

HAART and Hepatotoxicity

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ABSTRACT

Antiretroviral (ARV) drugs are given in combination to treat the human immunodeficiency virus (HIV) infection and to prolong the life expectancy of the patient. The increase in the levels of hepatotoxicity due to the use of above drugs has been the concern till date. Lactic acidosis, hepatocytes fatty infiltration and oxidative stress are the commonly associated hepatotoxic effects with the administration of nucleoside reverse transcriptase inhibitors. Non-nucleoside reverse transcriptase inhibitors such as nevirapine and efavirenz inhibit bile acid transport causing cholestasis which in turn causes apoptosis to the hepatocytes. Furthermore, hepatitis C and B virus co-infection and *Tuberculus bacilli* in HIV infected patients remains a vital risk factor for the development of hepatotoxicity associated with highly active antiretroviral therapy (HAART). Overwhelming evidences clearly shows that the ARV drugs mediated hepatotoxicity has been attributed due to their mitochondrial interference. Although a low grade of hepatotoxicity resolves, high levels of toxicity leads to discontinuation of the therapy. Hence, careful observation is necessary especially during and after HAART to study the drug-induced liver diseases.

INTRODUCTION

Human immunodeficiency virus (HIV) related mortality and the risk of opportunistic infections has greatly decreased in recent years due to the use of highly active antiretroviral therapy (HAART) which employs the combination of two or more antiretroviral drugs for its treatment and are often referred as antiretroviral therapy (ART) (Egger *et al.*, 2002). Though HAART have its potential to reduce progression of the disease in patients, they still have certain side effects which include liver toxicity, hematuria, decreased bone density, cardiovascular disease, gastrointestinal tract infection, hypersensitivity reaction, lactic acidosis, lipodystrophy, myopathy and Steven-Johns syndrome, etc. (Soriano *et al.*, 2008). One of the major side effects caused by ART is

hepatotoxicity (Priyanka and Ezhilarasan, 2014). In fact, according to a recent report, AIDS- related illnesses account only around 50 % of the deaths, whereas HAART-induced liver injury has appears as a primary cause of death in HIV infected patients (Puri and Kumar, 2016). Hence, overwhelming research is being focused on HAART-related liver injury; especially in patients infected with both HIV and HCV (Bonacci *et al.*, 2016; Casado *et al.*, 2014) and remedial measure to protect the above drug-induced liver injury is the need of the hour.

The objective of this review is to discuss our knowledge in understanding the mechanisms of toxicity induced by antiretroviral (ARV) drugs in context to its hepatic physiology. The following section emphasizes on the importance of liver injury and its mechanisms, which results as a consequence of metabolism and/or due to direct cell toxicity by ARV drugs. The mechanism by which ARV drugs induced toxicity arises includes bile acid retention and apoptosis, mitochondrial dysfunction, endoplasmic reticulum (ER) stress and hepatocytes membrane damage by reactive oxygen species (ROS) (Figure1).

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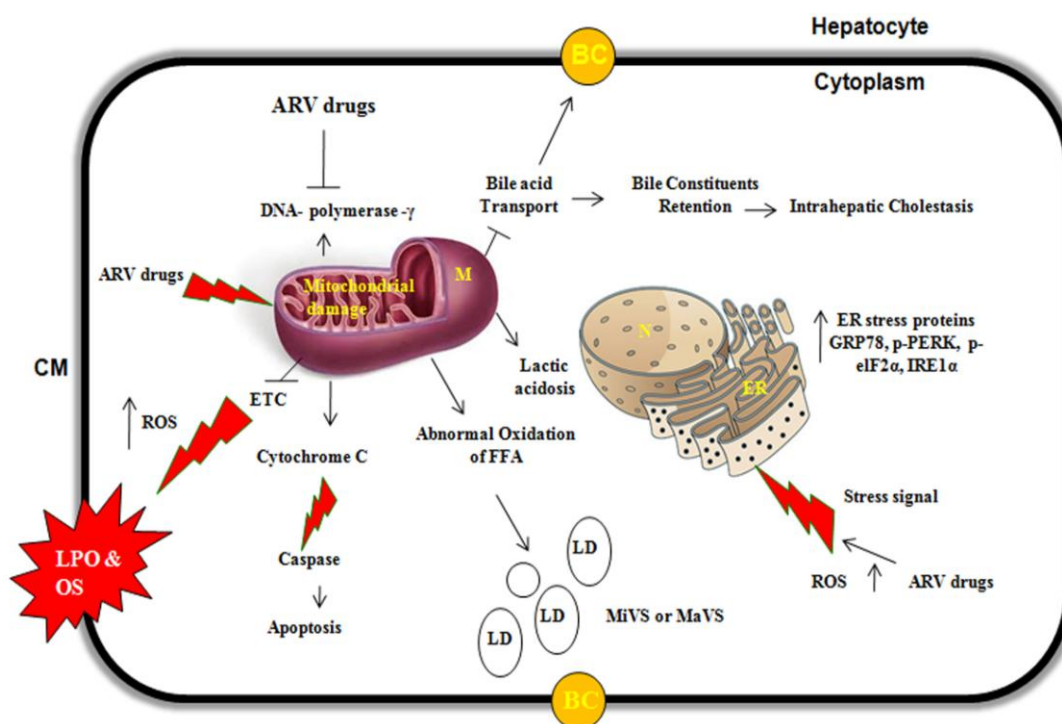


