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RESEARCH ARTICLE

COINFECTION WITH HEPATITIS B AND HEPATITIS C VIRUS: NEW INSIGHTS OF TREATMENT IN THE ERA OF DIRECT ACTING ANTIVIRALS.

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Abstract

Coinfection with hepatitis B (HBV) and C virus (HCV) is a major public health issue globally because coinfecting patients may experience more rapid and severe liver disease progression. Subsequently, treatment should be prioritized for these patients. Both the European Association for the Study of the Liver (EASL) and The American Association for the Study of Liver Diseases (AASLD) suggested that the criteria for optimum treatment for patients who are coinfecting based on the viral dominance after viral interactions should be similar to those patients who have hepatitis B or hepatitis C mono-infection. The new drugs for HCV treatment, the direct acting antivirals (DAAs), have brought new pathways in treating HCV alone and should be evaluated in HBV/HCV-coinfecting patients. Unfortunately, there is an unpredictable risk of HBV reactivation in patients with dual HBV/HCV infection under the new free-interferon regimens using DAAs. Both the EASL and AASLD up-to-date recommendations suggesting close monitoring HBV coinfection, regardless of the infection stage (chronic, occult, resolved), of the HCV genotype or the class of DAAs used. In HBV dominance, nucleos(t)ide analogue (NA) with high antiviral activity (potency) and high genetic barrier should always be considered. Both HBV and HCV treatment could be implemented in synchronously active HCV coinfection or HBV reactivation during HCV treatment.

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Introduction:-

Chronic hepatitis B (HBV) and C virus (HCV) infections are major public health issues globally.^[1] Several studies reported different coinfection rates depending on the geographical region. The prevalence rates are 0.7% in Egypt,^[2] 16% in India^[3] and 2.6% in Turkey.^[4] Other countries, Italy,^{[5],[6]} Spain,^[7] Japan,^{[8],[9]} Taiwan,^[10] and Iran^[11] have demonstrated that approximately 10-15% of patients with chronic HBV infection are also infected with HCV. But, about 2-10% of anti-HCV-positive patients are HBsAg positive.

Regarding, the virological interactions of HBV/HCV coinfection, these are poorly understood. HCV is an RNA pathogen while HBV is a DNA viral pathogen with a different life cycle. Coinfection mostly leads to the viral suppression of one of the viral agents. Two major specific patterns of infection have been described: the HCV superinfection of a chronic HBV infected individual followed by suppression of the HBV replication^[12] and the

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acute infection of HBV of a patient with chronic HCV infection followed by inhibition of HCV replication.^[13] This inverse relationship of the replicative patterns of the two viruses suggests direct or indirect (i.e., mediated by host immune responses) viral interference.^{[14],[15],[16]}

The primary concern with chronic HBV and HCV co-infection is that co-infection seems to result in more severe liver disease progression than mono-infections,^{[13],[17],[18]} with an increased risk of hepatocellular cancer (HCC)^{[19],[20],[21]} and of fulminant hepatitis.^[22] New findings confirmed that HBV/HCV coinfecting patients may experience more rapid progression of severe liver disease compared to those with hepatitis B alone although similar data for Asian and African patients with the highest prevalence of HBV infection worldwide are still missing.^[23] Furthermore, coinfection did not worsen HCV liver disease progression in the same study.

Nevertheless, treatment should be prioritized for HCV/HBV dually infected patients to avoid severe liver disease progression.^[24] The recently published EASL and ASSLD recommendations, suggesting that therapeutic criteria should be similar for both the patients who are coinfecting based on the viral dominance after hepatitis B and C viral interactions as for patients with either HBV or HCV mono-infection.^{[24],[25]} The DAAs have brought new therapeutic options in treating HCV and the new regimens should be evaluated in patients with HBV/HCV dual infection. But it seems reasonable as a first-line therapy based on existing data for DAAs therapies in HCV mono-infected patients. The aim of this review is to describe the evolution of treatment for patients with HBV/HCV coinfection liver disease with the new therapeutic options for this special category of patients.

