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The impact of human immunodeficiency virus on viral hepatitis

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Abstract

The combination of antiretroviral (ARV) therapies introduced at the end of the 1990s profoundly changed the natural history of human immunodeficiency virus (HIV) infection. Liver diseases are one of the three primary causes of 'non-AIDS-related' death in people living with HIV for three reasons: the high prevalence of hepatotropic viral co-infections, the hepatotoxicity of ARV drugs and new emerging liver diseases, including nodular regenerative hyperplasia and hepatitis E virus infection. The impact of HIV infection on the natural history of hepatitis C virus (HCV) or hepatitis B virus (HBV)/HIV co-infection has markedly changed in the past few decades with the progress made in ARV treatment and the improved definition of therapeutic strategies for HCV or HBV. Initially, HIV had a negative impact on hepatotropic infections. Today, HIV does not appear to significantly modify the natural history of HCV and HBV infection. This is associated with fair immune restoration, viral suppression associated with analogues having dual activity against HBV and HIV and with the increasing efficacy of antiviral treatments against HCV. A significant decline is expected in the morbidity and mortality associated with chronic liver infection in co-infected patients. Nevertheless, today, there are three major issues: (i) improving preventive measures including vaccination and risk reduction; (ii) screening patients infected with HBV or HCV and evaluating the impact of chronic infection on the liver and finally; (iii) early screening of hepatocellular carcinoma whose occurrence is higher and that evolves more rapidly in co-infected than in mono-infected patients.

Hepatitis C virus co-infection

Epidemiology

Approximately 25% of people with human immunodeficiency virus (HIV) infection are co-infected with hepatitis C virus (HCV). In the past, HIV co-infection worsened the natural history of chronic HCV infection, with progression to fibrosis occurring twice as fast and in the presence of cirrhosis, a risk of complications five times higher than in patients infected with HCV mono-infection (1, 2). After 10–15 years of HIV–HCV co-infection, without specific treatment, 25% of co-infected patients will develop cirrhosis (compared with 2–6% of patients with HCV mono-infection). In France, it has been shown that the annual mortality associated with hepatitis B virus (HBV) or HCV infection was substantial (4000–5000 cases) (3). Male gender, older age and especially excessive alcohol consumption and HIV co-infection are associated with increased mortality rates. Despite the harmful impact of HIV on HCV, and even though eradication of HCV modifies the long-term prognosis of these patients, access to HCV treatment in co-infected patients has been limited but this is also improving (4).

Today, this negative impact is debated because of improved control of comorbidities (chronic alcohol intake, metabolic syndrome, poor immune status) and earlier treatment of HCV-infected patients, with increasingly effective therapeutic schedules resulting in earlier and better immune restoration with antiretrovirals (ARV) that are less hepatotoxic compared with first-generation analogues (Fig. 1).

Treatments

Treatment of acute hepatitis C infection

Hepatitis C virus transmission occurs in high-risk groups: drug users and patients with high-risk sexual practices (exposure to blood). HCV is more easily transmitted in patients with sexually transmitted diseases (genital ulcers) and HIV infection. Although the probability of spontaneous clearance of HCV is lower in HIV-co-infected than in HIV-negative individuals (15 vs 30% respectively), a spontaneous cure is possible. Treatment of acute HCV should be begun within 12 weeks after the diagnosis if HCV RNA is still detectable. Present recommendations are to treat patients with HIV–HCV co-infection with 24 weeks of pegylated interferon

