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HEPATITIS B VIRUS INFECTION AND HEPATOCELLULAR CARCINOMA IN PLWH: EPIDEMIOLOGY, PATHOGENESIS AND TREATMENT

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Abstract – *Combined Antiretroviral therapy altered the natural history of Human Immunodeficiency Virus (HIV) infection, leading to a substantial decline in morbidity and mortality of patients living with HIV. Due to the shared transmission routes, co-infection with HBV and HIV is not uncommon, especially in those patients with similar socioeconomic vulnerabilities and psycho-social conditions. HBV is a known cause of HCC even in absence of cirrhosis, and HIV-HBV-coinfected patients may have faster progression of hepatic fibrosis and a higher risk of cirrhosis and consequently HCC.*

In this article we review the epidemiology, the etiology, the role of coinfection HIV/HBV in the pathogenesis of liver cancer, the management and prevention of HBV infection in HIV-infected patients in the era of combined antiretroviral treatment.

KEYWORDS: *HIV, HBV, B Hepatitis, Cancer, Liver, HCC*

INTRODUCTION

Combined Antiretroviral therapy (cART) altered the natural history of Human Immunodeficiency Virus (HIV) infection, leading to a substantial decline in morbidity and mortality of patients living with HIV (PLWH). Moreover, causes of death changed, shifting from AIDS-defining pathologies to non-AIDS defining pathologies[1-13].

Among the non-AIDS defining pathologies, cancers (NADCs) are the most frequent cause of morbidity and mortality in PLWH[14-25]. Virus-related hepatocellular carcinoma (HCC) is especially important[26]. We already discussed elsewhere HCV-related HCC in PLWH, and we will focus here on HBV-related HCC[27].

Hepatitis B virus (HBV) infection is highly accountable for chronic hepatitis, liver cirrhosis and HCC all over the world[28]. Moreover, HBV co-infection in PLWH is associated with a decreased lifespan, an increased risk of progression of chronic liver disease and hepatotoxicity associated with HAART[29,30].

HBV causes an acute infection eliciting a rapid immune response, which in adults habitually ends in protective immunity as an acute self-limited infection, while in infants and children it more often becomes a chronic one[28,31].

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Due to the shared transmission routes, co-infection with HBV and HIV is not uncommon, especially in those patients with similar socioeconomic vulnerabilities and psycho-social conditions (i.e. mental illness, drug use, alcohol use, homelessness)[28,30]. Nonetheless, the introduction of antiretrovirals (ARVs) active also against HBV led to improvements in outcomes of this co-infection[32].

In this article we review the epidemiology, the etiology, the role of coinfection HIV/HBV in the pathogenesis of liver cancer, the management and prevention of HBV infection in HIV-infected patients in the era of cART.

EPIDEMIOLOGY

Globally, HBV incidence is 10 times higher than HIV[29]. However, among the estimated 40 million individuals infected with HIV worldwide, only about 6-14% is reportedly affected by a chronic HBV infection[33-35]. About one sixth of the mortality related to a liver disorder in PLWH is caused by HBV co-infection[29].

Although being more prevalent in low-income areas, such as Sub-Saharan Africa and South-East Asia, HBV infection affects a significant part of the population in North America and Western Europe[30,31]. Last data presented by World Health Organization (WHO) states that the prevalence is higher in the Western Pacific Region (6.2 %), which includes 37 countries, among which China, Japan, Malaysia, Philippines and Viet Nam, and the African Region (6.1%)[36]. The Eastern Mediterranean Region, the South-East Asia Region and the European Region have, respectively, a prevalence of 3.3 %, 2.0 % and 1.6 %[36]. America has the lowest prevalence rate, 0.7 %[36]. Ten different genotypes have been identified. Curiously, different regions have a different distribution of HBV genotypes[37]. As a matter of fact, genotype A is more frequently found in Africa, India, Europe and America; genotype B and C in Pacific regions of Asia; genotype D is prevalent in India, Africa, Mediterranean regions and Europe; genotype E is only retrieved in West Africa, while F is characteristic of South and Central Americas. Genotype I and J are also predominant in the Pacific regions of Asia (Viet Nam and Japan, respectively)[37].

