Tesamorelin, liver fat, and NAFLD in the setting of HIV

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Management of abnormal liver function tests and cirrhosis, in the absence of hepatis B or C coinfection and high alcohol intake, has become an important issue in people with HIV on antiretroviral therapy (ART). One of the most common causes for abnormal liver function in both the general population and people living with HIV is non-alcoholic fatty liver disease (NAFLD), which has two forms: non-alcoholic steatohepatitis (NASH) or hepatic steatosis (figure). Between 6% and 35% of people globally[1] have NASH-related cirrhosis, and it is the fastest growing indication for liver transplantation in the USA.[2] In people living with HIV on ART, the prevalence of NAFLD is higher (26–65%)[3] and they can have more severe clinical and biochemical manifestations and a faster rate of liver fibrosis progression.[4] Surprisingly, there are few treatment options available for this very common disease and even fewer have been evaluated in people with HIV.

In *The Lancet HIV*, Takara L Stanley and colleagues[5] present promising results from their randomised, double-blind, multicentre trial in which they administered daily injections of tesamorelin or placebo to people living with HIV and NAFLD.[5] Tesamorelin is a synthetic peptide analogue of growth hormone-releasing hormone that restores the pulsatile release of growth hormone in people with HIV and reduces visceral abdominal fat in HIV-associated lipodystrophy.[6,7] Tesamorelin is approved by the US Food and Drug Administration to reduce visceral fat in people living with HIV and central adiposity. Tesamorelin is thought to reduce fat by stimulating lipolysis through increasing endogenous growth hormone.[7]

The primary endpoint of the study was change in hepatic fat fraction (HFF) after 12 months of treatment. The primary safety endpoint was blood glucose, because tesamorelin can reduce insulin sensitivity leading to hyperglycaemia. HFF was calculated following proton magnetic resonance spectroscopy (MRS) and MRI and has been shown to have a high specificity for hepatic steatosis compared with liver biopsy. An HFF of 5% or more on MRI was used to define hepatic steatosis. Additionally, a liver biopsy was done at study entry and at 12 months.

61 participants were enrolled. Compared with placebo, participants who received tesamorelin had a significant reduction in HFF with a greater proportion having a reduction of HFF to less than 5%. 38% of participants in the placebo group had liver disease progression, highlighting the importance of developing new treatment strategies for NAFLD. Tesamorelin prevented the progression of liver fibrosis during the treatment period but did not improve existing fibrosis. There was no significant effect of tesamorelin on liver enzymes or blood lipids. Finally, although tesamorelin was well tolerated with no overall change in fasting glucose or glycated haemoglobin, there were two study discontinuations in the tesamorelin group due to hyperglycaemia.

Meta-analyses[8] of NAFLD in HIV have identified associations with traditional risk factors rather than HIV-related risk factors or antiretroviral drugs. The current approach to managing NAFLD and NASH is primarily related to lifestyle changes, including treatment of comorbidities such as diabetes, hypertension, dyslipidaemias, and reducing the cardiovascular risk profile. In the general population, a weight loss of 5–10% of body mass is recommended, but it is unclear if this amount of weight loss will also lead to improved outcomes for people living with HIV.

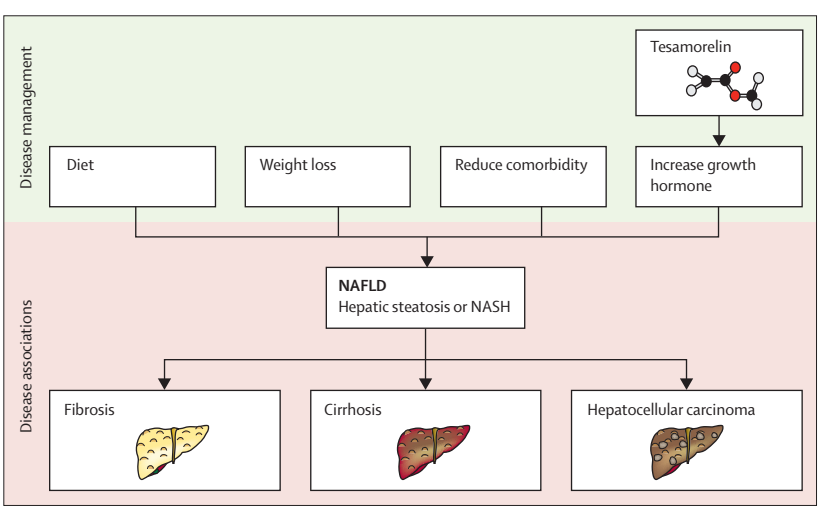

Figure: **Disease associations and management strategies for NAFLD**
Non-alcoholic fatty liver disease (NAFLD) is defined as an increased amount of fat in the liver in the absence of hepatitis B or C or substantial alcohol intake. NAFLD includes hepatic steatosis (defined as fat accumulation in ≥5% of hepatocytes) through to non-alcoholic steatohepatitis (NASH; characterised by inflammation in addition to fat accumulation in the liver). All forms of NALFD can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. Multiple interventions are used for the management of NAFLD, including modification of diet, a reduction in body weight, control of co-morbidities such as diabetes, hypertension of hyperlipidaemia or pharmacological interventions. Tesamorelin is a synthetic peptide analogue of human growth hormone-releasing hormone, which binds to human growth hormone-releasing factor receptors and restores the pulsatile release of growth hormone. Tesamorelin can stimulate lipolysis through increased endogenous growth hormone, although multiple mechanisms are likely involved in liver fat reduction.

Because there are very few therapeutic drugs available for NASH or NAFLD, Stanley and colleagues' study[5] is an important therapeutic advance. However, several issues require further consideration. First, it is unclear what will happen after stopping tesamorelin, specifically whether declines in the HFF will be maintained. Second, if tesamorelin is required for a longer duration, there are no long-term data on safety. Third, tesamorelin requires refrigeration and access to a supply of clean needles and syringes, which could reduce its use in some low-income and middle-income countries, where NAFLD prevalence is substantial and increasing, such as in India.[9] Finally, tesamorelin had no effect on participants with established fibrosis at entry, which means that the greatest clinical benefit of the drug will be achieved through early detection of NAFLD. Increased investment will be needed to increase the awareness of the condition to allow for early diagnosis and a focus on prevention. Tesamorelin provides a new therapeutic approach that is important to managing people living with HIV and NAFLD and warrants further investigation.

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We declare no competing interests.

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