Drug that reduces abdominal fat in HIV patients also may reduce fat in liver

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The only drug to receive FDA approval for reduction of the abdominal fat deposits that develop in some patients receiving antiviral therapy for HIV infection may also reduce the incidence of fatty liver disease in such patients. In a paper that will appear in the July 23/28 issue of *JAMA* – a theme issue on HIV/AIDS receiving early online release to coincide with the International AIDS Conference – Massachusetts General Hospital (MGH) investigators report that daily injections of tesamorelin significantly reduced fat in the liver without affecting glucose metabolism.

"Tesamorelin's ability to reduce liver fat in conjunction with the reduction of abdominal fat may be clinically important for patients with HIV infection who have fatty liver disease along with increased abdominal fat," says Steven Grinspoon, MD, of the MGH Neuroendocrine Unit and Program in Nutrition Metabolism, the study's senior author. "While some patients with nonalcoholic fatty liver disease have a benign course, others may develop a more serious condition involving liver inflammation, cellular damage and fibrosis, which can progress to cirrhosis and end-stage liver disease or to liver cancer."

Between 30 and 40 percent of HIV-infected patients develop nonalcoholic fatty liver disease (NAFLD), often but not always in conjunction with lipodystrophy, the abnormal abdominal fat accumulation that develops in 20 to 30 percent of patients receiving antiretroviral drugs. Tesamorelin stimulates the body's release of growth hormone, which is reduced in HIV lipodystrophy, and several studies by

Grinspoon's team and others led to the 2010 approval of the drug to treat the lipodystrophy.

In designing the current study, the MGH team originally planned to further investigate tesamorelin's effects on abdominal fat with a secondary focus on fat in the liver and muscle, and on markers of inflammation and cardiovascular risk. But since several studies suggested a significant incidence of NAFLD in HIV-infected patients, the study's goals were broadened to focus on tesamorelin's ability to reduce fatty deposits in the liver as well as abdominal fat in general.

The study enrolled 48 adult patients who were receiving antiretroviral treatment for HIV and had developed excessive abdominal fat deposits. Participants were first randomized to receive daily injections of either tesamorelin or a placebo. In addition, since growth hormone treatment can lead to increased blood sugar levels and reduced insulin sensitivity, half of those in each group also had a procedure that analyzes insulin secretion and resistance at the study's outset and at assessment sessions conducted at three months and at the end of the six-month study. The assessments also included comprehensive measures of factors related to HIV infection, lipid and glucose metabolism, along with analysis of abdominal fat by CT scan and of liver fat by MR spectroscopy.

At the end of the study period, participants receiving tesamorelin had a significant, modestly sized decrease in liver fat along with the expected reduction in overall abdominal fat. Those receiving placebo treatment had increases in both measures. Although tesamorelin treatment did appear to have reduced insulin sensitivity and raised blood sugar levels at the three-month assessment, by six months both measures had returned to levels observed at the study's outset, implying that the drug's impact on glucose metabolism was only temporary.

"Tesamorelin's neutral long-term effects on insulin sensitivity and

glucose are important, since HIV patients with abdominal fat accumulation may have underlying insulin resistance; so it's important to know that won't be worsened by this treatment," says Grinspoon, a professor of Medicine at Harvard Medical School. "Since we know that liver fat is associated with inflammation in the liver, reducing it may result in less inflammation. Indeed levels of AST, a marker of liver inflammation, were reduced in response to tesamorelin in our study.

"Now we need to investigate the effects of tesamorelin in patients with the severe form of liver inflammation called nonalcoholic steatohepatitis, which can cause significant damage to liver cells, and examine whether reduced liver fat has other metabolic benefits," he adds. "Tesamorelin also may be an effective treatment for non-HIV-infected patients with NAFLD, and that needs to be studied as well."

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