AIDS Reviews 2005;7:197-209

Liver Steatosis in HIV-infected Patients

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Abstract

Liver steatosis, defined as abnormal fat accumulation in hepatocytes, may be related to different pathogenic mechanisms, in particular metabolic abnormalities, toxic injuries, and viral infections. Since most of these mechanisms are frequently encountered in HIV-infected patients, and since HIV infection *per se* and antiretroviral treatments may be involved in the pathogenesis of liver steatosis, it could be speculated that HIV-infected patients are at a high risk of developing the condition. However, studies on steatosis in HIV-infected patients are still rare and do not reveal any significant increase, prevalence or clinical impact. Nevertheless, while waiting for prospective studies in HIV-infected patients, improved recognition, diagnosis and management of steatosis are required in these patients. (AIDS Reviews 2005;7:197-209)

Key words

Liver steatosis. Hepatotoxicity. Hepatitis C. Antiretroviral drugs. HIV.

Introduction

Liver steatosis is a classical pathologic finding in liver biopsy. It has been associated with chronic excessive alcohol consumption for a long time. Nonalcoholic liver steatosis has been more recently found to be a common disease in other populations, in particular in patients with visceral obesity and in those infected with hepatitis C virus (HCV). Since coinfections and metabolic alterations (in particular those linked to antiretroviral treatment) are often encountered in HIV-infected patients, it could be speculated that in these patients there is a particularly high risk of developing liver steatosis. However, the prevalence, possible pathogenesis, and the clinical relevance of nonalcoholic liver steatosis in these patients have not yet been established.

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What is liver steatosis?

Hepatic steatosis is defined as abnormally frequent collections of triglycerides within hepatocytes. In routine practice, a semi-quantitative approach is used to assess the importance of steatosis. There are two patterns of liver fat accumulation: macrovesicular steatosis where a single large fat droplet displaces the nucleus in the hepatocyte, and microvesicular steatosis characterized by multiple intracellular droplets within the hepatocyte. The latter can be assessed by using greater magnification, and are often associated with mitochondrial injury. Steatohepatitis is defined by the presence of cytological ballooning, scattered inflammation, perisinusoidal fibrosis and Mallory hyaline deposition in addition to steatosis[1-4].

Despite these histologic definitions, it may be difficult to confirm the existence and assess the extent of liver steatosis precisely, which leads to difficulties in the interpretation of the results from different studies.

Indeed, triglycerides can be observed in some hepatocytes in normal livers[1], at a frequency which is not clearly established (probably < 5%)[5]. Thus the diagnosis of steatosis does not seem to be relevant when the proportion of fatty hepatocytes is below this limit[6]. On the other hand, a percentage of fatty hepatocytes > 30% is without doubt clearly relevant.

The development of steatosis may (rarely) be focal[7], and thus liver biopsy may either under- or overestimate steatosis according to the part of the liver assessed.

In many clinical studies, either only macrovesicular steatosis is quantified and taken into account, or no difference is made between the two types. However, macrovesicular and microvesicular steatosis may correspond to different pathogenic mechanisms, and most likely to different diseases; this has to be kept in mind when analyzing the results of these studies. The two types of steatosis may be found together, and macrovesicular is not as "benign" nor microvesicular as "severe" as initially thought in early reports[1,5].

Differentiating between alcoholic hepatitis and nonalcoholic steatohepatitis (NASH) on purely histologic grounds may be impossible without clinical data, thus leading to under- or overestimation of their respective incidences in a given population.

Since no universally accepted grading and staging system has yet been established, although proposals have been made[8], discrepancies between interpretations made by two different expert pathologists may be observed quite often (up to 30%, personal unpublished data), as already seen in the evaluation of histologic activity despite the existence of a validated score (METAVIR)[9].

How to diagnose liver steatosis?

Liver steatosis is often clinically asymptomatic, or associated with mild gastrointestinal symptoms[5,10-13]. Physical examination may find hepatomegaly in some cases (in particular in severe and/or rapidly evolving steatosis)[13-16]. The diagnosis is thus frequently made during the evaluation of liver enzyme abnormalities. Elevation of ALT levels up to 2-3 times the upper limit of normal is the most frequent lab abnormality encountered, although many patients may have normal hepatic enzyme levels[5,10,11,13,17,18]. However, other causes of liver enzyme elevation frequently observed in HIV-infected patients, such as opportunistic infections, viral hepatitis, or non-steatosis antiretroviral toxicity have to be considered and investigated as well.

Ultrasound may be a useful tool in detecting liver steatosis, even though it provides qualitative rather than quantitative assessment of fatty liver infiltration. In a retrospective study comparing ultrasound examinations to liver histology findings in 48 HIV-infected patients (most of them with abnormal liver enzyme values), a good correlation between hyper-echoic aspect of the liver and steatosis was found[19]. In this study, the sensitivity of ultrasound was 71%, whereas the specificity was better (90%). Ultrasound was found to be more sensitive and more reliable than liver enzyme tests in another study[18]. In non-HIV-infected patients, the estimated sensitivity of ultrasound ranges from 60-94%, with a specificity from 84-95%[20].

Often, only a moderate or severe degree of liver steatosis may be seen on ultrasound, CT, or MRI, whereas mild steatosis is often undetectable with imaging techniques[13]. However, the relatively insufficient sensitivity and specificity of CT and MRI can be improved by using special procedures[12,21]. Proton spectroscopy, which seems to offer better sensitivity, has been used in some research studies, since it allows noninvasive quantification of liver fat, without exposure to radiation, and correlates closely with liver histology from liver biopsies[22,23].

However, none of these examinations can distinguish between micro- and macrovesicular steatosis, and inflammatory or fibrotic changes suggestive of steatohepatitis. Moreover, the distinction between steatosis and other associated pathologies (as high as 44% in the pre-HAART era in HIV-infected patients[19]) is often not possible with these techniques. Thus, the gold standard remains liver biopsy[12,13].

