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**REVIEW ARTICLE**

# Therapeutic Exploitation of Viral Interference

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**Abstract:** Viral interference, originally, referred to a state of temporary immunity, is a state whereby infection with a virus limits replication or production of a second infecting virus. However, replication of a second virus could also be dominant over the first virus. In fact, dominance can alternate between the two viruses. Expression of type I interferon genes is many times upregulated in infected epithelial cells. Since the interferon system can control most, if not all, virus infections in the absence of adaptive immunity, it was proposed that viral induction of a nonspecific localized temporary state of immunity may provide a strategy to control viral infections. Clinical observations also support such a theory, which gave credence to the development of superinfection therapy (SIT). SIT is an innovative therapeutic approach where a non-pathogenic virus is used to infect patients harboring a pathogenic virus.

For the functional cure of persistent viral infections and for the development of broad- spectrum antivirals against emerging viruses a paradigm shift was recently proposed. Instead of the virus, the therapy should be directed at the host. Such a host-directed-therapy (HDT) strategy could be the activation of endogenous innate immune response *via* toll-like receptors (TLRs). Superinfection therapy is such a host-directed-therapy, which has been validated in patients infected with two completely different viruses, the hepatitis B (DNA), and hepatitis C (RNA) viruses. SIT exerts post-infection interference *via* the constant presence of an attenuated non-pathogenic avian double-stranded (ds) RNA viral vector which boosts the endogenous innate (IFN) response. SIT could, therefore, be developed into a biological platform for a new "one drug, multiple bugs" broad-spectrum antiviral treatment approach.

**Keywords:** Viral interference, persistent HBV infection, viral superinfection, dsRNA virus, antiviral gene responses, pandemic preparedness.

## 1. VIRAL INTERFERENCE: A SHORT BACKGROUND

Viral interference is a state of temporary immunity, whereby infection with one virus limits infection, replication or production of a second virus. Schultz-Cherry and Laurie *et al.* [1, 2] provided an overview on the history of viral interference, which is summarized here briefly.

Probably Jenner reported first on viral interference in 1804 that herpetic infections may prevent the development of vaccinia lesions. Viral interference was described for plant viruses [3], for bacteriophages [4] for animal [5], and then for human viruses [6-12].

Alick Isaacs and Jean Lindenmann discovered in the 1950s that following influenza A virus (IAV) infection a soluble agent was made by infected cells which interfered with new IAV infection [13]. The interference was generated from membrane exposure to this soluble product from the virus-exposed membranes, which was therefore named interferon (IFN).

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Today, we know that IFNs make up an important family of cytokines that have antimicrobial, proapoptotic, immunomodulatory, and antiproliferative actions, which are mediated by hundreds of IFN-stimulated genes suppressing viral infections. These original reports on virus-virus interactions have been well supported through epidemiological studies for a variety of viruses. One can study the impact of viral interference in populations as to how one virus influences the susceptibility or resistance to other circulating viruses.

For example, different respiratory viruses reach their epidemic peaks at different times within populations probably due to interference [14-18]. Similarly, separate peaks of infection with different influenza virus (sub)types were observed [19, 20]. Influenza vaccination may prevent induction of temporary immunity that could protect against subsequent respiratory infections [12, 21, 22]. Preventing seasonal influenza virus infection by vaccination increased the risk of infection with A(H1N1) pdm09 virus [23-25]. Influenza vaccine recipients displayed higher rates of infection with non-influenza respiratory viruses, compared with unvaccinated subjects [26, 27]. This effect is observed only within specific periods, which was estimated to be weeks to months [12, 22, 26, 28]. The different intervals between initial infection and

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subsequent exposure may explain the inconsistent findings between epidemiological studies [12, 23].

During influenza season, numerous strains of influenza A and B viruses cocirculate within populations. Influenza A(H3N2) viruses cocirculated with influenza B viruses, while influenza A(H1N1) pdm09 viruses were reported only rarely during the 2014–2015 season in the United States [29]. Cocirculation of other respiratory viruses complicate further the situation [30]. Several viruses have been hypothesized to influence influenza virus infection in humans [10] or directly shown to cause viral interference in animal models [31-33].

