



People With HIV Are at Risk for Liver Fibrosis and Fatty Liver

Metabolic disorders are linked to liver scarring and fat accumulation in HIV-positive people.

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Metabolic syndrome, diabetes and obesity are risk factors for the development of liver fibrosis and fat accumulation among people living with HIV, even if they don't also have hepatitis B or C, according to a pair of studies presented last week at the 9th International AIDS Society Conference on HIV Science in Paris (IAS 2017).

In the era of effective antiretroviral therapy (ART), which has reduced the number of deaths from opportunistic infections, liver disease has become a major cause of illness and death among people with HIV. In many cases coinfection with hepatitis B virus (HBV) or hepatitis C virus (HCV) plays a role, but people can develop serious liver disease even without these viruses.

Viruses, heavy alcohol consumption, exposure to toxins and other causes of liver injury can lead to fibrosis and steatosis. Fibrosis occurs when scar tissue replaces normal liver cells known as hepatocytes. Cirrhosis is the most advanced stage of fibrosis. Steatosis occurs when hepatocytes start to fill up with fat. [Non-alcoholic fatty liver disease](#) (NAFLD) develops in people who do not drink heavily; its more advanced stage is known as non-alcoholic steatohepatitis (NASH). Over time, these progressive conditions can lead to liver function impairment, liver cancer and the need for a liver transplant.

Maud Lemoine, MD, of Imperial College London presented findings from a study looking at the effect of metabolic syndrome on the prevalence and severity of liver fibrosis in HIV-positive people without viral hepatitis (known as HIV mono-infection).

[Metabolic syndrome](#) is a cluster of risk factors associated with elevated cardiovascular risk, including abdominal obesity (having a "beer belly" or "spare tire"), high blood pressure, abnormal blood fat levels (high triglycerides and low HDL cholesterol) and high blood glucose, a sign of insulin resistance and type 2 diabetes.

The METAFIB study, conducted at a single center in France, included 478 HIV-positive people without HBV or HCV infection who reported that they were not heavy alcohol drinkers and did not have other causes of chronic liver disease.

Liver fibrosis was assessed using a noninvasive imaging method known as transient elastography (FibroScan), which measures liver stiffness using sound waves. Among the participants with valid liver stiffness results, 203 people who had metabolic syndrome were matched according to age and sex with 202 people who did not.

Nearly 90 percent were men and the average age was 53. Participants had been HIV positive for around 17 years on average. Most were on ART with an undetectable viral load, and the mean CD4 count was over 600 cells/mm³.

People with metabolic syndrome had a higher body mass index than those without the condition (26.0 versus 23.2), and they were more likely to be obese, defined as a BMI of 30 or higher (13.3 percent versus 3.5 percent). Those with metabolic syndrome were also more likely to have insulin resistance (49.0 percent versus 8.5 percent) or type 2 diabetes (15.3 percent versus 1.0 percent). This group also had higher levels of liver enzymes and various inflammatory markers in their blood.

The researchers found that participants with metabolic syndrome were significantly more likely than those without it to have liver fibrosis. A quarter of people with metabolic syndrome had moderate fibrosis, compared with about 7 percent of those without. Advanced fibrosis (about 15 percent versus about 3 percent) and cirrhosis (about 8 percent versus around 1 percent) followed similar patterns.

People with moderate or worse fibrosis had significantly higher levels of inflammatory markers than people without fibrosis or with only mild fibrosis, including C-reactive protein, interleukin 6, leptin and adiponectin (two hormones produced by adipose or fat tissue) and a marker linked to activation of macrophages (a type of immune system white blood cell). The same pattern was seen when comparing people with and without cirrhosis.

After adjusting for other factors, people with metabolic syndrome were four times more likely to have advanced or worse fibrosis and eight times more likely to have cirrhosis. Obese people were three times more likely to have advanced fibrosis and four times more likely to have cirrhosis. However, HIV-related factors, including ART use, did not predict fibrosis or cirrhosis status.

“HIV-monoinfected patients with metabolic syndrome are at risk of liver fibrosis and should be systematically screened for liver fibrosis irrespective of transaminases [liver enzyme levels] or HIV parameters,” the researchers concluded.

They suggested that adipose tissue, insulin resistance and macrophage activation “are probably key players” in the development of liver fibrosis in HIV-positive people without viral hepatitis.

In a related study, Hugo Perazzo of Fundação Oswaldo Cruz in Rio de Janeiro and colleagues looked at factors associated with liver fibrosis and steatosis among HIV-positive people without viral hepatitis who were on long-term ART. Fibrosis and steatosis were determined using FibroScan.

The researchers hypothesized that a single “hit”—such as type 2 diabetes, obesity or a genetic risk factor—could cause simple steatosis but that progression to cirrhosis or NASH may require additional hits. Chronic inflammation and immune activation associated with HIV might be one such factor or perhaps use of hepatotoxic antiretroviral drugs, they suggested.

This analysis included 395 participants from the PROSPEC-HIV cohort. In contrast to the previous study, a majority (60 percent) were women and the average age was 45. Again, they had well-controlled HIV, with 80 percent having an undetectable viral load and the median CD4 count was over 660 cells/mm³. They had been on ART for a median of seven years, and many of them had used older antiretrovirals that can cause metabolic or liver-related side effects.

About a third of study participants had metabolic syndrome, but even more had at least one of its components, such as abdominal obesity (68 percent) or abnormal blood fat levels (61 percent). Ten percent had type 2 diabetes.

The researchers found that 9 percent met the criteria for fibrosis and 35 percent met the criteria for steatosis. Women and men were equally likely to have fibrosis, but men were significantly more likely to have steatosis. Older age was a risk factor for fibrosis but not for steatosis.

In a multivariate analysis, having type 2 diabetes more than doubled the risk for fibrosis, while having a CD4 count under 200 cells/mm³ increased the risk by nearly eightfold. Looking at steatosis, metabolic syndrome overall was associated with a fourfold higher risk, while two of its components features—obesity and type 2 diabetes—raised the risk even more (by nearly 11 and 10 times, respectively).

In addition, longer duration of ART use was “associated with steatosis independently of metabolic factors,” the researchers concluded. This was especially true for older nucleoside reverse transcriptase inhibitors such as Retrovir (AZT or zidovudine) and Zerit (d4T or stavudine).

The researchers recommended that prevention and management of noninfectious conditions such as metabolic syndrome should be integrated into HIV care to decrease the burden of liver disease.