of neutrophils (a type of white blood cell)
- elevated levels of the waste product bilirubin, a known side effect linked to the use of atazanavir (Reyataz)

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2. Hammer SM. Antiretroviral treatment as prevention. *New England Journal of Medicine*. 2011 Aug 11;365(6):561-2.

C. Treatment and transmission issues arising from HTPN 052

Early use of ART in trial 052 resulted in a 41% relative decrease in the number of serious HIV-related illnesses. This suggests that it is beneficial for people to start treatment when they have between 350 and 550 cells rather than delay initiation of treatment until CD4+ cells fall below the 250-cell mark.

Transmission issues

The study team calculated that there was a relative reduction of 96% in HIV transmissions because of the initiation of early ART.

Most transmissions (82%) occurred in participants who lived in Africa. This arose, in part, because of the large proportion of participants enrolled from that continent. Other factors that probably played a role in the high number of transmissions in African countries in trial 052 may have included:

- On average, viral loads in HIV-positive people in Africa tend to be greater than those in HIV-positive people from other regions; the reason for this difference in viral loads is not clear.
- The strain or subtype (also called clade) of HIV that is commonly found in Southern Africa, clade C, may be more easily sexually transmitted than other subtypes of HIV.

Other possible factors to account for the higher proportion of HIV infections in the African study

sites, such as more frequent sex and less frequent use of condoms, are under investigation.

Infectious despite relatively high CD4+ cell counts

The researchers note that other studies have found that people with AIDS and those who have recently been infected with HIV are highly sexually infectious. However, they also stated in their report that the results from trial 052 and other studies "emphasize that HIV can be transmitted from infected persons who are asymptomatic or minimally symptomatic and who have high CD4+ counts. Since most persons with established HIV infection fall into the latter category, such transmission, albeit not maximally efficient, must help fuel the spread of HIV."

Unfinished business

Researchers are still analyzing blood samples from four cases of transmission that occurred in the study. Investigation is still needed to find out why more transmissions occurred in Africa.

Unprotected anal sex is the most infectious sexual route for HIV transmission. We do not yet have details about the role that unprotected anal sex may have played in the transmission of HIV infections in trial 052.

Extending the benefits

Results from the present study clearly show that early initiation of ART in a population with a low rate of sexually transmitted infections (STIs) can greatly reduce the rate of HIV transmission to partners in stable, overwhelmingly *heterosexual* couples.

Although the results from trial 052 are greatly encouraging, as the proportion of MSM (men who have sex with men) couples in this trial was relatively small, firm conclusions cannot yet be drawn about the impact of ART on HIV transmission via unprotected anal sex among MSM.

The results from trial 052 support approaches commonly called "Test and Treat" or "Seek and Treat." Such approaches applied at the level of a community or town or region with widespread HIV testing as part of a comprehensive HIV prevention package (testing, counselling, care) can lead to more diagnoses of HIV infection and offer early initiation of treatment. In such cases, early treatment helps preserve the health of the HIV-positive person and can help reduce the further spread of HIV in the community.

STIs

Sexually transmitted infections can cause inflammation on or inside delicate ano-genital tissue, providing an entryway for HIV. In trial 052, rates of STIs were relatively low and people were regularly screened and treated for STIs.

In the real world outside of a clinical trial, comprehensive programs are needed to extend the benefits of ART on HIV transmission to communities where HIV and STIs are common and people are at high risk for HIV infection. Such programs should include at least the following:

- regular counselling for serodiscordant couples about preventing HIV transmission, including the correct and consistent use of condoms
- regular counselling about taking ART exactly as directed and tips to maintain adherence
- advice about how to cope with the side effects and drug interactions that can occur with ART and other medicines commonly used by HIV-positive people
- regular screening for STIs
- treatment for diagnosed STIs

The role of ART in context

In an editorial that accompanied the publication of HTPN 052's results in the *New England Journal of Medicine*, Dr. Scott Hammer from the Columbia University Medical Centre in New York City stated:

> "Antiretroviral therapy is by no means perfect and is not the ultimate answer to controlling and ending the HIV epidemic. Adverse effects, emergence of drug-resistant viral strains, maintenance of adherence, sustainability, and cost are just some of the concerns." However, "aggressive programs to diagnose and treat HIV infection as part of a comprehensive care package and multiple approaches to the prevention of HIV transmission that have been tested in well-designed clinical trials have the potential to preserve health and control the epidemic until a safe and effective HIV vaccine is a reality."

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II NUTRITION

A. Vitamin D – a busy little vitamin often caught in the wrong studies

Interest in vitamin D, which was discovered nearly 100 years ago, has resurged in the past decade as researchers have found a range of health conditions in which vitamin D may play a role. A glance at some of the many recent scientific papers on vitamin D suggests the possibility that it may help to prevent or reduce certain health complications. However, readers should note that many of the studies that the media use to underscore the role of vitamin D in human health are problematic. A major source of this problem is the design of the studies.

Many vitamin D studies are cross-sectional or observational in nature. Such studies are good at finding associations between vitamin D and a range of health conditions, but they cannot prove that a deficiency of vitamin D causes diseases or that taking very high doses of vitamin D can prevent or treat a specific condition such as cancer, insulin resistance or heart attacks. Cross-sectional and observational studies are prone to inadvertent bias in their interpretation because of many factors for which they cannot be adjusted.

An example of how an observational study can lead one to draw the wrong conclusions is that at least one study suggested that HIV-positive people who had high levels of vitamin D in their blood also had a high CD4+ cell count. Conversely, people in the same study who had low levels of vitamin D had low CD4+ counts. A simplistic reading of this study would suggest that achieving a high concentration of vitamin D in the blood (by taking large doses) would lead to increased CD4+ cell counts. Yet, to date, two prospective clinical trials—one in HIV-positive adults and the other in HIV-positive children—that tested high doses of vitamin D supplementation have not found any subsequent changes in CD4+ cell counts with vitamin D.