In high-income low-prevalence areas such as Western Europe, North America and Australia, HBV infection is usually acquired during adulthood[28,31]. According to a study by McKee et al[31], injection drug users (IDUs) and men who have sex with men (MSMs) are at high risk for co-infection with HIV and HBV. However, a study by Sharma et al[30] showed that also heterosexual contact can be an important transmission route. The difference between the two studies is in the setting. While McKee works in a high-income setting, such as the Canadian British Columbia, Sharma's research is set in a low-income area, India[29,30]. As a matter of fact, in low-income countries most HBV infections occur during early childhood by vertical transmission, close contact, medical procedures or cultural customs[31,35,38]. Moreover, the majority of HIV-HBV co-infected individuals are in the 31-40 age group[29,39].

The shared transmission routes between HIV and HBV mentioned earlier can be referred as a syndemic. Risk behaviors for HIV-HBV co-infection not necessarily correlate with poverty in a high-income area[30].

A possible situation increasing the prevalence of HIV-HBV co-infection is the occult HBV infection, defined as the presence of HBV-DNA in serum or liver despite the absence of Hepatitis B surface Antigen (HBsAg). Such condition can be only diagnosed by testing for HBV-DNA, but the cost of this test is too high to even think to screen for occult HBV infection[40]. Moreover, occult HBV infection is more frequent in older patients[41]. However, HBV infection can be suspected in the presence of Hepatitis B core Antibody (HBcAb) associated with a negative HBsAg. A recent study by Hyun et al[42] studied the prevalence of isolated HBcAb prevalence in an endemic population. They show that within the Korean American sub-population, the prevalence of isolated HBcAb positivity is 10.8 %[42]. However, they did not measure HBV-DNA levels in positive individuals; therefore, it was not possible to determine the exact occult HBV infection prevalence[42]. In a recent study, Majzoobi et al[43] showed that in a population of HIV infected people, the 46.6% showed an isolated HBcAb positivity, but none of those patients had detectable HBV-DNA levels. However, another recent study by Bivigou-Mboumba et al[44], showed that in a HIV-infected population screened for HBV co-infection, 35 % of the patients showing an isolated HBcAb positivity had a detectable HBV-DNA.

Considering only primary liver cancers, HCC is the most prevalent. It accounts for about 90% of them. It is the fifth most common cancer in men worldwide and the seventh among women. With more than 700,000 new cases and over 600,000 deaths per year, it represents 9.2% of all new diagnosis of cancer worldwide (7.9% in men; 3.7% in women) and it is the second leading cause of cancer-related death, exceeded only by lung cancers[28,29,32]. The high male to female ratio is thought to be linked to the fact that HBV infection occurs more frequently in men than women and that HCC is thought to be a hormone-responsive cancer[41]. In support of this hypothesis there is the fact that HCC is more frequent in women older than 65 years[41].

Geographical distribution of HCC is highly variable. In middle and low-income countries, it is more frequently diagnosed than in developed ones. Moreover, HCC distribution traces endemic areas for HBV infection[32,36]. Despite the significant improvements in HBV viral control, obtained with the inclusion of tenofovir in ART regimens, overall mortality, liver related mortality, hospital utilization rates and risk of HCC are still elevated in HIV-HBV co-infected individuals[33]. In a study by Moore et al[45], HCC is shown to be associated to HCV rather than HBV with a 2:1 ratio.

HEPATITIS B VIRUS: LIFE CYCLE AND DIAGNOSIS OF THE INFECTION

HBV is a small encapsulated DNA virus belonging to the family of hepadnaviridae[46]. It is a non-cytopathic virus, and liver damage in its presence is caused by a dysregulated immune response[47].

Eight genotypes, A to H, which have separate geographic distribution, are described[36,46].

