Chapter 4

Human Immunodeficiency Virus-Hepatitis B Virus (HIV-HBV) Coinfection

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.78567

Abstract

The global epidemics of hepatitis B and HIV have led to a new understanding of the complex interactions between these two viruses. Due to similar patterns of contamination, the high prevalence of HBV infection among the 33 million people living with HIV (PLHIV) across the world is about 10%. In highly endemic areas such as sub-Saharan Africa, this prevalence can be as high as 15% and leads us systematically to seek HIV/HBV co-infection. According to WHO, nearly 240 million people are chronically infected with HBV worldwide. Of these, 4 million are co-infected with HIV. Overall, co-infection rates range from 5 to 14% in areas of low prevalence of HBV infection and 5–73% in areas of high prevalence for HBV infection. Studies have revealed the complexity of the infection relationship between HIV and HBV. This complex relationship is thought to be responsible for greater morbidity and mortality of hepatic origin in co-infected patients than in mono-infected individuals. This chapter will highlight the following main points:

- Concomitant negative impact of HIV and HBV on their natural histories
- Implication of concomitant negative impact on the overall management of HIV-HBV coinfection
- Treatment and management.

Keywords: HIV, HBV, HIV-HBV coinfection, occult hepatitis B infection

1. Introduction

1.1. General information on HIV

The human immunodeficiency virus (HIV) is an enveloped RNA virus (two copies) belonging to the family of Retroviridae, genus Lentivirus. HIV infection and its natural evolution lead

to a set of opportunistic, infectious, or tumoral manifestations, consequences of an immunodepression qualified as acquired immunodeficiency syndrome (AIDS). To date, there are two types of HIV: the first, called HIV-1, is responsible for the pandemic and HIV-2 is more common in West Africa [1].

1.2. Genomic structure and organization

Morphologically, HIV is a single spherical particle with a diameter ranging from 90 to 120 nm. The virion has a spiky envelope and a dense nucleocapsid, sometimes trapezoidal or bar-shaped.

Structurally it is described as follows (**Figure 1**).

The viral body comprises two identical RNA molecules; three viral enzymes (reverse transcriptase (p66/p51); protease (p10) and integrase (p32)]; and three internal proteins [24 kDa capsid protein (p24); the 7KDa nucleocapsid protein (p7) that is associated with the RNA molecules; and the outermost protein, associated with the viral protease, the 17 kDa matrix protein (p17)].

The viral envelope, emanation of the cellular cytoplasmic membrane, carries two viral glycoproteins (gp) essential in the virus-host cell interaction. This is the gp41 (41 kDa glycoprotein found in the transmembrane position) and the gp120 (120 kDa glycoprotein, lining the outer surface and thus allowing the attachment to its cellular receptor, the CD4 molecule) [1].

HIV has gag, pol, and env as structural genes that encode internal proteins, viral enzymes, and envelope glycoproteins, respectively [2], and it has six regulatory genes: tat, rev, nef, alive, vpr, vpu (for HIV-1), and vpx (for HIV-2) [1] (**Figure 2**).

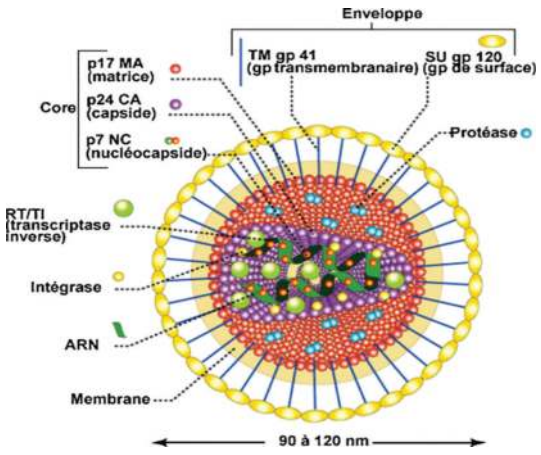

Figure 1. HIV structure (from HIV genetic diversity and its consequences, [1].