Cross-sectional and observational studies are often faster, cheaper and simpler to conduct than large randomized placebo-controlled clinical trials. Cross-sectional and observational studies can serve as a useful starting point for formulating theories that can be tested in clinical trials of a more robust statistical design. However, cross-sectional and observational studies cannot produce definitive results.

A further complication in understanding the applicability of the results of vitamin D studies is that different studies have used different populations, doses and durations of vitamin D supplementation. Also, emerging research suggests that some people may have certain genes that influence a cell's ability to respond to vitamin D. All of these factors can affect the outcome of a study. Now, nearly a century since its discovery, in some ways vitamin D research is still in its infancy.

In this issue of *TreatmentUpdate* we have collected and synthesized important recent data on vitamin D, dosing issues and its potential role for a number of health conditions that can affect people with HIV infection.

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B. Overview of vitamin D – sources, dosing, drug interactions, toxicity

When it was first discovered nearly a century ago, researchers initially classed the compound associated with protection from tuberculosis (TB) and bone disease as vitamin D. However, researchers in the modern era have re-classed it as a hormone, though it is still commonly called a vitamin. As a result of its reclassification, a range of different doctors and researchers have been studying vitamin D, including endocrinologists, nutritionists, cardiologists, immunologists and oncologists. These different fields have enriched our understanding of vitamin D and its potential role in human health.

Where does vitamin D come from?

In general, people get vitamin D from exposure to sunlight, from small amounts in certain foods and from supplements.

A series of steps is involved in the body's production of vitamin D. First, ultraviolet B radiation in sunlight interacts with a fatty molecule (7-dehydrocholesterol) found in the skin and forms pre-vitamin D. This is then transported to the liver, where vitamin D_2 is formed. This is then taken to the kidneys, where vitamin D_2 is converted to vitamin D_3 (sometimes called ergocalciferol). Vitamin D_3 is the form of vitamin D that is used by the body's cells. The formation of vitamin D_3 from its precursor molecules is enabled by enzymes.

If the body produces excessive amounts of vitamin D_3 from sunlight, enzymes are activated that convert vitamin D_3 into its *inactive* forms.

Many possible roles for vitamin D

Vitamin D helps the intestine absorb minerals such as calcium and phosphorus. Without sufficient levels of this vitamin, researchers estimate that "only 10% to 15% of dietary calcium and about 60% of phosphorus are absorbed." These minerals are used to help build bones.

Receptors for vitamin D are found in many tissues, including the following:

- bones
- brain
- hormone-producing glands – pancreas and thyroid
- immune system – T-cells, B-cells and macrophages
- liver
- muscles (including the heart)
- reproductive system – ovary, uterus, prostate and testicles
- skin

The presence of vitamin D receptors in so many different tissues suggests the possibility that vitamin D has a role to play in each one.

Ideal vitamin D levels in the blood

The American Endocrine Society recently released comprehensive guidelines about vitamin D. According to these guidelines, vitamin D deficiency occurs when the level of vitamin D_2 in the blood is less than 50 nmol/l (this is equivalent to 20 ng/ml). Much of our overview of vitamin D is based on the Endocrine Society's comprehensive recommendations and research.

The ideal level of vitamin D for human health is not known. For maintaining a healthy skeleton, the Endocrine Society recommends maintaining an intake of vitamin D such that the levels in the blood are at least 75 nmol/litre. In some cases, to achieve non-skeletal health benefits, perhaps higher concentrations of vitamin D in the blood will be needed. However, there is insufficient data at present to justify higher levels of vitamin D.

Why is vitamin D_2 often assessed?

Vitamin D_2 is the most common form of this vitamin found in the blood. It has a half-life of between two and three weeks. In contrast, vitamin D_3 is present in the blood at levels that are about one thousand times less than vitamin D_2. Moreover, levels of vitamin D_3 in the blood are tightly controlled by the kidneys. The concentration of vitamin D_3 in the blood does not reflect the body's store of vitamin D, and such concentrations are not generally useful for making assessments of human health. Another issue is that the half-life of vitamin D_3 is about four hours. Also, researchers have found that people with vitamin D deficiency tend to have normal or even elevated levels of vitamin D_3 in their blood. Thus, most researchers prefer to assess vitamin D_2 levels.

Vitamin D and parathyroid hormone

The amount of vitamin D_3 produced by the kidneys is controlled by the body, depending on levels of the minerals calcium and phosphorus in the blood. When the body's sensors detect less-than-normal levels of these minerals in the blood, the parathyroid glands, located in the chest, release a hormone called parathyroid hormone (PTH). This hormone causes the kidneys to reabsorb calcium from urine and stimulates enzymes to convert vitamin D_2 into its active form, vitamin D_3.

PTH also stimulates the tearing down of bone so that calcium can be released into the blood. This raises calcium levels in the blood, but at the cost of weakening bone. Prolonged exposure to elevated PTH levels can accelerate vitamin D deficiency and likely plays a role in osteopenia and the more severe loss of bone mineral density called osteoporosis.

Studies have found that PTH levels tend to be higher in cases of vitamin D deficiency but PTH levels tend to reach their lowest levels when the concentration of vitamin D_2 in the blood is between 75 nmol/litre and 100 nmol/litre.

Researchers have found that intestinal absorption of calcium increased between 45% and 65% when the concentration of vitamin D_2 in the blood rose from 50 nmol/litre to 80 nmol/litre.

Based on these and other studies about PTH, calcium and bone health, leading vitamin D researchers have suggested the following:

- When vitamin D_2 levels are 49 nmol/litre or less, vitamin D "deficiency" has occurred.
- When the concentration of vitamin D_2 is between 50 nmol/litre and 74 nmol/litre, people have vitamin D "insufficiency."
- When the concentration of vitamin D_2 is greater than 75 nmol/litre, there is sufficient vitamin D present in the body.

However, there is still considerable debate about what the ideal levels of vitamin D_2 should be for people with a range of health conditions, including osteoporosis, cardiovascular disease and HIV infection. It is possible that even higher concentrations of vitamin D_2 may be necessary for people with these and other health conditions, but research is needed to resolve this controversy.

Who is at risk for vitamin D deficiency?

