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TOPIC HIGHLIGHT

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Human immunodeficiency virus infection and the liver

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Abstract

Liver disease in human immunodeficiency virus (HIV)-infected individuals encompasses the spectrum from abnormal liver function tests, liver decompensation, with and without evidence of cirrhosis on biopsy, to non-alcoholic liver disease and its more severe form, non-alcoholic steatohepatitis and hepatocellular cancer. HIV can infect multiple cells in the liver, leading to enhanced intrahepatic apoptosis, activation and fibrosis. HIV can also alter gastro-intestinal tract permeability, leading to increased levels of circulating lipopolysaccharide that may have an impact on liver function. This review focuses on recent changes in the epidemiology, pathogenesis and clinical presentation of liver disease in HIV-infected patients, in the absence of co-infection with hepatitis B virus or hepatitis C virus, with a specific focus on issues relevant to low and middle income countries.

Key words: Human immunodeficiency virus; Liver disease; Low-middle income settings

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INTRODUCTION

There are 33 million people infected with human immunodeficiency virus (HIV) globally with the greatest burden of disease in low and middle income countries. With the increased availability of antiretroviral therapy (ART), the number of people surviving with HIV and presenting with liver disease is increasing[1]. Most clinical trials and cohort studies have studied liver disease in HIV-infected individuals living in high income countries but liver disease is likely to emerge as an important co-morbidity in HIV-infected patients in low and middle income countries.

In the absence of co-infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV), liver disease in HIV-infected individuals encompasses the spectrum from abnormal liver function tests, liver decompensation, with and without evidence of cirrhosis on biopsy, to non-alcoholic liver disease (NAFLD) and its more severe form, non-alcoholic steatohepatitis (NASH) and hepatocellular cancer (HCC)[2-6]. This review focuses on recent changes in the epidemiology, pathogenesis and clinical presentation of

liver disease in HIV-infected patients with a specific focus on issues relevant to low and middle income countries.

EPIDEMIOLOGY OF HIV AND LIVER DISEASE

Liver disease, including liver-related mortality secondary to chronic liver disease and HCC, is an emerging management problem in HIV-infected individuals in high income countries, where people are surviving longer on ART[1]. In the most recent data collection on adverse events of anti-HIV drugs (D:A:D) study of over 33 000 individuals, liver related deaths were the commonest cause of non-acquired immunodeficiency syndrome (AIDS) mortality amongst HIV-infected individuals[1]. While liver related deaths were strongly associated with viral hepatitis (84% of liver related deaths, 11% of total deaths), 16% of the liver related deaths (or 2.3% of the total deaths) in this population occurred in the absence of viral hepatitis[1].

Liver-related mortality in HIV-infected patients not co-infected with HBV or HCV has not been widely studied in low and middle income countries. In a retrospective South American study of serious non-AIDS events in the LATINA cohort (comprising over 6000 HIV-infected individuals on ART from Brazil, Mexico, Peru and Argentina), terminal liver failure or cirrhosis was the leading cause of death with 54/130 (42%) confirmed or probable cases based on clinical, laboratory and histological findings[7]. In this study, co-infection with HBV or HCV and low CD4 count were the major risk factors[7]. Similarly, a post-mortem study of 86 HIV-infected individuals undergoing autopsy in rural South Africa demonstrated that 10% had liver related conditions at the time of death[8]; however, it is likely that co-infection with viral hepatitis was a contributing factor.

Chronic liver disease, as measured by raised alanine aminotransferase (ALT), has been widely studied in HIV-infected individuals, particularly in high income settings. In a Swiss cohort of 2365 HIV-infected individuals not co-infected with either HBV or HCV, 385 (16%) had chronically elevated ALT (defined as > 2 × upper limit of normal)[9]. Risk factors associated with elevated ALT were high HIV RNA and prolonged ART exposure as well as high body mass index (BMI), alcohol abuse and increasing age[9]. A number of studies have now shown a link between BMI, high cholesterol levels, diabetes mellitus and liver disease in HIV mono-infection in high income countries[9-11], indicating lifestyle may play a significant role in the development of liver disease amongst HIV-infected individuals. Of concern, high BMI and diabetes mellitus are increasingly reported in low and middle income countries[12]. Ocama *et al*[13] recently reported that following 36 mo of ART in a cohort of 546 individuals in Kampala, only 1.5% had grade 3 aspartate aminotransferase (AST) elevations. In this study, a subset (n = 470) of patients were tested for HBV surface antigen and 9% were positive. A study of 59 individuals in Mexico showed a moderately strong positive correlation between elevated transaminases and HIV RNA in individuals not receiving ART and without viral hepatitis co-infection[14], consistent with reports from North America[11].