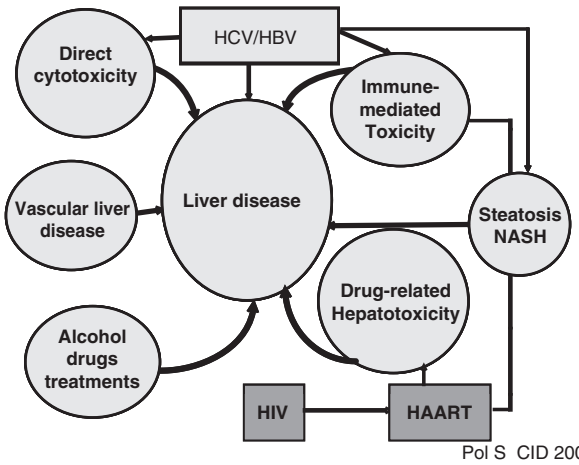

Fig. 1. Causes of liver disease in people living with HIV during the era of HAART. The mechanisms of action are often combined and one disease can mask another. Co-infections with hepatotropic viruses top the list. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

(PEG-IFN) ribavirin (RBV) combination therapy, even if the addition of RBV has not been shown to be beneficial in HIV-negative patients (5).

Treatment of chronic hepatitis C virus infection

Patients with a Metavir score of $F > 1$ according to a liver biopsy (or Fibroscan® [Echosens, Paris, France] if the patient has never been treated) should be treated. If possible, HCV treatment should be begun before ARV treatment. If HCV therapy cannot be begun (or if it is unsuccessful), ARV treatment should be begun (even if CD4 levels are above 350/mm^3) to limit the progression of fibrosis. This is because the delay between the date of HIV infection and the beginning of ARV treatment is a factor associated with the progression of liver fibrosis. To reduce the risk of haematotoxicity (anaemia and neutropenia for zidovudine), mitochondrial toxicity (didanosine, stavudine) or even an interaction with the absorption of RBV (abacavir, for example), ARV treatment should be adjusted before beginning anti-HCV combination therapy (6). Patients with decompensated cirrhosis should be considered as candidates for transplantation before antiviral treatment is begun because of the risk of sudden worsening of liver disease during treatment. The sustained virological response (SVR) with the association of PEG-IFN and RBV was at most 44% in pivotal trials. The predictive factors for achieving SVR are genotypes 2 and 3, a low HCV viral load ($< 350\,000$ UI/ml), transaminases levels > 3 times the upper limit of normal and the lack of treatment with HIV protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

Early viral kinetics are an essential tool for monitoring treatment efficacy. If patients respond to treatment, this provides supportive information, and in the case of a non-response, it is possible to discontinue unnecessary treatment. Undetectable serum HCV RNA at week 4 of treatment [rapid virological response (RVR)] is the best predictive marker of a SVR (positive predictive value 97%). Failure to obtain an HCV RNA load reduction of > 2 log UI/ml after 12 weeks of IFN is predictive of a lack of SVR in $> 99\%$ of cases. The positive predictive value of a complete virological response at week 12 (HCV RNA negativity) is only 60%. If HCV RNA remains > 350 UI/ml at week 12, SVR cannot be expected. In practice, a patient with positive HCV RNA at week 4 and week 12 will not be cured after 48 weeks of treatment and treatment should be discontinued (7).

The disappointing results of the four pivotal trials of HCV treatment in HIV-co-infected patients were probably because of insufficient doses of RBV and frequent treatment discontinuation. Currently, the tendency is to administer 'high doses' of RBV (nearly 15 mg/kg/day) associated with haematopoietic growth factors, and adapt the duration to early viral kinetics as in HCV mono-infection from 24 weeks (RVR and positive predictive factors such as a low baseline HCV viral load) to 72 weeks (slow virological response) even if the current duration of therapy is 48 weeks. Because of the results of phase II and III studies of HCV protease inhibitors in patients with HCV mono-infection, there are high hopes for these agents in co-infected patients: the first trials began gradually because of expected reactions between HCV protease inhibitors, cytochrome P450 and ARV.

The benefits of treatment

Sustained virological response after HCV therapy corresponds to eradication of the HCV virus. The consequential reduction in liver necro-inflammation results in stabilization and then in an improvement in liver fibrosis and in the absence of co-morbidities (8). As in patients with mono-infection, the long-term prognosis changes in patients with SVR, especially those with F3–F4 liver fibrosis. Nevertheless, these patients are still at risk of complications, in particular the development of hepatocellular carcinoma; hence, the real aim of treatment could be improvement of fibrosis/cirrhosis defined as a two-unit improvement in the Metavir activity score on post-treatment biopsy (9).