Several studies have documented that less-than-ideal levels of vitamin D are common in both HIV-positive and HIV-negative people living in North America and Western Europe. Furthermore, several studies have found that deficiencies of vitamin D are even common in HIV-positive people who live in relatively sunny countries such as Brazil, India and Tanzania.

In part, these low levels of vitamin D may occur because the average person spends a lot of time indoors and so does not get sufficient exposure to sunlight. But there might be other factors that affect vitamin D levels, including the following:

Air pollution

Smog can absorb, scatter or reflect ultraviolet radiation (UV), thereby reducing the amount of UV light that hits the skin and subsequent vitamin D production.

Sunscreen

Wearing sunscreen with a sun protection factor (SPF) of 30 reduces the production of vitamin D in the skin by 95%.

Skin tone

Dark-skinned people require between three and five times as much sun exposure to make the same amount of vitamin D as light-skinned people.

Skin temperature

Conversion of pre-vitamin D to vitamin D_3 is affected by temperature. More vitamin D is produced at higher temperatures than at lower temperatures. In general, under normal conditions, the temperature of the skin on the body is lower than core body temperature. On cold days, exposed skin temperature may be even lower than usual. This decrease in skin temperature can affect the production of vitamin D.

Age

The skin of elderly people contains less of the compounds used to make vitamin D than the skin of younger people. Therefore, given the same sun exposure, elderly people likely produce less vitamin D than younger people.

Weight

Very overweight and obese people—those with a body mass index (BMI) of 30 or greater—tend to have vitamin D deficiency.

Medications and herbs

As enzymes in the liver and kidneys help convert pre-vitamin D into its active form, drugs or substances that interfere with these enzymes have the potential to reduce vitamin D levels. Also, drugs that speed up or activate the enzymes that help break down vitamin D_3 and vitamin D_2 into inactive forms have the potential to reduce levels of this vitamin. Here are some of the medicines and herbs with the potential to reduce vitamin D levels:

- 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
- anti-cancer drugs – Taxol and related compounds
- antifungal agents – clotrimazole and ketoconazole
- 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)
- anti-inflammatory drugs – corticosteroids

Health conditions

There are many health conditions that are associated with vitamin D deficiency, including the following:

- intestinal inflammation (occurring in Crohn's disease, cystic fibrosis and so on)
- receipt of transplanted organs – perhaps the medicines used to suppress the immune system interfere with vitamin D production
- liver damage – a healthy liver helps to produce vitamin D_2
- kidney damage – the kidneys help to produce vitamin D_3
- Increasingly, HIV infection has become associated with vitamin D deficiency. It is not clear why this is the case. Some researchers think that because HIV triggers ongoing inflammation, this somehow alters or reduces the body's ability to produce vitamin D. Another possible explanation is that vitamin D deficiency and insufficiency are common in most HIV-negative people, so it should not be surprising to see the same issues in people at high risk for or who have HIV infection. More research will be needed to understand why vitamin D deficiency and insufficiency are so common in HIV-positive people and if vitamin D deficiency is clearly linked to co-morbidities such as cardiovascular disease, insulin resistance, kidney disease and other issues.

Sources of vitamin D

Vitamin D is not found in many foods. But here are some foods that are relatively rich in vitamin D_3, with their approximate amounts per serving shown:

- salmon (fresh and wild caught) – between 600 international units (IU) and 1,000 IU of vitamin D_3 per 100 grams
- salmon (fresh, farmed) – between 100 and 250 IU per 100 grams
- salmon (wild, canned) – between 300 and 600 IU per 100 grams
- sardines (canned) – 300 IU per 100 grams
- tuna (canned) – 236 IU per 100 grams
- egg yolk – 20 IU

Some foods are rich in vitamin D_2, such as these:

- shiitake mushrooms, fresh – 100,000 IU per 100 grams
- shiitake mushrooms, sun-dried – 1,600 IU per 100 grams

Some foods in North America and parts of Europe are fortified, or have added vitamin D_2 or D_3:

- fortified milk – 100 IU per 236 ml
- fortified yoghurt – 100 IU per 236 ml
- fortified breakfast cereals – 100 IU per serving
- fortified margarine – 429 IU per 100 grams

The amount of vitamin D that can be made from exposure to sunlight is affected by many factors, including:

- season
- time of day
- distance from the equator (latitude)
- skin tone
- age

When taking the complexities of these factors into account it is difficult to make general recommendations for the ideal amount of time to be in the sun in order to achieve sufficient vitamin D.

The panel noted that the skin of older people contains fewer of the precursor molecules needed to make vitamin D from sunlight. However, intestinal absorption of high doses of vitamin D from supplements is not affected by this change in the skin.

Vitamin D and bone density

The Endocrine Society's vitamin D panel examined data from a large observational study involving 13,432 adults of diverse ethno-racial backgrounds. In general, it found that greater concentrations of vitamin D_2 in the blood were associated with modestly increased bone density.

A healthy skeleton

German researchers extracted samples of bone from 401 men (average age: 58 years) and 270 women (average age: 68 years) for analysis. They did not find bone abnormalities (less-than-normal levels of bone density) in samples from patients whose vitamin D levels in the blood were greater than 75 nmol/litre. They concluded that in order to maintain a healthy skeleton, sufficient calcium should be taken and vitamin D intake should be enough to achieve a minimum of 75 nmol/litre in the blood.

Analysis of several randomized placebo-controlled studies in which elderly participants received 400 IU/day of vitamin D found that this dose was too low to significantly raise the concentration of vitamin D in the blood.

In a clinical trial that used doses between 400 and 1,000 IU/day, researchers found that the process of slowly wearing down the skeleton was significantly reduced. Moreover, a randomized placebo-controlled study in elderly women with a combination of calcium and 800 IU/day of vitamin D significantly reduced rates of fractures.

Analysis of many vitamin D studies has found that vitamin D's anti-fracture effects become apparent when the concentration of vitamin D in the blood is at least 75 nmol/litre.

While vitamin D is essential for a healthy skeleton, by itself it is not enough to help rebuild bone density that has been lost as a result of age or other factors. Medically supervised assessments and therapy with drugs that help maintain or increase bone density, increased calcium intake and prescribed or supervised exercise are all necessary to help strengthen bones.

