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HIV and liver disease

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Abstract

Liver-related diseases are associated with the high levels of morbidity and mortality in people living with HIV. Between 13% and 18% of all-cause mortality in HIV-infected patients involves a liver-related damage, this being one of the main causes of death not related to acquired immunodeficiency syndrome (AIDS). People living with HIV, even when the disease is under control, are more likely to develop pathologies and complications of a liver-related origin than the general population, both due to common causes such as alcoholism, non-alcoholic fatty liver disease, hepatic viral infections and ageing, in addition to specific HIV-related processes such as antiretroviral treatment toxicity and liver damage inherent to HIV infection. On the other hand, some antiretroviral drugs may have a beneficial effect in reversing liver fibrosis in patients with HIV and chronic liver disease. This paper reviews the main risk factors associated with liver disease in people living with HIV and the role of antiretroviral therapy (ART) in this disease.

Keywords

HIV. Liver disease. Chemical and drug-induced liver disease. Antiretroviral treatment.

Introduction

Liver-related mortality accounted for 3% of all deaths in Europe in 2019. That year, chronic liver disease caused 287,000 deaths in Europe, 63,500 of which were due to hepatocellular cancer (HCC). Compared to 1990, mortality from chronic liver disease has increased by 25% and deaths due to HCC by 70%[1,2]. Hence, liver disease is a major health threat in Europe[2]. However, the profile of liver disease in our environment is changing due to the cure of hepatitis caused by the hepatitis C virus (HCV), the control of hepatitis caused by the hepatitis B virus (HBV), the ever-increasing abusive use of alcohol and the obesity epidemic[2]. In addition, we are facing the challenge of undiagnosed or untreated liver disease, particularly among the immigrant population[2].

Liver disease is more prevalent in people living with HIV/AIDS (PLWHA) than in the general population[2]. The virus itself can induce liver damage[3]. Furthermore, other factors such as opportunistic diseases that may appear, alcohol consumption, the sequelae of continued immunosuppression, ageing, HIV, and HCV or HBV coinfection, as well as the chronic use of ARTs may contribute to the development or exacerbation of liver disease[4].

This paper conducts a review of the main risk factors associated with liver disease in PLWHA and the role of ART in that disease.

Liver disease in HIV patients

After the introduction of ART in triple therapy in 1996, the main causes of morbidity and mortality in PLWHA in industrialized countries are now events unrelated to AIDS, particularly cardiovascular disorders and liver pathologies[3,5].

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The prevalence of liver disease in PLWHA ranges from 4% to 18% according to different studies, while deaths related to liver damage are 10 times more frequent among PLWHA than in the general population[3]. It is estimated that liver-related diseases account for between 13% and 18% of all-cause mortality in PLWHA, this being one of the main causes of death not related to AIDs[6].

Once HIV infection was controlled, the main causes of liver disease in PLWHA changed from opportunistic infections and lymphomas to HCV and HBV coinfections, drug-induced liver injury (DILI), alcoholic disease, and non-alcoholic fatty liver disease (NAFLD)[3]. The main causes of liver damage in PLWHA are summarized in table 1[3,6,7].

Cirrhosis and hepatocellular carcinoma (HCC) are the final complications of PLWHA with underlying liver disorders such as viral hepatitis and alcohol abuse.[4] HCC develops primarily in patients with advanced fibrosis, but also affects people without cirrhosis, particularly in patients with HBV infection or NAFLD[2]. The risk of HCC in PLWHA could triple the risk of the general population and has been increasing in recent years[8]. Furthermore, the rate of early diagnosis of HCC is low[9].

Table 1. Factors that promote liver disease in the HIV-infected population

Factors associated with HIV	– Direct injury to hepatocytes – Increased oxidative stress – Metabolic alterations due to the direct effect of the virus on the liver – Immune-mediated injuries – Depletion of intestinal CD4+lymphocytes and intestinal microbial translocation – Systemic inflammation – Cellular senescence – Pro-fibrogenic and pro-inflammatory effects on hepatic non-parenchymal cells
Factors associated with antiretroviral treatment	– Hepatotoxicity of antiretrovirals – Drug interactions – Metabolic alterations due to antiretrovirals – Immune reconstitution
Factors associated with patient characteristics	– Coinfections with viral hepatitis – Alcohol consumption – Ageing – Consumption of drugs – Obesity, insulin resistance, diabetes, and dyslipidemia

Viral hepatitis

Viral hepatitis is a major cause of mortality among PLWHA. Around 2.9 million PLWHA are coinfected with HCV, and 2.6 million with HBV worldwide[10]. In Europe, it is estimated that between 1.6% and 3.1% of the general population is infected with HBV or HCV, while the prevalence of these infections is between 15 and 50 times higher in PLWHA than in the general population[2]. It is estimated that 8.4% and 35.4% of HIV patients could be coinfected with HBV or HCV, respectively[11].