Potential etiologies and pathogenesis of liver steatosis in HIV-infected patients

Apart from histologic considerations, different classifications of steatosis have been used from the suspected etiologic factor, either differentiating between alcohol-induced steatosis and nonalcoholic fatty liver disease (NAFLD), or distinguishing between hepatitis-related steatosis and NAFLD, or differentiating between primary steatosis (related to host factors such as the metabolic syndrome) and secondary steatosis (including alcohol- and drug-related steatosis)[5]. Since the pathogenic pathways and the potential consequences may differ from one cause to another, we will consider steatosis as a whole, while keeping in mind the histologic limitations previously discussed, according to the potential causative factors in HIV-infected patients.

Several causes may be associated with liver steatosis in HIV-infected patients. However, whatever the cause, liver steatosis is intrinsically related to troubles in fat metabolism and energy production in hepatocytes, in particular to hepatic free fatty acids (FFA).

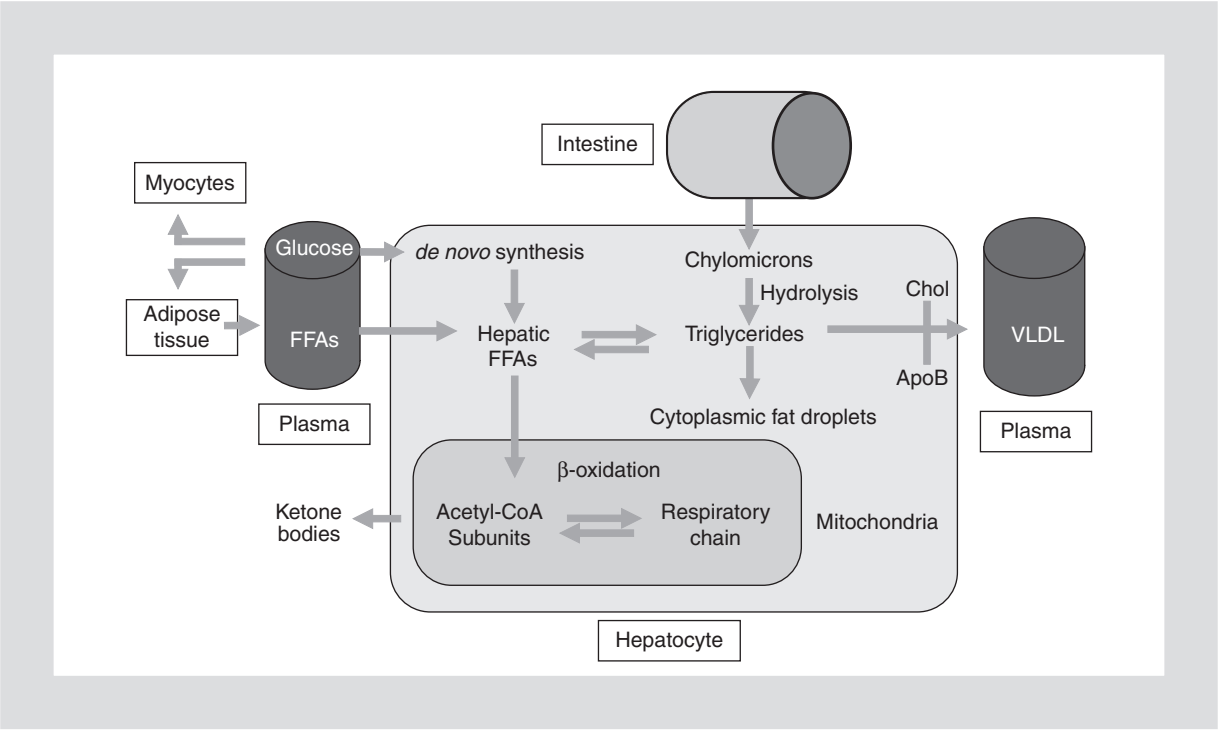

Figure 1. *Fat metabolism and energy production in hepatocytes* (adapted from Pessayre, et al.[24]).

Lipid metabolism and energy production in hepatocytes

Fat metabolism and energy production in hepatocytes are summarized in figure 1 from the review of Pessayre, et al[24]. FFA have several origins. They are synthesized *de novo* within the hepatocytes, or they are taken up by the liver from plasma FFA released from adipose tissue, or they are generated in the liver from the hydrolysis of intestinal chylomicrons.

Then, hepatic FFA may be esterified into triglycerides. Hepatic triglycerides are either secreted as very low density lipoproteins (VLDL), corresponding to a droplet of triglycerides, cholesterol, phospholipids and a large protein termed apolipoprotein-B, or they accumulate as fat droplets within the cytoplasm of hepatocytes.

Hepatic FFA can also go into mitochondria where they undergo mitochondrial beta-oxidation. The oxidation of FFA in mitochondria is associated with the conversion of oxidized into reduced factors (NADH and FADH2), which can be then be re-oxidized by the mitochondrial respiratory chain, further allowing the conversion of adenosine diphosphate (ADP) into adenosine triphosphate (ATP) which can be used to provide energy to the cell.

The entry of FFA into the mitochondria is regulated according to physiologic conditions. After a carbohydrate meal, high glucose and insulin levels cause brisk hepatic fatty acid synthesis, which is preferentially directed toward the formation of triglycerides. In contrast, in the fasting state, FFA are released from adipose tissue and taken up by the liver. Hepatic FFA synthesis is low, thus leading to a massive mitochondrial import of FFA and extensive mitochondrial beta-oxidation allowing ATP production. Successive beta-oxidations split FFA into acetyl-coenzyme A (CoA) subunits, which are mostly condensed into ketone bodies that are secreted by the hepatocyte.

Hepatic fat accumulation is due to a variety of causes, including the increased delivery of FFA to the liver, increased *de novo* lipogenesis, and possibly impaired VLDL formation in some cases. Moreover, impaired beta-oxidation is probably involved in this context, especially in steatohepatitis as opposed to simple steatosis.