Fig. 1: mechanism of ARV drug induced hepatotoxicity. CM- hepatocyte membrane; M- Mitochondria; N-Nucleus; ER-Endoplasmic reticulum; BC-bile canaliculi; LPO- lipid peroxidation; OS-Oxidative stress; LD- Lipoid droplets; MiVS- Microvesicular steatosis; MaVS- Macrovesicular steatosis; ETC- Electron Transfer; p-eIF2 α –eukaryotic translation initiation factor-2 α ; GRP78-glucose-regulated protein 78; p-PERK – protein kinase-like endoplasmic reticulum kinase; IRE1 α inositolrequiring and ER-to-nucleus signaling protein.

Highly active antiretroviral therapy (HAART)

The name HAART was introduced in the late 1990s to report the usefulness of combination drug therapies to treat HIV. The HAART regimen includes the combination of three or more antiretroviral drugs used effectively to suppress a wide variety of HIV infection. The main aim of employing HAART in HIV infected individuals is that if one drug is not able to suppress, the other drugs used in this combination will be more likely to suppress the HIV (Priyanka and Ezhilarasan, 2014). In context to liver, onset of severe liver injury initiating after HAART ranges from 2 to 18% and in USA, approximately 2000 cases of acute liver failure are being reported annually due to drug abuse which accounts for about 50% and 2-5% of these patients are being hospitalized with jaundice and approximately 10% with acute hepatitis (Núñez, 2010). Co-infection with hepatitis C virus (HCV) has also been documented as one of the foremost causes of chronic liver disease during HAART. Pre-existing hepatic fibrosis and accumulation of extracellular matrix during HAART is said to aggravate the risk of liver toxicity associated with ART (Wambani *et al.*, 2015).

HAART-induced hepatotoxicity

Hepatotoxicity arises due to chemical / drug intake leading to severe liver damage. When some drugs taken in combination or even at therapeutic levels, overdose cause liver injury (Ezhilarasan and Karthikeyan, 2016; Ezhilarasan, 2016; Pandit *et al.*, 2012). There are several risk factors which are said

to play a pivotal role in the onset of hepatotoxicity in patients who are under therapy. The prophylaxis for HIV infections are influenced by many factors such as race, age, sex and hepatic drug reactions which are more common in females, and alcoholic persons. Liver disease patients with cirrhosis are at increased risk of developing drug toxicity due to drug formulations or genetic factors in patients under ARV therapy (Yang *et al.*, 2016). Liver toxicity is one of the common manifestations in patients under ART and the role of HAART in HCV has been widely discussed. Antiretroviral therapy can initially increase hepatic inflammation, necrosis and accelerate chronic HCV progression. Therefore, many studies propose that HIV/HCV co-infection may augment the risk of developing hepatotoxicity after ART and HCV act as an independent risk factor for the progression of hepatic disease in co-infected individuals during HAART. Hence, it has been advised that patients should be monitor for pre-existing liver diseases and most notably hepatitis B and C before initiating ART (Labarga *et al.*, 2007).