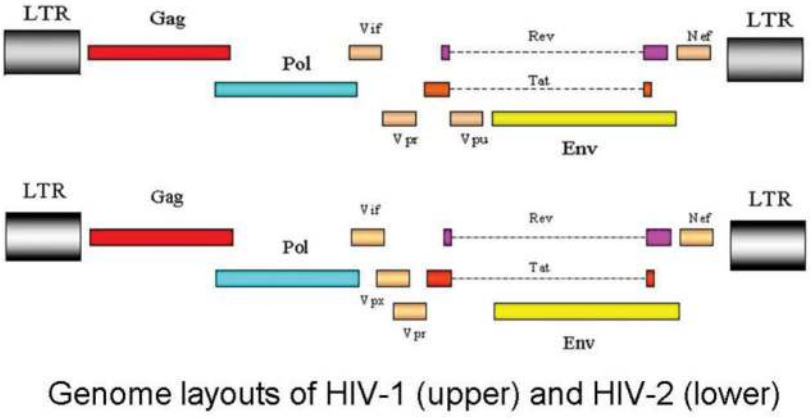

Figure 2. Genomic organisation of HIV-1 and HIV-2 [2].

The reverse transcriptase (RT) allows the viral genome (RNA) to be retro-transcribed into DNA, thus promoting integration into the chromosomal DNA of the host cell: at this stage, the HIV is called "provirus." In its proviral form, HIV is flanked on both sides by repetitive sequences, strongly implicated in the transcription and integration of the virus. These sequences are called LTR for long terminal repeat and consist of three non-coding regions (U3, R, and U5), allowing the integration of double-stranded DNA into the chromosomal DNA of the host cell. These regions contain, at the 5 'ends of the LTRs, promoters that control the initiation and regulation of viral genome transcription, under the influence of viral and cellular factors [2].

1.3. Prevalence of HIV in the world

In 2015, the number of HIV-related deaths ranged from 930,000 to 1,300,000 worldwide [3]. According to Global AIDS in 2016, approximately, 37 million people live with HIV and 21 million are under treatment.

The distribution of HIV infection is not equitable in the world, sub-Saharan Africa is the most affected region. In 2015, it alone counted 25,600,000 people living with HIV (PLHIV) or nearly 70% of the world's PLHIV. The overall prevalence in this part of the world is 5.0% (95% CI, 4.7–5.2), with 1,900,000 new infections per year.

1.4. Pathophysiology

Infection caused by HIV is responsible for the progressive destruction of the immune system, primarily by the removal of CD4 T-cells. These are the targets of the virus to ensure its replication. Lymphocyte homeostasis, which allows proliferation of lymphocyte cells, is gradually becoming ineffective. The immune system thus weakened leads to the appearance of so-called

"opportunistic" infections. Eventually, the infected subject dies as a result of this generalized immunosuppression (AIDS stage).

The natural history of HIV infection has been divided into two major phases. The seroconversion stage occurs in the first 6 weeks after infection, a period between the time of infection and the appearance of antibodies. In some patients this phase is accompanied by an influenza state. During this phase, viral replication is intense (every day 1 billion viruses are produced), where viral load levels up to more than 1 million copies per mL of plasma [4], and the patient is very infectious. CD4 T-cell level drops transient but usually returns to baseline.

The chronic phase has two stages.

Asymptomatic phase: This is the clinical latency phase. The immune system continuously destroys the viruses to keep the viral load low (no virological latency). At the same time the CD4 count will gradually decrease. This phase may persist for several years (up to 15 years).

Symptomatic phase: It lasts from a few months to several years. The immune system begins to weaken and no longer effectively controls viral replication. The number of CD4 T lymphocytes then decreases significantly. The lymphoid organs no longer compensate for this destruction. Opportunistic infections make their appearance, defining the AIDS stage.