Host factors: the metabolic syndrome, first step to steatosis

Many studies on nonalcoholic steatosis have shown a clear relationship between a fatty liver and troubles in glucose and fat metabolism. Obesity has very often been found to be the strongest predictor of NAFLD. The more obese the patient, the higher the risk of fatty

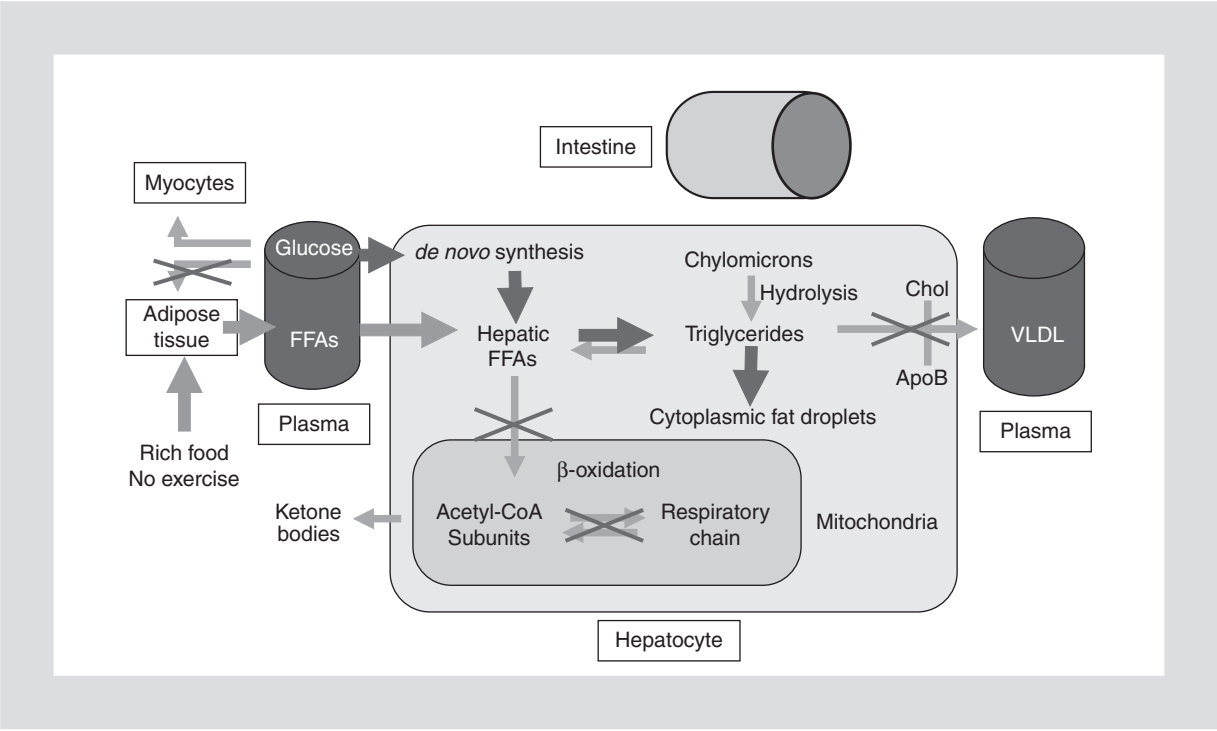

Figure 2. *Changes in fat and glucose metabolism in obesity* (adapted from Pessayre, et al.[24]).

liver disease[17]. In the USA, the prevalence of fatty liver disease is estimated at 20-30%. In a recent European study, 47% of morbidly obese females and 85% of males had more than 30% of hepatocytes filled with fat droplets[17].

In fact, obesity is often part of the metabolic syndrome, a clinical and biological entity associating abdominal obesity, high blood pressure, hypertriglyceridemia, low HDL, and insulin resistance[25]. Indeed, obesity increases plasmatic FFA and also causes resistance to the action of insulin, resulting in a decrease in glucose uptake and its utilization by adipocytes and muscle cells. The increased load of FFA within hepatocytes results from an increased uptake from plasma and increased *de novo* synthesis. This may lead to increased beta-oxidation. However, this increase is not sufficient to control the excess FFA, which leads both to increased secretion of VLDL (causing hypertriglyceridemia) and to increased formation of triglycerides. These are partly stored in the cytoplasm, causing macrovesicular steatosis[24].

From steatosis to steatohepatitis

Nonalcoholic simple liver steatosis mostly runs a non-progressive clinical course in cohort studies[26,27], but in overweight patients, necrosis and inflammatory infiltrate will develop in association with steatosis, thus defining steatohepatitis. In these patients, mitochondrial beta oxidation of FFA may be lowered and/or uncoupled from the respiratory chain, with a decreased activity of respiratory chain complexes with low ATP hepatic levels (Fig. 2). The production of reactive oxygen species (ROS) oxidizes the unsaturated fat deposits and causes lipid peroxidation, which in turn will alter mitochondrial DNA (mtDNA), and increase tumor necrosis factor-alpha (TNFα) release by hepatocytes[24].

Steatohepatitis is probably a crucial stage in the progression of steatosis to advanced liver disease, since it is believed that steatohepatitis can evolve to cirrhosis in 15-20% of cases[28]. What makes steatosis evolve into steatohepatitis still needs to be demonstrated clearly. It is likely that the genesis of steatohepatitis, as opposed to steatosis, requires either a more severe and prolonged exposure to a causal factor or additional physiopathologic abnormalities. This concept is referred to as the “two hits” or “multiple hits” hypothesis[4]. The first hit, frequently imbalance in lipid homeostasis associated with insulin resistance, leads to the development of steatosis. The genetic background may influence the probability of developing steatosis. The second hit may be an intrahepatic abnormality (such as mitochondrial injury resulting in