Coinfection by HIV and HBV or HCV can give rise to an aggravation of certain pathological processes and can occur in patients with chronic hepatitis in which the fibrosis process may be accelerated and increase the risk of HCC[11,12]. In addition, the toxicity of ARVs is generally greater in patients coinfected with HBV or HCV[11,13]. When choosing ART in a patient coinfected with the hepatitis virus, potential hepatotoxicity, the existence of liver cirrhosis, and whether the coinfection is due to HBV and/or HCV and/or hepatitis D virus should be taken into account[14]. Moreover, immune reconstitution arising from ART in patients with underlying chronic hepatitis B or C may be associated with a transient outbreak of hepatitis. This effect occurs with many powerful antiretroviral regimens[13]. Although they are often self-limited reactions, this liver damage can give rise to hepatic decompensation in patients with pre-existing cirrhosis[6].

Moreover, there are various ARTs with activity against HBV, more specifically lamivudine (3TC), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), which determines the treatment of patients coinfected with HIV/HBV[15]. In addition, there are multiple interactions between ARTs and direct-action antiviral drugs for the treatment of HCV that gives rise to the need to change the ART regimen or to find an HCV regimen with less risk of interactions[14].

NAFLD

NAFLD includes a wide range of histological and clinical disorders, including early-stage liver damage, steatohepatitis, cirrhosis, and end-stage liver disease[16]. It is characterized by an excessive accumulation of fat in the liver, in the absence of excessive alcohol consumption and other etiologies such as chronic viral hepatitis or the use of steatosis-inducing

drugs. Although it is widely associated with obesity, it can also occur in individuals of normal weight, especially in Asian populations[17].

It is estimated that between 20% and 63% of PLWHA could suffer from non-alcoholic steatohepatitis (NASH) and 14-63% have NASH with fibrosis[18]. There are several factors that can contribute to the development of NASH in PLWHA, such as the viral infection itself, metabolic abnormalities, adipose tissue dysfunction, mitochondrial toxicity of old ARTs, immune activation and dysregulation, and microbial translocation[18].

In addition to its impact on the liver, NAFLD is an independent risk factor for cardiovascular disease, diabetes mellitus, and all-cause mortality[18]. Cirrhosis caused by NAFLD is one of the most frequent causes of liver transplantation in PLWHA[12,18].

Alcoholic liver disease

Europe has the highest level of alcohol consumption in the world, which, together with the consumption of ultra-processed foods and the high prevalence of obesity are the main reasons for liver-related morbidity and mortality[2]. More than 50% of end-stage liver disease is due to excessive alcohol consumption[2]. It is a common cause of end-stage liver disease and HCC in PLWHA, in addition to being responsible for the need for liver transplantation[12,19].

Drug-induced liver injury

DILI, due to the use of prescription and non-prescription drugs in people with or without HIV, is one of the leading causes of acute liver failure and transplantation in Western countries. Although rare, it should be regarded as a serious problem due to its unpredictable nature and potential fatal outcome[20]. It can be caused by the use of ARTs and other types of drugs, including non-steroidal anti-inflammatory drugs, antibiotics, antiarrhythmics, and anticonvulsants.[20] It should be pointed out that drug-induced steatosis and drug-induced steatohepatitis are rare but well-documented types of DILI. It is known that the differential diagnosis of which with NAFLD can be difficult[20].

Furthermore, it is also known that PLWHA has a higher risk of drug hypersensitivity reactions compared to the general population and a higher probability of DILI due to drugs such as trimethoprim-sulfamethoxazole and acyclovir[6]. In addition, drug interactions can enhance the hepatotoxic effects of drugs[6].