HBV virion, known as Dane particle, is spherical. A double walled structure with a lipid envelope covered in HBsAg surrounds the nucleocapsid. Nucleocapsid consists of hepatitis B core antigen (HBcAg), which is complexed with a virally encoded polymerase and the viral DNA. HBV genome is 3.2 kb in size and is made up of a partially double-stranded circular DNA[41]. HBV entire life cycle happens in hepatocytes. After entering the cell and the nucleus, HBV-DNA is released as a relaxed circular (rc) DNA which is converted in a covalently closed circular (ccc) DNA chromosome[33]. This structure, cccDNA, is able to persist for a long time and represents the main barrier to clearance of the virus[33,48].

cccDNA encodes the core proteins, HBcAg and its soluble form Hepatitis B e Antigen (HBeAg), and the envelope proteins, HBsAg, polymerase and X protein (HBx). HBx has transcriptional trans-activating potential[43]. HBV can integrate into human genome, as HIV does. As a matter of fact, HBV polymerase encodes the large pre-genomic RNA (pgRNA) which is the template for HBcAg and the polymerase protein. However, pgRNA can also have another destiny. It can serve as a template for the formation of double stranded DNA, which integrates into human genome[33].

One of the pathogenic mechanisms of HBV is completed through HBsAg. The surface antigen is able to control the adaptive immunity, inhibiting it and decreasing the production of anti-HBV surface antibodies (HBsAb), which are required for long-term HBV control[33]. Moreover, some viruses, especially in chronic untreated HBV infection, develop mutations of the pre-core region. These mutants are not able to secrete HBeAg. In addition, they are able to replicate at high levels for long periods, leading to an enhanced necro-inflammatory activity in the liver[33]. Other mutants are instead associated with a higher risk of HCC onset[33]. Moreover, in a study by Choi et al[49], reverse transcriptase mutations spontaneously occurring have been associated with an increased rate of potential antiviral drug resistance and liver disease progression.

Diagnosis of the infection

An HBsAg qualitative dosing test is sufficient to diagnose an HBV infection.

Quantification of HBsAg has been used as a proxy for predicting more active phases of chronic HBV infection and severe liver-related disease[50]. The same technique is used in HIV-HBV co-infected patients to predict HBsAg plasma clearance. A progressively decreasing HBsAg is, as a matter of fact, a good prognostic factor for liver disease, while persistently high levels of HBsAg are associated with a higher risk of HCC onset in untreated infection[33,49]. Boyd et al[50] showed that quantitation of HBsAg and HBV-DNA are influenced by the presence of S-gene mutations (MUPIQHs) already present before the beginning of ART. However, these mutations are not related to the co-infection with HIV, do not influence the response to the treatment and are generally not selected by the treatment[49]. Moreover, HIV-related immune suppression seems to have a protective role against MUPIQHs[49].

Dinesha et al[40] proposed a method of pooled Nucleic Acid Testing (NAT) to screen co-infected patients for occult HBV infection. Applying a method already studied for other infectious diseases, they showed that in a high prevalence area, at least 10% of the HBV-infections in PLWH is not diagnosed because of a negative HBsAg[40].

TUMORIGENESIS

Among PLWH, the risk of developing HCC is five- to six-fold higher than the general population. The introduction of ART did not modify this difference[29,33]. HCC is the most common type of liver cancer[27]. Virus-related HCC is more frequent than non-virus-related HCC[29,33]. Establishment of a chronic HBV infection is influenced by immune tolerance, suppression of CD4+ T-lymphocyte responsiveness to the infection or impairment of the innate immune responses[47]. An increased number of regulatory T lymphocytes and induced apoptosis of Fas-expressing lymphocytes are other mechanisms

through which immune tolerance to HBV, and therefore, a chronic HBV infection, is established[47]. Moreover, in PLWH, HCC has been associated with lower CD4+ T-lymphocyte count and higher HBV-DNA[34]. However, the exact role of HIV in promoting HCC has still been poorly understood[29,34]. Chronic HBV infection is responsible for around 50-80% of HCC cases worldwide[36].

A study by Moore et al[45] showed that HIV infection is associated with a lower odd of developing HCC, probably because the patients died before developing HCC or HCC is underdiagnosed[45]. Moreover, PLWH who develop HCC in presence of HBV co-infection are affected by a higher mortality rate than individuals affected by HBV infection only.

HBV is a known cause of HCC even in absence of cirrhosis. However, around 70-90% HBV-related HCC develops in cirrhotic livers[46,48]. Cirrhosis development is accelerated in PLWH[33].

Other risk factors may increase HCC risk among persons with chronic HBV infection. These include older age, male sex, cirrhosis, diabetes mellitus, exposure to environmental carcinogens (aflatoxin B1, alcohol and tobacco consumption and HDV superinfection[32,36]. HBV-infected individuals with an undetectable HBV-DNA have a lower risk of developing HCC, although this risk is not zero[33].

