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REVIEW

Pegylated Interferon-α-Induced Functional Cure for Special Populations with Chronic Hepatitis B Virus Infection: Current Trends, Challenges and Prospection

Ye Zhang[1,*], Yu Li[2,*], Jian-Qi Lian[1], Wen Kang[1]

[1]Department of Infectious Diseases, Tangdu Hospital, Fourth Military Medical University, Xi'an, Shaanxi, 710038, People's Republic of China; [2]Department of Infectious Diseases, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, 710068, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wen Kang; Jian-Qi Lian, Department of Infectious Diseases, Tangdu Hospital, Fourth Military Medical University, 569 Xinsi Road, Baqiao District, Xi'an, Shaanxi, People's Republic of China, Email 82399536@qq.com; lianjq@fmmu.edu.cn

Abstract: Chronic hepatitis B virus (HBV) infection affects 257 million people globally, causing 880,000 deaths annually owing to end-stage liver disease. Current first-line therapies include nucleos(t)ide analogs (NAs) and pegylated interferon-α (PEG-IFN-α). A functional cure, defined as sustained HBsAg loss for ≥ 24 weeks, undetectable hepatitis B e antigen/HBV DNA, and normal liver function, is the ideal and achievable treatment endpoint for chronic HBV infection. This review focuses on PEG-IFN-α-induced functional cure in special populations with chronic HBV infection, including patients with partial response or low-level viremia (LLV), fibrosis or compensated cirrhosis, HBV-related hepatocellular carcinoma (HCC), HBV/human immunodeficiency virus-1 (HIV-1) coinfection, and pediatric patients. PEG-IFN-α enhances the complete virological response and HBsAg loss rate in CHB patients with partial virological responses to NAs or LLV. PEG-IFN-α improves liver histology and promotes liver fibrosis regression in compensated cirrhosis. PEG-IFN-α not only decreases HCC incidence and recurrence but also improves overall survival in patients with HBV-related HCC after curative treatment. Patients living with HBV/HIV-1 coinfection have a high rate of HBsAg loss/seroconversion in response to effective antiretroviral therapy, and the administration of add-on PEG-IFN-α may further increase the rate of HBV functional cure. IFN-α/PEG-IFN-α-based therapy is beneficial for younger children with chronic HBV infection despite the viral load, HBeAg, and liver inflammation status. Adverse events associated with PEG-IFN-α are manageable in specific HBV populations. PEG-IFN-α is a valuable strategy for a functional cure in special populations with chronic HBV infection, supporting clinical decision-making for HBV management.

Keywords: chronic hepatitis B, pegylated interferon-α, functional cure, special population

Introduction

Chronic hepatitis B virus (HBV) infection induces viral persistence in approximately 257 million patients worldwide, resulting in 880,000 deaths annually due to HBV-related liver diseases such as decompensated cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[1,2] It is important to inhibit HBV replication and suppress hepatitis B surface antigen (HBsAg) expression using antiviral agents to achieve the World Health Organization goals for the elimination of HBV infection worldwide by 2030, with a 90% reduction in incidence and 65% reduction in mortality.[2,3]

There are two main first-line therapeutic recommendations for chronic hepatitis B (CHB) patients: oral nucleos(t)ide analog (NAs) therapy [including entecavir (ETV), tenofovir (TDF), tenofovir alafenamide (TAF), and tenofovir aminufenamide (TMF)], and pegylated interferon-α (PEG-IFN-α) subcutaneous injection.[4–7] NAs act as viral DNA polymerase inhibitors to block HBV replication mainly through competition with natural deoxy-ribonucleoside triphosphates to bind

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HBV DNA polymerase, leading to DNA chain termination to block viral DNA synthesis.[8] NAs treatment was well-tolerated by most patients. Long-term first-line NAs treatments can achieve a sustained virological response with undetectable circulating HBV DNA in more than 95% of CHB patients, but the cumulative rate of HBsAg loss is low (approximately 1%).[9] IFN-α is an important immune modulator that exerts dual antiviral effects by both direct inhibition of HBV covalently closed circular DNA (cccDNA) transcription as well as viral particle assembly and induction of antiviral genes to enhance immune cells function.[10] Administration of PEG-IFN-α leads to a relatively high rate of HBsAg loss (approximately 20–50%) due to its antiviral and immunoregulatory properties,[11–15] especially for those with low baseline HBsAg level.[16–19]

Functional cure is defined as sustained HBsAg loss (≥ 24 weeks post-therapy) with or without the appearance of hepatitis B surface antibodies (anti-HBs), undetectable hepatitis B e antigen (HBeAg), undetectable serum HBV DNA, and normal liver function after a finite course of therapy,[20–22] which is regarded as an achievable and ideal end-point for antiviral therapy in terms of drug withdrawal safety.[23] PEG-IFN-α-induced durable HBsAg loss was found in approximately 80% of patients during more than 48 weeks of follow-up after discontinuation of medications in both CHB patients and inactive HBsAg carriers (IHC).[24–28] The appearance of a high anti-HBs titer and longer consolidation treatment time are potential predictors of a sustained functional cure.[24–28]

PEG-IFN-α-induced HBsAg loss/seroconversion has mainly been investigated in adult CHB patients and IHC. This review explores PEG-IFN-α-induced functional cure in special populations with chronic HBV infection, including patients with partial virological response to NAs therapy, compensated HBV-related liver cirrhosis, HBV-related HCC, HBV and human immunodeficiency virus-1 (HIV-1) co-infection, and pediatric HBV-infected patients. This study aimed to highlight the potential efficacy and safety profile of PEG-IFN-α administration in enhancing the functional cure rate of these special populations.