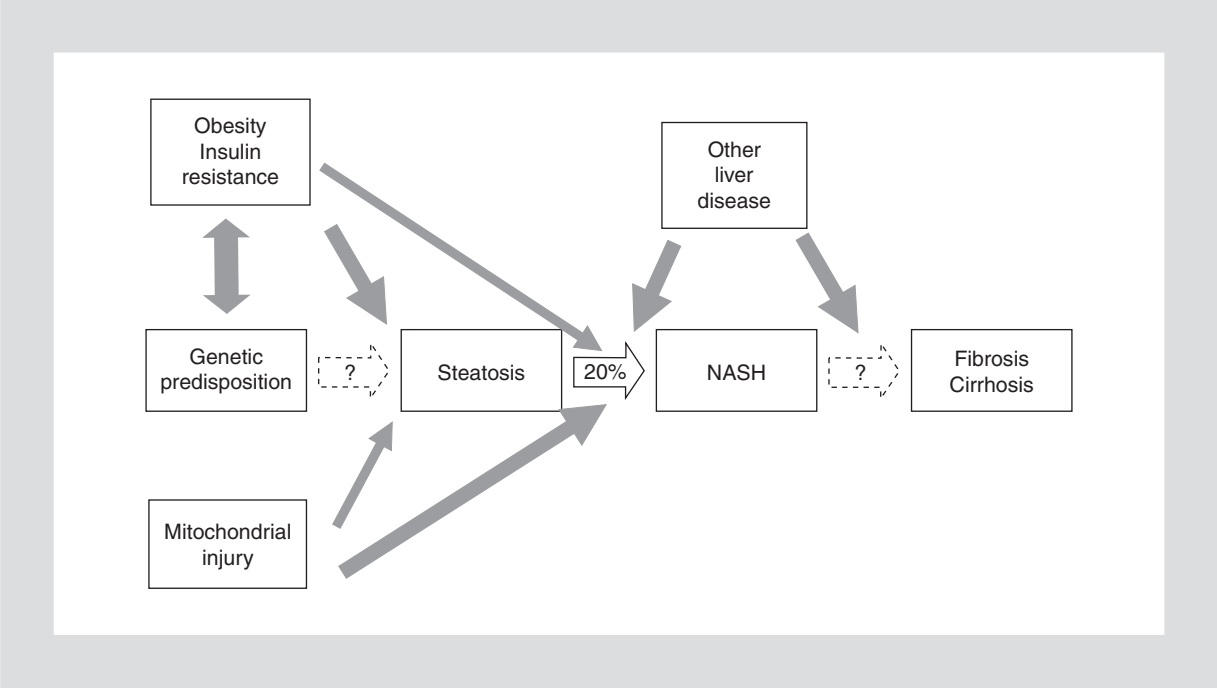

Figure 3. *The two hits hypothesis* (adapted from Ristig, et al.[4]).

chronic impairment of mitochondrial beta-oxidation and of the respiratory chain) that develops as a response to the first hit, or is present independently, and linked to other causes such as toxic drugs, alcohol intake, or viral coinfections (Fig. 3).

Alcohol and drugs

Excessive alcohol intake is the most classical hit leading to steatosis and steatohepatitis. Alcohol causes impairment of mitochondrial oxidation of FFA through oxidative damage to the mitochondrial enzymes[29]. The amount of alcohol necessary to induce fatty liver is unclear, but women will develop steatosis and steatohepatitis at lower doses than do men, with a 1 to 2 ratio[30]. Since excessive alcohol intake may frequently be encountered in HIV-infected patients[31], and even though the quantities consumed are not precisely known, it has to be taken into account in the prevention and management of liver steatosis in HIV-infected patients.

Some drugs, such as aspirin, ibuprofen, nonsteroidal anti-inflammatory agents, amiodarone, calcium channel blockers, chloroquine, estrogen, methotrexate, anthracycline, tetracycline, chloramphenicol, linezolid, or valproic acid may also be associated with mitochondrial impairment[5,32,33]. However, their ability to promote liver steatosis has not been established.

Hepatitis C virus infection

Prevalence of liver steatosis in HCV-infected patients

Among the factors involved in fatty liver disease onset which could be the second "hit", hepatitis infections have to be considered, since these infections are common in HIV-infected patients, with nearly 20-30% of those coinfected with HCV and 6-8% with chronic positive HBs antigenemia. However, even though steatosis seems to be frequent in hepatitis B (27-51%[34]), most studies have been conducted in HCV-infected patients.

It is, however, difficult to clearly assess the real prevalence of steatosis in HCV-infected patients, since most studies are cross sectional or retrospective, with liver biopsies not being systematically performed in a whole cohort, but in selected patients (thus probably leading to an overestimation of the prevalence), and using different cut-off values. Moreover, these studies do not make it possible to draw definite conclusions on causal relationships; i.e. if liver steatosis is a cause, a concomitant factor, or a consequence of associated factors.

Taking into account these limitations, it could be suggested that steatosis, whatever the level, is observed in 30-70% of liver biopsies[34]. When using a

threshold of 30% of fatty hepatocytes, the prevalence ranges from 6-24%[6,35-39]. The few longitudinal data available seem to indicate that steatosis, once present, persists and tends to increase with time.

Mechanisms of liver steatosis in HCV-infected patients

Most studies indicate that the presence of steatosis is dependent on a complex interaction of viral and host-related factors. The role of obesity, insulin resistance, and dyslipidemia has been clearly highlighted[34,38,40-42]. Of interest, HCV has also been associated with a higher risk of insulin resistance in HIV-infected patients[43]. In HCV mono-infected patients, steatosis also appears to be associated with increased age and male sex[34,38,40,41]. All of these host-related factors appear to be of highest importance in patients infected with HCV genotype 1, who are more likely to develop "metabolic" steatosis[44].

On the other hand, steatosis may be of a "viral" origin, since many studies indicate that HCV genotype 3 is independently associated with steatosis[6,34,42,44-47]. The quantitative association between steatosis and hepatic HCV-RNA[44-46,48], the loss of steatosis after viral eradication[6,38,45,49], and the development of steatosis in *in vitro* or animal models of HCV infection[50] all support the hypothesis of a direct effect of HCV via a different pathogenic mechanism. Since patients chronically infected by HCV genotype 3 have decreased levels of beta lipoproteins, it has been suggested that HCV core proteins may impair the incorporation of triglycerides into VLDL[45,49,51-53].