Muscles are anchored to bones and exercising them can help strengthen bones. Clinical trials have found that vitamin D can help improve muscle strength and reduce the risk of falls in elderly people, particularly those who are deficient in vitamin D.

Used for analysis

The Endocrine Society's vitamin D panel also incorporated into its analysis other findings from clinical trials with women before and after menopause, and data from trials of men who received 10,000 IU per day of vitamin D_3 for months, as well as additional data from a study in adults who were given 50,000 IU of vitamin D_2 (equivalent to 3,000 IU of vitamin D_3 daily) for up to six consecutive years. In these studies there were no alterations in calcium concentrations in the blood or urine. This suggests that in the absence of other health conditions, high doses of vitamin D by itself do not cause unsafe increases in the amount of calcium in the blood. Also, there were no reports of toxicity in these particular high-dose studies.

Vitamin D panel's dosing recommendations

Based on the wealth of accumulated data, including those from many studies as well as their own clinical and research experience, the vitamin D panel made the following recommendations for people at risk of vitamin D deficiency:

- Keep the level of vitamin D_2 in the blood consistently above 75 nmol/litre (30 ng/ml).
- Adults aged 19–70 years "require at least 600 IU/day of vitamin D to maximize bone health and muscle function." It is unknown if 600 IU/day is enough to provide "all the potential non-skeletal health benefits associated with vitamin D. However, to raise the blood level of vitamin D_2 consistently above 75 nmol/litre may require at least 1,500 to 2,000 IU/day of vitamin D."
- Adults should **not** take more than 4,000 IU/day without medical supervision.
- Adults aged 70 years or older require "at least…800 IU/day." Again, the panel remarked that to achieve levels of 75 nmol/litre in the blood might require daily doses of between 1,500 and 2,000 IU/day.
- The panel suggested using either vitamin D_2 or vitamin D_3 for the prevention and treatment of deficiency.
- Physicians treating adults who have vitamin D deficiency may prescribe "50,000 IU of vitamin D_2 or D_3 once weekly for eight weeks or its equivalent of 6,000 IU/day of vitamin D_2 or D_3" also for eight weeks. The purpose of such a high dose is to raise vitamin D levels in the blood to at least 75 nmol/litre within eight weeks. After this point, a maintenance dose of 1,500 to 2,000 IU/day of vitamin D can be used.
- Special populations – in people who are "obese or who have malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6,000 to 10,000 IU/day) of vitamin D to treat vitamin D deficiency to maintain a vitamin D level [in the blood] above 75 nmol/litre, followed by maintenance therapy of 3,000 to 6,000 IU/day."
- Special populations – people who are HIV positive and/or those who are taking anti-seizure drugs, corticosteroids or antifungal agents such as ketoconazole "should be given at least two to three times more vitamin D for their age group to satisfy their body's vitamin D requirement." Obviously the appropriate dose of vitamin D for adults with HIV infection is going to vary from one person to the next, depending on the concentration of vitamin D in their blood. However, the panel's recommendations provide plenty of guidance for physicians seeking to raise and then maintain vitamin D levels.

Although vitamin D is dissolved in fat, it can be taken with or without a meal, as it does not appear to require fat for absorption.

Concerns about toxicity

Vitamin D is fat soluble, and is therefore stored in the body's fat. As a result, levels of this vitamin can build up, so some researchers are concerned about its potential for toxicity.

In adults, a dose of 50,000 IU/day of vitamin D can eventually increase levels in the blood to more than 374 nmol/litre. At such a concentration, abnormal levels of calcium and phosphorus can also build up in the blood.

Several studies that have lasted for up to five months have found that doses of 10,000 IU/day of vitamin D_3 are not toxic to adults.

A study in people with multiple sclerosis who received an average of 14,000 IU/day of vitamin D for one year also did not detect toxicity.

Based on these and other studies, the panel recommends an upper limit of 10,000 IU/day of vitamin D for adults.

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C. Caution needed with vitamin D in certain conditions

The American Endocrine Society's guidelines state: "Vitamin D supplementation should not be a major concern *except* in certain populations who may be more sensitive to it." Such populations are those who have chronic granuloma-forming disorders, including the following conditions:

- sarcoidosis
- tuberculosis
- chronic fungal infections
- lymphoma

In these conditions, cells of the immune system called macrophages become activated and sometimes produce vitamin D_3 in excessive amounts. As a result, people with these conditions can absorb higher-than-normal amounts of calcium from their intestine. Also, having these inflammatory conditions often triggers the release of calcium from the skeleton into the blood. This leads to higher-than-normal levels of calcium in the blood and in the urine as the body tries to flush out this mineral. The Endocrine Society states that vitamin D and calcium levels in patients with these disorders should be carefully monitored. Excess calcium in the blood and urine of these patients tends to occur when the amount of vitamin D in the blood is greater than 75 nmol/litre.

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D. Controversy in vitamin D dosing

As interest in vitamin D has greatly increased over the past decade given the many studies on this vitamin, doctors and patients seek credible sources of information to guide daily dosing. In November 2010, the Institute of Medicine (IOM), a non-profit group affiliated with the prestigious US National Academy of Sciences, issued a report that took an extremely conservative view on vitamin D. In essence, the report stated that the high blood levels of vitamin D advocated by many physicians and researchers were not necessary. Moreover, it generally suggested that most adults should be satisfied with a daily dosage between 400 and 600 IU of vitamin D.

In June 2011, the American Endocrine Society—an association of 14,000 researchers, physicians and other health and scientific professionals—issued comprehensive evidence-based guidelines that specifically focused on the use of vitamin D not just by healthy people, but also those people with chronic health conditions. Its analysis and recommendations are extensively covered in this issue of *TreatmentUpdate*. We have focused on the Endocrine Society's guidelines in part because the Society has been regularly reviewing the literature on vitamin D research and also because it address the specific health needs of people living with HIV. Also, HIV-positive people appear to be at increased risk for thinner-than-normal bones and the Endocrine Society's guidelines partially addresses that issue. Moreover, the Endocrine Society's recommendations about dosing are similar to what scientists conducting clinical trials with HIV-positive people have found: Generally, larger-than-normal doses are required to raise vitamin D to levels associated with health, particularly skeletal health. Indeed, researchers at Toronto's Hospital for Sick Children, commenting on their experience with a randomized trial of vitamin D supplementation in children with HIV, suggested that higher doses than those recommended by the IOM may be necessary in children and adults with HIV infection and perhaps other chronic medical conditions.