HCC onset in chronic HBV infection is associated to a dysregulation of the immune system; however, the exact mechanisms is still unknown[4]. Whenever a Th2-like inflammatory response prevail on a Th1-like immune response in presence of HBV, the infection persists and becomes chronic[47].

HBV causes HCC through a complex pathway starting with viral interactions with endogenous mutagens, such as reactive oxygen species, and pro-inflammatory cytokines and products. Immune dysregulation is also accountable for HBV-related HCC in PLWH[46]. Especially, interleukin (IL)-8 and tumor growth factor (TGF)-β1 are major regulator of liver fibrosis and have been associated with the HCC onset in chronic HBV infection[47]. Moreover, immune senescence mediated by PD-1/PD-L1 interactions and sPD-1 are reportedly related with the onset of HCC[47].

The disruption of the host DNA through integration of HBV-DNA is a fundamental step in HCC pathogenesis. The *x* gene properties of promoting cell cycle progression, inactivating negative growth regulators and inhibiting the expression of tumor suppressor genes, such as p53, carry out a specific role in the carcinogenesis[29,32,36,48]. Chronic necro-inflammation due to HBV-infection leads to a hyper stimulated regeneration, which is afflicted by a high DNA damage rate[47,48]. As previously said, it is the balance between virus clearance and tolerance to determine the outcome of the infection[51]. As a matter of fact, during self-limited acute HBV infection, the efficient HBV-specific immune response plays a key role. A response of CD4+ and CD8+ T-lymphocytes is generated to control and clear HBV[47,51]. Especially, HBV-specific CD8+ T cells produce IFN-γ and TNF-α, cytokines with a potent antiviral activity, but can also carry out their function by stimulating the lysis of the infected hepatocytes[52].

T-helper CD4+ lymphocytes stimulate B cells to produce antibodies. In addition, NK cells and NKT cells efficiently control HBV[51]. However, this immune response does not take place during chronic HBV infection. As a matter of fact, the early phase of the chronic HBV infection is a stage of immune tolerance during which HBV-DNA replicates at high-levels and pro-inflammatory cytokines are found in low concentrations[53,54]. However, after this tolerance phase we assist to an immune active stage, during which with hyper active HBV-specific CD8+ T-lymphocytes attack infected hepatocytes, causing chronic liver injuries, inflammation and stimulating liver regeneration[52,54].

Low level of HBV replication and limited inflammation are characteristic of the third and last stage, the immune inactive one.

It is in this stage that an inactive carrier can relapse, causing the progression of their chronic hepatitis to liver fibrosis and cirrhosis[52,55]. Eventually, HBV activates oncogenic pathways that result in immune escape and promote the onset of HCC[33].

Chronic inflammation is considered an important element contributing to tumorigenesis: patients with more cumulative immune mediated hepatocyte damage would be more susceptible to HCC[33,53-55].

Diagnosis of HCC

There are many differences between diagnosis in high-income countries, where it is usually done by performing imaging, either computed tomography or magnetic resonance, and cytology/histology, and diagnosis in low-income countries, where it relies on a series of abdominal ultrasounds combined with plasmatic a-fetoprotein (AFP) for confirmation[41].

Nowadays, circulating micro-RNAs (miRNAs) are under investigation as a diagnostic tool that can be useful to screen patients with HCC, especially in low-income countries and hyper-endemic HIV settings[28,56].

THE ROLE OF CO-INFECTION WITH HIV

In PLWH, HBV infection doubles the events of AIDS and death[40,47]. HIV/HBV-coinfected patients are burdened by faster progression of hepatic fibro-

sis and a higher risk of cirrhosis. Consequently, they have a higher risk of HCC than HBV-monoinfected patients[29,57]. Moreover, they also have a higher risk of acute hepatitis, hepatic decompensation, and liver-related mortality[47,58].

The spectrum of HIV-induced liver diseases includes hepatitis, alcohol-associated steatohepatitis, nonalcoholic steatohepatitis (NASH) and endothelialitis[52] These damages might be worsened by malnutrition or administration of possible hepatotoxic antiretroviral drugs[30].