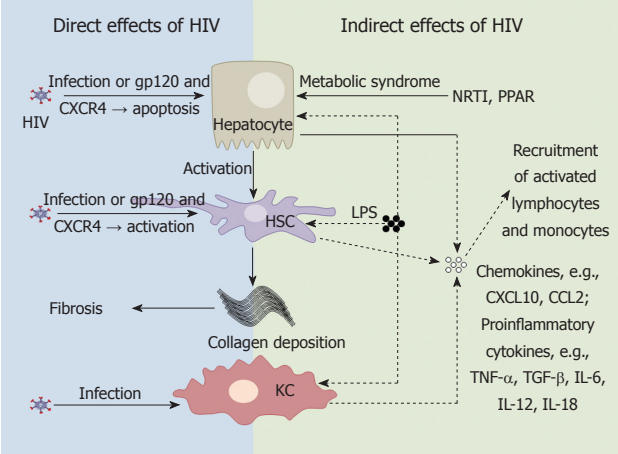

Figure 1 Human immunodeficiency infection and the liver. Mechanisms by which human immunodeficiency virus (HIV) infection of liver cells can contribute to liver disease progression by either direct (left panel) or indirect (right panel) mechanisms. HIV can directly infect hepatocytes, hepatic stellate cells (HSCs) and Kupffer cells (KCs). In the absence of productive infection, gp120 binding to CXCR4 may induce hepatocyte apoptosis and activation of HSCs, both contributing to fibrosis. Nucleoside reverse transcriptase inhibitors (NRTIs) and HIV itself [*via* peroxisome proliferator-activated receptor (PPAR) effects] may also contribute to liver disease by inducing the metabolic syndrome. HIV infection of the gastrointestinal tract leads to an increase in lipopolysaccharide (LPS) which can stimulate hepatocytes, KCs and HSCs to produce pro-inflammatory cytokines and chemokines which attract activated lymphocytes and monocytes to the liver which may further drive fibrosis. TNF-α: Tumor necrosis factor-α; TGF-β: Transforming growth factor-β; IL: Interleukin.

Data on HCC in HIV mono-infection in both low and high income countries is limited. In a study of over 3500 HIV-infected Chinese individuals, HCC was one of the leading causes of morbidity and mortality; however, this was primarily due to co-infection with viral hepatitis[15]. In a French prospective database study, a low CD4 count was a major risk factor for HCC with the rate ratio, or risk, increasing from 2 to 7.6 when comparing patients with a high CD4 count (> 500 cells/mL) to those with a low CD4 count (< 50 cells/mL) respectively[16]. Importantly for low and middle income countries, it has been demonstrated that the use of ART in individuals with low CD4 count (< 350 cells/mL) was associated with a reduced risk of hospitalization for liver related complications[17].

PATHOGENESIS OF HIV AND LIVER DISEASE

HIV may alter liver function by either direct or indirect mechanisms. HIV predominantly infects CD4+ T-cells, monocyte/macrophages and dendritic cells. However, there are multiple studies now showing HIV infection of a wide range of non hemapoietic cells, including cells in the liver. In addition, changes in gastrointestinal (GI) tract permeability *via* massive depletion of GI tract associated

CD4+ T-cells by HIV may have indirect consequences on immune activation and liver disease (Figure 1).

Direct effects of HIV on the liver

There are numerous studies demonstrating HIV infection of hepatic cells. Kupffer cells, differentiated tissue macrophages that reside in the liver, can be infected by HIV *in vivo*[18-20]. *In vitro* studies suggest that HIV infection of primary Kupffer cells leads to productive infection[21,22].