Clinical features of Hepatitis C and Hepatitis B Co-infection:-

Hepatitis B and C viruses can be transmitted synchronously since they share a common route of transmission, blood-to-blood contact. However, an individual might get infected with one of the viruses and later in life may have a concurrent infection with the other virus through the same or another mode of transmission. In either case, the problem is that coinfection can result in severe liver disease progression such as cirrhosis and HCC.^[13, 23, 26, 27]

Overall more than 90% of adults with acute HBV infection develop icteric hepatitis as a result of an appropriate immune response followed by a spontaneous resolve of the virus, and develop antibodies against hepatitis B virus (anti-hepatitis B surface (anti-HBs))^{[28],[29]} Few patients develop chronic HBV hepatitis and remain surface antigen (HBsAg) positive. In contrast, most adults exposed to hepatitis C virus develop an acute hepatitis without icterus and approximately 80 to 85% develop chronic infection.^[30] These patients with a history of HCV exposure whether they develop chronic infection or resolve HCV virus, are anti-HCV positive.

In co-infection with hepatitis B and C virus, the following clinical outcomes may occur as shown in Figure 1. Patients may resolve hepatitis B virus or hepatitis B infection may become silent (occult HBV infection)^[31] and develop chronic HCV hepatitis;^[32] they may resolve hepatitis C and develop chronic HBV hepatitis;^[26] they may resolve both viruses; or they may develop chronic infection with both hepatitis B and C viruses.^[13] Clinical, serological and virological characteristics of these infectious scenarios are outlined in Table 1.

Table 1:-Clinical, serological and virological characteristics of dual infection of HBV and HCV in patients with chronic hepatitis.

The clinical spectrum	Serological and virological characteristics				
	HBsAg	HBeAg/anti-HBe	HBV-DNA	Anti-HCV	HCV RNA
Chronic HBeAg (-) hepatitis and HCV hepatitis	+	-/+	>2000 IU/ml	+	+
Chronic HBeAg (+) hepatitis and HCV hepatitis		+/-	>2000 IU/ml		
Occult HBV in chronic HCV hepatitis	-	-/-	<2000 IU/ml	+	+
Chronic HCV hepatitis in HBsAg carrier	+	-/+	<2000 IU/ml	+	+
both viruses resolved	-	-/+	-	+	-

Management and Treatment of patients with HBV/HCV coinfection:-

In patients with chronic HBV/HCV hepatitis, it is necessary to determine the dominant virus that should be eradicated. It is uncommon to have a co-dominance of both viruses. HBV dominance means high serum HBV DNA

levels and low serum HCV RNA levels. However, some of these patients have fluctuating serum HBV DNA levels there is a need for a long term follow-up^[33] in order to evaluate viral loads before initiating any treatment. NA treatment might be considered in patients with HBV dominance (persistent or fluctuating serum HBV DNA levels above 2000 IU/ml). In HCV dominance, serum HBV DNA levels are often undetectable or very low and serum HCV RNA levels are high. These patients should receive treatment for chronic HCV hepatitis.^[34] Viral interactions will affect the therapeutic options in dually infected patients with HBV and HCV.

Evolution of HBV/HCV coinfection therapy:-

The goal of HBV/HCV coinfection treatment is to achieve sustained virological response (SVR) which means undetectable serum HCV-RNA levels at 24 weeks (SVR24) or recently at 12 weeks (SVR12) with the introduction of DAAs but also HBsAg seroconversion and clearance of serum HDV-DNA after the end of antiviral therapy.^{[24],[25],[31]}

Treatment of HCV in dually infected HCV/HBV patients with chronic HCV hepatitis:-

The treatment of hepatitis c and B have evolved over the years. Initially, Interferon containing regimen has been the only therapy to eradicate HBV or HCV infection for years. However, this regimen associated with low rates of HBV and HCV virological responses. In Villa et al^[35] study, patients with HCV/HBV coinfection treated with 9 million IU of standard IFN 3 times weekly for 3 months and 31% of these patients showed clearance of HCV. Also, it has been described a poor response of IFN in patients with occult HBV infection and chronic HCV hepatitis.^{[36],[37]}

Later, the addition of guanosine analog (ribavirin) in co-infected patients with HCV dominant disease, has been well studied and has proven poor efficacy in several studies. A study by Liu et al^[38] treated coinfecting patients with standard IFN and RBV reported SVR up to 21% of those patients who lost HBsAg. SVR rates were comparable to those in patients with HCV alone.

Then, pegylation of interferon modified the pharmacokinetic profile of IFN- α -2. Compare to conventional IFN, pegylated interferon alpha showed a slower absorption rate, more reduced distribution and slower clearance rate. Subsequently, this molecule proven to be superior to standard interferon alfa for both chronic hepatitis B and C treatment.

