

The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viral interactions and management

Dimitris Konstantinou, Melanie Deutsch

Athens University Medical School, Hippokration General Hospital of Athens, Greece

Abstract

Monoinfection with either hepatitis B (HBV) or C virus (HCV) represents one of the major causes of chronic liver disease globally. However, in endemic areas a substantial number of patients are infected with both viruses mainly as a result of the common routes of transmission. Numerous studies have demonstrated that dually infected patients carry a greater risk of advanced liver disease, cirrhosis and hepatocellular carcinoma compared with monoinfected patients. The choice of treatment is based on the virological profile of each patient taking into account the dominant virus pattern. In predominant HCV, standard combination treatment with pegylated interferon and ribavirin has proven equally effective in HBV/HCV-coinfected patients as well as in HCV-monoinfected patients. Strikingly, approximately 60% of patients with inactive HBV infection before HCV treatment may present HBV reactivation while others experience hepatitis B surface antigen seroconversion after clearing HCV, demonstrating the complexity of the interaction between the two viruses during the follow up. The therapeutic strategies for the predominant HBV dually infected patients are more vague, although high genetic barrier nucleos(t)ide analogues play an indisputable role. Finally, the recently approved combination treatments for chronic hepatitis C containing direct-acting antivirals may definitely change the treatment protocols in the future although there is no experience with these drugs in dually infected patients until today.

Keywords Hepatitis B virus, hepatitis C virus, occult hepatitis B virus, pegylated interferon, ribavirin

Ann Gastroenterol 2015; 28 (2): 221-228

Introduction

Chronic hepatitis B (HBV) and C virus (HCV) infections represent significant public health issues globally. An estimated 400 million persons are carriers of HBV in worldwide, 75% of whom reside in Asia and the Western Pacific. Likewise, HCV infection is estimated at approximately 170 million people globally [1-3], and a marked geographic variation exists, with infection rates ranging from 1.3-1.6% in the USA to 15% in Egypt [4]. Because of the shared modes of transmission, HBV/HCV coinfection is not uncommon in highly endemic areas and among subjects with a high risk of parenteral transmission. Patients with dual HBV/HCV infection have

a higher risk of progression to cirrhosis and decompensated liver disease [5,6], and have an increased risk of hepatocellular cancer (HCC) [7,8]. Coinfected patients represent a diverse group with various patterns of viral replication and great variations of immune profiles. The aim of this review article is to summarize the risk factors and epidemiology of HBV/HCV coinfection, to describe its clinical features and impact on liver disease pointing out the therapeutic options for this special category of patients.

Epidemiology

Due to lack of large-scale population-based studies the exact number of HBV/HCV coinfecting patients is unknown. Moreover, the true number of patients with HBV/HCV coinfection is further underestimated due to the unknown prevalence of occult HBV infection (negative hepatitis B surface antigen [HBsAg] but detectable serum HBV DNA) in patients with chronic HCV infection. The reported prevalence of HBV/HCV infection in different studies reveals wide differences depending on the geographical region, the study population, the method of the patients' selection criteria and the study design.

2nd Department of Internal Medicine, Athens University Medical School, Hippokration General Hospital of Athens, Greece

Conflict of Interest: None

Correspondence to: Dimitris Konstantinou, 2nd Department of Internal Medicine, Athens University Medical School, "Hippokration" General Hospital of Athens, 114 Vas. Sophias Ave., 115 27 Athens, Greece, Tel.: +30 210 7774742, Fax: +30 210 7706871, e-mail: dkonstantinou@gmail.com

Received 1 September 2014; accepted 22 October 2014

In this context, for example, two studies, one from India [9] and one from Egypt [10], report contradictory results with a prevalence of dual infection of 16% and 0.7% respectively. Another study from Turkey recruited 51 cases with dual infection of 1950 tested patients (2.6%) [11]. Other data from Spain [12], Italy [13,14], Japan [15,16], Taiwan [17], and Iran [18] have demonstrated that approximately 10-15% of patients with chronic HBV infection are also infected with HCV. On the other hand, about 2-10% of anti-HCV-positive patients are HBsAg positive. HBV/HCV coinfection is more frequently found in several high-risk populations, i.e., persons who inject drugs, patients on hemodialysis, patients undergoing organ transplantation, HIV-positive and β -thalassemia patients [19-23].

In a large multicenter Italian study [24], the prevalence and risk factors for dual HBV/HCV coinfection have been assessed. Anti-HCV was present in 7% of chronic HBV carriers and about 40% of these patients also had detectable HCV RNA. In this study, independent predictors of dual infection were: age >42 years, history of IV drug use, blood transfusion, and residence in the South of the country. In another prospective American study the prevalence of HBV coinfection in a total of 1257 patients with chronic HCV infection was 5.8% [2]. Age <40 years, Asian race, injection drug use, and a greater number of lifetime sexual partners were independent risk factors for dual infection. Likewise, Tyson *et al* [25] estimated the prevalence and the predictors of HBV coinfection in a US cohort of HCV-infected patients. The prevalence of HBV coinfection compared with HCV mono-infection were age \leq 50 years, male sex, positive HIV status, history of hemophilia, sickle cell anemia or thalassemia, history of blood transfusion, cocaine and other drug use while there was decreased risk in patients of Hispanic ethnicity.