Avian influenza virus (H9N2) and Newcastle disease virus (NDV) are endemic in the Middle East, in particular in Israel [34]. It was observed that the impact of velogenic NDV (vNDV) was more severe with a concomitant circulation of low pathogenicity avian influenza virus. A H9N2 challenge made birds more susceptible to vNDV, lowering the minimum dose required to cause an infection, exacerbating the clinical outcome; however, delayed the onset of the disease and time of death. Interestingly, the presence and degree of these effects were dose-dependent and not mutually exclusive. These examples indicate that concomitant viral infections can have different effects of the viruses involved depending on a large number of known and presently unknown factors.

While viral interference referred originally to the phenomenon when the first infecting virus suppressed the replication of a second infecting virus, clinical observations, mainly in hepatitis B and C virus (HBV/ HCV) infections, demonstrated that replication of the second virus could also be dominant over the first virus (see below). In fact, dominance can alternate between the two viruses but it is more common for HBV to appear to be suppressed by HCV [35]. In this paper, interference caused by accidental natural infection of a second virus will be referred to as *coinfection*, while deliberate iatrogenic infection using a second nonpathogenic virus as *superinfection*.

## 2. DETERMINANTS OF VIRAL INTERFERENCE

### 2.1. Ordered Hierarchy of Viruses May Contribute to their Dominance During Coinfection

The continued presence of an influenza virus prevented or modified a subsequent infection with a different influenza virus [1]. The outcome depended on the virus combinations, indicating a hierarchy of influenza viruses inducing different levels of temporary immunity [36]. Different patterns were observed: (1) prevention of secondary infection, (2) coinfection, (3) shortened secondary infection, (4) delayed secondary infection, and (5) no effect as compared to the control group. Upon virus infection, expression of type I interferons is upregulated in infected epithelial cells, and proinflammatory cytokines and chemokines are released from cells of the innate immune system [37]. Interference was only observed if the primary infection occurred up to 7 days before secondary challenge, suggesting that continued shedding of the primary virus may induce a temporary state of immunity. It was proposed that induction of a nonspecific localized temporary state of immunity may provide a strategy to control infection with emerging influenza viruses in the absence of a specific vaccine [1].

### 2.2. The Interferon System is Capable of Controlling Most, if not all, Virus Infections in the Absence of Adaptive Immunity

Interferon (IFN) was discovered in 1957 by Isaacs and Lindenmann [8, 38]. IFNs are secreted cytokines that elicit distinct antiviral effects. They are grouped into three classes called type I, II and III IFNs, according to their amino acid sequence. Type I IFNs comprise a large group of molecules; mammals have multiple distinct IFN-α genes (13 in man). Type II IFN has a single member, also called IFN-γ and is secreted by mitogenically activated T cells, natural killer (NK) cells and macrophages. IFN-α/β acts through a common heterodimeric receptor, which appears to be expressed ubiquitously, to activate a signal-transduction pathway, which triggers the transcription of a diverse set of IFN-inducible genes establishing an antiviral response in target cells [39].

Both RNA and DNA viruses induce IFNs through the production of viral double-stranded (ds) RNA [40, 41]. Dependent upon transcription, negative-stranded RNA viruses generate a dsRNA molecule, positive-stranded RNA viruses generate a dsRNA molecule *via* replication, and even DNA viruses generate dsRNA following convergent transcription. While dsRNA is an efficient inducer of IFN-α/β, it is not the only inducer. There are multiple routes by which hosts can recognize viruses and signal the induction of IFNs.

The innate immune response is crucial in detecting RNA viruses for the establishment of proper inflammatory and antiviral responses. Viruses seen by our cells *via* the so-called pattern recognition receptors (PRRs) in the cytoplasm, endosomes and on the cellular surface. PRRs sense the presence of viral nucleic acids recognizing pathogen-associated molecular patterns (PAMPs) [42].

Toll-like receptors (TLRs) are PRRs that recognize molecular patterns associated with double-stranded RNA (dsRNA), which is a molecular pattern associated with viral infection, because it is produced by most viruses at some point during their replication. Mammalian TLR3 recognizes dsRNA, activation of the receptor induces the activation of NF-kappaB and the production of type I interferons [43]. These bind to their receptor on neighboring uninfected cells (and also on the infected cell) and activate an intracellular signaling cascade leading to upregulation of several hundred IFN responsive genes. Viruses released from the primary infected cell replicate inefficiently in cells that are in the antiviral state.