Earlier studies showed that, compared to HIV-uninfected subjects, adult patients with HIV infection have a higher risk of chronicity after acute HBV infection, with reduced clearance of the HBV e antigen (HBeAg) and increased levels of HBV replication[29,58,59]. Moreover, co-infection leads to a higher liver-related mortality compared with individuals affected by mono-infection, even when ART is successful[33,42,56]. In addition, HIV/HBV co-infected individuals tend to have a lower socio-economic status and a higher number of comorbidities[58].

Despite being associated with a higher mortality, co-infected PLWH show higher rates of either HBsAg loss or seroconversion during treatment. This is especially true in patients starting treatment with a low CD4+ T-lymphocyte count or with a low HBsAg level[33]. However, there are discordant data about the association of HBsAg levels with seroconversion[33]. Moreover, this higher rate of seroconversion might be associated with Immune Reconstitution Inflammatory Syndrome (IRIS)[33].

When occult HBV infection occurs in PLWH, it is clinically significant[40]. As a matter of fact, they are co-infected patients who are not recognized as such. Therefore, their condition is even worse than a real co-infected one, as the clinician could choose sub-optimal ART regimens, doomed to fail in controlling the infection or leading to a worsening of a pre-existing liver damage. Moreover, occult infection often happens in older patients, who lived longer with it[41].

Co-infected people who seroconvert to protective antibody have a higher risk of reactivation of HBV.

They are also more at risk of developing HCC with a higher severity and more complications[46]. HIV accelerates the progression of HBV-related liver disease by several different mechanisms, such as direct interaction between HIV and HBC, direct HIV infection of multiple cells in the liver, increased microbial translocation with increased liver inflammation, exhaustion of HBV-specific T-cells[33,45,59]. Moreover, in a study by Shata et al[47], it was demonstrated that Fas mediated apoptosis is of utmost importance in determining liver damage. Although the level of soluble Fas ligand (sFasL) levels in patients with HIV-HBV co-infection are lower than in healthy controls, this is thought to be caused just by the fact that FasL is mainly expressed by CD4+ T-lymphocytes which, in HIV infection, are decreased in number, thus leading to a lower shedding[47].

Hepatic stellate cells (HSC), Kupffer cells and hepatocytes are permissive to HIV infection. Moreover, HIV sequences retrieved from liver cells are different from those found in other tissues[33]. Therefore, it is possible to hypothesize that HIV can persist in Kupffer cells even during ART and contribute to liver inflammation and fibrosis by binding of gp120 to the CXCR4 co-receptor expressed on hepatocytes and HSC[33,60].

As HIV destroys CD4+ T-lymphocytes, compromising host immunity against HBV, PLWH are more frequently HBsAg positive than the general population[61,62].

Oshitani et al[63] showed that HIV-positive pregnant women have a 3-fold higher HBeAg positive rate than HIV-uninfected pregnant women. Moreover, Rouet et al[64] showed that HBV DNA was detected in 26.7% of pregnant women with HIV/HBV coinfection *vs.* 9.4% of those with HBV mono-infection.

Several studies showed that HIV-related immune suppression worsens the natural course of HBV infection. The Swiss HIV cohort study firstly reported a significant association between the number of CD4+ T-lymphocytes and HCC risk, directly linking HIV to HCC[29,32,36,46,48,51,52,59,62,64].

The Multicenter Cohort Study highlighted a correlation between CD4+ T-lymphocyte nadir counts and risk for liver-related mortality in HIV-HBV co-infected individuals[47,54,55,58,59,62].

Moreover, HBV genotype A is the most prevalent in PLWH in Western countries[29,32,36,48]. Nonetheless, the distribution of HBV genotypes might vary according to clustering by risk factors, geographic origin, and co-infection with other hepatitis viruses. Non-A genotypes are correlated with a quicker evolution to cirrhosis and HCC than A genotypes[62-64].

SYMPTOMS

Signs and symptoms of HCC do not differ between HIV-infected and HIV-negative patients. Clinical signs and symptoms of HCC often does not appear until an advanced tumor stage. Moreover, as HCC often happens in the context of an advanced liver disease, it is very difficult to distinguish which one is the cause of the sign[65].