Viral interactions

The virological and molecular aspects of HBV/HCV coinfection are poorly comprehended. Although liver disease activity and progression are generally more severe in the presence of double infection, an inverse relationship in the replicative levels of the two viruses exists, suggesting direct or indirect (i.e., mediated by host immune responses) viral interference [26,27]. Patients with chronic HBV who developed acute HCV infection presented a suppression of the HBV replication [28]. Likewise, inhibition of HCV replication has been noted in patients with chronic HCV superinfected with HBV infection [29]. Finally, HBV reactivation was observed in some coinfecting patients after successful clearance of HCV with pegylated interferon- α (peg-IFN- α) and ribavirin (RBV) [30]. An interesting example is described in the study of Hamzaoui *et al* [31]. A dually infected patient received initially treatment with (peg-IFN- α) and RBV for the dominant HCV component resulting in HCV early virological response but an increase in HBV DNA, requiring the use of a nucleoside analogue. This was followed by a good response

regarding HBV but a relapse of HCV, posing a therapeutic dilemma for the continuation of the treatment. Two recent publications by Eyre *et al* [32] and Bellecave *et al* [33] analyzed this subject. The Huh-7 human HCC cell line can support HBV replication and HBV virion formation together with the HCV life cycle. By applying this cell culture system, these authors independently concluded that HBV and HCV could replicate *in vitro* in the same hepatocyte without evidence of interference. Therefore, the viral interference observed in coinfecting patients is probably due to indirect mechanisms mediated by innate and/or adaptive host immune responses. Moreover, the HCV core inhibited HBV replication and HBsAg expression in the mouse models of acute and chronic HBV infections [34]. In the clinical setting, studies have also revealed that HCV can suppress HBV replication and this effect is mediated by the HCV core protein. One study found that the inhibitory effect of HCV was genotype-dependent being more evident in the case of genotype 1 [35]. Finally, an Italian study [36], demonstrated that HBV/HCV coinfection is not a stable condition, but may present dynamic and possibly evolving profiles. The study enrolled 133 untreated HBV/HCV-positive patients, longitudinally followed up for 1 year with evaluation HBV/HCV viremia levels and liver biochemistry. Approximately one third of the patients presented alternating phases of inhibition and recurrence of the activity of one or both the viruses. Furthermore, patients with chronic HBV infection superinfected with HCV can undergo seroconversion of HBeAg and HBsAg [37-39]. Sheen *et al* [40] estimated an annual rate of HBsAg seroconversion of 2.08% in HBV/HCV coinfection patients compared to 0.43% in patients with HBV mono-infection. The reverse is also true: there is an inhibitory effect of HCV on HBV [41,42]. Zarski *et al* [42] showed that HCV RNA levels were significantly decreased in HBV/HCV co-infected patients with positive serum HBV DNA as compared to HBV DNA-negative cases. One study showed that co-infected patients had a higher rate of HCV RNA clearance compared to those with HCV mono-infection (71% vs. 14%) [43].

In summary, patients with combined HBV and HCV infection show a large spectrum of virological profiles. Although, most HBV/HCV coinfecting patients appear to have active HCV and inactive HBV replication, some patients experience high HBV DNA levels and undetectable HCV RNA, while others present alternating phases of dominance of one virus over the other [44].

Clinical features of HBV/HCV coinfection

Acute coinfection of HBV/HCV is rare but more prevalent in IV drug abusers [45-47]. In acute infection with HBV and HCV, patients showed delayed HBsAg appearance and a shorter HBs antigenemia compared to those with acute HBV alone [48]. A study from Italy [26] included 30 patients presenting with acute hepatitis and markers of active HBV/HCV coinfection. The chronicity rates were comparable to patients with mono-infection with either of the viruses, although a biphasic alanine aminotransferase elevation was

observed in some patients. The latter phenomenon was also evident in a patient with acute coinfection and a subsequent spontaneous clearance of both viruses [49]. In the context of acute coinfection, spontaneous clearance of either or both viruses has been documented in the literature [26,49-51].

HCV superinfection is frequent in endemic areas of HBV infection, such as Asia, South America and sub-Saharan Africa [52]. Several reports have documented that *de novo* HCV superinfection in the setting of chronic HBV infection can result in HBeAg seroconversion and, in some cases, clearance of HBsAg. Fulminant hepatic failure was significantly higher among patients with underlying HBV infection than those without (23% vs. 3%) [53]. In a more recent study [29] during a follow-up period of 1-21 years, patients with HCV superinfection had a significantly higher cumulative incidence of cirrhosis and HCC than acute hepatitis Delta superinfection or active chronic HBV infection.

HBV superinfection was less frequently reported than HCV superinfection. In one report a patient became seronegative for HCV RNA after HBV superinfection [54]. Sagnelli *et al* [30] have shown that HBV superinfection may be associated with acute deterioration of liver function among patients with chronic HCV infection, and the risk of fulminant hepatitis may be increased.

Finally, a more recent study by the same authors [6] examined the impact of HBV superinfection in chronic HCV infection during a long-term follow up of 29 chronic anti-HCV-positive patients with acute hepatitis B and 29 anti-HCV-negative patients with acute hepatitis B. Acute hepatitis B had a more severe course in the first group of patients in comparison with the second (34.5% vs. 6.9%, $P < 0.05$), nevertheless, some patients experienced HCV RNA clearance.