It has also been suggested that HCV core protein may induce mitochondrial dysfunction, either by promoting oxidative injury and thus adversely affecting mitochondrial function, and/or by direct interaction of viral proteins on mitochondria, and/or via immune-mediated activation of cell apoptosis[2,54]. Hence, the decrease in mtDNA content of PBMC observed in HIV-HCV coinfected patients is higher than in mono-infected ones[54].

Consequences of liver steatosis in HCV-infected patients

Regarding the potential consequences of steatosis, around 30% of the patients with chronic hepatitis C and steatosis are affected by steatohepatitis[34]. An independent association between steatosis and the degree of fibrosis in HCV-infected patients has also been shown[6,34,35,38,42,45,55-57]. To support the potential independent role of steatosis in promoting fibrosis, another recent study in HCV mono-infected patients showed that the probability of fibrosis progression was higher in patients with significant steatosis (> 30% seven years after biopsy) than in those without steatosis[36]. Conversely, no clear relationship exists between the degree of necrotic-inflammatory activity and steatosis. On the other hand, steatosis was less prevalent in cirrhotic patients[41].

Though necrosis and inflammation are well known factors in the progression of fibrosis, these data suggest that steatosis and necrotic-inflammatory activity may act independently in the mechanisms generating fibrosis. It has also been suggested that steatosis could not only increase the risk of progression to cirrhosis, via stellate-cell activation and collagen synthesis, but perhaps also to hepatocellular carcinoma (HCC)[58].

However, this causal relationship still needs to be argued, since different studies that took insulin resistance into account (which was not done in many previous studies) observed in multivariate analysis that fibrosis was associated with insulin resistance, but not with steatosis, whatever the HCV genotype[39,59-63]. There is, thus, growing evidence that steatosis is an innocent marker of the real fibrogenic factor – insulin resistance.

Another possible consequence may be the negative impact of steatosis on the response to anti-HCV treatment. Indeed, recent studies have observed a lower response rate to anti-HCV treatment in patients with significant steatosis, after adjustment for HCV genotype, and independent of other factors such as body mass index (BMI), age and fibrosis[6,35,38,64-66]. A decreased pharmacologic effect of interferon and/or ribavirin has been discussed as a potential explanation of this lower rate of response[64], but this seems unlikely since the virologic response is lower in patients infected with HCV genotype 3 and with a high viral load (these patients often have a high level of steatosis, but not a higher BMI), compared with those with low viral load or infected with HCV genotype 2[67].

On the other hand, we could face a paradox since HCV genotype 3 is a risk factor for steatosis and is also a positive prognostic factor of virologic response to anti-HCV treatment. An explanation could be that the prevalence of steatosis in patients infected with HCV genotype 1 is often close to that observed in those infected with genotype 3, since these HCV genotype 1-infected patients are more often older, and thus in-

fected by HCV for a longer period of time, and more often obese than HCV genotype 3-infected ones. However, the prevalence of steatosis in HCV genotype 3-infected patients is high in many studies, suggesting that other factors (in particular host- and viral-related) play a more important part in the response to anti-HCV treatment.

The effect of anti-HCV treatment on liver steatosis has also been assessed in several studies[6,37]. Improvement in steatosis is often associated with sustained virologic response (SVR) in HCV genotype 3-infected patients[6,37]. In a large study on 574 HCV mono-infected patients with paired liver biopsies[38], steatosis was markedly improved in HCV genotype 3-infected patients who achieved SVR. This finding was independent of BMI. In contrast, patients with non-genotype 3 infection had no significant changes in steatosis following treatment, as was the case with patients infected with genotype 1, whatever the response to treatment. This argues for the responsibility of host-related factors in non-genotype 3 infection, and for the interest of anti-HCV therapy in treating steatosis in patients infected with genotype 3. These results were also observed in HIV-HCV coinfected patients in the recent therapeutic trial, RIBAVIC[68].

HIV infection per se *and antiretroviral treatment*

Another hit in the pathogenesis of steatosis and steatohepatitis may be HIV infection *per se* or antiretroviral treatment. In the pre-HAART era, steatosis was found in 30-50% of HIV-infected patients[69-71]. A more recent study on 27 HIV-infected children (12 of whom underwent liver biopsy) found a high prevalence of nonspecific steatosis in these children, with no clear relationship to the antiretroviral treatment[18]. Since HIV is not known to infect hepatocytes directly, the potential mechanisms of HIV toxicity directly leading to steatosis are unclear. It could be suggested that HIV promotes hepatocyte apoptosis, as shown *in vitro* and in HIV-HCV coinfected patients[72,73], but such a pathogenic mechanism cannot explain fat deposition without inflammation observed in the clinical reports. Another associated explanation could be that advanced HIV infection was found to be associated with increased TNFα release[74], which can impair mitochondrial respiration and block the respiratory chain, increasing mitochondrial ROS formation and lipid peroxidation[24]. Nevertheless, it is likely that comorbidity induced by factors such as alcohol abuse, malnutrition, and chronic illnesses played a significant part in these end-stage or postmortem evaluations.

Rather than HIV *per se*, the potential role of antiretroviral therapy appears to be more important. In the HAART era, it has been suggested that 40% of HIV-infected patients treated with a protease inhibitor (PI) for longer than one year will develop acquired lipodystrophy[75]. Lipodystrophy is more often associated with insulin resistance, hypertriglyceridemia, and low serum levels of HDL cholesterol, these abnormalities being mostly linked to PI use. Lipodystrophy, and in particular lipoatrophy, is also observed in patients treated with nucleoside reverse transcriptase inhibitors (NRTI), and this may be associated with hyperlactatemia[76].