HIV RNA has also been detected in sinusoidal cells and hepatocytes *in vivo*[18,19]. Primary human sinusoidal cells have also been shown to be permissive to HIV infection *in vitro*[23]. A number of studies have demonstrated HIV infection of hepatocyte cell lines[24]. Infection of hepatocyte cell lines is thought to be CD4-independent as most hepatocyte cell lines, as well as primary hepatocytes, do not express CD4[24]. HIV infection of hepatocytes cells may therefore occur *via* receptor-mediated endocytosis or alternative co-receptors[25]. Hepatocytes may act as a transient HIV reservoir and promote CD4+ T cell infection by cell-cell contact[26].

HIV can also induce hepatocyte apoptosis *in vitro via* gp120 signalling through CXCR4 in the absence of infection[27]. Hepatocyte apoptosis can trigger pro-fibrotic activity of hepatic stellate cells (HSC) activity, as has been demonstrated in both HIV-HBV co-infection and HIV-HCV co-infection[28,29]. Further work is needed to determine the precise role of HIV-induced hepatic cell apoptosis and liver disease in HIV mono-infection.

HSCs are lipid storing cells and the main cells responsible for fibrogenesis in the liver. HIV infection of HSCs, including primary HSCs and the LX-2 stellate cell line, has recently been reported[30]. While HSCs express the HIV co-receptors CCR5 and CXCR4, HIV infection of HSCs appeared to be CD4-independent[30]. However, gp120 has also recently been shown to activate HSC *via* ligation of CXCR4[31]. HSCs infected with HIV or exposed to gp120 showed increased activation and fibrogenesis, as measured by alpha-smooth muscle actin and collagen production and increased levels of monocyte chemotactic protein-1 (MCP-1 or CCL-2). CCL-2 binds to CCR2 which is primarily expressed on activated pro-inflammatory monocytes and migration of these cells into the liver could potentially contribute to hepatic fibrosis and the accelerated progression to liver disease observed in HIV-HCV co-infected individuals[30,31].

Indirect effects of HIV on the liver

HIV infection of GI tract associated CD4+ T-cells leads to increased permeability to bacterial endotoxins such as lipopolysaccharide (LPS). Increased systemic levels of LPS are hypothesised to contribute to chronic immune activation in HIV-infected patients *via* activation of monocytes[32]. Kupffer cells are the main cell type in the liver that responds to LPS. When stimulated through ligation of the LPS receptor, toll like receptor (TLR)-4, Kupffer cells produce pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), interleukin-6 (IL-6), IL-12 and IL-18[33]. Under normal physiological conditions, Kupffer cells remain tolerant, or refractory, to repeated LPS stimulation[33]. Elevated LPS has been shown to contribute to liver disease progression in alcoholic liver disease[34], as well as in NAFLD and NASH[35-37], chronic HCV[38] and HIV-HCV co-infection[39]. In addition to activation of Kupffer cells, LPS also directly activates HSC to produce CCL-2[40], and *in vitro* following co-culture with monocytes, induces hepatocytes to produce chemokines CXCL9, 10 and 11[41]. These chemokines will induce chemotaxis of both T-cells and monocytes to the liver. In HIV-infected individuals, an increase in systemic LPS levels may therefore potentially contribute to liver disease progression, although to date this has not been demonstrated in the setting of HIV alone (Figure 1).

Finally, HIV may also contribute to the metabolic syndrome associated with NAFLD or NASH *via* several mechanisms. ART and chronic inflammation can promote insulin resistance[42], where free fatty acids are released from adipose tissue, leading to increased intrahepatic triglyceride droplets (macrosteatosis) or *via* mitochondrial toxicity (microsteatosis) and oxidative stress[43,44]. HIV has also been shown to modify the activity of peroxisome proliferator-activated receptors (PPAR)[45]. PPARs are a family of nuclear receptor transcription factors that regulate insulin sensitivity, glucose and lipid metabolism, as well as inflammation, tissue repair, carcinogenesis and fibrosis, and are expressed by hepatocytes, HSCs and Kupffer cells[46-48]. Two HIV accessory proteins, Vpr and Nef, have been shown to suppress PPAR-γ subtype activity *in vitro*[49,50]. One small study in HIV-infected individuals also showed a reduction in the mRNA levels of PPAR-γ and a correlation with increased liver fibrosis[51]. Suppression of PPAR-γ activity by HIV may therefore represent another mechanism by which HIV contributes to liver disease progression.