Usually the IOM's reports are taken very seriously and set the agenda for a particular issue in North America and elsewhere. However, instead of addressing some of the confusion about vitamin D, the IOM's report has triggered unease and in some cases outright unrest—unusual reactions to an IOM report.

Researcher and endocrinologist Michael Holick, based at Boston University's School of Medicine, said: "The IOM was too definitive in its recommendations." A proponent of evidence-based medicine, Canadian researcher and professor Gordon Guyatt from McMaster University said,

"Basically, the [IOM's] vitamin D recommendations are based on low-quality evidence." He adds, "I think that admitting that would have made some of the angst disappear."

In the past decade, because vitamin D has become associated with many health conditions, the "medical and scientific communities have become preoccupied with how it might prevent chronic disease," reported the scientific journal *Nature*. The publication also noted that some physicians "recommend doses of up to 6,000 IU/day to make up for the time that people spend indoors. This is less than the amount a fair-skinned person without sunblock might make in half an hour of exposure to the midday summer sun."

Not for everyone

According to *Nature*, the IOM's mandate was to "set the levels [of vitamin D] that protect most people, but not all." Furthermore, according to bone researchers in Germany and Switzerland and bio-statisticians in California, the IOM made a mathematical mistake in its calculations of the ideal level of vitamin D in the blood that is associated with strong bones. The IOM choose a level of 50 nmol/litre. However, an examination of the evidence suggests that setting the level of vitamin D at 75 nmol/litre (as done by the American Endocrine Society) would likely protect more people.

Members of the IOM's panel stand by their calculations, saying that their methodology is "standard procedure for dietary recommendations."

Tension about toxicity

One criticism of the IOM report is that it cited a clinical trial in which elderly women given 500,000 IU of vitamin D annually in a single dose experienced more falls and fractures than women of similar age who were given placebo. According to *Nature*, many researchers found that study "ridiculous." Edward Giovannucci, a nutritional epidemiologist at the Harvard University School of Public Health, said, "No one absorbs 500,000 IU a day from the sun, so why would you give that as a supplemental dose?" But another Harvard University epidemiologist, JoAnn Manson, says that the mega-dose clinical trial should be factored into concerns about toxicity. She notes, "Within the first three weeks of this trial, when serum levels were at or above 100 nmol/litre, there was an increased risk of falls and fractures."

Clinical trials to the rescue

Many clinical trials testing different doses and schedules of vitamin D are underway (some are mentioned later in this issue of *TreatmentUpdate*). Harvard's JoAnn Manson is one of the scientists leading a five-year, 20,000-person study designed to assess the impact of vitamin D supplementation on cancer and cardiovascular disease.

Not all researchers are patient with the current pace of clinical trials of vitamin D. Reinhold Vieth, PhD, a world-renowned vitamin D scientist at the University of Toronto, calls the demand for huge clinical trials a "cop-out." He says that there is good evidence that higher doses of vitamin D would reduce rates of multiple sclerosis, but a clinical trial to test this would require thousands of people and 30 years."

Experts vs. data

Nature has suggested that the IOM panel members "underestimated the passion present in the vitamin D field." Dr. Clifford Rosen, a member of the IOM panel and a respected member of the bone-research community, summarized the ongoing controversy about the IOM report as follows:

> "This is the beginning of a whole new phase…. In the old days of medicine we believed experts, and now we say, show us the data."

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E. Excessive immune activation and vitamin D – lessons from multiple sclerosis

HIV infection causes prolonged and excessive activation of the immune system. As cells of the immune system interact with many organ systems, prolonged activation of the immune system causes many cells in the body to release chemical messengers that incite inflammation. Although the use of potent combination anti-HIV therapy—commonly called ART or HAART—greatly reduces HIV-related inflammation, this problem of immune activation persists. Some researchers think that prolonged inflammation seen in HIV infection likely plays a role in the apparent accelerated aging of the brain, bone, cardiovascular, kidney and other organ-systems.

Researchers have been testing different compounds for their ability to reduce HIV-related inflammation. Most recently, such compounds have included the cholesterol-lowering medications called statins and concentrated fish oil. Clinical trials with one statin—atorvastatin (Lipitor)—have found only modest reductions in immune activation in HIV-positive people. A clinical trial with low-dose fish oil has found minimal changes in immune activation in HIV-positive people. So researchers are considering other compounds, such as high-dose vitamin D_3.

A lesson from MS

With multiple sclerosis (MS), inflammation in the central nervous system—the brain and spinal cord—occurs. Also, the layer of insulation that sheaths nerve fibres is attacked by T-cells. These attacks cause the electrical signals to leak, rendering nerve impulses weaker. This helps weaken control of muscles, affects balance and causes other problems.

Laboratory experiments with cells and animals suggest that vitamin D_3 may be able to partially suppress the activity of T-cells. These and other cells of the immune system, such as macrophages, have receptors for vitamin D. Also, these cells can convert vitamin D_2 into vitamin D_3. Other cells of the immune system, such as dendritic cells, whose function is to help amplify the immune response, can also have some of their functions weakened by vitamin D.

In addition to having the insulation that covers nerves attacked, people with MS have other abnormalities—for instance, their immune system may respond abnormally to common proteins in the body and environment. Lab experiments have found that vitamin D_3 can reduce these abnormalities in cells taken from patients with MS.

A recent Canadian clinical trial has found that very high doses of vitamin D_3 decreased symptoms of MS and reduced excessive T-cell activation. This finding may be of interest to researchers who study the long-term effects of HIV on the immune system.