Occult hepatitis B (OHB) is defined as the presence of HBV DNA, in serum and/or the liver tissue without detectable HBsAg with or without anti-HBc or anti-HBs outside the pre-seroconversion window period [55]. Occult HBV infection has been identified in up to 50% of patients with chronic HCV infection [56]. Moreover, Georgiadou *et al* [57] investigated 540 subjects for the presence of occult HBV in Greek HCV patients, in patients with nonviral liver diseases, and in healthy donors. The authors showed that HBV DNA was detected in 26.2% of HCV-infected patients in the absence of HBsAg, while in the non-HCV group the ratio was significantly lower. Considerable data suggest that occult HBV coinfection with HCV may contribute to chronic liver damage and the development of HCC. Cacciola *et al* [58] studied the prevalence and clinical significance of occult HBV infection in patients with chronic HCV infection. The result showed that 21 of the 66 patients with HCV infection and OHB (33%) had cirrhosis compared to 26 of the 134 patients with HCV infection and no OHB (19.8%, $P = 0.04$). This finding suggests that OHB in patients with chronic HCV infection present a greater danger of evolution to cirrhosis and progressive liver disease. In contrast, a more recent study found that occult HBV infection occurred in almost half of the patients with HCV examined, but was not of clinical significance [59]. Finally, while several studies have implicated occult HBV infection in a kind of "resistance" to treatment with IFN in patients with chronic

HCV infection [60,61], others have reported contradictory results concluding that virological responses to combined peg-IFN and RBV therapy are similar in chronic HCV patients with and without occult HBV infection [62].

HBV/HCV coinfection and cirrhosis

Compared with HBV monoinfected patients, higher rates of cirrhosis (44% vs. 21%) and decompensated liver disease (24% vs. 6%) are reported in coinfecting patients [63]. Likewise, compared to HCV-monoinfected patients, a higher rate of cirrhosis (95% vs. 49%) and more decompensated liver disease (Child-Pugh class C 37% vs. 0%) were also demonstrated in HBV/HCV-coinfecting patients [64]. There are, however, studies that do not support these conclusions [65,66]. Recently, in a cohort of Egyptians dually infected, patients had no difference regarding the histologic score in comparison to monoinfected patients [10]. These discrepancies can be explained by biases in the design of the studies (small sample size, retrospective design) and technical reasons (sensitivity of anti-HCV assays). On the other hand, the fact that the dual infection of HBV and HCV ends up in the dominance of either virus and the suppression of the other could partially explain the similarity in histologic findings between dually infected and monoinfected patients [67].

Impact of HBV/HCV coinfection on development of HCC

Epidemiologic studies in patients with dual HBV/HCV infection have documented an increased risk of HCC confirmed by three meta-analyses [7,8,67]. Given the role of the chronic necroinflammation and especially cirrhosis in the pathogenesis of HCC together with the higher incidence of cirrhosis and a greater degree of hepatic damage in dual infection, a synergistic carcinogenic interaction between the two viruses is most probable. The different mechanisms that have been hypothesized as being associated with the development of HBV- or HCV-related HCC suggest that both viruses could play an active role at different steps of the carcinogenic process when they are present together in hepatocytes. Most evidence suggests that HBV is capable of initiating the neoplastic process, while HCV could act as a promoter, and that they may be synergistic in causing HCC [7].

A prospective analysis evaluated the role of HBV/HCV dual infection in 290 cirrhotic patients regarding the risk of HCC [68]. The authors concluded by both univariate and multivariate analyses that, apart from male sex and previous alcohol abuse, dual infection with HBV and HCV is the greatest predictor for developing HCC in cirrhotics. In a longitudinal study [69], the incidence of HCC was 6.4 per 100 person years in HCV/HBV-coinfecting patients compared to 2.0 in HBV and 3.7 in HCV mono-infection. In the same study, the cumulative risk of developing HCC after 10 years was 45% in HBV/HCV-coinfecting patients compared to 16% in HBV- and 28% in HCV-monoinfected patients. Finally, Liu *et al* conducted a

retrospective cohort study which principally examined the impact of treatment in dually infected HBV/HCV patients in respect of diminishing the risk of HCC. They reached the conclusion that combination therapy with peg-IFN+RBV significantly reduced the risk of HCC and improved overall survival [70].

Treatment issues

In patients with dual chronic HCV and HBV infections, the disease outcomes, including the development of liver cirrhosis and HCC, are generally more severe than those in patients with mono-infection [71-73]. In addition, it has been confirmed that the incidence of HCC in co-infected patients is higher than in mono-infected patients [74]. As previously mentioned [70], Liu *et al* proceeded in a comparison of HCC risk, liver-related mortality and all-cause mortality between treated and untreated HBV/HCV-coinfected patients; the authors assessed the same outcomes in treated HBV/HCV-coinfected patients and treated HCV-mono-infected patients. They demonstrated that peg-IFN/RBV therapy is not only safe and effective, but translates into important clinical benefits such as reduction in liver-related complications and improved patient survival. Therefore, patients dually infected with HCV and HBV require effective treatments.

HBV/HCV-coinfected patients are very heterogeneous both in terms of infection modality with most patients from Asia acquiring HBV infection at birth and later having HCV superinfection, whereas patients from Europe and the USA either acquire both infections concomitantly or present a superinfection of HBV on chronic HCV infection [75]. In terms of viral dominance, it is not often to have a co-dominance of both viruses. There is either HBV dominance, which means high HBV DNA levels and low HCV RNA levels or HCV dominance defined by the high HCV RNA levels and absent HBV DNA. The first pattern is more common in Asian patients and shows a disease progression similar to that of HBV mono-infection, while the second pattern is typical of North American and European patients and is met in HCV-mono-infected patients.