CLINICAL PRESENTATIONS OF LIVER DISEASE IN HIV MONO-INFECTION

Noncirrhotic portal hypertension

Portal hypertension has been described recently in HIV mono-infected individuals without other known risk factors for liver disease. Individuals may present with decompensated portal hypertension, such as ascites or bleeding esophageal varices, without histological cirrhosis on liver biopsy[2-5]. This clinical scenario has been variably termed "noncirrhotic portal hypertension" (NCPH)[52], idiopathic portal hypertension[3] or "cryptogenic pseudocirrhosis"[4] to differentiate it from cirrhosis from other etiologies.

Numerous case reports and series of individuals with NCPH in HIV have been described[2,52-60], including those undergoing liver transplantation[61]. NCPH has not yet been described in low and middle income countries. It is possible that NCPH has not been recognized due to limited availability of liver biopsy. Alternatively, the

Table 1 Potential causes for liver disease in human immunodeficiency virus infection[43]

Viral hepatitis	HBV, HCV, (HDV)	Co-infection common (up to 10%)
	HAV, HEV	Self-limited acute increase in ALT
Drug hepatotoxicity	Alcohol	Limited data in low and middle income countries
ART[1]	Nevirapine	Hypersensitivity, usually early (< 12 wk)
	Efavirenz	Direct liver cell stress or hypersensitivity
	Abacavir	Hypersensitivity, (predominantly in HLA B57 carriers)
	ddI, d4T	Mitochondrial toxicity with long-term use
	Ritonavir	Steatosis, metabolic disturbance
	Darunavir	Hypersensitivity
	Tipranavir	Hepatic failure reported with ritonavir 200 mg
	Maraviroc	Hypersensitivity with liver involvement
Anti-TB therapy[2]	Rifampicin	Drug interactions with ART and direct hepatotoxicity
	Isoniazid	Hepatotoxicity may be increased in HIV
	Pyrazinamide	Dose-related hepatotoxicity
Hepatotropic infections	Schistosomiasis	Leads to portal hypertension
	Leishmaniasis	Fever +/- hepatosplenomegaly
	Herpes viruses inc EBV CMV HHV6 HSV	Often cause raised transaminases, occasionally symptomatic hepatitis
	Liver abscess	Unlikely to cause chronic liver disease
HIV cholangiopathy		Usually when CD4 < 200 cells/μL
NAFLD		ART-related, prevalence unknown

[1]Raltegravir rarely causes hepatitis; [2]Ethambutol rarely associated with hepatitis, and may be due to concurrent therapy. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; HAV: Hepatitis A virus; HEV: Hepatitis E virus; ART: Anti-retroviral therapy; ddI: Didanosine; d4T: Stavudine; TB: Tuberculosis; NAFLD: Non-alcoholic fatty liver disease; EBV: Epstein barr virus; CMV: Cytomegalovirus; HHV: Human herpesvirus; HSV: Herpes simplex virus; HIV: Human immunodeficiency virus; ALT: Alanine aminotransferase; HLA: Human leukocyte antigen.

impact of NCPH may be overshadowed by more common diseases such as co-infection with viral hepatitis, pyogenic infections or tuberculosis[8,62,63]. NCPH has been described in adolescence[64] but the lead time prior to clinical presentation of NCPH may mean it remains a future problem for low and middle income countries.

Liver histology from individuals with HIV mono-infection and NCPH is variable and includes periportal or perisinusoidal fibrosis, low grade inflammation and steatosis[65]. However, a common pattern appears to be portal vein occlusion and focal fibrous obliteration of small portal veins, so-called "hepatic venopathy", often in the setting of nodular regenerative hyperplasia (NRH)[52,57].

A hypercoagulable state may contribute to the hepatic venopathy and NRH, as described in the antiphospholipid syndrome associated with rheumatoid arthritis[66]. Hypercoagulable states were identified in 8 out of 10 individuals with NCPH in one case series[57]. In a recent case-control study, NRH was seen in all 5 out of 11 individuals with NCPH where histology was available, and protein C and S activity was lower in cases than controls[67]. In another small case-control study including 15 individuals with confirmed esophageal varices and absence of cirrhosis on liver biopsy, periportal fibrosis was the most common hepatic lesion described and NRH was only seen in 1 patient[65]. A strong association between prolonged exposure to didanosine (ddI) and the development of NCPH was found in this study. Two cross sectional studies looking at associations between multiple clinical factors and NCPH have also demonstrated an association with prior and current use of ddI[2], as well as NASH[5]. ddI is now almost never used in high income countries but still frequently used in low and middle income countries, and therefore NCPH may soon be seen more frequently in these settings[68].