Ironically, in a recent study, it has been reported that use of HAART therapy has shown the beneficial effect on the onset of liver fibrosis in HIV/HCV co-infected patients with advanced liver fibrosis (Chou *et al.*, 2015). Despite the improved understanding of HAART mediated hepatotoxicity in HIV/HCV co-infected patients, the interaction remains controversial. To overcome the above scenario, patients can be routinely checked for basic liver function tests such as transaminases, bilirubin, urea and creatin levels after commencing HAART for the first 3 months.

Table 1: Spectrum of antiretroviral drug induced hepatotoxicity.

Drug	Spectrum of hepatotoxicity	References
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Zidovudine	Acute cholestatic hepatitis, inhibits DNA polymerase- γ in mitochondria, ER stress, oxidative stress	Raghu and Karthikeyan, 2016; Raghu <i>et al.</i> , 2015; Banerjee <i>et al.</i> , 2013; Brinkman <i>et al.</i> , 1998; Dubin and Braffman, 1989
Stavudine	Elevation of liver toxicity marker enzymes, lactic acidosis, inhibition of mitochondrial oxidation of FFA – macrovesicular steatosis	van Griensven <i>et al.</i> , 2010; Gerschenson <i>et al.</i> , 2001; Johri <i>et al.</i> , 2000; Lea and Faulds, 1996
Lamivudine	Elevation in serum ALT levels in patients co-infected with chronic HBV, elevation of hepatotoxic and lipid marker enzymes in serum and plasma	Jesudas <i>et al.</i> , 2016; Johri <i>et al.</i> , 2000
Non- nucleoside reverse transcriptase inhibitors (NNRTIs)		
Nevirapine	Jaundice, hepatitis, hepatic necrosis, hepatic failure, elevation of liver marker enzymes (AST/ALT) in chronic therapy	Ajulo <i>et al.</i> , 2015; Bera <i>et al.</i> , 2012; Hitti <i>et al.</i> , 2004
Efavirenz	Retention of bile constituents in hepatocytes – cholestasis – hepatocytes apoptosis, inhibits bile acid transport in human/rat hepatocytes, high levels of elevation of AST/ALT, hepatic steatotic changes, mitochondria and ER stress	Thamrongwonglert <i>et al.</i> , 2016; Patil <i>et al.</i> , 2015; Apostolova <i>et al.</i> , 2013; McRae <i>et al.</i> , 2006
Protease inhibitors (PIs)		
Ritonavir	Induction of hepatocytes apoptosis through caspase-3 cascade system Inhibits bile acid transport in human/rat hepatocytes Increased risk of hepatotoxicity in HIV+TB infected patients with rifampicin treatment	Mchunu <i>et al.</i> , 2016; Kuang <i>et al.</i> , 2014; Schmitt <i>et al.</i> , 2009
Nelfinavir	Liver fibrosis, increased risk of severe hepatotoxicity along with nevirapine	Mira <i>et al.</i> , 2006
Saquinavir	Hindrance in bile acid transport inside the hepatocytes	McRae <i>et al.</i> , 2006
Indinavir	Combination with Saquinavir can cause elevation of liver marker enzymes	Sulkowski <i>et al.</i> , 2003

In patients with the history of the pre-existing liver disease, investigation of liver function tests can be performed more frequently *i.e.*, every 2 weeks after initiating the therapy. Clinically, it is in practice that once the liver marker enzymes of hepatotoxicity become stable; then the other less hepatotoxic drugs such as lamivudine and abacavir can be prescribe in patients who are at greater risk for developing hepatotoxicity (Kontorinis and Dieterich, 2003). In HIV-infected pregnant women using ARV therapy with an elevation of alanine aminotransferase (ALT) has been documented previously and is directly linked to liver toxicity (Huntington *et al.*, 2014) (Table.1).