The first step in the treatment of HBV/HCV-coinfected patients is to determine which is the dominant virus that should be eradicated. Careful longitudinal follow up of serum HBV DNA and HCV RNA levels is essential before the diagnosis of the viral dominance [36]. These viral interactions will very likely influence the therapeutic strategies in dually infected patients.

Treatment of HCV in dual HCV/HBV patients with active HCV infection

Villa *et al* [76] reported that 9 million IU of standard IFN 3 times weekly for 3 months could clear HCV in 31% of patients with HCV/HBV coinfection. Liu *et al* [77] used standard IFN and RBV and discovered that sustained HCV eradication (sustained virological response, SVR) was achieved

at rates comparable to those in patients with HCV alone while, interestingly, up to 21% of their patients lost HBsAg.

In 2008 Potthoff *et al* [30] published a small prospective multicenter pilot study that evaluated the efficacy of weight-adjusted peg-IFN- α -2 β and RBV for 48 weeks in 19 patients with chronic HBV/HCV coinfection (all were HBsAg/HCV RNA-positive and 6 were HBV DNA-positive and 13 negative). A fraction of 15 patients fulfilled treatment schedule with an SVR rate of 93% (86% in genotype 1 and 100% in genotypes 2 or 3).

Liu *et al* [78] subsequently conducted a multicenter study using peg-IFN and RBV in HCV/HBV-coinfected patients. This regimen proved equally effective in patients with HCV mono-infection and in those with chronic HCV/HBV infection. This study represents the largest prospective, randomized, controlled trial using peg-IFN and RBV therapy in HBV/HCV coinfection, and reports a high SVR rate (72% and 83% in genotypes 1 and 2/3 respectively). The same authors investigated the durability of HCV clearance in HCV-mono-infected and HCV/HBV dually infected patients by conducting a 5-year prospective follow-up study [79]. The findings revealed that after a median follow up of 4.6 \pm 1.0 years, HCV reappearance developed only in 6 (2.6%) of the 232 patients who achieved SVR. This suggests that the durability of the SVR obtained by using peg-IFN and RBV therapy was satisfactory and not influenced by HBV coinfections.

As peg-IFN is one of the first-line choices for the treatment of chronic HBV infection [80], it is reasonable to conclude that peg-IFN-based therapy in dually infected patients will also act on the HBV. Indeed, the 2 previous studies remarkably found that HBsAg disappeared 6 months after the end of therapy in 18 (11.2%) of the 161 dually infected patients with a rate of HBsAg seroclearance of 5.4% per year. Baseline low pretreatment serum HBsAg level correlated significantly with HBsAg seroclearance. In another study [81], the rs9277535 polymorphism for HLA-DPB1 region was recognized as a host genetic factor associated with spontaneous HBsAg seroclearance.

The reactivation of HBV activity is another clinical entity in dually infected patients receiving anti-HCV therapy. In a treatment cohort of 76 patients with pretreatment serum HBV DNA <200 IU/mL, reappearance of HBV DNA was found in 47 (61.8%) patients [79]. These patients should be put under surveillance and treatment should be initiated if clinically indicated.

At present, no data have been published regarding the efficacy of direct-acting antivirals (DAAs) in combination with peg-IFN plus RBV or with IFN-free regimens in treating patients with chronic HBV/HCV coinfection. Whether the new DAA-based therapies will be effective in HBV/HCV coinfection represents an issue for further studies.

Treatment of HBV in dual HCV/HBV patients with active HBV infection

The data published on the use of anti-HBV drugs for patients with chronic HBV/HCV coinfection are scanty,

Table 1 Pegylated interferon and ribavirin for HBV/HCV coinfection

Patients (n)	HCV SVR (%)	HBV DNA negative (%)	HBsAg loss (%)	HBV reactivation (HBV DNA negative pretreatment) (%)	Reference
19	70*,78**	33	0	31	Potthoff 2008 [30]
161		56	11	35	Liu 2009 [78]
17	6	N/A	N/A	N/A	Senturk 2008 [84]
50	40*,75**	100	0	24	Yu 2009 [85]
18	60*,88**	12	N/A	N/A	Kim 2011 [86]

*HCV genotype 1, **HCV genotype 2/3, N/A, not applicable; SVR, sustained virological response; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus

Table 2 Standard interferon with ribavirin for HBV/HCV coinfection

Patients (n)	Serology	HCV RNA/HBV DNA	HCV SVR	HBV response	References
21	Anti-HCV+, HBsAg +	+/+ *N=17(81%)	N=9 (43%)	HBsAg loss (0%) HBeAg loss (N=3, 100%) HBV DNA (N=6, 35%)	Liu <i>et al</i> (2003) [77]
36	Anti-HCV+, HBsAg +	+/+ *N=18 (50%)	N=25 (69%)	HBsAg loss (0%) HBeAg loss (0%) HBV DNA (N=2, 11%)	Hung <i>et al</i> (2005) [87]
42	Anti-HCV+, HBsAg +	+/+ *N=16 (38%)	69%	HBsAg loss (N=5, 12%) HBeAg loss (50%) HBV DNA (N=5, 31%)	Chuang <i>et al</i> (2005) [88]
51	Anti-HCV+, HBsAg +	+/N/A	N=23 (17%)	N/A	Myers <i>et al</i> (2003) [89]
51	Anti-HCV+, HBsAg +	+/+ *N=15 (29%) liver tissue	N=20 (40%)	N/A	Fabris <i>et al</i> (2004) [90]
47	Anti-HCV+, HBsAg +	+/+	N=11 (28%)	N/A	Mrani <i>et al</i> (2007) [91]