In a small prospective multi-center pilot study study by Potthoff et al^[39] 19 patients with chronic HBV/HCV coinfection (6 were HBV DNA-positive and 13 negative) treated with weight-adjusted peg-IFN- α -2 β and RBV for 48 weeks achieved SVR rate 93% (86% in genotype 1 and 100% in genotypes 2 or 3).

Moreover, a large prospective randomized, controlled, multicenter study by Liu et al^[40] evaluated peg-IFN and RBV in HCV/HBV-coinfecting patients. High SVR rates (72% and 83% in genotypes 1 and 2/3 respectively) achieved. Also, the same authors investigated the sustained HCV clearance both in patients with HCV/HBV coinfection and HCV infection alone for a follow-up period of 5-years.^[41] They reported that HCV reappearance occurred only in 6 (2.6%) of the 232 patients who achieved SVR and concluded that sustained HCV clearance is not influenced by HBV coinfections.

Finally, other study with the combined regimens of peg-IFN and RBV showed similar virological responses in chronic HCV patients with and without occult HBV infection.^[42]

Although the above authors reported on a high effectiveness of peg-IFN α plus RBV in HBV/HCV-coinfections, SVR rates are affected by the HCV genotypes and the IL28B genotype.

Furthermore, adverse events are common with interferon based regimens such as fatigue, flu-like symptoms, depression, skin rash and gastrointestinal manifestations. Also, pegylated interferon alfa is contraindicated in patients with untreated or severe depression and with decompensated cirrhosis. These factors have driven the urgent need for more effective and safer such as the DAAs including inhibitors of nonstructural proteins such as NS3/4A pro-tease, NS5A and NS5B polymerase for the treatment of chronic hepatitis C.

DAA greatly improves SVR rates independently of whether the patient is treatment naïve or previously unsuccessfully treated with peginterferon and ribavirin, of fibrosis stage and IL28B genotype. Subsequently, therapeutic management of HCV infected adults includes only DAAs.^[1]

New therapies including regimens with high potency and high genetic barrier were administered orally and this resulted in better compliance and high rates of virological responses for eradication of HCV.

Direct-acting antivirals (DAAs) for HCV/HBV coinfection: reactivation of hepatitis B virus as a further challenge during DAAs-based anti-HCV treatment:-

At the moment little data is available whether the new DAA-based therapies will be effective in HBV/HCV coinfection. Collins et al^[43] reported two coinfecting HCV/HBV cases treated with potent, interferon-free, direct-acting antiviral regimens simeprevir and sofosbuvir with no activity against HBV who had HBV reactivation. They suggested that early start of anti-HBV therapy because of abrupt rise in the serum HBV DNA levels should be strongly implemented to prevent significant hepatitis as recommended by EASL and AASLD guidelines recently.^{[24],[25]}

Hepatitis B virus reactivation, defined as an abrupt increase in HBV replication, marked by a rise in serum HBV DNA levels, in patients with inactive or resolved HBV infection. Reactivation may result in liver injury (hepatitis flare) as shown by elevations in serum alanine aminotransferase (ALT) levels.^[31]

For the period from November 2013 to October 2016, the US Food and Drug Administration (FDA) has reported 29 cases of HBV reactivation in patients with dual HCV/HBV infection who received DAAs regimens as anti-HCV therapy.^[44] As a result, FDA now issued a warning about the risk of HBV reactivation in those patients who are going to be treated with DAAs.

Of those 29 patients, at baseline, 9 had detectable serum HBV DNA levels, 7 were HBsAg-positive and had undetectable serum HBV DNA levels, and 3 were HBsAg-negative and undetectable HBV-DNA levels. For the remaining 10 patients, data were not available or uninterpretable. Two deaths and 1 case of liver transplantation were reported.