Liver damage from HIV

HIV infection *per se* is associated with liver damage and an increased risk of liver fibrosis through multiple pathways[3]. HIV has a direct cytopathic effect on hepatocytes, mainly triggering apoptosis through the gp120 protein receptor signaling pathway[6]. In addition, it can cause indirect liver damage through numerous mechanisms (Table 1)[3,6,7].

Control of HIV infection is beneficial for liver histopathology. The START trial, which included more than 4500 patients, illustrated that liver fibrosis is rare in PLWHA that start antiretroviral treatment at an early stage, demonstrating the important role played by early therapeutic intervention in the progression of fibrosis[21,22]. Moreover, ART improves liver fibrosis in people coinfected with HIV/HCV and significant fibrosis at baseline[23] and the discontinuation of ART in coinfected patients leads to an increased likelihood of liver fibrosis[24].

Antiretroviral treatment and liver damage

In general, currently used ART drugs have a low risk of liver damage. If they do generate disorders, most episodes are mild and self-limited[14]. The main mechanisms by which ARTs cause hepatotoxicity are summarized in table 2[3,13].

There is no specific contraindication for any ART for patients with Child-Pugh Stage A cirrhosis. However, there are still insufficient data for patients with hepatocellular insufficiency (Child-Pugh stages B and C) (Table 3)[14].

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

NRTIs are an essential part of ART. Older NRTIs such as zidovudine (AZT), stavudine (d4T), and didanosine (DDI) were associated with significant liver toxicity primarily due to mitochondrial toxicity[3]. Mitochondrial toxicity is due to the inhibition of mitochondrial DNA (mtDNA) replication through the binding of NRTIs to mtDNA polymerase gamma, which is the enzyme responsible for it. This gives rise to impaired oxidative phosphorylation which, in turn, promotes the formation of reactive oxygen species which, in turn, damage mtDNA, causing mitochondrial dysfunction. Moreover, impaired mitochondrial function induces the production of lactate and has a negative effect on free fatty acid oxidation within hepatic mitochondria, two factors that can result in a spectrum of lesions: from varying degrees of macrovesicular and microvesicular hepatic steatosis to lactic acidosis and life-threatening

Table 2. Main mechanisms of hepatotoxicity of antiretrovirals

Type of antiretroviral drug	Mechanism of hepatotoxicity production
NRTIs	Mitochondrial toxicity – Altered fatty acid oxidation in hepatic mitochondria>hepatic steatosis – Hypersensitivity reactions (ABC) – Immune reconstitution at the start of treatment. – Flares when developing resistance or when discontinuing treatment with activity against HBV (3TC, FTC, TDF, and TAF) in patients with hepatitis B
NNRTIs	– Hypersensitivity reactions – Mitochondrial toxicity – Direct cholestatic injuries – Immune reconstitution
PIs	– Direct toxicity (rare) – Hypersensitivity reactions – Immune reconstitution at the start of treatment.
INIs	– Unknown individual mechanisms – Immune reconstitution at the start of treatment.
Entry inhibitors	– Hypersensitivity reactions – Immune reconstitution at the start of treatment.

3TC: lamivudine; ABC: abacavir; FTC: emtricitabine; INI: integrase inhibitor; PI: protease inhibitor;; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; VHB: hepatitis B virus.

hepatotoxicity[20]. Furthermore, AZT and DDI can be associated with hepatic fibrosis and d4T with hepatic steatosis, which can progress to hepatic fibrosis[3].

With regard to abacavir (ABC), in a cohort study of 314 patients coinfected with HIV/HCV, the combination of ABC and 3TC was associated with an increase in the APRI index (a non-invasive index for the prediction of liver fibrosis based on platelet and AST levels). This study estimated that a mean 16% increase in APRI values every 5 years was observed when ABC/3TC was used in combination with a PI and an 11% increase every 5 years when used with an NNRTI[25].

FTC and 3TC are regarded as safe drugs in terms of liver toxicity[13]. FTC has not been associated with liver fibrosis progression[3]. It is worth to note that naive patients with chronic HBV starting ART with activity against HBV (such as FTC, 3TC, TDF and TAF) may experience flares of hepatitis the first days of taking the regimen. However, this reactivation can occur when starting any powerful regimen in a patient with HCV and/or HBV coinfection as part of an immune reconstitution syndrome. In addition, they may also experience exacerbations of HBV infection if resistance develops or if treatment is discontinued, particularly in the absence of HBeAg seroconversion[27]. The incidence of exacerbations after the discontinuation of treatment in an evaluation of long-term studies of FTC monotherapy in the treatment of HBV ranged from 7% to 23% with treatment lasting from 24 to 48 weeks, respectively. The median time to the onset of the exacerbations was around 11 months, and only transient transaminase elevations were registered in most cases.[28] As such, it is important to use active regimens against HBV both in treatment-naive patients and when changing the treatment for any reason. In this regard, it should be pointed out that monotherapy with 3TC or FTC is not recommended regimens due to the high risk of the appearance of short-term resistance and the exacerbation of HBV. This does not happen when TDF of TAF are used[29].