*number of HBV DNA-positive patients. HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; N/A, not applicable; SVR, sustained virologic response

Table 3 Serologic and virological profiles in HBV/HCV-coinfected patients with chronic hepatitis

	HBV and HCV active	Occult HBV in chronic active HCV	HCV active in HBsAg carrier
HBsAg	+	-	+
HBV DNA	+	+	-
Anti-HCV	+	+	+
HCV RNA	+	+	+

HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen

most probably because HBV predominates less frequently than HCV. In a small study [82], 8 patients with dually active HBV and HCV were treated with 5 MU IFN and 100 mg/day lamivudine (LAM) for 12 months, followed by LAM alone for 6 more months. The SVR for HCV was 50%. HBeAg clearance was observed in three patients, two of them seroconverted to anti-HBe. HBV DNA became undetectable in 3 patients at the end of treatment, but appeared again later in two patients.

In a recent study, tolerability and efficacy of anti-HBV nucleos(t)ide analogues [LAM plus adefovir (n=10), entecavir

(n=7), telbivudine (n=4), tenofovir disoproxil fumarate (n=3)] was investigated in a cohort of 24 HBV/HCV-coinfected cirrhotic patients [83]. Clearance of HBV DNA was found in 96% of patients after 18 months, while HCV reactivation was low (12.5%). However, while the virological response was favorable in all patients and treatment was well tolerated, progression of liver cirrhosis was seen in as many as 33%. HCV RNA-positive patients at baseline deteriorated more frequently. Thus, a favorable clinical impact in HBV/HCV cirrhotic patients was seen only in HCV RNA-negative patients at baseline.

Concluding remarks

HBV/HCV dual infection is not uncommon in endemic areas and among subjects at risk of parenterally transmissible infections. The first step in initiating treatment is to define which the dominant virus is, by performing serological and virological examinations. For dually infected patients with active HCV infection, the same genotype-dependent treatment recommendations as for HCV mono-infection apply. In these

patients treatment with peg-IFN and RBV has been well studied and proven effective. The introduction of new DAAs has opened new pathways in treating HCV, which need to be evaluated in HBV/HCV-coinfected patients, but currently no data exist for DAA-based therapies. HBV DNA and HCV RNA positivity in chronic hepatitis patients occurs infrequently since a dominant pattern is the usual result of viral interaction. The information on the treatment of this subset is scanty but it seems reasonable that a first-line therapy could be peg-IFN plus RBV with the addition of or a shift to a high potency and high genetic barrier nucleos(t)ide analogue for patients with HBV DNA persistence.

It should be pointed out that a high level of clinical suspicion is required during treatment in order to early diagnose any reactivation of HBV or HCV replication and start an appropriate treatment.