According to Randall and Goodbourn [44], there are five main ways by which viruses circumvent the IFN response; 1) interfering with host cell gene expression and/or protein synthesis; 2) limiting the production of viral PAMPs minimizes IFN induction and/or blocking IFN-induction cascades; 3) inhibiting IFN signalling; 4) blocking the action of IFN-induced enzymes with antiviral activity; and 5) some viruses have a replication strategy which is insensitive to the action of IFN. Some viruses also use combinations of these strategies. Even small RNA viruses with limited coding capacity

produce proteins whose primary function is to counteract some aspect of the IFN pathway.

## 3. CLINICALLY RELEVANT NATURAL CO-INFECTIONS (I): GB VIRUS C REDUCED MORTALITY AMONG HIV PATIENTS

### 3.1. Is GB Virus Infection a Silent anti-HIV Panacea Within?

The GB virus C (GBV-C) is a common non-pathogenic, positive-sense RNA virus classified in the Flaviviridae family with worldwide distribution. The GBV-C and hepatitis G virus (HGV) are two isolates of the same virus, independently identified in humans in the 1990s and were initially considered a potential cause of liver disease. Studies, however, failed to associate the virus with hepatitis or any known human disease. GBV-C is related to hepatitis C virus (HCV) and it is transmitted parenterally. GBV-C infection is common in people with HIV infection and among intravenous drug users. There is a strong association between GBV and HIV infections. This suggests that the two viruses may share similar epidemiological and transmission features.

Favorable clinical course and reduced mortality among HIV infected patients were demonstrated by several studies with patients coinfected with the GBV-C [45]. The potential benefit of GBV-C coinfection was demonstrated in the pre-HAART (highly active antiretroviral therapy) and post-HAART eras. GBV-C decreased HIV replication in *in vitro* models, suggesting the interference of persistent GBV-C viremia. The beneficial effect of GBV-C appears to be mediated *via* changes in the cellular immune response. Elucidation of putative protective effects of GBV-C in HIV coinfection could potentially identify novel targets for anti-HIV agents [46, 47].

GBV-C reappeared in the scientific scene when two research groups, in an attempt to find viral interference among HIV seropositive patients, reported a lower mortality rate and slower disease progression among coinfected patients. Although several mechanisms have been proposed for this putative benefit, the question of whether GBV-C exerts a protective effect in HIV infected patients should be further investigated [48].

Tillmann, *et al.* [49] published in 2001 that among HIV infected patients who tested positive for GBV-C RNA, survival was significantly longer, and there was a slower progression to acquired immunodeficiency syndrome (AIDS). Survival after the development of AIDS was also better among GBV-C positive patients. Also, HIV load was lower in GBV-C-positive patients than in GBV-C negative patients. GBV-C load correlated inversely with HIV load but did not correlate with the CD4+ cell count. Since coinfection with GBV-C was associated with a reduced mortality rate in HIV infected patients, it was proposed that the presence of GBV-C leads to an inhibition of HIV replication. GBV infection could also prolong HIV disease progression by decreasing the HIV viral load and increasing the CD4(+) T-cell level [50] or inhibiting HIV-1 entry [51].

Xiang, *et al.* [52] published simultaneously with Tillmann, *et al.* in the same issue of the NEJM that GBV-C coinfection was associated with significantly improved survival in HIV infected patients. The mortality rate among the 144 patients with GBV-C coinfection was significantly lower than that among the 218 HIV infected patients without GBV-C coinfection. GBV-C coinfection reproducibly inhibited HIV replication in cultures of peripheral-blood mononuclear cells.

In fact, several cross-sectional studies performed worldwide noted that GBV-C coinfected patients had reduced HIV-1 loads, higher CD4+ T cell counts, a delay in AIDS prognosis and a longer lifespan, compared with patients infected with HIV-1 only [53-59].

Also, GBV-C and HIV-1 coinfection has been associated with prolonged survival among HIV-1 infected patients in clinical studies [60], therefore, GBV-C could be an attractive target for the development of novel anti-HIV/AIDS therapies [61].