Tenofovir appears to have little or no direct hepatotoxicity. Minor elevations in serum ALT and AST are more common in patients with no HBV or HIV infection receiving tenofovir as part of pre-exposure prophylaxis than receiving placebo, but rarely exceed 5 times the upper limit of normal (ULN) (< 1%)[30]. A pre-exposure prophylaxis study of 5857 individuals receiving FTC/TAF (2,694 patients) or FTC/TDF (n = 2,693) reported grade 3/4 AST/ALT elevations in 2% in both groups[31]. Like FTC and 3TC, tenofovir can cause exacerbations of hepatitis B at initiation or discontinuation of treatment in patients coinfected with HIV/HBV[27]. Emergence of resTenofovir is associated with a low rate of HBV resistance emergence amd thus, due to the fact, tenofovir is associated with a very low rate of HBV resistance (< 1% after 4 years), exacerbations of hepatitis B due to such resistance are highly unlikely[30]. On the other hand, some studies have associated the use of TDF with an improvement in liver fibrosis in patients not coinfected with HBV[32] and in patients coinfected with HIV/HBV[33,34], although the results are not replicated in all these studies[22,35].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Not all NNRTIs have the same risk of hepatotoxicity[13]. Older NNRTIs such as efavirenz (EFV), and especially nevirapine (NVP), have historically been associated with liver toxicity[13]. The risk of grade 3/4 hepatotoxicity

Table 3. Recommendations for the use of the main antiretrovirals in accordance with the degree of liver fibrosis

	Child-Pugh A	Child-Pugh B	Child-Pugh C
NRTIs			
TDF	+	+	+
TAF	+	+	+
FTC	+	+	+
3TC	+	+	+
ABC	+	NR	NR
NNRTIs (± NRTIs)			
EFV	+ (precaution)	PD; NR	Contraindicated
ETR	+	+ (precaution)	SD; precaution
DOR	+	+	SD; precaution
RPV	+	+	SD; precaution
RPV-TDF-FTC	+	+ (precaution)	SD; precaution
INIs (± NRTIs)			
DTG	+	+	SD; precaution
DTG-ABC-3TC	+	NR	NR
RAL	+	+	PD; precaution
EVG-TDF-FTC	+	+	NR
BIC	+	+	SD; precaution
PIs			
DRV/r or DRV/c	+	+	NR
ATV/r	+ (precaution)	+ (precaution) 300 mg without ritonavir	NR
ATV/c	+ (precaution)	NR	NR
LPV/r	+	+	NR
FPV/r	700 mg/100 mg/12 h	450 mg/12 h 100 mg/24 h	300 mg/12 h 100 mg24 h
Entry inhibitors			
MVC	+	Precaution	SD; precaution
Enfuvirtide	+	+	+

+Safe drug, no dose adjustment required.
PD: insufficient data, SD: insufficient data for recommended dose or safety, NR: not recommended.
3TC: lamivudine; ABC: abacavir; ATV: atazanavir; BIC: bictegravir; CAB: cabotegravir; c: cobicistat; DRV: darunavir; DTG: dolutegravir; DOR: doravirina; EFV: efavirenz; ETR: etravirine; EVG: elvitegravir; EVG/c: elvitegravir/cobicistat; FTC: emtricitabine; INI: integrase inhibitor; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; LPV: lopinavir; MVC: maraviroc; NVP: nevirapine; RAL: raltegravir; RPV: rilpivirine; r: ritonavir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.
Adapted from https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new-guidelines (2022)[15].

can be as high as 1-8% with EFV and as high as 15-20% with NVP[36-39]. Multiple mechanisms of NNRTI toxicity have been suggested, such as direct cholestatic injury or immune reconstitution; however, early hypersensitivity reactions at the beginning of treatment are the most commonly reported causes of hepatotoxicity in the literature[3,13]. These hypersensitivity reactions are likely due to an intermediate metabolite generated during metabolism through the cytochrome P450 pathway, which leads to an immunogenic reaction[13].