The impact of steatosis

Steatosis is frequent ($> 80\%$) in HIV-infected patients and increases the risk of the progression of fibrosis. The role of insulin resistance (IR), observed in one out of three co-infected patients, is more controversial. As in patients with HCV mono-infection, IR seems to be predictive of a poor response to PEG-IFN bitherapy (10) but this is still under debate. Improved sensitivity to insulin with molecules such as metformine or

glitazones is an interesting line of research, even if results in patients with mono-infection are disappointing for the moment.

Hepatitis B virus co-infection

Epidemiology

The prevalence of HBV–HIV co-infection is high: serological markers of HBV show that signs of past or present infection (HBsAg, antibody to HBc) are found in one out of three HIV patients, and chronic HBV infection, confirmed by the presence of HBsAg or HBV DNA, is found in 7% of these patients (11).

Two-thirds of patients are infected with 'wild-type' HBV co-infection that is expressing HBeAg. Approximately 6% of HIV–HBV co-infected patients have a delta co- or super-infection. The increase in sexually transmitted diseases and acute hepatitis A, B, D and C in patients with HIV infection emphasizes the risk of HBV infection in this population: this suggests that systematic and regular screening of HBV infection is indispensable in people living with HIV, with regular monitoring of antibodies to HBs and an active preventive vaccination campaign in this high-risk population against HAV and HBV.

Human immunodeficiency virus changes the natural history of chronic hepatitis B virus infection

Progression to chronic infection is more frequent in patients with HIV and acute HBV infection than in those without HIV: 20 vs 5% and probably more if the CD4 count is low. HIV infection worsens the course of chronic HBV, resulting in faster progression of fibrosis, faster development of cirrhosis and hepatocellular carcinoma, a lower rate of spontaneous HBe or HBs seroconversion and a greater risk of HBV reactivation in inactive carriers. On the other hand, HBV does not influence the natural history of HIV.

Early ARV tritherapies that restored normal immune function initially resulted in the worsening of liver lesions (immune restoration) in the absence of control of HBV replication. As ARV that are active in both HIV and HBV are used more extensively, the natural history of liver disease is expected to change once again with a reduced incidence of cirrhosis and stabilization or even an improvement in severe HBV-related liver disease (12).

Treatment of hepatitis B virus in the presence of human immunodeficiency virus co-infection

Interferon-α

With the arrival of nucleoside and nucleotide analogues, the role of IFN-α in the treatment of chronic HBV–HIV co-infected patients has considerably diminished and almost disappeared.

Nucleot(s)ide analogues

Five nucleot(s)ide analogues have been approved to treat chronic HBV infection: lamivudine, adefovir, entecavir, telbivudine and tenofovir. Most of these molecules are also effective against HIV but if they are prescribed as mono-therapy, which is not recommended, they will select HIV-resistant mutants. Lamivudine, emtricitabine and tenofovir have received approval for the treatment of HIV and HBV. Emtricitabine is of interest because it has been commercialized in association with tenofovir in the form of a single pill. Adefovir dipivoxil (nucleotide analogue) has the disadvantage of being less potent than tenofovir, with the emergence of resistant mutants (30% at 5 years). Entecavir (nucleoside analogue) is more potent than lamivudine and adefovir and has a better resistance profile than the latter molecules in patients who have never been treated by lamivudine (1.2% at 6 years). However, entecavir-resistant mutants develop faster in patients with lamivudine resistance (one out of two patients at 5 years). Like the other analogues, entecavir should always be prescribed in combination therapy to prevent the selection of HIV-resistant mutants. Tenofovir disoproxil fumarate (nucleotide analogue) is the molecule of choice in these cases. It is more potent than lamivudine and adefovir. It is effective against lamivudine- and some adefovir-resistant viruses as well as in cases with an incomplete response to adefovir. No clinical resistance has been identified with tenofovir to date. Tenofovir is used in HBV in combination with lamivudine or emitricabine. This is associated with a third molecule that is active against HIV. Like adefovir, tenofovir may rarely cause renal toxicity, usually proximal tubular dysfunction, which can result in altered phosphorus reabsorption, diabetes and secondary osteopenia.