## 4. CLINICALLY RELEVANT NATURAL CO-INFECTIONS (II): HCV DOMINATES OVER HBV REPLICATION IN COINFECTED HEPATITIS PATIENTS

### 4.1. More than 2 Billion People could be at Risk for HBV Reactivation Associated with Immune-suppressive Therapies Because Eradicative HBV Therapy is Not Available Yet

Hepatitis B virus (HBV) infections contribute significantly to the global health problem and, with more than 250 million people chronically infected, it is a major health priority. Unfortunately, there is still no reliable cure for HBV infection. A compounding problem is that approximately 1 in every 3 individuals worldwide may have been exposed to HBV infection [62-64]. Importantly, after recovery from HBV infection, a covalently closed circular DNA (cccDNA) episome can persist in a latent state for decades. In infected individuals, this is a reservoir for HBV reactivation [65]. Current anti-HBV treatment cannot eliminate the viral cccDNA and emergence of resistance remains a problem [66]. HBV infection is therefore difficult to eradicate, and its persistence explains the potential of HBV reactivation in any individuals who have been infected with the virus once the immune control mechanisms are perturbed or suppressed. At present, no validated tests are available to determine whether a particular drug or biologic can be associated with HBV reactivation, thus the risk of a new class of drug before its clinical application cannot be assessed. Importantly, no reporting system is available to accurately track cases of HBV reactivation that potentially are associated with these drugs until these cases are being reported in the literature [67].

HBV reactivation may occur from latent episomal cccDNA reservoirs following cessation of therapy, patient non-compliance, the development of escape mutants, during HCV direct-acting antiviral (DAA) therapy, cancer chemotherapy, immunosuppressive therapies for the management of rheumatologic conditions, malignancies, inflammatory bowel disease, dermatologic conditions, solid organ or bone marrow transplantation [68]. Therefore, despite effective HBV vaccines and therapies, HBV will remain a major public health burden in terms of global morbidity and possibly mortality for decades to come.

Coinfection of HBV with HCV, hepatitis D virus, or human immunodeficiency virus infection presents an unusual setting for potential HBV reactivation [69]. Treatment of coinfected patients with antivirals directed at the virus such as direct-acting antivirals for HCV, lonafarnib for hepatitis D virus, and non-B antiretroviral therapy for human immunodeficiency virus can result in HBV reactivation [70-72].

### 4.2. Increasing Awareness of HBV Reactivation in HBV/HCV Coinfected Patients Treated with DAAs

When a person has active HBV and HCV coinfection, usually one of the viruses dominates (typically HCV). Such individuals probably account for 200,000 to 400,000 people just in the United States today. However, if their HCV infection is suppressed, their HBV can reactivate, or become more aggressive with high HBV DNA levels and low HCV RNA quantification [73].

Because of shared modes of transmission, HBV/HCV coinfection is common in highly endemic areas and among subjects with a high risk of parenteral infections. The worldwide prevalence of HBV/HCV coinfection is not known [74]. Due to the phenomenon of silent (occult) HBV infection, it might be underestimated. The most common coinfection in Asia-Pacific countries was HCV superinfection in patients with chronic HBV infection. Viral interference usually leads to a predominance of one of the two viruses, which in most cases is HCV [75]. HBV/HCV coinfected persons tend to have a more severe liver injury, a higher probability of liver cirrhosis and hepatic decompensation, and a higher incidence of hepatocellular carcinoma compared with patients infected by one virus. Treatment-induced eradication of one virus may result in the reactivation of the other. Reciprocal viral interference can also happen, and a "flare" of hepatitis activity may cause liver function deterioration [76, 77]. DAAs remain a safe and highly effective treatment for the management of HCV infection. Consistent with this, DAAs are used increasingly to treat HCV infection. DAA therapy for chronic HCV infection, however, might pose a risk for HBV reactivation in HBV/HCV coinfected patients [78, 79].

HBV reactivation is defined as an abrupt increase in HBV replication in patients with inactive or resolved HBV infection, after the initiation of DAA therapy. Reports were published on HBV reactivation (HBV-R) in patients with HBV/HCV coinfection. HBV reactivation may result in clinically significant hepatitis. The FDA identified 29 reports of HBV-R in patients receiving DAAs from 22 November 2013 to 15 October 2016. Two patients died while one patient underwent liver transplantation. Therefore, HBV reactivation is a newly identified safety concern in HBV/HCV coinfected patients who are treated with DAAs. Indeed, the FDA issued a black box warning that all patients who are being treated with DAA agents for HCV infection must undergo HBV panel testing [80].

## 5. HOST-DIRECTED THERAPIES FOR VIRAL INFECTIONS

In contrast to antibiotics, conventional antiviral drugs are limited to a distinct virus group. The constant emergence of infections with new virus species with pandemic potential, however, emphasize the need for broad-spectrum antiviral drugs [81].