Although, it is now clear that there is a potential risk of HBV reactivation associated with DAAs therapy, the risk is unpredictable. One recent study reported that out of 103 patients with resolved HBV infection treated with DAAs none experienced reactivation.^[45] Other study reported out of the 327 patients who received DAAs as antiviral therapy, 124 were anti-HBc positive, with none showing HBV reactivation.^[46]

Few interesting cases of HBV reactivation with the DAAs for HCV therapy were recently reported. In the study of Takayama et al^[47] a dually infected patient received initially treatment with asunaprevir and daclatasvir for the HCV dominance resulting in HCV early virological response but an increase in HBV DNA, requiring the use of a nucleoside analogue entecavir. Other case study also reported HBV reactivation of a patient infected with HCV genotype 4 and HIV during anti-HCV treatment with DAAs ledipasvir /sofosbuvir.^[48] Finally, similar three cases of HBV reactivation in HBV/HCV (genotype 1) coinfecting patients were recently reported.^{[49],[50]} These three patients had been previously received HCV treatment with peginterferon/ribavirin without achieving SVR. During antiviral HCV therapy with the combination of DAAs sofosbuvir and simeprevir HBV reactivation occurred. The patients were at different stage of HBV infection One patient had HBeAg-negative chronic HBV infection, previously termed 'inactive carrier' (HBsAg positive, HBeAg (-), anti-HBe (+), very low or undetectable serum HBV DNA levels and normal serum aminotransferases), one had occult HBV infection (HBsAg (-) and low serum HBV DNA levels) and the last one resolved infection (HBsAg (-), anti-HBc (+), anti-HBs (±) and undetectable serum HBV DNA levels). Although patients treated with NA in addition to DAAs, one patient required liver transplantation after fulminant hepatic failure.

There has been also one report of HBV reactivation with the triple therapy of peginterferon- α , ribavirin and simeprevir in patient with HBV/HCV coinfection. Entecavir administered in addition to triple anti-HCV treatment and serum HBV DNA levels became undetectable.^[51]

The phenomenon of HBV reactivation has not solely be described for HBV/HCV coinfecting patients treated with DAAs. In the past, HBV reactivation had been reported in HBV/HCV coinfection treated with regimens containing

pegIFN- α which shows significant antiviral activity against hepatitis C but also against hepatitis B.^{[24],[25],[52]} Despite the antiviral activity of interferon against hepatitis B, interferon-based HCV treatment can result in loss of HBV suppression and HBV reactivation. Indeed, in some patients with HBV/HCV dual infection after eradication of the dominant virus such as clearance of serum HCV RNA with peg-IFN- α and RBV the other virus then may become active (HBV reactivation).^{[34],[39]} A recent meta-analysis showed that dually infected patients who received peg-IFN- α and ribavirin appeared with an increase in HBV replication (23%) and particularly those who achieved SVR with the anti-HCV treatment.^[53] But, this phenomenon is not frequent,^[23] and acute hepatitis appears to more rare.^[54]

The introduction of new DAAs has opened new pathways in treating HCV alone or HBV/HCV coinfecting patients but these direct antiviral drugs has no antiviral activity against hepatitis B. So the risk of HBV reactivation may be greater with the DAAs since the newer DAAs have high antiviral potency against HCV only and not for HBV. ASSLD HCV treatment guidelines are not clear about how to monitor these patients.^[25] But current EASL HCV treatment guidelines suggested how to monitor these patients on DAAs with an unpredictable risk of HBV reactivation although the new regimens need to be evaluated in HBV/HCV-coinfecting patients.^[24] At the moment, up-to-date EASL recommendations suggest close monitoring of HBV coinfection, regardless of the stage of HBV infection (occult, past infection or chronic), HCV genotype or class of DAAs used. This is due to the unpredictable risk of the HBV reactivation in HCV/HBV-coinfecting patients during or after combined antiviral therapy with interferon-free regimens.^[24] Serum aminotransferase levels monitoring is indicated in patients with resolved HBV infection (anti-HBs and anti-HBc antibody-positive patients). If serum ALT levels elevated on treatment a test for HBs antigen and/or serum HBV DNA levels should be done. In case of chronic hepatitis B or "occult" HBV infection the addition of NA therapy is strongly recommended. However, in the future, routine initiation of dual treatment for HCV and HBV might be the standard of care for all coinfecting patients. At the moment, there are still ongoing studies in HBV/HCV coinfecting patients treated with DAAs based antiviral therapy.