Indeed, NRTI are the backbone of most antiretroviral therapies. But they have been compromised by long-term toxicity, in particular mitochondrial toxicity. Mitochondrial toxicity is frequent in treated HIV-infected patients, with an incidence ranging from 2-8% per year (and an incidence of new lactate elevation from 0.4-0.8/100 patients per year in prospective studies[5,32]). This toxicity seems to be related to the inhibition or the alteration of the human DNA polymerase gamma, which is a key regulatory enzyme of mtDNA replication, and far more susceptible to NRTI than nuclear polymerases at physiologic concentrations. Inhibition of DNA polymerase gamma leads to reduced respiratory chain enzyme activity[77] and mtDNA depletion, even though differences can be observed between the different tissues. In the liver, ultrastructural mitochondrial abnormalities were observed in 30 HCV-HIV coinfected patients under HAART[78]. The inhibition of DNA polymerase gamma in the liver seems to occur more frequently with D drugs (ddC, ddI, d4t) than with non-D drugs[79,80]. Toxicity may be aggravated by the concomitant use of other drugs such as ribavirin or hydroxyurea with ddI[54]. Other mechanisms, such as the incorporation of nucleosides analogues in mtDNA or competitive inhibition of ATP/ADP translocation may be involved in toxicity[5]. Overall, this toxicity results in increased ROS, in increased lipid peroxidation, in fatty-acid accumulation in hepatocytes, in impaired glycolysis and also in lactate accumulation (since the liver is essential for lactate homeostasis). This combination has been reported by some authors in HIV-infected patients as the steatosis-lactic acidosis syndrome[15]. However, a recent study in 80 HIV-HCV coinfected patients did not show a clear correlation between liver mtDNA levels and macro- or microvesicular steatosis[80], emphasizing the combined, even synergetic, effect of other cofactors. In addition to mitochondrial toxicity, it

is possible that NRTI (in particular d4T) are associated with a greater risk of insulin resistance and hypertriglyceridemia[81,82], and thus with a greater risk of liver steatosis via other pathways.

Several cases of fatty liver disease with fatal outcome have been reported in HIV-infected patients treated with NRTI[10,14,16,83-89]. In the pre-HAART era, liver histology in patients treated with NRTI who subsequently developed severe liver disease, often with lactic acidosis, nearly always found steatosis[10,16,84,87,89-91], which was more often microvesicular. Similar findings were observed in the HAART era. In a study on six HIV-infected patients with NRTI-induced hyperlactatemia and hepatic abnormalities who underwent liver biopsy, microvesicular steatosis was observed in four cases, whereas mixed diffuse steatosis was found in one case[14]. Similar findings were observed in four patients who developed lactic acidosis and aminotransferase elevation while on antiretroviral treatment including stavudine[11], or in patients who underwent liver transplantation for hepatitis C-related end-stage liver disease, all of them on antiretroviral therapy that included NRTI[92].

Protease inhibitors may inhibit lipid and adipocyte regulatory proteins that have partial homology to the catalytic site of HIV protease, to which all PI bind[76]. Indeed, they can inhibit the differentiation of proliferating pre-adipocytes into mature adipocytes. They suppress the breakdown of the nuclear form of sterol regulatory element binding proteins (SREBP) and reduce the expression of peroxisome proliferator activated receptor gamma (PPAR-γ) in the liver and adipose tissues. This results in increased fatty acid and cholesterol synthesis in hepatocytes and decreased pre-adipocyte differentiation, reduced leptin expression, and insulin resistance in adipocytes[40,93]. They can also suppress proteasome-mediated breakdown of nascent apolipoprotein B, both in adipocytes and in hepatocytes[40,94]. They also inhibit insulin-mediated glucose uptake via GLUT-4, which is a key receptor in adipocytes and skeletal muscle cells[40,95].

Since the mechanisms underlying antiretroviral therapy-induced lipodystrophy and NAFLD are close and perhaps the same, it is likely that the two diseases are correlated[96]. A cross-sectional study comparing 25 HIV-positive men with HAART-associated lipodystrophy, nine treated HIV-infected men without lipodystrophy, and 35 HIV-negative healthy men showed that the severity of insulin-resistance syndrome in patients with HAART-associated lipodystrophy was related to the extent of fat accumulation in the liver (assessed by proton spectroscopy), rather than in the intraabdominal region[23]. It was also suggested that fat accumulation in the liver may play a causative role in the development of insulin resistance in these patients.

Moreover, the multiple-hit hypothesis applies to HIV-infected patients. The probability of developing steatosis or even steatohepatitis depends on the genetic background of the patient. As for lactic acidosis, steatosis was observed more often in women than in men in several case reports[10,11,16,84]. Overweight or obese patients also seemed to be at higher risk[14].

What do we currently observe in HIV-infected patients?

All of the potential causes of steatosis and its potential implications previously discussed are summarized in figure 4. However, clinical studies on steatosis and its related risk factors in HIV infection are rare and retrospectively include HIV-HCV coinfected patients. The first reason for this is that liver steatosis has only recently been studied in HCV mono-infected people. The second reason is that since liver biopsy is the main diagnostic tool, it is more frequently performed in HCV-HIV coinfected patients than in HIV mono-infected ones.

Prevalence of liver steatosis in HIV-infected patients

Considering the risk factors associated at least with antiretroviral treatment, it could be speculated that HIV-HCV coinfected patients are at a higher risk of liver steatosis than HCV mono-infected ones.

In a recent study which examined liver tissue from a random sample of 112 antiretroviral-experienced HIV-HCV coinfected patients, all but one of whom was infected with HCV genotype 1, 60% had no histologic evidence of liver steatosis, and only 18% had steatosis with more than 5% hepatocytes affected[97]. In 106 HIV-HCV coinfected patients, no steatosis was observed in 44%, whereas only 9% had moderate to severe steatosis (> 33%), most of which were macrovesicular[98]. In another report, no steatosis was observed in 33% of 148 HCV-HIV coinfected patients who underwent liver biopsy, whereas 19% of the patients had 11-30% of fatty hepatocytes and 11.5% had > 30% of fatty hepatocytes[47]. Steatosis was most often macrovesicular (40%) or mixed (53%). Yet another study reported no steatosis in 46% of 92 coinfected patients and moderate to severe steatosis in 24%[99].