Mechanism of ARV drug-induced hepatotoxicity

Antiretroviral drugs are metabolized in the liver through cytochrome and its metabolizing enzymes which may even cause liver toxicity due to its polymorphisms (Bissell *et al.*, 2001). Antiretroviral drugs inhibit the human mitochondrial DNA resulting in inhibition of normal mitochondrial replication which in turn decrease cellular respiratory chain thereby inhibits fatty acid β -oxidation pathway. There are previous reports suggesting ARV drugs-induced mitochondrial toxicity such as microvesicular hepatic steatosis, giant mitochondria and intrahepatic cholestasis. Studies have also concretely proved that interruption in electron transport chain results in the release of increased intracellular ROS leading to oxidative stress. These free radicals can cause lipid peroxidation of fatty acid present in the hepatocytes membrane consequently to release profibrogenic cytokines, fibrosis, and nuclear factor κ B to counteract the effect. Due to mitochondrial interaction cytochrome c, an inter membrane protein is also released into cytosol which activates caspases pathway thereby triggers cellular apoptosis in hepatocytes (Kontorinis and Dieterich, 2003; Spengler *et al.*, 2002).

HEPATOTOXIC POTENTIALS OF NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Zidovudine (AZT)

Zidovudine, a nucleoside analogue is commonly used in combination with other ARV agents for the prophylaxis and treatment of the HIV infection (Martín Fernández *et al.*, 1998). It was the first antiretroviral agent which received Food and Drug Administration (FDA) approval on March 19, 1987, for the treatment of HIV infection. In the same year, in October, Melamed and co-workers have reported the possible role of AZT-induced hepatotoxicity clinically (Melamed *et al.*, 1987). Few studies have also reported acute cholestatic hepatitis after AZT administration (Raghu *et al.*, 2015; Dubin and Braffman, 1989). Several experimental studies using rats and mice have also shown to develop oxidative stress leading to hepatotoxicity with AZT (Raghu *et al.*, 2015). The AZT-induced hepatotoxicity could be suggested due to the impairment of mitochondrial DNA transcription and inhibition of DNA polymerase γ in hepatocytes (Brinkman *et al.*, 1998; Fromenty and Pessayre, 1995). The severity of AZT-induced hepatotoxicity is reported in experimental animals and such studies found that the mild and transient elevation of marker enzymes of hepatotoxicity to severe manifestations like inflammation, ER stress, fatty infiltration, lactic acidosis and hepatic failure leading to death. For this reasons, the clinical use of AZT is limited (Raghu *et al.*, 2015; Banerjee *et al.*, 2013).

Stavudine (d4T)

Stavudine is a thymidine analogue and is well-known ARV drug for its potential to induce hepatotoxicity and even acute liver failure. The d4T treatment can cause mild to transient

elevation in liver marker enzymes due to hepatotoxicity which occurs in up to 50% of patients and lactic acidosis is often reported in these patients with high mortality rate (van Griensven *et al.*, 2010; Lea and Faulds, 1996). In primates, chronic exposure of d4T has been reported to induce mitochondrial toxicity and there was a significant destruction of hepatocytes mitochondrial DNA found in the liver of d4T-exposed monkeys (Gerschenson, *et al.*, 2001). Like other ARV drugs, d4T also interferes with mitochondrial catabolic beta-oxidation of free fatty acids causing the infiltration of lipid droplets in liver cells, manifesting as severe macrovesicular steatosis with hepatomegaly (Johri *et al.*, 2000).

Lamivudine (3-TC)

Lamivudine is an L-enantiomer, substituted analogue of cytidine is said to be effective against both HIV and hepatitis B virus (HBV) infections. It was observed that lamivudine treatment elevated the liver aminotransferase levels in patients with chronic hepatitis B (Johri *et al.*, 2000). These elevations appear due to a transient rise in patients with chronic HBV infection. Hence, patients should be carefully monitored after discontinuation of lamivudine therapy and if necessary treatment regimen should be started again promptly when decrease in clinical symptoms of hepatotoxicity (Núñez, 2010). Recent experimental studies have proved that chronic 3-TC administration consequently leads to an elevation in hepatotoxic and lipid marker enzymes in plasma of rats. The study also showed that ethanol intake could aggravate the 3-TC-induced hepatotoxicity in rats (Jesudas *et al.*, 2016).