Host-directed therapy (HDT) is an emerging anti-infective approach [81]. HDT interferes with host cell factors that are required by a pathogen for replication or persistence, in order to enhance protective immune responses. HDTs administering interferons have been well established for the treatment of chronic viral hepatitis. In fact, administration of recombinant IFN-α or its pegylated derivatives remain the only HTD drugs licensed for management of chronic HBV infection because they can eliminate cccDNA of HBV [66]. Unfortunately, the severe side effects of systemic IFN treatment, which include influenza-like symptoms with fever and fatigue, depression, bone marrow suppression, exacerbated autoimmunity and, mainly due to ribavirin, hemolytic anemia, represent a major shortcoming of this therapy.

Therefore, various approaches have been developed to boost the endogenous innate (IFN) response, most of them relying on the activation of Toll-like receptors (TLRs) [82]. Both RNA and DNA viruses induce IFN through the production of viral double-stranded (ds) RNA. dsRNA is an efficient inducer of IFN-α/β *via* a signaling cascade that leads to the activation of several hundred IFN-stimulated genes (ISGs). ISGs enhance adaptive immunity by upregulating major histocompatibility complex class I (MHC-I) and thus antigen presentation. Furthermore, many of these genes contribute, directly or indirectly, to the antiviral state of a cell. As a net result, IFN-stimulated cells are barely able to be infected by viruses, a property that is reflected in the name of these cytokines (interference).

In fact, Kaufmann *et al*. proposed that the activation of the endogenous innate immune response *via* TLRs could be an HDT strategy for the functional cure of persistent viral infections and for the development of broad-spectrum antivirals against emerging viruses [81].

### 5.1. Post-exposure Treatment with Virus-like Particles (VLPs) for Ebola and Marburg Virus Infections in Patients are Not Effective Yet

Ebola virus and Marburg virus (filoviruses) cause lethal haemorrhagic fever in humans and non-human primates (NHPs). Filoviruses represent a double global health threat as naturally acquired diseases and as potential agents of bioterrorism. An Ebola virus outbreak can spread from a remote area to any major city in the world in 36 hours or less [83, 84]. Studies suggest that if an early innate response slows down Ebola virus replication a protective adaptive immune response can be mounted. All patients with a viral load <7.71 log copies per milliliter of blood survived, whereas all those with counts above this threshold died [85]. In a mouse model of Ebola virus (EBOV) infection it was found that virus-like particles (VLPs) lead to accelerated induction of IFN stimulated genes (ISGs) in liver and spleen of wild type mice, but not in mice deficient in *Stat1*, a transcription factor required for IFN induction, or *Ifnar1*, encoding the membrane receptor for type I IFNs. Therefore, VLPs seem to be promising vaccine candidates to facilitate post-exposure protection against EBOV [86]. Post-exposure vaccines may be useful if treatment occurs very soon after expo-

sure. Unfortunately, the most promising therapies for post-exposure use with demonstrated efficacy in the gold-standard NHP models of filovirus disease were unable to show statistically significant protection in patients infected with Ebola virus [83].

### 5.2. Post-exposure Superinfection Therapy (SIT) Using a Non-pathogenic Virus was Safe and Effective in Acute and Chronic HBV and HCV Patients, Respectively

Between 1990 and 2013, viral hepatitis deaths due to acute infection, cirrhosis, and liver cancer have risen from the tenth to the seventh leading cause of mortality worldwide. About 5% of the world population is chronically infected with HBV and close to 700 thousand people die every year due to complications of hepatitis B, including cirrhosis and liver cancer [87]. This is in spite of the extensive use of hepatitis B vaccine globally.

These facts justify alternative antiviral management approaches such as superinfection therapy (SIT). SIT is an innovative HDT, which boosts the endogenous innate (IFN) response by an attenuated non-pathogenic avian double-stranded (ds) RNA viral vector [88]. SIT has been shown to be safe and effective in patients infected with two completely different viruses, the hepatitis B, and hepatitis C viruses. Therefore, SIT could be developed into a safe, effective and affordable medicine for hepatitis patients with unmet needs.

Currently, SIT is based on a non-pathogenic, attenuated infectious bursal disease virus (IBDV). Since IBDV is easy to produce and store, it could be developed into a pandemic therapeutic to mitigate the world-changing effects of the next pandemic. The development of affordable SIT, which is an entirely different modality from the DAA drugs currently in pipelines, could complement DAA drug development efforts.