Study details

Researchers in Montreal and Toronto recruited 49 volunteers who had signs and symptoms of MS and randomly assigned them to be in one of the following groups:

- vitamin D_3 (25 participants)
- control (they did not receive vitamin D)

Vitamin D_3 was given in a complex regimen of increasing doses between 4,000 IU and 40,000 IU per day over the course of one year. On average, participants in the vitamin D group received 14,000 IU of vitamin D_3 daily over the course of the study. Additionally, participants in the vitamin D group received 1,200 mg of calcium per day.

Participants assigned to the control group were not provided with vitamin D_3 by the research team but were allowed to take up to 4,000 IU of vitamin D_3 if they wished.

Results

At the start of the study, all participants had about 78 nmol/litre of vitamin D in their blood, and this level was not different between the two study groups.

A year later, vitamin D levels in the control group were 83 nmol/litre and 179 nmol/litre among people who took high doses of this vitamin.

Cells of the immune system of people with MS tend to react abnormally to a range of proteins in lab tests. Specifically, the immune cells of patients with MS unnecessarily attack proteins that they should not. At the start of the study, such abnormalities were similar in both study groups. However, by the end of the study, participants who received high-dose vitamin D_3 had a more normal level of immunological responses to proteins associated with MS. These proteins represented about 38% of all test proteins used to assess immunologic responses during the study. So the results suggest that excessive immune activation was normalized in people who received high-dose vitamin D_3. This change was statistically significant, not only within the vitamin D_3 group but also in comparison to the control group.

Researchers also found that as vitamin D levels in the blood increased there was a measurable decrease in immunologic reactivity to certain proteins from milk and brain tissue.

Levels of a molecule in the blood called hsCRP (high-sensitivity C-reactive protein) rise during periods of inflammation and fall when inflammation decreases. There were no changes to CRP levels in this study. The researchers speculated that perhaps the lack of change was due to the already high levels of vitamin D in participants.

There were no significant changes in levels of proteins in the blood associated with the building up or tearing down of bone. This should not be surprising because previous studies have found that when the concentration of vitamin D in the blood is at 75 nmol/litre or greater, markers or proteins associated with bone metabolism do not generally change when additional vitamin D is taken.

A previous study found that high-dose vitamin D_3 (20,000 IU per day) for 12 consecutive weeks can cause CD4+ cells to increase their production of anti-inflammatory chemicals. However, no significant changes were found in levels of such chemicals in the present study.

No toxicity due to high-dose vitamin D_3 was reported.

The present study in MS patients showed that high doses of vitamin D_3 are safe. Moreover, such doses of vitamin D_3 have the ability to reduce the immune system's attacks on the body—such attacks are called autoimmunity. The findings from the present study support large, randomized placebo-controlled clinical trials of high-dose vitamin D_3 in other health conditions where excess immune activation and autoimmunity are present, such as HIV infection.

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F. Raising vitamin D levels in HIV-positive people

Vitamin D is not like other vitamins; it acts as a hormone and has complex and poorly understood functions within the body. Vitamin D deficiency and insufficiency are common in people with HIV infection. Anecdotal reports from physicians caring for HIV-positive people and results from clinical trials suggest that getting vitamin D levels in the

blood into the optimal range (75 nmol/litre or greater) is not easy and may take several months or up to a year even when relatively high doses (such as 4,000 IU/day) are taken with over-the-counter oral supplements. Researchers in Los Angeles conducted a 12-week study of oral vitamin D_3 supplementation. Their results suggest that it is possible to significantly raise vitamin D levels in the blood with over-the-counter supplements but very high doses are needed, particularly in cases of pre-existing deficiency.

Study details

Researchers recruited 82 HIV-positive people—78 men and four women. All participants were on stable ART. Their average profile at the start of the study was as follows:

- age – 48 years
- CD4+ count – 552 cells
- viral load – less than 200 copies/ml

Problems such as higher-than-normal blood pressure and abnormal levels of cholesterol in the blood were common.

Prior to entry in the study, none of the volunteers were taking more than 400 IU per day of vitamin D. And the level of vitamin D in their blood was less than 50 nmol/litre, suggesting deficiency.

All participants were supplied with a liquid formulation of vitamin D_3 called Ddrops, with each drop containing 2,000 IU of vitamin D. In Canada, the maximum allowable amount of vitamin D per tablet, capsule or drop sold over the counter is 1,000 IU.

Each participant was instructed to take 50,000 IU twice weekly for five consecutive weeks. After this, participants were told to reduce their dose to 2,000 IU per day for seven additional weeks.

Results

Overall, 81% of participants had their levels of vitamin D rise to 75 nmol/litre or greater after 12 weeks of supplementation. Ten participants (12%) disclosed that they had difficulty taking Ddrops as directed.

About 60% of participants were taking efavirenz (Sustiva, Stocrin and in Atripla) and 77% were taking tenofovir (Viread and in Truvada and Atripla). Exposure to efavirenz has been linked to decreased levels of vitamin D, and exposure to tenofovir, in theory, might have had a similar effect. However, in the present study, exposure to efavirenz or tenofovir or other anti-HIV medicines did not affect the ability of participants to increase their vitamin D levels.

No significant changes in viral load or CD4+ cell counts occurred as a result of taking high doses of vitamin D. Also, no toxicity was reported.

The results of the Los Angeles trial are reassuring in at least several ways, as follows:

- They confirm the effectiveness of the liquid formulation in popular use—Ddrops.
- It is possible for HIV-positive adults to achieve adequate levels of vitamin D in the blood with aggressive oral supplementation.
- High doses of oral vitamin D over the short-term were not associated with toxicity.
- Vitamin D had no negative effects on HIV viral load.
- Vitamin D supplementation did not increase (or decrease) CD4+ cell counts
- Vitamin D levels can rise with supplementation despite the use of medicines such as efavirenz.

The research team plans to continue to monitor the participants in this study to observe the long-term effect of vitamin D supplementation.

The best dose of vitamin D supplementation to move the concentration of this vitamin in the blood closer to ideal levels is not known and will probably vary from one person to another. But the present study may serve as one possible method for quickly raising vitamin D levels.