HEPATOTOXIC POTENTIAL OF NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Nevirapine

Nevirapine is a non-nucleoside reverse transcriptase inhibitor commonly prescribed as a part of combination with other ARV drugs in the treatment of HIV/AIDS (Ajulo *et al.*, 2015). It is commonly used ARV drug to treat HIV-1 infection in pregnant women to prevent gestational transmission. The nevirapine-induced hepatotoxicity is manifested as elevation of serum marker enzymes, bile duct obstruction and jaundice, hepatic necrosis, hepatitis and hepatic failure (Bera *et al.*, 2012; Hitti *et al.*, 2004). Clinical studies have reported that nevirapine is one of the well-characterized hepatotoxic ARV drug in spite of its efficacy and good tolerability with an occurrence of characteristic liver injury ranging from 10% to 18% in patients who are under therapy with nevirapine (Sanne *et al.*, 2005). Clinically, symptomatic hepatitis is reported in 4 % of patients taking nevirapine. The development of hepatotoxicity is reportedly high in female compared to male population. The liver hepatotoxic marker enzymes such as AST and ALT have shown to increase following chronic nevirapine therapy in children. Hence, it is advised that if the patients develop any clinical symptoms of hepatitis then the nevirapine treatment should be discontinued immediately. Generally, like other ARV drugs nevirapine also should be discontinued when elevation of serum aminotransferase levels occur associated with rashes (Ajulo

et al., 2015). The data regarding the nevirapine-associated hepatitis and risk of developing hepatitis from subsequent treatment with other NNRTIs are scanty and hence further studies are warranted on these lines. It is unfortunate that lack of clear guidelines till date regarding the discontinuation of nevirapine in HIV infected individuals who develop asymptomatic mild to moderate increases in hepatic aminotransferase levels are unavailable.

Efavirenz

Efavirenz is a non-nucleoside reverse transcriptase inhibitor which causes hepatotoxicity by blocking the bile acid transport. Bile formation is a vital function of the liver, and failure of bile formation and bile duct obstruction, retention of bile leads to cholestasis. The bile retention within the hepatocytes during cholestasis is associated with induction of apoptosis in hepatocytes (Patel *et al.*, 1998). Previous studies in human and rat hepatocytes using efavirenz is reported to inhibit bile acid transport (McRae *et al.*, 2006). Efavirenz, when administered in combination with Emtricitabine/Tenofovir (one of the first-line agents for the treatment of HIV), causes hepatotoxicity characterized by high levels of hepatic aminotransferases (Patil *et al.*, 2015). Rilpivirine, another NNRTI has shown to be more advantageous when compared to efavirenz. In a recent study, it has been confirmed that rilpivirine has better lipid profiles compared to efavirenz when these drugs are administered in HIV patients and it is also shown that efavirenz attributed to inducing abnormal lipid changes (Thamrongwongler *et al.*, 2016).

The mechanisms related to hepatotoxicity induced by efavirenz are not clear, nevertheless, a recent study has reported that the mitochondrial toxicity of this drug is accompanied by an induction of ER stress in human hepatocytes (Apostolova *et al.*, 2013). In light of the above literature, a recent study has confirmed the role of mitochondrial and ER stress to be the key factor for efavirenz-induced hepatotoxicity (Polo *et al.*, 2015). However, as we seen earlier the mechanism of efavirenz-induced hepatotoxicity is not well characterized till date but it is considered to occur less frequently than with nevirapine (Sonderup *et al.*, 2016).

PROTEASE INHIBITORS (PIs)

HIV protease inhibitors are the type of ART which inhibits the protein synthesis thereby inhibits viral replication. There are around nine HIV-PIs approved by FDA such as saquinavir, nelfinavir, lopinavir, amprenavir, atazanavir, darunavir, tipranavir, indinavir and most of these drugs are structural homologs to ritonavir (Wlodawer and Vondrasek, 1998).

Ritonavir

Ritonavir is the most widely and frequently used PI causing hepatotoxicity. This drug is mostly used in combination with other NRTIs or NNRTIs. Ritonavir is shown to inhibit hepatocyte proliferation and apoptosis via caspase-3 activation.