If not impairing liver function, HCC may progress silently and escape early diagnosis[66]. On the other hand, if liver function is impaired clinical symptoms can appear.

Non-specific signs and symptoms are mostly present in advanced stages of cancer, such as right upper quadrant abdominal pain, hepatomegaly, haemobilia, obstructive jaundice and fever. Anorexia, nausea, lethargy and weight loss are also often present[65,67].

Complications include hepatic vein occlusion evolving to Budd-Chiari syndrome, portal vein invasion, thrombosis, rupture causing acute abdomen and intraperitoneal bleeding[68].

Metastases can spread from HCC, both through the hematic and lymphatic system. The most frequent secondary localizations of HCC are abdominal and thoracic lymph nodes, lung, bones and adrenal glands[65]. Symptoms related to metastases often appear before the HCC signs. Moreover, metastases are present in 40 % of the cases at the diagnosis[65].

HCC can also present as a paraneoplastic syndrome, with symptoms of hypercalcemia, hypercholesterolemia, hypoglycemia or erythrocytosis[65,67]. Other paraneoplastic syndromes associated with HCC may present as thrombocytosis, arterial hypertension, diarrhea and femininization[65]. This kind of signs are more frequent in younger patients, with larger cancers and in the presence of portal vein thrombosis and may also appear in absence of previous hepatic cirrhosis[65]. Moreover, HCC frequently causes cutaneous manifestations, such as dermatomyositis, polymyositis, porphyria cutanea tarda, pityriasis rotunda and sign of Leser-Trelat[65]. In addition, HCC can also have neurologic manifestations[65].

PREVENTION AND MANAGEMENT

Current guidelines recommend testing for HAV, HBV and HCV[68,69].

Screening of chronic HBV infection is based on the research of serum HBsAg, HBsAb and HBcAb. PLWH who are HBcAb positive and HBsAg negative, especially when also showing increased levels of liver transaminases, should also undergo qualitative/quantitative HBV-DNA testing to rule out occult HBV infection. HDV antibodies should be tested in all HBsAg positive patients[68,69].

In all patients with chronic HBV infection, and in particular co-infected PLWH, all causes of liver disease should be ruled out. Alcohol consumption, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases and drug-induced hepatotoxicity should be investigated and treated when necessary[29].

All PLWH should be assessed periodically for any liver damage, by measuring complete blood count, liver transaminases, alkaline phosphatase, coagulation markers, albumin and cholinesterase. A more direct approach to stage liver fibrosis should include fibro-scan or liver biopsy. If HBsAb negative, with no other marker of HBV infection, PLWH should be vaccinated[67-69].

HBV vaccine is recommended only for individuals with CD4+ T-lymphocyte counts above 200 cells/μL. As a matter of fact, response to vaccine is poor below this level. Therefore, PLWH with CD4+ T-lymphocyte counts below 200 cells/μL should receive ART first and HBV vaccine later, when CD4 counts rise above 200/μL[27].

After vaccination, it is necessary to monitor HBsAb titre should be checked to verify seroconversion. Moreover, HBsAb levels should be tested once a year, in order to administer booster vaccine dose when those levels decline < 10 IU/l[66,67].

Since PLWH do not respond as well as the general population to the standard vaccine schedule, double dose at 3-4 time points (months 0, 1, 6 and 12) may help to improve response rates to the HBV vaccine[29,32,36,44,46].

Patients should be informed about prevention of liver damage: limitation of alcohol consumption, avoiding hepatotoxic drugs or abuse. They also should be vaccinated against HAV if not immune[67,68].

An abdominal ultrasound every 6 months should be performed in HBV co-infected PLWH to detect early HCC[67]. As a matter of fact, a study by Rajbhandari et al[58] showed that cirrhosis is a strong risk factor for mortality in PLWH. Therefore, they support the importance of prevention and early identification of HBV co-infection in PLWH.

Serum alpha-fetoprotein (AFP) can be associated in the surveillance of chronic hepatitis B. Cirrhotic patients should be monitored for the presence of esophageal varices using upper-gastrointestinal endoscopy every 1-2 year[68].