ART and liver disease

Hepatotoxicity due to ART may be related to agents from a number of classes, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors[43] (Table 1). The severity of hepatotoxicity may range from transient elevations in transaminase levels to hepatic failure and death, *via* a variety of mechanisms. NNRTI such as nevirapine and efavirenz may cause hypersensitivity[69-71]. NRTI, primarily ddI, may cause direct mitochondrial toxicity leading to abnormal liver function[72]. Other mechanisms by which ART causes liver-related toxicity include direct cell stress and disturbances in lipid/sugar metabolism and steatosis, as seen with protease inhibitors[43]. The protease inhibitors ritonavir, tipranavir and darunavir have all been associated with elevations in ALT[43].

Fatty liver disease in HIV

NAFLD is now commonly reported in many high income countries in the presence and absence of HIV infection. The spectrum of NAFLD ranges from mild steatosis to NASH, which may progress to severe fibrosis and cirrhosis. NAFLD may be associated with other features of the metabolic syndrome, including central obesity, insulin resistance, diabetes mellitus and dyslipidemia, such as raised triglycerides, low high-density lipoproteins and raised low-density lipoproteins. NAFLD has been identified in up to 30% of HIV mono-infected Americans, although this study was unable to demonstrate

whether the prevalence of NAFLD was different to HIV-negative individuals[6]. While risk factors for NAFLD may be similar in people with or without HIV[73], a small study has suggested that people with HIV and NAFLD may be more physically active and less obese than HIV-negative individuals with NAFLD, and that other factors such as HIV itself or ART may contribute to NAFLD[74]. NAFLD is frequently described in the setting of HIV-HCV co-infection[75-77] where ART including ddI or stavudine may also be implicated[75]. Insulin resistance and NASH have been described in individuals with liver disease in HIV mono-infection[5,52]. Insulin resistance and exposure to ddI and/or stavudine were factors associated with advanced fibrosis in 681 HIV-HCV co-infected individuals in Spain[78]. Few studies of NAFLD have been published from low and middle income countries.

Co-infections other than HBV or HCV

Co-infection with *Mycobacterium tuberculosis* and its treatment are also important causes of liver disease in low and middle income countries and are summarised in Table 1. Hepatitis related to isoniazid therapy is common[79], and HIV or ART may increase the risk of isoniazid-related hepatotoxicity, as demonstrated in a small Ethiopian study[80]. Concomitant anti-tuberculosis therapy was associated with a 5-fold increased risk of abnormal aminotransferase levels in Ugandan individuals commencing NNRTI-based ART[81].

Schistosomiasis may also cause liver disease but was an uncommon cause of liver disease in HIV-infected individuals in Uganda in one study of 77 patients[62]. In a recent study using transient elastography (TE, FibroScan®) in 1000 individuals in Uganda, 14% of the 500 HIV-infected individuals had positive schistosomiasis serology[82]. Significant fibrosis (≥ F2, liver stiffness measurement ≥ 9.3 kPa) was detected in 17% of HIV-infected individuals. Positive schistosomiasis serology was not a significant predictor of cirrhosis [odds ratio 1.7, (0.9-3.3); $P = 0.10$] in this study but the authors concluded that schistosomiasis may play a role in the burden of liver disease in HIV-infected individuals in Uganda[82]. Further work is required to better understand the true relationship between HIV, schistosomiasis and liver disease.

The impact of other infections, including visceral leishmaniasis (also known as Kala-Azar), on liver disease in HIV infection is unclear but has been reported[83] and may cause chronic disease[84]. Amebic liver abscesses are frequently described in HIV infection[85] but are usually treatable and are unlikely to contribute significantly to ongoing liver disease[62]. HIV cholangiopathy in individuals with CD4 T-cell counts < 200 cells/mL may be due to infections with cytomegalovirus, cryptosporidium or microsporidium[63], although prevalence in low and middle income countries has not been reported.

