Hormonally Challenged

June 24, 2008 By David Evans

For people living with HIV, testosterone replacement therapy (TRT)—injections, gels and patches that boost blood levels of the potent hormone—was, for many years, an imperfect but necessary tool for fighting debilitating AIDS-wasting syndrome. Although wasting, by which a person becomes skeletally thin and weak from loss of fat and muscle mass, is far less a threat today due to the widespread use of antiretroviral (ARV) therapy, studies reveal that as many as 17 percent of HIV-positive men remain testosterone deficient.

Testosterone deficiency, or hypogonadism, occurs when a man loses his ability to produce enough testosterone, potentially resulting in loss of muscle mass, bone loss, fatigue, depression and sexual dysfunction. HIV-negative men typically don't become hypogonadal until their 60s and 70s. Among HIV-positive men, however, the condition can occur at any age.

While screening HIV-positive men for low testosterone seems like an obvious recommendation, diagnosing hypogonadism can be tricky. First, the "normal" range of testosterone in the blood is broad—any reading between 250 to 1100 nanograms per deciliter of blood is normal, according to one of the nation's largest laboratories Quest Diagnostics. Therefore, people with an average testosterone level on the high end of normal can see their testosterone levels drop to the lower end of normal—and exhibit symptoms of testosterone deficiency—but still not qualify for a treatable diagnosis of hypogonadism. Second, testosterone levels can fluctuate wildly from morning to night and over successive days, so a single test result that falls below normal doesn't necessarily mean a person is hypogonadal. What's more, people with low testosterone may not display symptoms, raising the question of whether treatment is either useful or necessary in these individuals.

While most hormone specialists, known as endocrinologists, agree that men with exceptionally low testosterone should be given replacement therapy, the treatment can have side effects. Most troublesome: It can fuel the growth of abnormal prostate cells, potentially leading to cancer. Also, long-term use of high-dose oral steroids has been linked to liver cancer. This is a growing concern for men living with HIV, many of whom are entering their 50s and are at increased risk for both liver disease and a number of non-AIDS-related cancers.

Given these risks, when is testosterone therapy appropriate for use in HIV-positive men? Jim Scott, PharmD, an associate professor of pharmacy practice at Western University of Health Sciences in Pomona, California, has conducted testosterone replacement research in HIV-positive men. Scott feels that testosterone replacement for hypogonadism is medically sound and relatively safe, but

encourages people with HIV and their health care providers to weigh the potential risks as well as the rewards. What follows is a guide to the possible benefits and side effects of TRT to help you make an informed decision.

Testing Testosterone

If you're experiencing fatigue, depression or problems in the sex department, talk to your health care provider about checking your testosterone levels. In fact, ask about making it routine—check your levels while you're feeling good so that you can check future numbers against what is healthy for you. But keep in mind:

Reference ranges—the range of what's normal—can vary from one lab company to another, and this range is massive. The normal range for the total amount of circulating testosterone is below 250 ng/dL to well over 1,000 ng/dL. If you have a normal-high level and it drops to normal-low, you might not have hypogonadism, but the decrease may be significant enough to warrant replacement therapy, especially if you have symptoms.

Testosterone is typically highest in the morning, making it the best time to test. Repeated tests, using the same lab, should involve samples taken at the same time, every time.

Some doctors prefer to look at your level of "free" testosterone, which is the proportion of testosterone that is not bound to proteins and is thus available to go to work where needed. Free testosterone generally makes up 2 to 3 percent of the total testosterone level.

Hormones 101

Testosterone is a sex hormone, also known as androgen, found in both men and women. In females it is typically produced at very low levels by the ovaries and adrenal glands and helps regulate muscle and bone development. In men, it is produced by the testes and adrenal glands at much higher levels and helps maintain sex drive, the production of sperm cells, male hair patterns, and muscle and bone mass.

In the years before the introduction of combination ARV treatment, AIDS-wasting syndrome was quite common. Scientists eventually learned that more than half of all men with the syndrome also had hypogonadism, and they began experimenting with synthetic testosterone and its chemical cousins, anabolic steroids, as a way to counteract wasting. Early studies showed significant success with TRT in helping people regain muscle mass, and the use of this therapy became highly prevalent.

Research on testosterone continued into the late 1990s—testing ranged from daily applications of gels and patches to potentially painful weekly or biweekly injections—but eventually stopped because the number of people with wasting syndrome had diminished to the extent that study enrollment became very difficult.

Treatment Benefits and Risks

Judith Rabkin, PhD, MPH, a professor of clinical psychology at Columbia University's College of Physicians and Surgeons, has spearheaded several studies of TRT in hypogonadal HIV-positive men. Her research has focused on fighting the more common symptoms of hypogonadism, including depression, fatigue, decreased libido and erectile dysfunction.

In one study, which compared injections of 400 milligrams of testosterone cypionate every other week with a placebo, Rabkin found that men who received testosterone were more than twice as likely as placebo recipients to report improvements in physical energy, mood and sexual function.

In 2006, the Endocrine Society, the leading group representing hormone-specializing endocrinologists in the United States, issued guidelines on testosterone replacement in hypogonadal men. Because of the potential for side effects with TRT, and the fact that plenty of men do not display symptoms of hypogonadism despite low testosterone levels, the group recommended against routine screening of the general male population. They did, however, acknowledge that HIV-positive men are at increased risk for hypogonadism and recommend short-term TRT for those found to be testosterone-deficient, just to bring testosterone levels back within the normal range. Rabkin agrees with these recommendations, saying, "When [testosterone levels] are below the reference range, there's no question that, medically, [TRT is] indicated."

Some studies have revealed that non-injectable TRT may offer safer results without the pain of a needle stick. Scott's research focused on testosterone gel, which is rubbed into the skin daily and can do a better job of keeping testosterone levels steady, as opposed to the "peaks and valleys" frequently seen with injections. "When we give somebody injectable testosterone they get really high levels…and then they crash lower than they should be, and they feel bad. The gel levels that

out," says Scott.

But long-term research on the safety, tolerability and efficacy of TRT in older HIV-positive men is lacking. Indeed, Rabkin acknowledges that most of the research on testosterone in HIV-positive men has involved men in their thirties.

Additionally, as most men pass the age of 50, their risk for developing problems with their prostate gland, including prostate cancer, increases—and TRT can increase this risk and exacerbate prostate problems. According to Rabkin, "Testosterone becomes a little risky for older men, and the age of our patients has increased over time." The Endocrine Society guidelines recommend that men be carefully screened and monitored for prostate problems before and after being given testosterone therapy.

Prostate troubles aren't the only concern with testosterone. Other side effects can include worsening of a sleep disorder called sleep apnea, growth of breast tissue, acne, mood volatility, testicular atrophy, reduced sperm count and male-pattern baldness.

Though the guidelines recommend at least short-term use of testosterone in HIV-positive men to augment ARV treatment in reducing muscle wasting, Rabkin found that men's testosterone levels plummeted within days after stopping treatment to the same levels they were before treatment started. She asserts that most men with hypogonadism cannot sustain normal hormone ranges after initial TRT and will probably require life-long testosterone augmentation.

People with HIV should consult with their physician and weigh all the potential risks and benefits of TRT. If they're found to have testosterone levels lower than the normal reference range on at least two tests and are experiencing symptoms, therapy may be warranted. For people without symptoms, the data are less clear, and safety concerns may weigh more heavily.