Many clinical trials of vitamin D are planned or underway in the U.S. with a variety of populations affected or infected with HIV. Here are just a few examples of these trials:

- women who have entered menopause
- comparing the effects of frequent low-doses (between 2,000 and 4,000 IU per day) and very high doses such as 50,000 IU/week for up to eight weeks
- the government-funded AIDS Clinical Trials Group (ACTG) is planning to test whether high-dose vitamin D can prevent the bone loss that often occurs when ART is initiated

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G. Possible roles for vitamin D in selected infections—TB, colds and flu, HIV, hepatitis C virus and bacterial vaginosis

Lab experiments with cells of the immune system—monocytes and macrophages—have found that these cells produce an enzyme that converts vitamin D into its active form. This suggests that these cells use vitamin D as part of the process of fighting infections and possibly tumours. Other experiments have found that exposure to vitamin D_3 stimulates macrophages to release small molecules that can attack germs.

Tuberculosis (TB)

Before potent antibiotics were available, physicians encouraged people with TB to get exposure to sunlight and in some cases vitamin D supplements were administered. However, well-designed clinical trials in the 21st century have found that vitamin D supplements in addition to antibiotics do not confer a major increase in survival or recovery from TB compared to antibiotics alone. Some researchers have suggested that instead of being used as part of treatment, perhaps vitamin D supplements might be more useful in helping to prevent infection with TB. Clinical trials to test this idea have not been done.

Colds and flu

Cells lining the lungs can produce high levels of enzymes that convert vitamin D into its active form, vitamin D_3. This finding suggests that these cells may use vitamin D as part of their defense system against infections. Indeed, in laboratory experiments when these cells are treated with vitamin D_3, they also produce small molecules that help protect cells from infection by viruses and bacteria.

Several clinical trials that have tested vitamin D_3 to assess its ability to reduce the risk of developing respiratory tract infections—the common cold and flu—have had mixed results. It is therefore difficult to draw firm conclusions about the role of vitamin D in preventing respiratory infections. Part of the problem arises from issues related to different study designs and methodology.

HIV

Observational studies have found that HIV-positive people usually have less-than-ideal levels of vitamin D in the blood and, in some cases, deficiency. Vitamin D deficiency in the setting of HIV infection even occurs in sunny tropical countries. Researchers are not certain why this is the case. One possible explanation is that HIV infection triggers ongoing inflammation in the immune system. By inciting the immune system to overproduce inflammation-related chemical signals or cytokines, it is possible that HIV infection indirectly speeds up enzymes that convert vitamin D_3 into inactive forms.

Supplementation with large amounts of vitamin D does not increase HIV replication in people who are taking ART. Results from two clinical trials suggest that vitamin D_3 does not affect CD4+ cell counts in HIV-positive adults and children.

Larger observational studies have found that vitamin D deficiency has been linked to an increased risk of death among HIV-negative people, particularly from cardiovascular disease. A recent European study with about 2,000 participants has found an association between low vitamin D levels and reduced survival among HIV-positive people. Details about this study appear in *TreatmentUpdate* 181. As the study is observational in nature, it cannot prove that low vitamin D levels are the cause of death. However, the same European researchers are also conducting a large study of vitamin D supplementation, hoping to improve survival rates in HIV-positive people. Interim results from this study of supplementation should be available in several years.

Researchers have found associations between low levels of vitamin D and pre-diabetes or diabetes in HIV-positive people in several studies. However, it is not clear if vitamin D deficiency led to problems with insulin and blood sugar. Clinical trials are needed to understand the relationship between vitamin D supplementation and pre-diabetes or diabetes in HIV-positive people.

Hepatitis C virus (HCV)—antiviral and other effects

Researchers in Israel have performed laboratory experiments with vitamin D, liver cells and HCV. In these experiments, treating HCV-infected cells with vitamin D_3 reduced their production of this virus, likely by stimulating the release of interferon. Treating these cells with low concentrations of both vitamin D_3 and interferon-alpha also reduced HCV production.

Note that lab experiments with cells and viruses do not reproduce the complexity of an organ or system. These experiments are an interesting first step on the path to conducting further experiments with vitamin D_3 and HCV-infected cells. Hopefully they will eventually lead to clinical trials.

Studies with HCV-infected people suggest that some of those with vitamin D deficiency are less likely to respond to HCV therapy than people with higher concentrations of vitamin D in their blood. Also, vitamin D is associated with a reduced risk of rejecting transplanted liver. Vitamin D is also associated with reduced liver inflammation in HCV infection. Unfortunately, due to the observational nature of these studies, firm conclusions about vitamin D's effects cannot be drawn at this time. Such findings need to be confirmed in robustly designed clinical trials so that the role of vitamin D in HCV infection can be better understood.

Bacterial vaginosis

The vagina normally contains a mix of mostly good bacteria and small amounts of bad bacteria. Sometimes women develop an imbalance in the bacteria that live in their vagina, whereby the proportion of bad bacteria increases—bacterial vaginosis (BV). In cases of BV, women can experience such symptoms as itching, burning, pain and discharge, while in some cases BV can occur without causing symptoms. BV does not normally cause serious complications, however, it can do so in cases where the woman is pregnant. BV can increase the risk for HIV transmission and the risk for becoming infected with STIs.

Observational studies have found an association between BV in pregnant, HIV-negative women and vitamin D deficiency. Recently, in a study of 600 non-pregnant women, researchers in the U.S. found an association between BV and vitamin D deficiency among women who were HIV positive. As with so many studies of vitamin D, this was an observational study so it can only find associations and does not prove that vitamin D deficiency causes BV. Indeed, in general, researchers are not certain why some women develop BV, though there are several theories. The present study provides a foundation to conduct more rigorous research to explore this link between BV and vitamin D, particularly among HIV-positive women.

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H. Can vitamin D increase testosterone concentrations in men?