References

- Williams R. Global challenges in liver disease. *Hepatology* 2006;**44**:521-526.
- Bini EJ, Perumalswami PV. Hepatitis B virus infection among American patients with chronic hepatitis C virus infection: prevalence, racial/ethnic differences, and viral interactions. *Hepatology* 2010;**51**:759-766.
- Crockett SD, Keeffe EB. Natural history and treatment of hepatitis B virus and hepatitis C virus coinfection. *Ann Clin Microbiol Antimicrob* 2005;**4**:13.
- Karoney MJ, Siika AM. Hepatitis C virus (HCV) infection in Africa: a review. *Pan Afr Med J* 2013;**14**:44.
- Lee LP, Dai CY, Chuang WL, et al. Comparison of liver histopathology between chronic hepatitis C patients and chronic hepatitis B and C coinfecting patients. *J Gastroenterol Hepatol* 2007;**22**:515-517.
- Sagnelli E, Coppola N, Pisaturo M, et al. HBV superinfection in HCV chronic carriers: a disease that is frequently severe but associated with the eradication of HCV. *Hepatology* 2009;**49**:1090-1097.
- Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer* 1998;**75**:347-354.
- Shi J, Zhu L, Liu S, Xie WF. A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. *Br J Cancer* 2005;**92**:607-612.
- Chakravarti A, Verma V, Jain M, Kar P. Characteristics of dual infection of hepatitis B and C viruses among patients with chronic liver disease: a study from tertiary care hospital. *Trop Gastroenterol* 2005;**26**:183-187.
- Mekky Ma, Nasr AM, Saleh MA, et al. Virologic and histologic characterisation of dual hepatitis B and C co-infection in Egyptian patients. *Arab J Gastroenterol* 2013;**14**:143-147.
- Senturk H, Tahan V, Canbakan B, et al. Clinicopathologic features of dual chronic hepatitis B and C infection: a comparison with single hepatitis B, C and delta infections. *Ann Hepatol* 2008;**7**:52-58.
- Crespo J, Lozano JL, de la CF, et al. Prevalence and significance of hepatitis C viremia in chronic active hepatitis B. *Am J Gastroenterol* 1994;**89**:1147-1151.
- Di Marco V, Lo Iacono O, Camma C, et al. The long term course of chronic hepatitis B. *Hepatology* 1999;**30**:257-264.
- Fattovich G, Tagger A, Brollo L, et al. Hepatitis C virus infection in chronic hepatitis B virus carriers. *J Infect Dis* 1991;**163**:400-402.
- Ohkawa K, Hayashi N, Yuki N, et al. Hepatitis C virus antibody and hepatitis C virus replication in chronic hepatitis B patients. *J Hepatol* 1994;**21**:509-514.
- Sato S, Fujiyama S, Tanaka M, et al. Coinfection of hepatitis C virus in patients with chronic hepatitis B infection. *J Hepatol* 1994;**21**:159-166.
- Dai CY, Yu ML, Chuang WL, et al. Influence of hepatitis C virus on the profiles of patients with chronic hepatitis B virus infection. *J Gastroenterol Hepatol* 2001;**16**:636-640.
- Semnani S, Roshandel G, Abdolahi N, et al. Hepatitis B/C virus co-infection in Iran: a seroepidemiological study. *Turk J Gastroenterol* 2007;**18**:20-21.
- Pallas JR, Farinas-Alvarez C, Prieto D, Delgado-Rodriguez M. Coinfections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. *Eur J Epidemiol* 1999;**15**:699-704.
- Reddy GA, Dakshinamurthy KV, Neelaprasad P, Gangadhar T, Lakshmi V. Prevalence of HBV and HCV dual infection in patients on haemodialysis. *Indian J Med Microbiol* 2005;**23**:41-43.
- Aroldi A, Lampertico P, Montagnino G, et al. Natural history of hepatitis B and C in renal allograft recipients. *Transplantation* 2005;**79**:1132-1136.
- Kalinowska-Nowak A, Bociąga-Jasik M, Garlicki A, Skwara P. Prevalence of hepatotropic viruses HBV and HCV in HIV-infected patients from Southern region of Poland. *Acta Virologica* 2000;**44**:23-28.
- Irshad M, Peter S. Spectrum of viral hepatitis in thalassemic children receiving multiple blood transfusions. *Indian J Gastroenterol* 2002;**21**:183-184.
- Gaeta GB, Stornaiuolo G, Precone DF, et al. Epidemiological and clinical burden of chronic hepatitis B virus/hepatitis C virus infection. A multicenter Italian study. *J Hepatol* 2003;**39**:1036-1041.
- Tyson GL, Kramer JR, Duan Z, Davila JA, Richardson PA, El-Serag HB. Prevalence and predictors of hepatitis B virus coinfection in a United States cohort of hepatitis C virus infected patients. *Hepatology* 2013;**58**:538-545.
- Alberti A, Pontisso P, Chemello L, et al. The interaction between hepatitis B virus and hepatitis C virus in acute and chronic liver disease. *J Hepatol* 1995;**22**:38-41.
- Raimondo G, Saitta C. Treatment of the hepatitis B virus and hepatitis C virus co-infection: still a challenge for the hepatologist. *J Hepatol* 2008;**49**:677-679.
- Liaw YF, Chen YC, Sheen IS, Chien RN, Yeh CT, Chu CM. Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *Gastroenterology* 2004;**126**:1024-1029.
- Sagnelli E, Coppola N, Messina V, et al. HBV superinfection in hepatitis C virus chronic carriers, viral interaction, and clinical course. *Hepatology* 2002;**36**:1285-1291.
- Potthoff A, Wedemeyer H, Boecher WO, et al. The HEP-NET B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol* 2008;**49**:688-694.
- Hamzaoui L, El Bouchtili S, Siai K, Mahmoudi M, Azzouz MM. Hepatitis B virus and hepatitis C virus co-infection: A therapeutic challenge. *Clin Res Hepatol Gastroenterol* 2013;**37**:e16-e20.
- Eyre NS, Phillips RJ, Bowden S, et al. Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells. *J Hepatol* 2009;**51**:446-457.
- Bellecave P, Gouttenoire J, Gajer M, et al. Hepatitis B and C virus coinfection: a novel model system reveals the absence of direct viral interference. *Hepatology* 2009;**50**:46-55.
- Zhu W, Wu C, Deng W, et al. Inhibition of the HCV core protein on the immune response to HBV surface antigen and on HBV gene expression and replication in vivo. *PLoS One* 2012;**7**:e45146.