Much progress has been made in the fight against the HIV pandemic. Antiretroviral treatment (ART) is based on the use of three molecules (triple therapy) interacting with HIV on its different targets. ART aims to achieve and maintain undetectable plasma viral load. It must restore immunity, measurable by measuring the level of CD4. Finally, it significantly reduces the risk of transmission in patients controlling viral replication [5].

TAR blocks viral multiplication by acting on the replicative cycle stages of HIV by interference. Currently there are six classes of antiretrovirals for five targets located in the replicative cycle:

- Three enzymatic targets: nucleos(t)idic and non-nucleos(t)idic reverse transcriptase inhibitors (NRTIs and NNRTIs), protease inhibitors (PIs), and integrase inhibitors (IINs);
- One protein target: fusion inhibitor (IF); and
- One cell target: antagonist of the CCR5 co-receptor.

Nucleoside inhibitors of reverse transcriptase (NIRT)

Abacavir (ABC)

Stavudine (D4T)

Ténofovir (TDF)

Lamivudine (3TC)

Didanosine (DDI)

Zidovudine (AZT)

Emtricitabine (FTC)

Non-nucleosidic inhibitors of reverse transcriptase (NNIRT)

Efavirenz(EFV)

Etravirine (ETR)

Névirapine (NVP)

Rilpivirine (RPV)

Protease inhibitor (PI)

Atazanavir/r (ATV/r)

Darunavir/r (DRV/r)

Fosamprenavir/r (FPV/r)

Indinavir/r (IDV/r)

Lopinavir/r (LPV/r)

Nelfinavir (NFV)

Saquinavir/r (SQV/r)

Tipranavir/r (TPV/r)

Integrase inhibitors

Dolutégravir (DTG)

Elvitégravir (EVG)

Raltégravir (RAL)

Fusion inhibitor

Enfuvirtide (ENF ou T20)

CCR5 antagonist

Maraviroc (MRC)

The new 2015 WHO guidelines stipulate that anyone infected with HIV should be systematically put on ART, regardless of CD4 T-cell level or viral load.

2. General information on HIV-HBV coinfection

The global epidemics of hepatitis B and HIV have led to a new understanding of the complex interactions between these two viruses. Due to similar patterns of contamination (bloodstream, sexual pathway, and mother-to-child transmission), the high prevalence of HBV infection among the 33 million people living with HIV (PLHIV) across the world is about 10% [6]. In highly endemic areas such as the sub-Saharan Africa, this prevalence can be as high as 15% and leads us systematically to seek HIV/HBV coinfection.

According to the WHO, nearly 240 million people are chronically infected with HBV worldwide. Of these, 4 million are coinfected with HIV. Overall, coinfection rates range from 5 to

14% in areas of low prevalence of HBV infection and 5–73% in areas of high prevalence for HBV infection [7–9].

2.1. Concomitant negative impact of HIV and HBV on their natural histories

2.1.1. HIV impact

Studies have revealed the complexity of the infection relationship between HIV and HBV. This complex relationship is thought to be responsible for greater morbidity and mortality of hepatic origin in co-infected patients than in mono-infected individuals [10, 11].

The natural history of HBV infection has changed in people living with HIV, where the immune system is weakened by the destruction of HIV-infected CD4 T-cells [12]. The risk of developing chronic hepatitis B after contracting HBV is six times more common in HIV-infected people than in non-HIV-infected people [13]. Indeed, immunosuppression caused by HIV is associated with a change in the time of occurrence of each event in the natural history of HBV infection. The evolution of acute HBV infection is altered in PLHIV with serological, biochemical, immunological and molecular consequences:

Focus on the serological markers, the rates of anti-HBs and HBsAg loss and/or seroconversion might be higher in HIV-HBV coinfected patients compared with patients who are HBV monoinfected [14]. So occult hepatitis B infection, reactivation (reverse seroconversion) of chronic HBV infection and fulminate hepatitis, appears mainly in HIV virologic failure [15]. In PLHIV and those chronically infected by HBV, the related rate of hepatitis B e antigen (HBeAg) clearance is five times lower than in HBV-infected individuals alone [13]. Diminution of HBsAg quantity may be responsible for its non-detection by immunochromatographic tests, in cases of patients with HBV active replication.