Researchers in Germany have conducted a randomized placebo-controlled study of vitamin D_3 supplementation in overweight people who took part in a structured weight loss program for 12 months. They found that daily vitamin D_3 at a dose of 3,333 IU did not affect weight loss. However, small but significant decreases in levels of triglycerides and the cytokine TNF-alpha occurred in the blood of people who received vitamin D_3. Also, a small (+5%) but statistically significant increase in levels of bad cholesterol (LDL-C) occurred among vitamin D_3 recipients. Unexpectedly, a small but statistically significant increase in testosterone levels was detected in men who received vitamin D_3.

Study details

Two hundred HIV-negative overweight and otherwise healthy people were recruited for the weight loss study. As part of the program, participants were educated about nutrition and healthy eating habits and received weekly counselling via telephone with a nutritionist for the first six months of the study. Half of the participants received vitamin D_3 at a dose of 3,333 IU/day for 12 consecutive months, while the other half received placebo. Among a subset of 54 men—31 received vitamin D and 23 received placebo—extensive laboratory assessments of testosterone were performed. This report focuses on the 54 men.

The average age of the men was 48 years and half of them smoked tobacco. Vitamin D levels prior to randomization were suggestive of deficiency, about 30 nmol/litre.

Results

The men lost an average of 6 kg over the course of a year.

The men who received vitamin D had their levels rise to 86 nmol/litre.

Before we can present further results on testosterone, some background information is necessary.

About testosterone

In adult males, most testosterone (95%) is made by the testicles—between 3 mg and 10 mg each day. The adrenal glands produce the remaining amount of this hormone.

In the blood, most testosterone is bound to two proteins:

- sex-hormone-binding globulin (SHBG)
- albumin

In theory, only testosterone that has broken loose or becomes free from those previously mentioned proteins is available for use by tissues. This unbound testosterone is called "free testosterone" in laboratory tests.

Assessments of testosterone

Analysis of blood tests sometimes report testosterone assessments as follows:

- total testosterone – this includes testosterone bound to blood proteins and free testosterone
- free testosterone – this can be directly measured or calculated using total testosterone levels, SHBG and albumin concentration and equations
- bioavailable testosterone – this refers to free testosterone plus testosterone loosely bound to albumin

Different laboratories have different reference ranges for testosterone, and levels of this hormone tend to fall with age.

Note that testosterone levels often fall in cases of chronic infections such as HIV and inflammatory conditions such as cancer, severe kidney and lung disease. Also, some drugs and substances can decrease testosterone levels, including the following:

- chronic, excessive use of alcohol
- chemotherapy
- ketoconazole (Nizoral)
- marijuana
- spironolactone (Aldactone)

Results—Testosterone and vitamin D

In different assessments, participants who received vitamin D had relatively small but statistically significant increases in testosterone compared to placebo. For instance, total testosterone levels rose by 3 nmol/litre to 13.4 nmol/litre after 12 months. A similar trend occurred with bioavailable testosterone and free testosterone.

Why did an increase occur?

There are several pieces of evidence to suggest that vitamin D may have played a role in the increased testosterone levels detected in this study. Such evidence is important to consider because the

primary purpose of the study was to assess weight loss and **not** to assess changes in testosterone. Moreover, the numbers of men in the substudy were relatively small. Here is some evidence that may support the vitamin D findings of this study:

- In experiments on mice, those that do not have receptors for vitamin D suffer from less-than-normal levels of testosterone.
- The testicles have receptors for vitamin D, suggesting that this vitamin plays some role there.
- A previous cross-sectional study in people found a link between vitamin D levels in the blood and testosterone levels in the blood.

Taken together, these previous bits of research along with the present German study suggest that vitamin D may modestly alter testosterone levels in males. Because of the previously mentioned issues, the present study's results cannot be taken as definitive, only suggestive. Also, because researchers did not assess factors influenced by testosterone, such as sex drive, mood or muscle strength, the clinical significance of these changes in testosterone levels is not clear.

Still, the findings from the present study are intriguing and require confirmation in a large randomized clinical trial.

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I. Statins and vitamin D – an unusual relationship

Cholesterol-lowering medications, commonly called statins, are often prescribed by physicians for HIV-positive people. In general, when used correctly and in the right population, statins are generally safe, though they can sometimes affect the concentration of other medicines. In a minority of people who take statins, problems such as muscle weakness and pain can develop. Statins also have anti-inflammatory activity, which may aid in the ability of these drugs to help prevent heart attacks.

Observational studies have found associations between low levels of vitamin D in the blood and an increased risk for cardiovascular complications, including peripheral artery disease and heart attacks. However, because of built-in limitations, observational studies cannot prove that low levels of vitamin D are the cause of peripheral artery disease, heart attacks and other related complications. Still, some scientists remain intrigued by the potential of vitamin D in the area of cardiovascular health, perhaps for at least the following reasons:

- Cells lining blood vessels contain receptors for vitamin D. Exposure to this vitamin helps restrict the thickening of this lining. Such thickening would otherwise impede the flow of blood.
- Lab experiments have found that vitamin D can help reduce inflammation. Separate studies suggest that inflammation plays a role in accelerating cardiovascular disease.
- Vitamin D can very modestly help reduce blood pressure.

Researchers in several countries have conducted experiments with statins to assess their impact on vitamin D in HIV-negative people. Their findings suggest the following:

- Rosuvastatin (Crestor) can raise vitamin D levels about threefold in the blood.
- Atorvastatin (Lipitor) can have a similar effect on vitamin D as rosuvastatin.
- Other statins, such as lovastatin (Mevacor) and simvastatin (Zocor), can also increase the concentration of vitamin D in the blood.
- In contrast to the statins listed above, fluvastatin (Lescol) does not appear to raise vitamin D levels.

Small studies have found that vitamin D_3 supplements at a dose of 800 IU/day can lower levels of atorvastatin (by about 10%) and the chemicals into which it is broken down inside the body. Yet, despite these reduced levels of atorvastatin, the combination of vitamin D and atorvastatin appeared to have increased cholesterol-lowering activity more than either substance did alone.

In general, these studies exploring the impact of statins on vitamin D were small. Larger robust clinical trials will be needed to understand the complex ways in which statins and vitamin D might affect each other's properties and actions.

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