35. Shih CM, Chen CM, Chen SY, Lee YH. Modulation of the transsuppression activity of hepatitis C virus core protein by phosphorylation. *J Virol* 1995;**69**:1160-1171.
36. Raimondo G, Brunetto MR, Pontisso P, et al; Associazione Italiana Studio Fegato Cooperative Group. Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus coinfecting patients. *Hepatology* 2006;**43**:100-107.
37. Chu CM, Yeh CT, Liaw YF. Low-level viremia and intracellular expression of hepatitis B surface antigen (HBsAg) in HBsAg carriers with concurrent hepatitis C virus infection. *J Clin Microbiol* 1998;**36**:2084-2086.
38. Liaw YF, Tsai SL, Chang JJ, et al. Displacement of hepatitis B virus by hepatitis C virus as the cause of continuing chronic hepatitis. *Gastroenterology* 1994;**106**:1048-1053.
39. Liaw YF, Lin SM, Sheen IS, Chu CM. Acute hepatitis C virus superinfection followed by spontaneous HBeAg seroconversion and HBsAg elimination. *Infection* 1991;**19**:250-251.
40. Sheen IS, Liaw YF, Lin DY, Chu CM. Role of hepatitis C and delta viruses in the termination of chronic hepatitis B surface antigen carrier state: a multivariate analysis in a longitudinal follow-up study. *J Infect Dis* 1994;**170**:358-361.
41. Chen SY, Kao CF, Chen CM, et al. Mechanisms for inhibition of hepatitis B virus gene expression and replication by hepatitis C virus core protein. *J Biol Chem* 2003;**278**:591-607.
42. Zarski JP, Bohn B, Bastie A, et al. Characteristic of patients with dual infection by hepatitis B and C viruses. *J Hepatol* 1998;**28**:27-33.
43. Ohkawa K, Hayashi N, Yuki N, et al. Long-term follow-up of hepatitis B virus and hepatitis C virus replicative levels in chronic hepatitis patients co-infected with both viruses. *J Med Virol* 1995;**46**:258-264.
44. Pontisso P, Gerotto M, Ruvoletto MG, et al. Hepatitis C genotypes in patients with dual hepatitis B and C virus infection. *J Med Virol* 1996;**48**:157-160.
45. Rodriguez M, Navascues CA, Martinez A, et al. Hepatitis C virus infection in patients with acute hepatitis B. *Infection* 1992;**20**:316-319.
46. Liaw YF, Chu CM, Chang-Chien CS, Wui CS. Simultaneous acute infections with hepatitis non-A, non-B, and B viruses. *Dig Dis Sci* 1982;**27**:762-764.
47. Feray C, Gigou M, Samuel D, et al. Hepatitis C virus RNA and hepatitis B virus DNA in serum and liver of patients with fulminant hepatitis. *Gastroenterology* 1993;**104**:549-555.
48. Mimms LT, Mosley JW, Hollinger FB, et al. Effect of concurrent acute infection with hepatitis C virus on acute hepatitis B virus infection. *BMJ* 1993;**307**:1095-1097.
49. Yan BM, Lee SS. Acute coinfection with hepatitis B and hepatitis C viruses. *Can J Gastroenterol* 2005;**19**:729-730.
50. Coppola N, Marrocco C, Di Caprio D, et al. Acute hepatitis B and C virus coinfection: a virological and clinical study of 3 cases. *Clin Infect Dis* 2003;**36**:528-532.
51. Chu CM, Sheen IS, Liaw YF. The role of hepatitis C virus in fulminant viral hepatitis in an area with endemic hepatitis A and B. *Gastroenterology* 1994;**107**:189-195.
52. Liaw YF. Hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *J Gastroenterol* 2002;**37**(Suppl 13):65-68.
53. Wu JC, Chen CL, Hou MC, et al. Multiple viral infection as the most common cause of fulminant and subfulminant viral hepatitis in an area endemic for hepatitis B: application and limitations of the polymerase chain reaction. *Hepatology* 1994;**19**:836-840.
54. Liaw YF, Yeh CT, Tsai SL. Impact of acute hepatitis B virus superinfection on chronic hepatitis C virus infection. *Am J Gastroenterol* 2000;**95**:2978-2980.
55. Brechot C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Brechot P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely "occult"? *Hepatology* 2001;**34**:194-203.
56. Kannangai R, Vivekanandan P, Netski D, et al. Liver enzyme flares and occult hepatitis B in persons with chronic hepatitis C infection. *Clin Virol* 2007;**39**:101-105.
57. Georgiadou SP, Zachou K, Rigopoulou E, et al. Occult hepatitis B virus infection in Greek patients with chronic hepatitis C and in patients with diverse nonviral hepatic diseases. *J Viral Hepat* 2004;**11**:358-365.
58. Cacciola I, Pollicino T, Squadrito G, Cerenzia G, Orlando M, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. *N Engl J Med* 1999;**341**:22-26.
59. Cardoso C, Alves AL, Augusto F, et al. Occult hepatitis B infection in Portuguese patients with chronic hepatitis C liver disease: prevalence and clinical significance. *Eur J Gastroenterol Hepatol* 2013;**25**:142-146.
60. Fukuda R, Ishimura N, Hamamoto S, et al. Co-infection by serologically-silent hepatitis B virus may contribute to poor interferon response in patients with chronic hepatitis by down-regulation of type-I interferon receptor gene expression in the liver. *J Med Virol* 2001;**63**:220-227.
61. De Maria N, Colantoni A, Friedlander L, et al. The impact of previous HBV infection on the course of chronic hepatitis C. *Am J Gastroenterol* 2000;**95**:3529-3536.
62. Chen LW, Chien RN, Yen CL, Chang JJ, Liu CJ, Lin CL. Therapeutic effects of pegylated interferon plus ribavirin in chronic hepatitis C patients with occult hepatitis B virus dual infection. *J Gastroenterol Hepatol* 2010;**25**:259-263.
63. Fong TL, Di Bisceglie AM, Waggoner JG, et al. The significance of antibody to hepatitis C virus in patients with chronic hepatitis B. *Hepatology* 1991;**14**:64.
64. Mohamed Ael S, al Karawi MA, Mesa GA. Dual infection with hepatitis C and B viruses: clinical and histological study in Saudi patients. *Hepatogastroenterology* 1997;**44**:1404-1406.
65. Villari D, Pernice M, Spinella S, et al. Chronic hepatitis in patients with active hepatitis B virus and hepatitis C virus combined infections: a histological study. *Am J Gastroenterol* 1995;**90**:955-958.
66. Colombari R, Dhillon AP, Piazzola E, et al. Chronic hepatitis in multiple virus infection: histopathological evaluation. *Histopathology* 1993;**22**:319-325.
67. Cho LY, Yang JJ, Ko KP, et al. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. *Int J Cancer* 2011;**128**:176-184.
68. Benvegnù L, Fattovich G, Novera F, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. *Cancer* 1994;**74**:2442-2448.
69. Chiamonte M, Stroffolini T, Vian A, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;**85**:2132-2137.
70. Liu CJ, Chu YT, Shau WY, Kuo RN, Chen PJ, Lai MS. Treatment of patients with dual hepatitis C and B by peginterferon α and ribavirin reduced risk of hepatocellular carcinoma and mortality. *Gut* 2014;**63**:506-514.
71. Liu CJ, Liou JM, Chen DS, Chen PJ. Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. *J Formos Med Assoc* 2005;**104**:783-791.
72. Chen DS, Kuo GC, Sung JL, et al. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. *J Infect Dis* 1990;**162**:817-822.
73. D'Amelio R, Matricardi PM, Biselli R, et al. Changing epidemiology of hepatitis B in Italy: public health implications. *Am J Epidemiol* 1992;**135**:1012-1018.
74. Huang YT, Jen CL, Yang HI, et al. Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B