2.1.2. Fulminant hepatitis B (HBF)

A syndrome produced by the major dysfunction of certain functions of the liver, fulminant hepatitis occurs in less than 1% of cases of acute jaundice hepatitis. It may be due to isolated acute hepatitis B or coinfection with hepatitis delta virus. More rarely, fulminant hepatitis occurs in chronic HBV carriers due to spontaneous or chemo-induced reactivation or superinfection with HDV [16]. It is characterized by a reduction of more than 50% of coagulation factors of hepatic origin. The liver is no longer able to destroy the neurotoxic substances produced; they are found in the bloodstream and migrate to the brain where they cause hepatic encephalopathy. All this is in the absence of an underlying liver pathology [17]. Typically, HBV DNA and HBeAg become undetectable rapidly, while hepatocellular insufficiency occurs. The simultaneous presence of HBsAg and anti-HBs in immune complexes is implicated in the severity of the clinical picture.

2.1.3. Occult hepatitis B (HBO)

The Taormina conference held in Italy in 2008 defined occult hepatitis B (HBO) as "the presence of HBV DNA in the liver, detectable or undetectable in serum, in individuals tested negative for HBsAg by an internationally validated serological test" [18]. It is a chronic infection, therefore

persistent over time with low-noise viral replication: It is described as a silent infection. In fact, in most cases, the HBV CV associated with these infections is very low (<200 IU/mL), but it can vary to reach high levels [19]. Serologically, occult infections known as seronegative are characterized by the absence of anti-HBs and anti-HBc and are distinguished from occult infections called seropositive that are associated with the seroconversion of anti-HBs and/or anti-HBc. Numerous studies have shown that the presence of isolated anti-HBc antibodies is closely correlated with the occult status of HBV infection [18, 20]. However, in 20% of patients with occult infection, no serologic marker of HBV infection is observed [21]. The prevalence of HBOs varies from 1 to 87% [22], depending on the population studied, the sensitivity of the diagnostic tests, and the nature of the sample used [23, 24]. Studies also show that HBO is significantly associated with the endemicity of HBV infection but is not limited to hyper-endemic countries for HBV [23–26]. The actuality of this problem is related to the fact that HBO can be transmitted during blood transfusions, provoke the reactivation of chronic hepatitis B in immunocompromised persons, and facilitate the development of hepatic cirrhosis and hepatocellular carcinoma. In most cases, occult infection goes unnoticed, which poses significant health problems, such as the transmission of the virus through blood transfusions and transplants [27–30].

This type of hepatitis B also has the distinction of being the cause of fulminant hepatitis but also of promoting cirrhosis of the liver, HCC, and treatment failure in the case of coinfection with HCV [31, 32].

Variations in the genome including mutations in the major antigenic loop, mutations in viral polymerase, modifications resulting from alternative splicing, and mutations in the pre-S region have been associated with occult hepatitis B.

Studies have shown that HBV DNA is detected more often in people living with HIV than in non-HIV people [33, 34]. The severity and persistence of immunosuppression play an important role in reactivating HBO.

On the biochemical point of view, interaction between HIV and HBV, it is observed that Alanine aminotransferase (ALT) enzyme levels are often greater than 5 times the upper limit of the normal range (ALT normal range: 1–22 IU/L) [35]. This has consequences on physiopathology, by increasing the risk of liver-related morbidity and mortality compared to HIV monoinfected individuals. However, normal transaminase levels should not be interpreted to mean that there is no underlying hepatic fibrosis.

On the immunological point of view, HIV has been shown to directly infect hepatocytes, hepatic stellate cells (HSC), or Kupffer cells, which are implicated on intrahepatic injury. HIV can also significantly affect the integrity of the gastrointestinal tract leading to elevated levels of LPS. LPS can directly activate Kupffer cells and HSC leading to increased intrahepatic inflammation and fibrosis [36].