TREATMENT

The aim of HBV treatment in PLWH is to suppress HBV viral replication, thus minimizing the progression of liver damage by reducing necro-inflammatory activity[29,32,36,46,48]. Given the high rate of co-infection in MSM, integration of HBV and liver care with HIV can improve the health of these patients without much effort[31]. One of the main hurdles in managing HIV-HBV co-infection is that ART is a lifelong treatment for both HIV and HBV, since both viruses are characterized by persistence of the infection[33]. Moreover, IRIS have been described in presence of HIV-HBV co-infection, and are characterized by a significant increase in hepatic transaminases following the beginning of ART[33].

All HBV co-infected PLWH should undergo treatment whenever an abnormal aminotransferase value or HBV DNA levels of > 2000 IU/mL has been found[68,69]. Patients with an indication for HBV treatment should start cART with nucleos(t)ide analogues, regardless of the CD4+ T-lymphocyte count.

A number of different drugs are approved for chronic HBV infection treatment. These includes IFN, pegylated-interferon (peg-IFN), lamivudine (3TC), emtricitabine (FTC), ADV, entecavir (ETV), telbivudine (LdT) and tenofovir disoproxil fumarate (TDF)[70]. A study by Bihl et al[71] showed that a delayed response to drugs can be influenced by poor adherence, altered immune response, drug regimen, and genotype.

According to EACS Guidelines, if TDF or TAF is contraindicated, entecavir may be prescribed in PLWH with no prior 3TC exposure. A particular attention is required in PLWH with liver cirrhosis and low CD4+ T-lymphocyte count, especially during the first months after starting ART in order not to overlook signs of immune reconstitution syndrome[69].

The vast majority of HBV-infected individuals under an effective treatment reach an undetectable HBV viremia[33,70]. Sequence analysis in patients with residual viremia revealed that it was associated with active viral replication more than with passive release from reservoirs[33,72].

As for HBV-related HCC, the existence of PD-1 mediated T-lymphocyte exhaustion in chronic viral diseases, has led to the hypothesis of using immune checkpoint inhibitors for cancer treatment[66]. Nivolumab and pembrolizumab, PD-L1 blockers, are currently in a phase 3 study, although it has been recently demonstrated that the same drugs could worsen the HCC prognosis[73-78]. The only medical treatment available at the moment for HCC is Sorafenib, a tyrosine-kinase inhibitor[27]. Treatment of HCC is surgical, by resection or transplantation[27]. The choice depends on the stage of the disease. Makuuchi's criteria are applied to determine the best treatment based on the residual liver function. Surgical treatment consists in trans-arterial chemoembolization (TACE) when liver functions are preserved and there are no metastases[79]. However, this kind of approach is only seldomly applied in PLWH, as the diagnosis often happens in a late stage[27]. Therefore, portal vein embolization is the most widespread treatment, with the highest chance of survival, in these patients[80]. Transplantation still offer the best chance at survival[27].

RESEARCH FOR A CURE

ARVs can suppress replication of HBV-DNA, but do not eradicate the infection. As a consequence, after stopping the treatment, we always assist to a rebound. Eradication of cccDNA is the goal of cure strategies, which include pro-apoptosis, gene editing and immunomodulatory strategies[32]. Some of these strategies could also have an effect in curing HIV.

CONCLUSIONS

PLWH are affected by a higher mortality of liver-related deaths than the general population, because of higher risk of being co-infected with HBV. HBV can cause HCC even in absence of cirrhosis, and the wide range of clinical and serological presentations it can offer, make its diagnosis challenging for the clinician.

Nonetheless, it is of utmost importance to test each HIV-infected patient for HBV, especially those patients showing increase liver transaminases.

HIV and HBV share the mechanism of integration into the host DNA, which makes the eradication of the infection a real hurdle. Moreover, this common mechanism, together with the immune system impairment, lead to a quicker transformation of liver fibrosis into HCC.

Therefore, three things are fundamental. Testing every PLWH and treat the co-infected, propose the vaccination to every HBsAb negative patient and monitor the seroconversion, screen the HIV-HBV co-infected patients for HCC. Early diagnosis of HIV infection and initiation of cART to achieve suppression of both HIV and HBV replication are needed to ensure long-term success in the prevention of HBV-related chronic complications such ah HCC.

Conflict of interest:
The authors declare they do not have any conflict of interest.

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