Etravirine (ETR) is often associated with elevated transaminases; however, elevations of over 5 times the ULN occur in only 2-4% of patients[40,41]. Most studies showed the rate of liver enzyme elevations to be no different in patients treated with ETR than in the comparison arms[40]. Toxicity may be greater in patients coinfected with HCV[40,41], although some studies suggest that the use of ETR does not seem to increase the risk of hepatotoxicity in patients coinfected with HCV[42].

Doravirine (DOR) is also a safe drug in terms of hepatotoxicity[13]. Serum transaminase elevations have been reported in 13% of patients on DOR, but elevations of over 5 times the ULN are uncommon and occur in 1% or less of patients. The rate of serum transaminase elevations during DOR therapy is higher in patients coinfected with hepatitis B or C; however, the complications are rarely severe[43-46].

Rilpivirine (RPV) is associated with a low rate of transient elevations in serum transaminases during the treatment and may rarely be clinically apparent[47].

Elevations of over 5 times the ULN are infrequent (1-4% of patients) and lower than those registered for EFV[48,49]. An aggregated analysis of the data from Phase-3 clinical trials (ECHO[49] and THRIVE[48]) illustrated the hepatic toxicity of RPV versus EFV in patients coinfected with HBV and/or HCV. Hepatic adverse events were mild and similar in both treatment arms. Hepatic adverse events requiring the discontinuation of the treatment were infrequent: 0.4% (3/682) in RPV versus 1.3% (9/682) in EFV[50].

An interesting fact is that RPV has been associated with an improvement in hepatic fibrosis in both animal studies and PLWHA studies (Table 4)[51-54]. The results of a recent study suggest that RPV attenuates liver fibrosis through selective apoptosis mediated by Signal Transducer and Activator of Transcription 1 (STAT1) in hepatic stellate cells, which are the main source of extracellular matrix in the liver[51] Signaling through the Janus protein tyrosine kinase and STAT pathways regulates liver fibrosis and regeneration[55]. *In vitro* and *in vivo* mouse models have shown that RPV, by regulating STAT1, is capable of inducing apoptosis in stellate cells. The consequent expression of IL-6 activates the signaling pathway mediated by STAT-3 in hepatocytes in a manner that promotes liver regeneration[51]. This STAT1-mediated mechanism has been demonstrated in human tissue in a cross-sectional study conducted in PLWHA and NAFLD exposed or not to RPV[52]. Furthermore, a retrospective[53] and other prospective studies in PLWHA[54] have shown a reduction in fibrosis greater than that associated with PIs or integrase inhibitors (INIs) in patients registering a sustained viral response (SVR) with the treatment for HCV infection (Table 4). Moreover, switching from regimens including EFV to RPV-based treatment is associated with a reduction in hepatic steatosis as measured by controlled attenuation parameter (CAP)[56].

Integrase inhibitors (INIs)

INIs have a good safety profile in terms of hepatotoxicity. A review of the incidence of hepatotoxicity in the use of INIs in 4366 HIV-1 patients in the EuroAIDS cohort showed just one discontinuation of the treatment for hepatotoxicity after a median of 1.6 years with each treatment[57]. Although all INIs are extensively metabolized in the liver, they have little or no effect on cytochrome P450 enzymes and their mechanism of hepatotoxicity is unknown[3].

Treatment in clinical trials with raltegravir (RAL) was associated with ALT elevations in up to 10% of patients and elevations of over 5 times the ULN in 3-4%[58-62]. In patients coinfected with HBV or HCV, aggregate analyses of clinical trials showed that Grade 3 or 4 elevations in transaminases are more common in coinfected individuals than in HIV-only individuals (3% vs. 4%)[63]. The results of these studies were similar for both monoinfected and HBV or HCV-coinfected individuals and the control group. Other studies have shown that switching from EFV or IP to RAL led to an improvement in patients' hepatic steatosis as measured by CAP[64,65].