On the molecular point of view, in PLHIV, HBV DNA replication may be diminished due to hepatocytes' direct infection by HIV in competition with HBV.

HBV resistance mutations are more common in HIV patients than in non-HIV patients. This is linked to the massive consumption of reverse transcriptase inhibitors (active against both HIV and HBV) with a low genetic barrier, such as 3TC.

HBV reactivation is more prevalent in HIV-HBV co-infected individuals than in HBV mono-infected individuals. This reactivation is particularly found in patients with an isolated anti-HBc profile [37, 38].

HIV accelerates the risk of cirrhosis and HCC. HIV/HBV patients have higher HBV CVs and therefore more frequent cirrhosis compared to HBV-only patients [11, 39, 40].

HBV is not directly cytopathic and the physiopathogenesis of its infection is immunomodulated. Hepatic lesions are recorded due to inflammation and lysis of infected cells that express HBsAg on their surface as a consequence of an immune response of the host.

The evolution of the infection is thus conditioned by the intensity, the efficiency, and the speed of the activation of the immune response. Healing is easily associated with an early and effective immune response. On the other hand, viral persistence is associated with a defective immune response. Cells such as macrophages, neutrophils, NK, and NKT cells provide a nonspecific and early immune response, causing necroinflammatory lesions [41].

The fact that HIV attaches to the surface of hepatocytes using co-receptors CCR5 and CXCR4 and Kupffer cells (hepatic stellate cells, HSC) causes a direct cytopathic effect of HIV on the liver tissue. This results in the triggering of cellular apoptosis by TNF-α (TRAIL: TNF-α-related apoptosis-inducing ligand) [42, 43]. Moreover, by infecting HSCs, HIV increases myofibroblastic differentiation and leads to the acceleration of the fibrosis process [44]. Finally, there is the hepatotoxicity of HIV treatment taken on a continuous basis.

2.1.4. HBV impact

Likewise, HBV infection would have a negative impact on the natural history of HIV infection. Permanent activation of the immune system in patients chronically infected with HBV would result in the increased viral replication of HIV [45]. Other studies have shown that HBV can induce continuous replication of HIV due to the action of HBV gene X expression in synergy with the Kappa B cell enhancer and T cell activators on the cell [46, 47].

HBV has also been indexed in reducing CD4 levels, although the mechanism is not clearly known [9, 48]. In sum, studies indicate that the risk of progression to AIDS and/or dying is 3.6–6.8 times higher in coinfection (HIV-HBV) than in HIV mono-infection [49, 50].

Finally, HBV, by destroying hepatocytes, the regulator of toxins in the body, increases the risk of antiretroviral toxicity [51].

2.2. Implication of concomitant negative impact on the overall management of HIV-HBV coinfection

The goal of HBC treatment is to improve the quality of life and survival of infected people by preventing progression of cirrhosis, complications of chronic hepatitis B infection (HBF, HBO, reactivation…), and the hepatocellular carcinoma (HCC) [52, 53].

Therapeutic management of HBV infection was clearly defined in the WHO guidelines in 2015. It is therefore stipulated that in HIV-HBV co-infected individuals, antiretroviral therapy

(ART) should be introduced. For all those who have evidence of chronic hepatitis, regardless of the stage of hepatitis, specifically, for adults, adolescents, and children 3 years of age and older, the TDF + 3TC/FTC + EFV fixed-dose combination is recommended to begin antiretroviral therapy [54].

It is therefore imperative that the diagnosis be made. In case of resistance to 3TC, the addition of TDF to antiretroviral therapy including 3TC or FTC is the solution of choice [55].

It is true that the current WHO recommendations are "test and treat". However, as these measures are not yet universally adopted, the previous recommendations of the WHO and the European AIDS Clinical Society (EACS) will be proposed here for the global management of HIV-HBV coinfection.

These recommendations stem from the management of patients who are mono-infected with HBV. They take into account three parameters required to initiate treatment against HBV: (a) the level of serum HBV DNA (>2000 IU/ml), (b) the elevation of ALT to more than two times the normal rate, and (c) liver histological lesions following the METAVIR score (activity expressed as grade ≥A2 and/or fibrosis level expressed as ≥F2) [56].