An ongoing phase 3 trial (NCT02555943)^[55] is currently assessing the incidence, morbidity, mortality and predisposing factors for HBV reactivation during DAAs based antiviral therapy in HBV/HCV coinfecting patients. In one arm HCV/HBV coinfecting patients will be treated with NA such as Entecavir or Tenofovir disoproxil fumarate in case of HBV reactivation during HCV combined therapies with DAAs such as Ledipasvir/Sofosbuvir; or Sofosbuvir and Daclatasvir, or Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir; or Sofosbuvir+Ribavirin. In other arm, HCV/HBV coinfecting patients will be treated as in the previous arm but before or at the commencement of HCV combined therapies with DAAs.

There are still unresolved issues and unmet needs regarding treatment of dually infected patients with Peg-interferon plus ribavirin with or without a second-generation DAAs or DAAs-based and interferon-free regimens. The optimum treatment for HBV/HCV coinfection needs to be developed.

Treatment of HBV in dually infected HCV/HBV patients with chronic HBV hepatitis:-

Peg-IFN-based therapy in HCV/HBV coinfecting patients also act on the HBV as does in mono-infected HBV patients.^[31] Indeed, studies reported 11.2% (18/161) HBsAg loss 6 months after the end of treatment and HBsAg seroclearance rate of 5.4% per year in HBV/HCV coinfecting patients.^{[41],[42]} Baseline low serum HBsAg levels correlated significantly with HBsAg seroclearance. Another study^[56] showed that the host genetic polymorphism rs9277535 for HLA-DPB1 region was associated with spontaneous HBsAg seroclearance.

However, during antiviral treatment for HCV or after the end of treatment reactivation of HBV due to immune reconstitution may appear.^[44] In a study, 61.8% (47/76) of HBV/HCV coinfecting patients treated for HCV with baseline serum HBV DNA levels <200 IU/mL showed HBV DNA reappearance.^[38] Therefore, serum HBV DNA levels monitoring is necessary and in case of HBV reactivation treatment with NA(s) is necessary.

Little data is available on the use of anti-HBV drugs for patients coinfecting with HBV/HCV and hepatitis B dominant disease.

Interferon with or without Lamivudine was a reasonable option in the past, before the new antiviral molecules become available, for coinfecting patients. In a small study,^[57] 50% of 8 HBV/HCV coinfecting patients received combined treatment with MU IFN and 100 mg/day lamivudine (LAM) for 12 months, followed by a six months tail with LAM alone achieved SVR. Three patients showed HBeAg clearance of whom two seroconverted to anti-HBe. Serum HBV DNA levels became undetectable in 3 patients at the end of treatment, but reappeared in two patients later.

In a more recent study, Coppola et al^[58] studied in a cohort of 24 HBV/HCV-dually nfectcd cirrhotic patients the tolerability and efficacy of the following NA: lamivudine plus adefovir (n=10), entecavir (n=7), telbivudine (n=4), tenofovir disoproxil fumarate (n=3). Undetectable serum HBV DNA levels were found in 96% of patients after 18 months, while HCV reactivation was low (12.5%). But, 33% of these patients appeared with progression of liver cirrhosis. The authors reported that a favorable clinical outcome had only HBV/HCV cirrhotic patients with HCV RNA-negative at baseline.