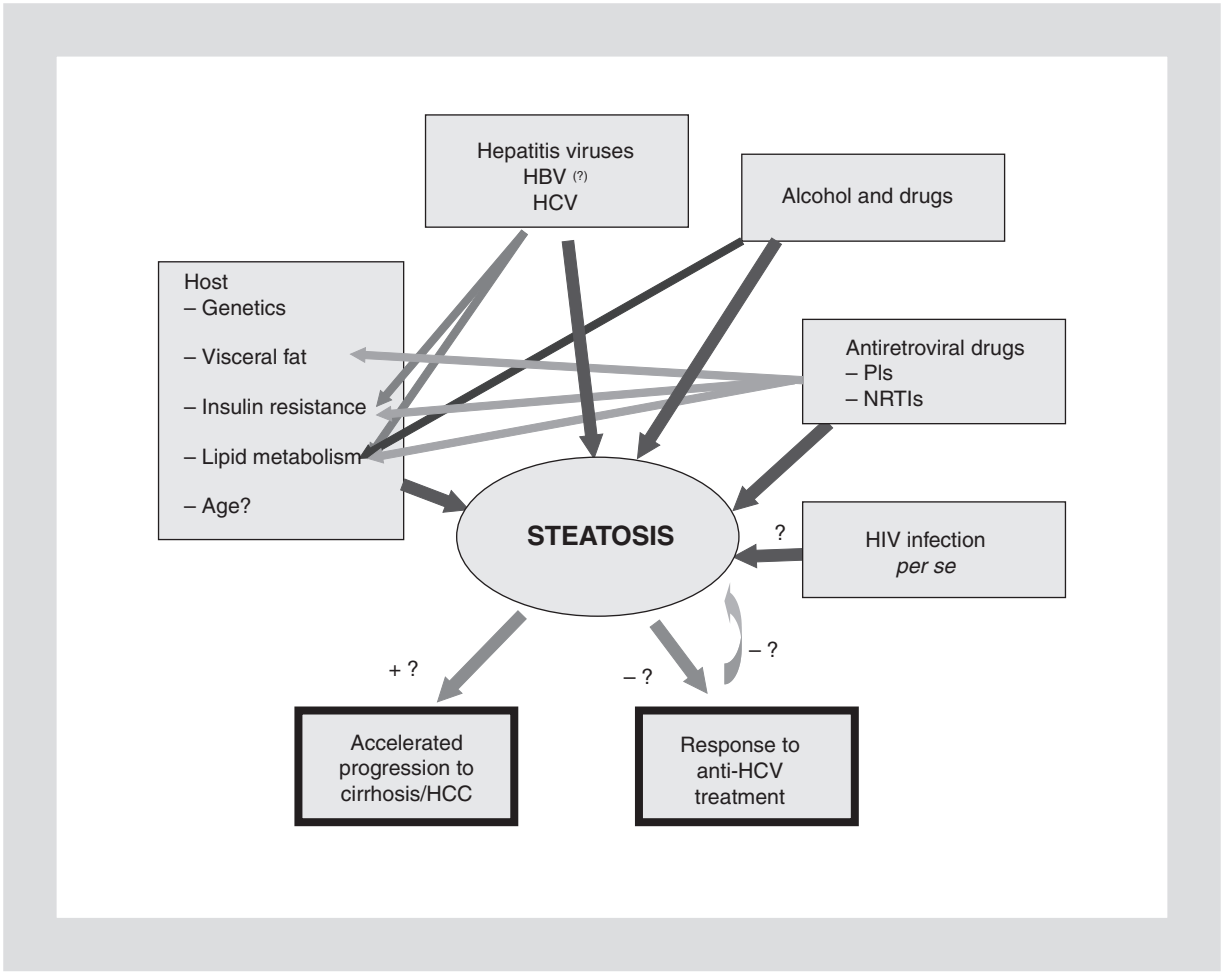

Figure 4. *Potential causes and consequences of liver steatosis in HIV-infected patients.*

Another recent study directly compared 92 HCV-HIV coinfected patients with 372 HCV mono-infected patients[100]. The coinfected patients were significantly younger, were less likely to have diabetes, had a lower BMI, a lower alcohol intake, a lesser degree of ALT elevation and were more frequently infected with HCV genotype 1. The steatosis observed in this study was predominantly macrovesicular. Though at least 1% of fatty hepatocytes were observed in 47% of coinfected patients, steatosis above a threshold of 33% was observed in only 2%. This compares with 9% in mono-infected patients.

According to these data, liver steatosis does not seem to be more frequent, and may even be less frequent, in HIV-HCV coinfected patients than in HCV mono-infected ones; 40-60% of coinfected patients do not have steatosis, and 5-10% have steatosis more than 33% of fatty hepatocytes. A possible explanation could be that the prevalence of genotype 3 is higher in HCV mono-infected patients, while the host-related factors are not more prevalent in coinfected ones. Another possibility could be that liver biopsies in HIV-HCV coinfected patients often reveal a higher prevalence of cirrhosis than in HCV mono-infected patients, and that steatosis could be lower in cirrhotic patients than in noncirrhotic ones[41].

Apart from these histologic data, it has to be kept in mind that HIV-infected patients while on antiretroviral treatment will often experience what is generally called hepatotoxicity (with a global proportion of grade III liver elevation of nearly 6% with a median follow-up of nearly two years[101]). This toxicity may be related to different mechanisms, such as direct drug toxicity, immune reconstitution in the presence of HCV and/or HBV coinfections, hypersensitivity reactions with liver involvement, but also liver steatosis and mitochondrial toxicity[54,102]. However, the histologic assessment of "liver toxicity" is not frequently performed, especially in mild liver-enzyme elevations. This leads to an underestimation of this phenomenon in HIV-infected patients.

Risk factors for liver steatosis in HIV- infected patients

The main classical host-related factors were found to be associated with steatosis in most studies, in particular BMI and insulin resistance[47,97,99,100].

In most studies including patients infected with HCV genotype 3, this genotype was also significantly (or almost significantly) associated with steatosis in multivariate and/or univariate analyses[47,99,100].