The therapeutic choice is based on two elements: (i) the indication or not of an antiretroviral treatment and (ii) the possible presence of cirrhosis.

In cases where HIV treatment is not indicated, that is, in patients with CD4 greater than 500 cells/mm^3, dual activity HIV and HBV molecules should not be used to avoid the resistance of HIV against these molecules [56] (**Figure 3**).

Surveillance and treatment include HBV viral load and ALT level. (1) The high rate of DNA is correlated with the risk of progression to cirrhosis and hepatocellular carcinoma, the analyses continue before treatment. (2) METAVIR score ≥A2 and/or APRI score ≥F2. (3) Treatment duration is 48 weeks for Peg IFN and nucleoside or nucleotide analogues may be discontinued 6 months after seroconversion HBs and/or Hbe. (4) The use of telbivudine and adefovir in this situation is difficult because of potential anti-HIV activity [55].

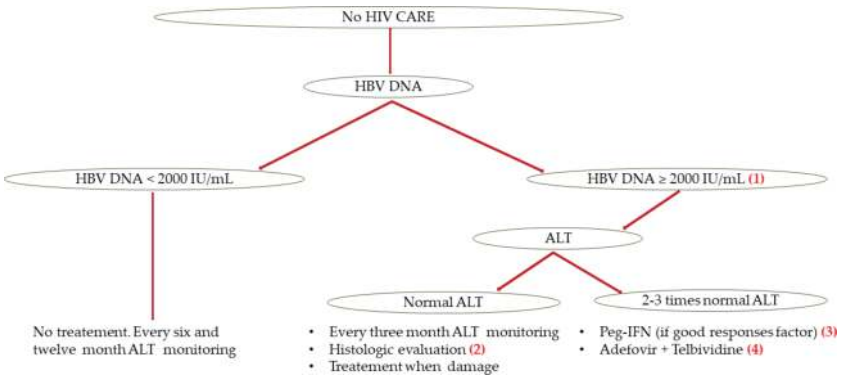

Figure 3. Therapeutic strategy in patients without indication of HIV treatment [56].

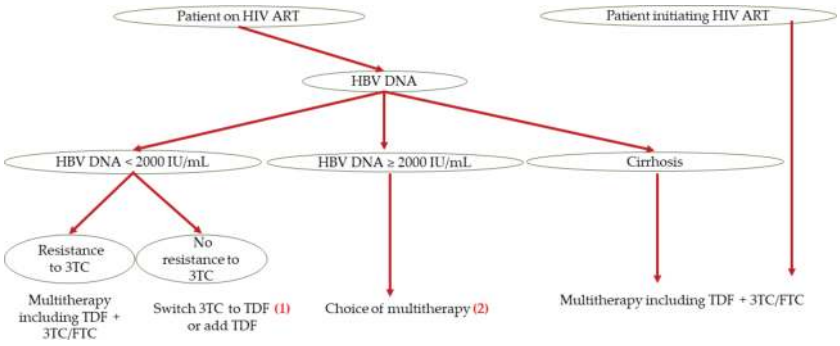

Figure 4. Therapeutic strategy in patients with indication of HIV treatment [56].

In cases where HIV treatment is recommended, the following pattern is adapted (**Figure 4**) [56]. HIV-infected patients should be routinely screened for HBV infection. In highly endemic areas, in patients with elevated transaminase levels, HBV DNA should be sought for the evidence of HBO.

Monitoring and treatment include HBV viral load, presence or absence of cirrhosis, and resistance to 3TC. TDF is the molecule with the highest genetic barrier; therefore, it is strongly recommended in all combinations against HIV-HBV coinfection: (1): if feasible and appropriate for maintaining control of HIV replication and (2): some experts recommend systematically including tenofovir plus emtricitabine/lamivudine if antiretroviral therapy is indicated, even if HBV treatment is not indicated [55].

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