## 6. SUPERINFECTION THERAPY (SIT)

### 6.1. The Idea of Viral Superinfection Therapy

Superinfection therapy adapts viral competition for the treatment of acute and persistent viral infections. The idea came from clinical observations when unrelated viruses interact in co-infected patients. Infection by one type of hepatitis virus (*e.g.* HCV) is often terminated after accidental infection by a second hepatitis virus (*e.g.* HBV). In such cases, one virus dominates over the replication of the other virus. Nevertheless, in cases when both viruses are pathogenic the disease persists, and hepatitis remains. However, the patient may benefit from superinfection with a non-pathogenic dsRNA virus such as the IBDV, which is a potent activator of the interferon-dependent antiviral gene program. Because of its major economic importance to the world's poultry industries, attenuated IBDV strains are used as commercial vaccines for decades and have an excellent safety record [89]. While wild type IBDV is a highly contagious disease of young chickens characterized by immunosuppression and mortality, the attenuated vaccine strains cause no disease. Furthermore, even the wild type IBDV is not known to be a hazard in transmitting to other species despite its worldwide distribution in the domestic fowl [90, 91]. Therefore, a non-pathogenic, attenuated vaccine strain of IBDV was administered to resolve acute and persistent HBV or HCV infections *via* viral interference. The intentional superinfection strategy was also discussed for the control and treatment of AIDS in view of the improved survival of HIV infected patients naturally infected with the GBV-C virus [92, 93].

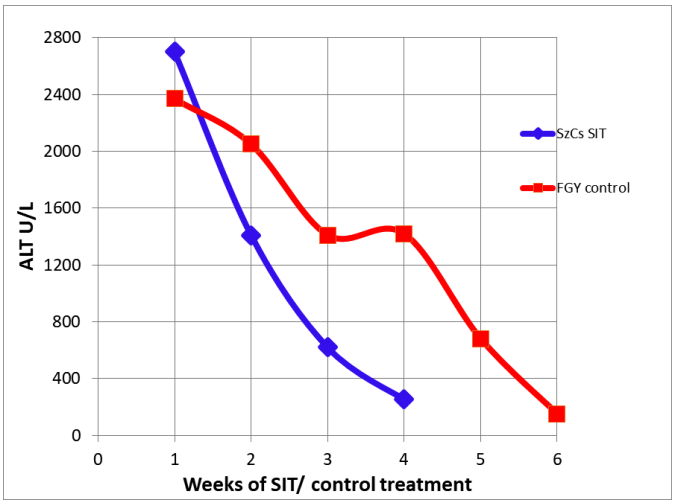
### 6.2. The Proof-of-concept of Viral Superinfection in Animals and Patients

It was demonstrated that IBDV was not toxic in rodents in doses 400 times that of proposed for human trials. Single and multiple oral administration of IBDV induced the production of neutralizing antibodies. However, despite the presence of neutralizing antibodies, repeat oral administration of IBDV was successful. Single oral administration, as well as intravenous administration, indicated that IBDV does not replicate in mammalian liver. This observation alleviates some safety-related concerns. These data support the development of an orally delivered anti-HBV and anti-HCV virus based drug agent for human use [94].