- and C. *J Clin Oncol* 2011;**29**:3643-3650.
75. Nguyen LH, Ko S, Wong SS, et al. Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection. *Hepatology* 2011;**53**:1839-1845.
 76. Villa E, Grotto A, Buttafoco P, et al. High doses of alpha-interferon are required in chronic hepatitis due to coinfection with hepatitis B virus and hepatitis C virus: long term results of a prospective randomized trial. *Am J Gastroenterol* 2001;**96**:2973-2977.
 77. Liu CJ, Chen PJ, Lai MY, Kao JH, Jeng YM, Chen DS. Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients. *Hepatology* 2003;**37**:568-576.
 78. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology* 2009;**136**:496-504.
 79. Yu ML, Lee CM, Chen CL, et al; Taiwan Liver-Net Consortium. Sustained hepatitis C virus clearance and increased hepatitis B surface antigen seroclearance in patients with dual chronic hepatitis C and B during posttreatment follow-up. *Hepatology* 2013;**57**:2135-2142.
 80. European association for the study of the liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012;**57**:167-185.
 81. Cheng HR, Liu CJ, Tseng TC, et al. Host genetic factors affecting spontaneous HBsAg sero-clearance in chronic hepatitis B patients. *PLoS One* 2013;**8**:e53008.
 82. Marrone A, Zampino R, D'Onofrio M, Ricciotti R, Ruggiero G, Utili R. Combined interferon plus lamivudine treatment in young patients with dual HBV (HBeAg positive) and HCV chronic infection. *J Hepatol* 2004;**41**:1064-1065.
 83. Coppola N, Stanzione M, Messina V, et al. Tolerability and efficacy of anti-HBV nucleos(t)ide analogues in HBV-DNA-positive cirrhotic patients with HBV/HCV dual infection. *J Viral Hepat* 2012;**19**:890-896.
 84. Senturk H, Tahan V, Canbakan B, et al. Chronic hepatitis C responds poorly to combination therapy in chronic hepatitis B carriers. *Neth J Med* 2008;**66**:191-195.
 85. Yu JW, Sun LJ, Zhao YH, et al. Analysis of the efficacy of treatment with peginterferon a-2a and ribavirin in patients coinfecting with hepatitis B virus and hepatitis C virus. *Liver Int* 2009;**29**:1485-1493.
 86. Kim YJ, Lee JW, Kim YS, et al. Clinical features and treatment efficacy of peginterferon alfa plus ribavirin in chronic hepatitis C patients coinfecting with hepatitis B virus. *Korean J Hepatol* 2011;**17**:199-205.
 87. Hung CH, Lee CM, Lu SN, et al. Combination therapy with interferon-alpha and ribavirin in patients with dual hepatitis B and hepatitis C virus infection. *J Gastroenterol Hepatol* 2005;**20**:727-732.
 88. Chuang WL, Dai CY, Chang WY, et al. Viral interaction and responses in chronic hepatitis C and B coinfecting patients with interferon-alpha plus ribavirin combination therapy. *Antivir Ther* 2005;**10**:125-133.
 89. Myers RP, Thibault V, Poynard T. The impact of prior hepatitis B virus infection on liver histology and the response to interferon therapy in chronic hepatitis C. *J Viral Hepat* 2003;**10**:103-110.
 90. Fabris P, Brown D, Tositti G, et al. Occult hepatitis B virus infection does not affect liver histology or response to therapy with interferon alpha and ribavirin in intravenous drug users with chronic hepatitis C. *J Clin Virol* 2004;**29**:160-166.
 91. Mrani S, Chemin I, Menouar K, et al. Occult HBV infection may represent a major risk factor of non-response to antiviral therapy of chronic hepatitis C. *J Med Virol* 2007;**79**:1075-1081.