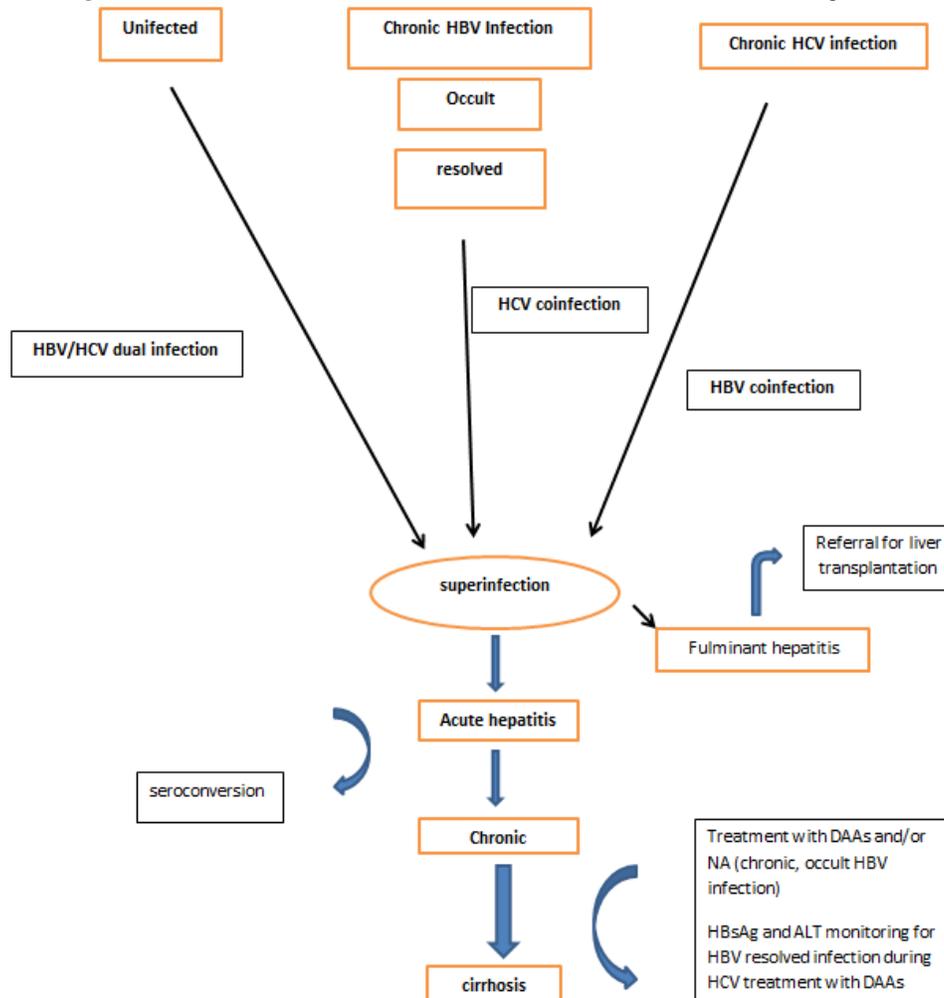
Today, after pegylated interferon discontinuation treatment of chronic HBV/HCV with HBV dominance should subsequently be with NAs. Over the last several years, several new agents have been added to the armamentarium of drugs against HBV infection. Currently, a potent antiviral NA with high genetic barrier i.e. entecavir, tenofovir disoproxil or tenofovir alafenamide, represents the optimal agents for first-line therapy.^[31] Other NAs such as lamivudine, adefovir and telbivudine are not recommended due the high viral resistance.

Guidelines for the treatment of coinfectcd HBV/HCV patients:-

Today, antiviral therapy for HCV/HBV coinfection is able to eradicate HCV infection and inhibit HBV replication. Evaluation of the predominant virus over the other and possibly comorbidities are essential for optimal antiviral regimens. For coinfectcd patients with active hepatitis C, the same regimens as for patients with hepatitis C infection alone should be applied following AASLD and EASL recommendations.^{[24],[25]} Regimens such as Peg-interferon plus ribavirin with or without a second-generation DAAs or DAAs-based interferon-free regimens should be implemented.^{[24],[25]} Hopefully, the high cost of direct acting drugs will not be a limitation to their use in developing countries. For HCV/HBV coinfectcd patients with active hepatitis B before, during or after DAAs based treatment for HCV, with or without cirrhosis NA treatment with entecavir, tenofovir disoproxil or tenofovir alafenamide is indicated.^{[24],[25],[31],[59]} Concurrent HBV therapy with DAAs combined treatment for HCV is strongly recommended if serum HBV DNA levels are detectable at a significant level before initiation of HCV treatment or there is a potential risk of HBV reactivation such as after initiation of a wide variety of immune-suppressive therapies for the treatment of cancer or autoimmune disease and in patients who are solid-organ transplant recipients.^{[24],[31]} In concurrent HBV/HCV treatment with the combination of simeprevir and tenofovir, eGFR and tubular function should be monitored frequently during treatment because simeprevir increases exposure to tenofovir.^[24] Thus, tenofovir doses should be consequently adjusted when required.

In resolved HBV infection or occult HBV infection, serum aminotransferase levels should be monitored and upon increase in ALT levels on treatment a test for HBs antigen and/or serum HBV DNA levels should be measured. The risk of HBV reactivation is unpredictable in the setting of the interferon-free HCV therapies with DAAs and close monitoring of HBV infection is necessary [Figure 1].

Further studies needed to clarify if all oral interferon free regimens with or without NA are the optimal regimens of both viruses at the same time for this population.

Figure 1:-Clinical course of HBV/HCV coinfection and treatment management**References:-**

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