Do integrase inhibitors affect testosterone levels in men?

Lower-than-normal levels of testosterone in men are associated with the following problems:

- decreased interest in sex
- erectile dysfunction
- reduced muscle mass and strength
- thinning bones
- fatigue
- in some cases, depression

Decreased testosterone levels occur as all men age.

In the time before potent HIV treatment (ART) became available, researchers found low testosterone levels in some men with HIV. In such cases this problem may have arisen for several reasons, including the following:

- unintentional and severe weight loss (due to HIV disease)
- HIV-related inflammation and injury to the body’s hormonal networks
- the development of life-threatening infections and prolonged and intense regimens of antibiotics, antifungals and antivirals needed to treat and later prevent infections from recurring

However, lower-than-normal levels of testosterone also have been found among HIV-positive men in the subsequent era who were using ART and never developed AIDS.

The reasons for this are not clear but may be related to dysfunction in the body’s production of some hormones, including testosterone, perhaps arising directly or indirectly from HIV infection.

Decreased testosterone levels have also been linked to the following:

- excessive intake of alcohol
- injecting street drugs
- hepatitis C virus infection

**Measuring testosterone**

There are antibodies in the blood that bind to hormones such as testosterone. The unbound (or “free”) testosterone is what is available for use by the body’s cells. Therefore, when assessing testosterone levels, endocrinologists usually ask the laboratory to measure the amount of free testosterone in the blood. Hormone levels in the body usually vary by time of day (because of internal 24-hour cellular clocks). Researchers who study testosterone recommend that measurements of free testosterone be done early in the morning.

Researchers in Paris and elsewhere in France have conducted a study with 113 HIV-positive men, all less than 50 years old, who did not have AIDS and who were taking ART and who had a viral load less than 50 copies/mL. The researchers published their findings in the January 28, 2017 issue of the journal *AIDS*. They found that about 12% of the men had lower-than-normal levels of testosterone (measured as free testosterone)—less than 70 pg/mL. This rate of low testosterone (called hypogonadism) is double the rate that would be seen in HIV-negative men of a similar range in age.

The researchers stated that they found a link between the use of integrase inhibitors and the presence of low testosterone. We caution readers that due to the study’s design and other issues, such a conclusion must be treated very cautiously, and we explain why the researchers may have inadvertently arrived at such a conclusion.

**Study details**

The average profile of the men when they were recruited for this study was as follows:

- age – 41 years
- CD4+ count – 627 cells/mm³
- estimated duration of HIV infection – six years

Bear in mind that blood and other tests were done largely at one point in time. We will return to this aspect of the
Results—Testosterone

- Levels of antibodies that bind to testosterone were elevated in 48% of participants.
- Lower-than normal levels of testosterone were found in 12% of men.
- Men who had low testosterone levels were more likely to have had HIV longer than men with normal testosterone levels.
- Some men with low testosterone levels also had thinner-than-normal bone density.
- Having a percentage of body fat greater than 19% was associated with decreased testosterone levels (excess belly fat can convert some of the body’s testosterone into estrogen).

Erectile dysfunction

Men with low testosterone were more likely to have ED. However, even among men with normal levels of testosterone, 54% had ED. Men with ED had been using ART longer (76 months) than men without ED (44 months).

Specific anti-HIV drugs

The researchers stated that they found a relationship between the use of integrase inhibitors for more than two years and the presence of hypogonadism. Note that only 14 men were using integrase inhibitors in this study. We urge readers to treat this finding with caution due to a number of factors, including the nature of the study, which is explained below.

Bear in mind

1. This study’s design is cross-sectional in nature; data were captured largely at one point in time. Cross-sectional studies are good at finding associations between a drug and, in this case, a problem (hypogonadism). However, cross-sectional studies by their nature can never prove cause and effect (that is, that integrase inhibitors cause hypogonadism). Cross-sectional studies are a good starting point to begin to explore a research question. If something interesting turns up, it can then be better understood in a study of a more robust statistical design.

2. There were only 14 men who used integrase inhibitors in the French study. This is insufficient for drawing robust conclusions about the impact of this class of medicines on testosterone levels (or anything else). The researchers stated that they were surprised by the association between integrase inhibitors and low testosterone, which is understandable because integrase inhibitors have been in use for about a decade in high-income countries. Also, it is odd that no other team of researchers has found this connection. Furthermore, in other studies, low testosterone has been found in HIV-positive men who were not taking ART and, in men who were taking ART before the introduction of integrase inhibitors.

3. The French researchers stated that they found an association between low testosterone and integrase inhibitors. However, this conclusion could have been skewed by other factors that were unmeasured by their study. For instance, why were some patients given integrase inhibitor–based therapy and others were not? What was the medical history of these patients? Researchers did not apparently screen participants for the presence of all major ED risk factors. Furthermore, the researchers did not address these points in their analysis. It may be that doctors had reasons for prescribing the anti-HIV drugs that they did, and that by chance people with low testosterone just happened to receive integrase inhibitor–based therapy. Such are some of the problems that can bedevil a cross-sectional study and the conclusions drawn from such studies.

4. What can be reasonably extracted from the present study is the following:

- free testosterone measurements are useful
- some HIV-positive men have lower-than-normal levels of testosterone
- ED is common among HIV-positive men

What needs to be done

The role of HIV treatment on testosterone levels (and ED) needs to be explored in a study of a more robust statistical design. Such a study would have many more participants, but size alone is insufficient to prove cause and effect. Ideally, as part of some randomized clinical trials, men would be screened for risk factors both for ED and low testosterone prior to initiation of ART and monitored while taking anti-HIV treatment. However, large, well-designed studies are expensive. In an era of austerity, it may take time to raise the funds necessary for such a large and well-designed study. The French researchers stated that they are engaged with a larger study to confirm their findings but did not state details as to that larger study’s design.
It is good that some researchers, such as the present French team, are interested in studying testosterone levels and why some HIV-positive men might have lower-than-normal levels. The findings from the French study are certainly interesting and should be seen as a beginning and not an end to understanding the issue of low testosterone and ED and their possible causes in HIV-positive men. Hopefully, the French study will stimulate other researchers to conduct further explorations on testosterone, ED and its relationship, if any, with HIV treatment. However, for now, any link between their findings on testosterone and the use of integrase inhibitors must be treated with caution until they are confirmed in a study that is statistically more robust.

Resource

Some issues related to sexual dysfunction in men

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REFERENCES:


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