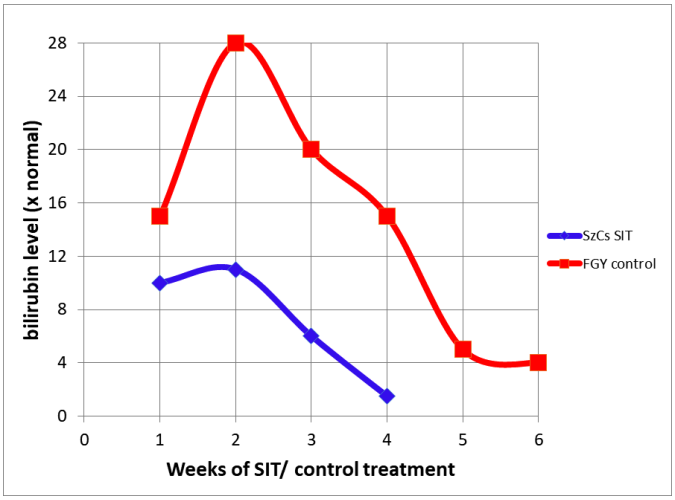
The proof of SIT concept was first demonstrated in marmoset monkeys proving for the first time that using of an apathogenic virus for the cure of a virus-induced disease is a realistic possibility [95]. Then, the proof of SIT concept was demonstrated in a preliminary clinical trial that included 84 patients, with either a diagnosis of acute B (43 patients) or acute C (41 patients) viral hepatitis [96]. IBDV treatment of two typical young male HBV patients is presented in Fig. (**1**). A, B with similarly striking elevation in serum alanine-aminotransaminase (ALT) activity and similarly high bilirubin levels. Statistically significant difference was observed between the IBDV treated and control groups, while no serious adverse events related to superinfection treatment were recorded. Most importantly, SIT was also safe and effective in two HBV and two HCV patients suffering from parenchymally decompensated chronic hepatitis with various life-threatening complications, *e.g.* portal hypertension, diuretic-resistant ascites, progressive jaundice, generalized edema, hepatic encephalopathy, etc. During IBDV treatment, all four patients went into long-lasting remission with spectacular clinical improvement, while conventional therapy was unable to stabilize the conditions of these patients. Conventional and SIT therapy of a decompensated chronic HCV patient is presented in Fig. (**2**). ALT enzyme levels declined after conventional IFN + ribavirin + thymosin treatment. When the patient became resistant to IFN, SIT was administered three times successfully over a period of three years suppressing ALT levels. No serious treatment associated toxicity was reported in the four decompensated patients. A striking feature of SIT was the regeneration of the cirrhotic liver over several years of follow up [88, 92, 97, 98].

### 6.3. The Safety Aspects of the IBDV Drug Candidate

IBDV is a double stranded RNA virus and expected to induce a very strong interferon (INF) response, however, there were no serious side effects observed during IBDV superinfection therapy even in parenchymally decompensated moribund patients. Systemic IFN-based therapy, in stark contrast, is associated with a wide array of adverse effects. The very different target range of the two therapies




(A)




(B)

**Fig. (1). A,B**. From the 42 acute hepatitis patients (Reference: Anticancer Res. 18:1279-82, 1998) two typical young male HBV patients (Sz.Cs. and F.Gy.; 21 and 34 years old, respectively) were selected with similarly striking elevation in serum alanine-aminotransaminase (ALT) activity (64- and 56-fold of normal level [42 U/L]) (A) and similarly high bilirubin levels (15- and 10-fold of normal [1.2 mg/dL]) (**B**). Sz.Cs. was treated by the attenuated IBDV viral preparation (as described in the Anticancer Res article), while F.Gy. received conventional symptomatic treatment. The efficiency of the SIT is measured by ALT and bilirubin levels, respectively. The IBDV therapy not only speeded up the recovery of Sz.Cs. by shortening the disease period about 30% but also prevented the elongated elevation of bilirubin level that was also characteristic of other control patients.

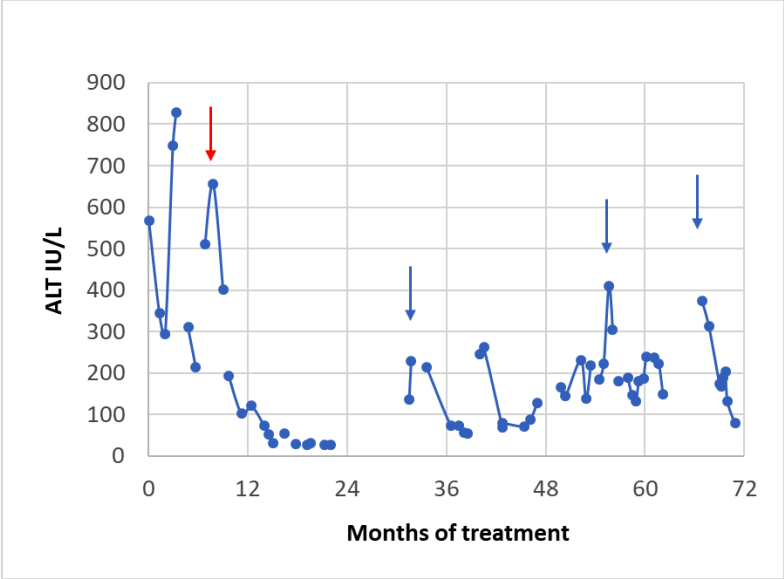



**Fig. (2).** Conventional and SIT therapy of a decompensated chronic HCV patient; ALT enzyme levels declined after conventional IFN + ribavirin + thymosin treatment (red arrow); then, patient became resistant to IFN. SIT was administered three times (blue arrows) over a period of three years successfully suppressing ALT levels.