Alcohol

Alcohol is a common cause of liver disease world-wide and is likely to be as important in low and middle income countries, as it is in HIV-infected individuals in high income countries[86]. Alcohol is responsible for significant morbidity and mortality in South Africa[87] and may also contribute to significant fibrosis detected by TE in Uganda[62]. However, data on alcohol consumption and its impact on liver disease in the setting of HIV in low and middle income countries are limited.

NON-INVASIVE ASSESSMENT OF LIVER DISEASE IN HIV MONO-INFECTION

The availability of liver biopsy is limited in low and middle income countries and non-invasive measures of liver fibrosis, such as TE, have been studied in many liver conditions but largely in high income countries[88]. Algorithms to diagnose liver disease severity based on a range of biochemical and hematological indices, such as FibroTest®, Hepascore or AST to platelet ratio index, have also been used[89]. Most data regarding TE come from studies of individuals with HCV[88]. TE is most reliable at detecting cirrhosis (F4) or severe fibrosis (F3/4) but is less reliable at differentiating absent or mild fibrosis (F0/1) from significant fibrosis or greater (F2/3/4)[88]. In many studies considered in a recent meta-analysis, the sensitivity for detecting at least significant fibrosis was less than 70%[88]. The mean area under the receiver operator characteristic curve (AUROC) was 0.84 (95% CI: 0.82-0.86), where a diagnostic tool is considered good if the AUROC is greater than 80% and excellent if the AUROC is greater than 90%[88]. The AUROC for the detection of cirrhosis was 0.94 (95% CI: 0.93-0.95).

Non-invasive measures like TE have been used to detect severe fibrosis in HIV-infected individuals with persistently elevated transaminase levels[2,5,90]. Few studies in low and middle income countries have been reported to date[82]. However, the convenience of TE and or biochemical or hematological indices offers great potential for screening and monitoring liver disease in large cohorts of HIV-infected individuals in low and middle income countries and there is a great need for further work in this area. A proposed algorithm for the use of TE in evaluating HIV-infected individuals is presented in Figure 2[91].

CONCLUSION

Liver disease in HIV-infected individuals, in the absence of co-infection with HBV or HCV, is an emerging issue in all settings. While ART related toxicities are an obvious cause, there is emerging evidence that HIV infection may have a direct impact on the pathogenesis of liver fibrosis, NAFLD and NASH and subsequent progression to liver disease. Further research is needed to determine the causal link between HIV infection and liver disease progression. Two potentially important risk factors for low and middle income countries in the development of liver disease are prolonged exposure to high HIV RNA and low CD4 count, providing further support for earlier initiation of ART. One of the major obstacles to

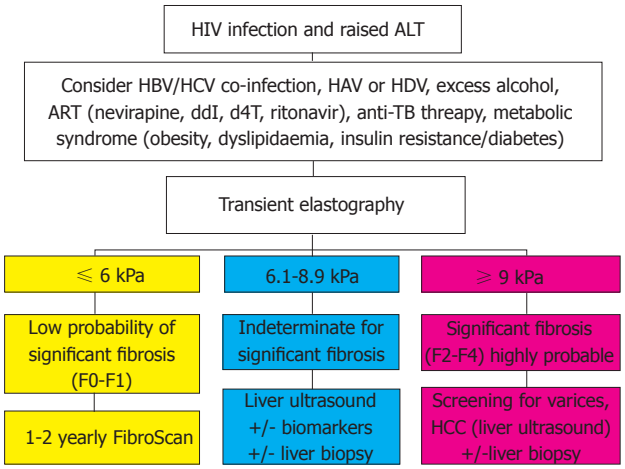

Figure 2 Proposed use of transient elastography (FibroScan) in human immunodeficiency virus infected individuals with raised liver enzymes (adapted from Ref.[91]). HIV: Human immunodeficiency virus; ALT: Alanine aminotransferase; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis delta; ART: Anti-retroviral therapy; ddI: Didanosine; d4T: Stavudine; TB: Tuberculosis; HCC: Hepatocellular carcinoma.

research into the epidemiology of the true incidence of liver disease in both high income and low and middle income countries is the lack of suitable non-invasive methods of determining liver disease progression. However, with the advent of newer convenient technologies, such as TE and non invasive plasma markers, we may see this change in the near future.

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