The aims of treatment

The aim of treatment is to improve survival in patients by reducing the progression to cirrhosis, hepatocellular insufficiency, hepatocellular carcinoma and death without negatively affecting HIV infection. This goal can only be reached with durable suppression of HBV (and HIV). This involves life-long treatment because of persistent prereplicative HBV in the nucleus of infected hepatocytes.

How to treat

Patients without an indication for antiretroviral treatment

Regular monitoring of ALT (during immunovirological monitoring of HIV) and monitoring of HBV DNA twice a year should be proposed in patients with HBV DNA below 2000 UI/ml, normal transaminases and liver fibrosis $\leq$ F2 on the Metavir score (Fig. 2).

If HBV DNA viral replication occurs (HBV DNA >2000 UI/ml), histological evaluation should be

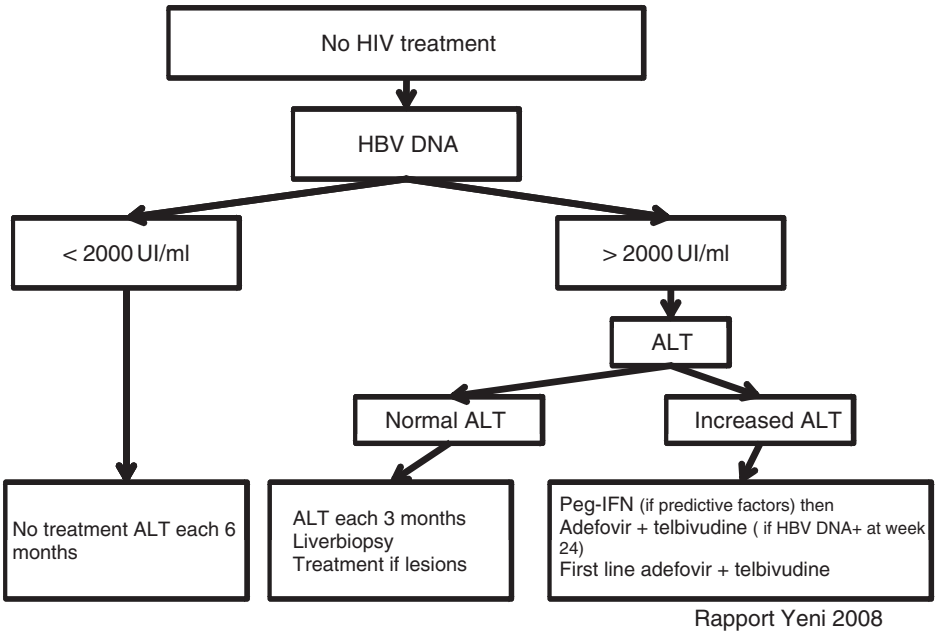

Fig. 2. Algorithm for HBV–HIV co-infection. All indications for treatment include active tritherapy for both viruses. HBV, hepatitis B virus; HIV, human immunodeficiency virus.