Treatment with dolutegravir (DTG) in clinical trials has been associated with ALT elevations of over 3 times the ULN in 2-5% of patients; however, these rates were similar to the patients in comparison groups receiving optimized antiretroviral therapy without DTG. These elevations were not associated with clinical symptoms and in general did not require any change in dose[66-70]. However, a few cases of acute liver injury with jaundice were reported in premarketing trials, having occurred in association with hypersensitivity reactions and resolved through the discontinuation of the drug. The association thereof with DTG has not been fully established[67]. Cases of acute hepatitis attributable to DTG have been reported since the drug was approved and its more widespread use. Latency to onset ranged from 1 to 8 months and the pattern of serum enzyme elevation was hepatocellular. No immunoallergic or autoimmune characteristics were registered[67,71,72]. At least one published case resulted in acute liver failure and the need for a liver transplant[73].

Treatment with bictegravir (BIC) combined with FTC and TDF in clinical trials has been associated with ALT elevations of over 1.5 times the ULN in 11% of patients; however, these rates were similar to those registered in the comparison groups (12-15%). Elevations of over 5 times the ULN occurred in 1.4% of subjects in the bictegravir arm compared to 0.9-1.3% of subjects in the comparator control arm. These elevations were not associated with clinical symptoms and in general did not require any change in dose. Furthermore, there were no cases of acute hepatocellular liver injury with jaundice[74-79]. There were no hepatic adverse effects or drug discontinuations due to hepatic abnormalities in patients coinfected with hepatitis B and HIV[76,79].

Cabotegravir (CAB) is the most recent INI[80]. Ninety-four subjects participating in a Phase 2a study conducted with CAB/RPV in HIV-negative individuals (ECLAIR study) started intramuscular treatment. One patient developed acute HIV-1 infection and had Grade 3 elevations in ALT and Grade 2 elevations in AST at week 53[81]. The aggregate analysis of the ATLAS and FLAIR studies regarding the use of the combination of CAB/RPV showed transaminase elevations

Table 4. Studies suggesting an antifibrotic effect of RPV

Author	Type of study	Result
Martí-Rodrigo et al.[51]	– *In vivo* and *in vitro* model of liver fibrosis and cirrhosis in mice – *In vitro* model of hepatic stellate cells	– Activation of STAT1 with induction of apoptosis in hepatic stellate cells associated with: • Antifibrotic and anti-inflammatory effect. • Paracrine effects with an increase in the proliferation of hepatocytes (through the activation of STAT3).
Montes et al.[52]	– Cross-sectional study in 42 patients with HIV and NAFLD exposed to RPV (n: 23) or not exposed to RPV (n: 19).	– Increase in the nuclear expression of STAT1 (activation) in liver tissue.
Montes et al.[53]	– Retrospective cohort study of patients exposed to RPV (n: 120) or not exposed to RPV (n: 120); 59% coinfected with HCV and around 10% coinfected with HBV; around 1/3 cured of hepatitis C	– After a median follow-up of 51 months, a reduction in hepatic fibrosis measured by elastography was registered in the group exposed to RPV (8.7 vs. 7.5 kPa; *P*=0.029) (median RPV exposure of 28.7 months). – The significant reduction in fibrosis was only registered in patients exposed to RPV and cured of hepatitis C (10.6 vs. 7.6 kPa; p < 0.0001). – There were no significant changes in fibrosis in the group not exposed to RPV, neither globally (8.4 vs. 7.8 kPa; p: 0.254) nor in patients cured of hepatitis C (9.4 vs. 8.1; p: 0.1).
Gonzalez -Serna et al.[54]	– Prospective study in 313 patients coinfected with HIV/HCV being treated with NNRTIs (n: 74; 53 with RPV and 16 with EFV) or PIs or INIs (n: 239) who started treatment with direct-acting antivirals and achieved SVR. Baseline hepatic fibrosis≥9.5 kPa.	– At the start of the study, the median fibrosis was 16.7 kPa in the NNRTI group and 17.3 kPa in the PI/INI group (p=0.278). – The median percentage decrease in fibrosis from baseline to SVR was 35.2% for NNRTI-based therapy and 29.5% for PI or INI-based therapy (p=0.018). – In the multivariate analysis, the use of an NNRTI-based regimen was associated with a greater decrease in liver fibrosis (p=0.021.)

INI: integrase inhibitors; PI: protease inhibitors; EFV: efavirenz; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; RPV: rilpivirine; SVR: sustained viral response; STAT: Signal Transducer and Activator of Transcription; HBV: hepatitis B virus; HCV: hepatitis C virus.