The mechanism of ritonavir-induced hepatotoxicity has been attributed due to induction of apoptosis of hepatocytes via the caspase-cascade system (Kuang *et al.*, 2014). In previous studies, ritonavir is reported to inhibit bile acid transport in human and rat hepatocytes (McRae *et al.*, 2006). HIV-infected individuals are often co-infected by many bacterial infections, including *Tuberculosis* bacilli. These patients are treated with anti-tubercular drugs daily, for several months, depending upon the severity of infection, in addition to their routinely administered regimens of anti-retroviral drugs (Mchunu *et al.*, 2016; Raghu and Karthikeyan, 2016). HIV-infected individuals are often co-infected by many bacterial infections, including *Tuberculosis* bacilli. These patients are treated with anti-tubercular drugs along with ARV drugs. Thus co-administration of PIs such as saquinavir/ritonavir (1000/100 mg twice daily) and rifampin (600 mg once daily) in HIV-negative volunteers showed a speedy and significant increase in liver enzymes. Hence, it has been suggested that the combination and co-administration of saquinavir/ritonavir and rifampicin show contraindication in HIV patients (Schmitt *et al.*, 2009).

Nelfinavir

Nelfinavir is widely used PIs as a first-line in HIV-infected patients. The nelfinavir-induced hepatotoxicity was reported to less when compared to NNRTIs and other PIs (Sulkowski *et al.*, 2004). Interestingly, the incidence of liver toxicity of nelfinavir-containing HAART regimens has been found low among HIV/HCV-coinfected patients with hepatic fibrosis. However, it is reported that nelfinavir administered with nevirapine, showed an increased risk of developing severe hepatotoxicity (Mira *et al.*, 2006).

Saquinavir and Indinavir

Saquinavir is the first PI approved by FDA and its toxicity is reported on a longer usage of ARV drugs. Saquinavir in combination with ritonavir causes rapid onset of acute hepatic injury (Wambani *et al.*, 2015). Saquinavir is reported to inhibit bile acid transport leading to retention of bile which causes apoptosis of human and rat hepatocytes (McRae *et al.*, 2006). The saquinavir and indinavir-induced liver toxicity ranges from mild transient elevation to severe causing hepatotoxicity. The injury is self-limited, but it can also cause acute liver failure and death (Sulkowski, 2003).

Management and Prevention of ARV-induced hepatotoxicity

In general, most of the drug-induced liver injury is difficult to predict and hence it has been advised that the clinician must be aware of the patient's predisposing risk factors for ARV drugs induced liver injury, which will help them in guiding and monitoring the patient (Soriano *et al.*, 2008). Regularly monitoring the levels of transaminases (AST and ALT) should be made mandatory before commencement and during ARV therapy. The less hepatotoxic ARV drugs such as lamivudine and abacavir can be prescribed to patients who are under high risk of developing

liver toxicity (Martinez *et al.*, 2001). Once the hepatotoxicity is confirmed in patients undergoing ARV therapy, the treatment can be discontinued for a short period so that the liver can recover from its injury as it has a natural regenerating capacity. Though liver can regenerate, its recovery depends on the dosage and the severity of the toxicity. As of now, the only effective treatment till date is discontinuation of the drug (Sulkowski *et al.*, 2004). Hence, as a remedial measure, the dosage of antiretroviral drugs can be prescribed to patients in accordance with Department of Health and Human Services guidelines to overcome the above issue (Soriano, 2014).

CONCLUSION

Undoubtedly, hepatotoxicity is one of the most serious complications in patients who is undergoing ARV therapy which further increases when they are co-infected with hepatitis virus. Hepatic steatosis and lactic acidosis are commonly observed in patients administered with antiretroviral nucleoside analogs, such as AZT, didanosine, zalcitabine, Combivir (AZT+3-TC) and 3-TC. While ARV drugs such as ritonavir, efavirenz and nevirapine are commonly reported for their hindrance in bile acid transport inside the liver.

These results clearly confirm that the ARV drugs induce hepatotoxicity due to its mitochondrial interference. Moreover, the corresponding triphosphate, produced by the virus also inhibits host DNA polymerase consequent to compensatory glycolysis and lactic acidosis leading to hepatotoxicity. Though the usage of ARV drugs during pregnancy is considered not to be safe, the HAART has significantly contributed to the reduction of mortality and morbidity in HIV-infected patients. To overcome the above challenge, the patients can be regularly monitored for the levels of toxicity and HAART regimen should be discontinued if the patients manifest hepatotoxicity due to the use of the above drugs. Pharmacovigilance of ARV drugs and HAART regimen-induced adverse drug reactions especially in liver is the need of the hour.

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