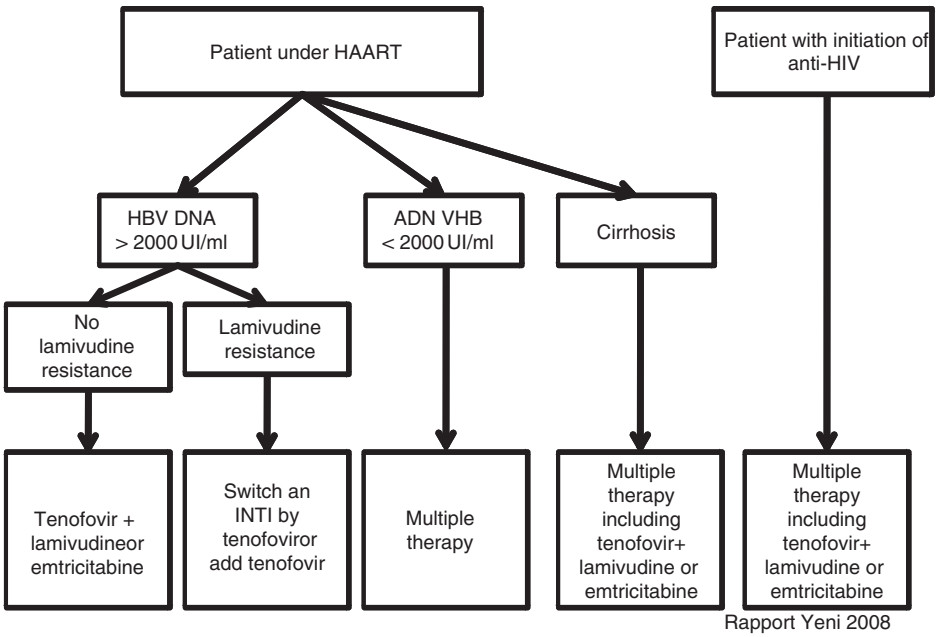

Fig. 3. Proposed algorithm for the management of HIV–HBV co-infected patients.

considered to begin treatment in the case of activity $A > 1$ and/or fibrosis $F > 1$ on the Metavir score (Fig. 3) (11). In this case, IFN (for HBeAg+ virus) or adefovir (for HBeAg− virus) could be considered. However, in practice, tenofovir is always the treatment of choice and thus a regimen of tenofovir, emtricitabine and a third ARV should be proposed to prevent the selection of HIV-resistant mutants.

Patients receiving antiretrovirals or who are supposed to begin antiretroviral treatment

Combination therapy with two molecules active against HBV (tenofovir+lamivudine or emtricitabine) is recommended in HBsAg patients who are supposed to begin ARV treatment, whatever the rate of HBV replication. However, the severity of liver disease should also be

evaluated to obtain a prognosis and determine how liver disease should be monitored. If ARV treatment must be changed, a regimen that is active against HBV must absolutely be maintained.

In conclusion, despite the initial differences in prognosis because of the harmful impact of HIV on the natural history of HCV and HBV, care of patients in 2010 is similar for co-infected and mono-infected patients. Progress in achieving more potent and safer immune restoration, on the one hand, and effective HCV or HBV viral suppression, on the other, has dramatically modified patient prognosis. Screening, evaluation of hepatotropic infection on the liver, treatment and virological follow-up including early viral kinetics to adjust the dose and duration of treatment are now similar, resulting in a better prognosis for co-infected as well as mono-infected patients who will soon benefit from new anti-HCV antivirals. HIV does not appear to significantly modify the natural history or the treatment of hepatotropic infections; nevertheless, three issues are now priorities: (i) improvement of preventive measures including vaccination and risk reduction; (ii) screening patients infected with HBV or HCV and evaluating the impact of chronic infection on the liver and finally; and (iii) early screening of hepatocellular carcinoma, which occurs more frequently and evolves more rapidly in co-infected than in mono-infected patients.

Conflicts of interest

Anaïs Vallet-Pichard has declared no potential conflicts.

Vincent Mallet is a speaker for Gilead, Merck, Schering Plough. Stanislas Pol is a Board Member of BMS, Boehringer Ingelheim, Tibotec, Janssen Cilag, Gilead, Roche, Merck, Schering-Plough, Abbott; a speaker for GSK; BMS, Boehringer Ingelheim, Tibotec, Janssen Cilag, Gilead, Roche, Schering-Plough; and receives grants from BMS, Gilead, Roche, Merck, Schering-Plough.

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