≥ 5 times the ULN in 2% of patients at week 48, compared to < 1% on the previous antiretroviral regimen. Minor increases in total bilirubin, without jaundice, were registered in the CAB/RPV groups. This was regarded as clinically insignificant and was thought to be secondary to competition between CAB and unconjugated bilirubin for clearance through UGT1A1[82].

Protease inhibitors (PI)

Older PIs have moderate-to-high rates of hepatotoxicity. Serum transaminase elevations > 5 times the ULN have been reported in up to 10% of patients on lopinavir[83] and atazanavir (ATV)[84], particularly in patients coinfected with HIV-HCV[85]. Characteristically, indinavir (an obsolete drug) and ATV increase serum unconjugated bilirubin due to the inhibition of UDP glucuronyl transferase in a manner similar to that of Gilbert syndrome, producing jaundice not indicative of liver injury[85].

The only PI in common use today is darunavir (DRV) combined with ritonavir or cobicistat as boosters. The toxicity of DRV/r and DRV/c is much lower than that of older PIs. Clinical trials with DRV/r showed serum ALT elevations of over 5 times the ULN in 2-3% of the patients; no subject developed clinically apparent liver injury with jaundice[86-88]. Serum enzyme elevations during treatment are usually asymptomatic and self-limiting and may even be resolved with continued medication[88]. Liver toxicity is even less with DRV/c[89,90]. DRV is metabolized by the liver, mainly through the cytochrome P450 (CYP3A4) system, and intermediate metabolites may be the cause of some liver disorders[88].

Entry inhibitors

Maraviroc selectively binds to the human chemokine receptor CCR5, blocking the interaction of GP120 and

CCR5 necessary for viral fusion and the entry of HIV into CD4 cells. It should be prescribed exclusively for patients infected with R5-tropic HIV-1 strains[15]. This drug is rarely used in the clinic[14]. When it began to be developed, there was concern as cases of severe liver disease were described; however, it has not been associated with a higher toxicity rate than that of other ARVs in subsequent studies and in the post-marketing phase[13,91,92]. The mechanism of hepatotoxicity may be related to hypersensitivity reactions or interactions with other drugs[3,93].

Ibalizumab is a humanized monoclonal antibody that binds to the second extracellular domain of the CD4 receptor, blocking it[14]. It is a human monoclonal antibody and is unlikely to be inherently hepatotoxic[94]. Pre-authorization clinical trials included a limited number of patients, many of which had other severe comorbidities such as cirrhosis and chronic hepatitis B and C. Serum aminotransferase elevations occurred in 14-25% of patients in these trials; however, abnormalities were generally mild and self-limited and often attributable to other underlying conditions[94,95].

Fostemsavir is an attachment inhibitor. It is a prodrug of temsavir, which binds directly to the HIV GP120 and prevents it from adhering to CD4 receptors[13]. The Phase 3 BRIGHTE study evaluated fostemsavir 600 mg twice daily in 371 treatment-experienced patients with HIV. Fostemsavir did not demonstrate any significant hepatotoxic potential in this study. The percentage of patients with Grade 3 or 4 laboratory abnormalities from baseline was low. There were three hepatobiliary adverse events that resulted in the discontinuation of the treatment (two cases of liver failure and one case of hepatorenal syndrome); however, all three events were attributed to the underlying disease and not to the ART[96]. The 96-week study on this population did not identify any fostemsavir-related hepatobiliary complications[97].

Conclusions

Liver-related diseases continue to be a major cause of morbidity and mortality in people infected with HIV, with an increasing impact of NAFLD. The rapid detection and diagnosis of liver disease in its early stages are essential to lessen the impact of this disease on the quality of life of this population. However, not every physician has the proper diagnostic hospital machinery to evaluate the underlying liver status of their patients. Therefore, it is important to standarize the use of laboratory liver diagnostic scores which will make it easier to analyze cohorts based on parameters already measured and provided by routine laboratory tests. Fortunately, modern ARTs in use are not associated with any major liver toxicity. However, taking into account the increasing prevalence of NAFLD among HIV population and the aging of most cohorts and the lack of specific treatments towards liver damage due to NAFLD, it would be interesting to further investigate the potential beneficial effect of certain treatments such as RPV with regard to the reversal of liver fibrosis.

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