could be one possible explanation. Receptors for the type I and II IFNs are found on the surface of most cell types such that systemic IFN therapy has an almost ubiquitous nature of signaling [99]. While one of the outstanding characteristics of viruses is their very restricted cellular and host tropism [100]. Importantly, IBDV interacts with appropriate cells such that its dsRNA is recognized by specific receptors (*e.g.* TLR3). These activate *several* gene families from within. For example, expression levels of IRF7 gene following intravenous injection of IBDV (R903/78) drug candidate, increased more than 250-fold as depicted in Fig. (**3**). This is another major difference between systemic IFN-based and superinfection therapy. Regardless of the specific mechanism of action, it is already clear that the two therapeutic modalities are not the same.

Hopefully, future preclinical and clinical studies will shed light on the exact mechanisms of viral interference that was seen in the above mentioned HCV and HBV clinical trials.

## 7. FUTURE PERSPECTIVES

Rare cancer successes instigated 'exceptional' research efforts. In many failed clinical trials there were exceptions,

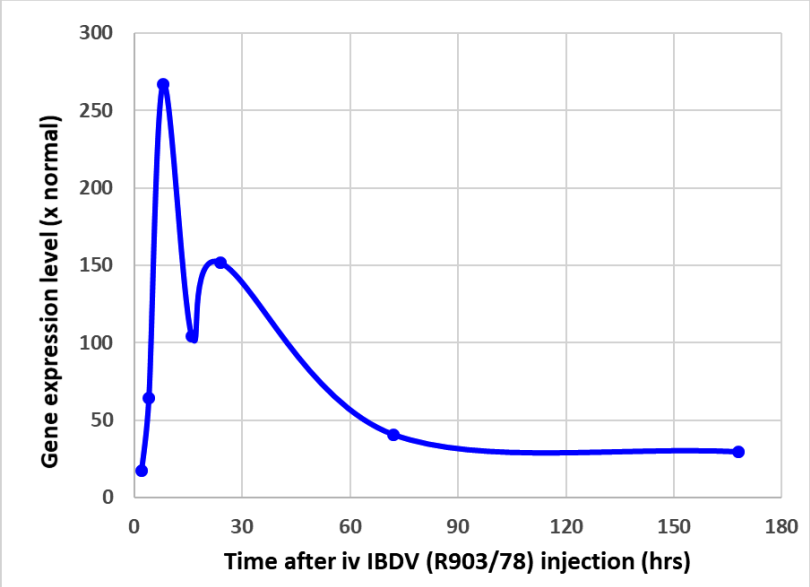



**Fig. (3).** Expression levels of IRF7 gene following intravenous injection of IBDV (R903/78) drug candidate.

rare patients with advanced cancer whose tumors shrank or even disappeared for many months or years [101]. Former NCI chief and Nobel-laureate Harold Varmus stated that we can really learn from such "outlier" cases, "exceptional responders." These cases may explain why a drug has sometimes dramatic beneficial effects in certain patients. Eventually, more people could benefit from the outlier cases. In our view, the published cases of the 4 parenchymally decompensated moribund patients with HBV and HCV infections treated successfully with IBDV superinfection should also instigate further research efforts. This would be beneficial to many millions of hepatitis patients worldwide with unmet needs.

The "one bug, one drug" approach (*e.g.* DAA drugs), which is currently used, is apparently inadequate to tackle the unresolved problem of treating viral diseases. Broad spectrum antiviral drugs effective against whole classes of viruses are urgently needed as *Science* called for [102].

Since the IBDV viral agent is easy to produce, store, stockpile and most importantly, it is effective against multiple unrelated viral diseases, SIT could be developed into a general post-infection viral therapy. This could become a plan "B" alleviating the logistic hurdles of surge capacity in vaccine production and increasing international pandemic preparedness [103, 104].

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| DAA | = | Direct Acting Antiviral Agent |
| dsRNA | = | Double Stranded RNA |
| HBV | = | Hepatitis B Virus |
| HCV | = | Hepatitis C Virus |
| SGPT | = | Serum Glutamic Pyruvic Transaminase |
| SIT | = | Superinfection Therapy |
| SVR | = | Sustained Virological Response |

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

Authors are shareholders of HepC, Inc.

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Declared none.

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