The potential impact of HIV infection *per se* or antiretroviral treatment on the onset of steatosis remains to be assessed. The only comparative study that set out to assess the impact of HIV infection did not find that HIV status, whatever the associated antiretroviral treatment, was associated with steatosis[100]. In the study of Sulkowski, et al.[97], nearly 90% of patients with hepatic steatosis had been exposed to a PI and d4T. After adjustment, exposure to d4T was associated with a more than fivefold higher risk of liver steatosis. More surprisingly, a positive association between steatosis and nonnucleoside reverse transcriptase inhibitor (NNRTI) treatment was found in univariate, but not in multivariate analysis in one study[47], and conversely, a negative association was found in another[98]. In all studies, no significant association with PI use was observed[47,98,99].

Clinical impact of liver steatosis

Though patients with steatosis were more likely to have bridging fibrosis or cirrhosis in univariate analysis in two studies[97,98], steatosis was not found to be independently associated with fibrosis in two others[47,100]. In contrast with other studies in HCV mono-infected patients, steatosis also seemed to be associated with necrotic-inflammatory activity in two studies[47,97], but not in two others[98,100].

The liver biopsies of seven HCV-HIV coinfected patients (mostly antiretroviral untreated), with clinically imminent liver death and advanced immune deficiency, were compared with seven asymptomatic patients (mostly treated with HAART), matched according to duration of their HCV infection[103]. Macrovesicular steatosis was a common finding, but with low percentages of fatty hepatocytes (always < 10%) whatever the study group. The extent of liver steatosis, inflammatory activity, and fibrosis was similar in both study groups. It cannot, however, be ascertained that the lack of difference observed can be linked to the antiretroviral treatment in the control group, or on the other hand to the fact that liver steatosis had reversed considering the advanced stage of liver disease[41].

Regarding the response to anti-HCV treatment, baseline insulin resistance showed a negative predictive value for week-12 early virologic response in 101 HCV-HIV coinfected patients[104]. Since insulin resistance is often associated with liver steatosis, it could be speculated that steatosis may be a negative prognostic factor of SVR, as already observed in HCV mono-infected patients.

Management of liver steatosis in HIV-infected patients

Even though the impact of subclinical steatosis in HIV-infected patients has not yet been established, it appears that improved recognition of steatosis and its risk factors is needed in the management of these patients[4]. A review of risk factors that contribute to liver abnormalities is required, including coinfections with hepatitis viruses, alcohol history, and metabolic abnormalities. Special attention must be paid to patients on high-risk antiretroviral therapy, in particular NRTI such as ddI, ddC and d4T. Most often, other NRTI have to be preferred in antiretroviral combinations, when possible. Nonspecific gastrointestinal syndrome or liver enzyme elevation should warn of the possible presence of steatosis. Other investigations to consider are noninvasive imaging techniques or even liver histology.

In HIV-infected patients with suspected or proven liver steatosis, alcohol intake has to be suppressed. Exercise and weight loss, when needed, are essential, as recommended in HIV-negative patients, even though their effect on steatosis reversal has still to be clearly proven. If necessary, diabetes and hypertriglyceridemia can be treated first with dietary, and then with specific pharmacologic therapies. Drugs such as aspirin, ibuprofen, and valproic acid, which are thought to induce liver mitochondrial injury, have to be used cautiously.

Treatment of other causes of liver steatosis, such as hepatitis C, has to be considered as well, in particular for HCV genotype 3, considering the significant reversal of steatosis in sustained virologic responders, HCV-treated, HIV coinfected patients[68]. For patients infected with HCV genotype 1, it seems more important to focus first on other factors, since steatosis in such cases may be predictive of decreased virologic response.

In HIV-infected patients without antiretroviral treatment, since both NRTI and PI may be associated with

liver steatosis, the need for such treatments and their risk/benefit ratio has to be weighed cautiously. NRTI other than d4T, ddC and ddI have to be preferred as the first-line treatment.

In treated patients, if liver steatosis is associated with symptomatic hyperlactatemia and/or lactic acidosis, immediate withdrawal of NRTI is mandatory, and should be associated with symptomatic treatments and other therapies such as antioxidants[5,32,33,105].

In other treated patients, antiretroviral interruption strategy may be considered, even if its efficacy is currently under investigation. If antiretroviral treatment is continued, it could be advocated that PI have to be replaced by NNRTI, or by atazanavir, which does not appear to promote significant dyslipidemia, but the efficacy of such switches is yet to be demonstrated. Once again, and when possible, d4T, ddC and ddI should be withdrawn, even if the possible improvement following the withdrawal of these drugs is also to be established.

Finally, different drugs, such as ursodeoxycholic acid, vitamin E, and N acetyl cysteine, have been studied for the specific treatment of NAFLD[13]. However, these drugs have been assessed in non-HIV infected patients and in non-controlled trials, and thus their efficacy is still to be demonstrated.

What do we need to know in HIV-infected patients?

HAART has led to a dramatic improvement in HIV-infected patients, by reducing the occurrence of HIV-related clinical events and allowing a greater life expectancy and quality of life. However, comorbidities such as viral coinfections and drug toxicity play a more important part in the management of these patients, generating a need for better knowledge of their prevalence, pathogenesis, clinical impact, and the therapeutic options offered.

In HIV-negative patients, liver steatosis appears as a significant factor of comorbidity, either as a marker of other disease, or due to its own potential evolution. The few data available in HIV-infected patients leave several questions unanswered:

- What is the real prevalence of liver steatosis, with special focus on microvesicular steatosis, in particular in patients with normal liver enzyme levels and/or without HCV coinfection?
- Is there a genetic background which could facilitate the onset on liver steatosis?
- Is there a clinical impact of liver steatosis, when assessed prospectively?
- If so, do we need to assess the presence of steatosis by liver biopsy? For which patients?
- Since fibrosis tends to be assessed via noninvasive tests (mainly biological fibrosis tests and elastometry), do we need a steatosis test?
- Is steatosis influencing the response to anti-HCV treatment? Is the lower response rate observed in HIV-HCV coinfected patients related to a higher prevalence of steatosis?
- What is the impact of withdrawal of NRTI on the evolution of steatosis, in particular on microvesicular steatosis?

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