Patients with Partial Virological Response or Low-Level Viremia

A partial virological response is defined as a decrease in HBV DNA level of > 1 $\log_{10}$ IU/mL, but still positive for HBV DNA in CHB patients with good compliance after NAs treatment for at least 12 months.[4–6] Low-level viremia (LLV) is defined as the persistent or intermittent detection of HBV DNA (< 2000 IU/mL, detection limit of 10 IU/mL) after 12 months of antiviral therapy.[7,29,30] Real-world experiences have shown that approximately 20–40% of patients still develop LLV, even with first-line NAs treatments.[30–32] Patients with high HBV DNA and RNA loads, high HBsAg levels, HBeAg positivity, and liver cirrhosis tend to have a high risk of LLV despite long-term NAs therapies.[33–36]

Chronic HBV-infected patients with LLV have high incidence of liver inflammation and fibrosis based on the pathological results of liver biopsy. G2–G4 inflammatory activity were observed in 76.2% (96/126) patients, while F2–F4 fibrosis was found in 61.1% (77/126) patients with LLV.[37] LLV is an independent risk factor for the progression of end-stage liver diseases.[29] Persistent LLV promotes progression of liver fibrosis progression during therapy,[31,38] and is associated with poor overall survival and tumor recurrence in patients with HBV-related HCC.[30,39–42] LLV also impairs the efficacy of immune checkpoint inhibitor-based therapy in patients with HBV-related unresectable HCC.[43,44] Although a report involving HBV-infected compensated cirrhotic patients from South Korea, Singapore, and Japan revealed that untreated LLV is not associated with an increased risk of disease progression compared with antiviral therapy-induced or spontaneously maintained virological response,[45] a head-to-head comparison strongly demonstrates that long-term antiviral therapy is still beneficial for CHB patients with compensated cirrhosis and LLV, leading to a significant reduction in annual HCC incidence.[46] Effective antiviral therapy also reduces mortality in HCC patients with low-level HBV viremia,[47] particularly in early stage HCC patients receiving transcatheter arterial chemoembolization (TACE).[48] Thus, treatment adjustments for CHB patients with partial response or LLV during therapy must be considered to achieve complete virological response (CVR).

The guideline recommendations for patients with partial virological response or LLV include switching to or combination therapy with more effective antiviral agents without sharing cross-resistance.[4–7] A novel HBV capsid assembly modulator also achieved high efficacy in suppressing residual HBV DNA and pregenomic RNA (pgRNA) in CHB patients with LLV in a phase II study.[49] However, the efficacy of these treatment strategies remains controversial. Furthermore, the intrahepatic HBV reservoir and HBV DNA integration mainly contribute to LLV in chronic HBV-infected patients.[29,50] PEG-IFN-α

robustly suppresses the transcriptional activity of integrated HBV DNA and cccDNA in intrahepatic HBsAg-negative patients with a functional cure.[51] Thus, the administration of PEG-IFN-α is also recommended for patients with a poor response to LLV in the Chinese guidelines for the prevention and treatment of CHB.[4] HBeAg-positive CHB patients with partial virological response (n=81) to NAs treatment were switched to PEG-IFN-α2a therapy for personalized duration. At the end of average 19.6 months (range: 15.5–33.3 months) PEG-IFN-α2a therapy, 38.3% (31/81) of the patients achieved HBeAg seroconversion and 8.6% (7/81) achieved HBsAg loss or seroconversion.[52] A retrospective study enrolled 97 LLV patients who were divided into three groups: NAs monotherapy (n=34), NAs combination therapy (n=16), and NAs+PEG-IFN-α therapy (n=47). After 96 weeks of treatment, NAs combination and NAs+PEG-IFN-α therapy achieved higher CVR rates (89.4% and 87.5%, respectively) than NAs monotherapy (55.9%).[53] Similarly, a prospective study involving HBeAg-negative, NA-treated CHB patients (n=240) with LLV was divided into two groups: PEG-IFN-α add-on (n=162) and NAs add-on (n=78) for 48 weeks of therapy. The PEG-IFN-α add-on group had a higher CVR rate (97.5% vs 85.9%) and an increased HBsAg loss/seroconversion rate (30.9% vs 5.1%) than the NAs add-on group.[54] The subgroup data from a multicenter, prospective real-world study (OASIS Project) from China focused on 1640 patients with CHB with LLV. Switching to (n=144) or add-on (n=969) PEG-IFN -α demonstrated an elevated HBsAg serovonversion rate compared with maintaining (n=489) or switching to (n=38) NAs (15.8% vs 3.4%) 48 weeks post therapy.[55] Thus, PEG-IFN-α-based therapy still has the benefit of achieving both CVR and functional cure in patients with a partial virological response or LLV.

Patients with Fibrosis or Compensated Liver Cirrhosis

PEG-IFN-α is absolutely contraindicated in patients with decompensated cirrhosis because of the possible risk of inducing hepatic flares and causing liver failure,[56] but can be administered for HBV-related fibrosis and compensated cirrhosis. In a subanalysis of Phase III studies, PEG-IFN-α showed similar or even better efficacy in both HBeAg-positive and HBeAg-negative patients with compensated cirrhosis.[56–58] PEG-IFN-α2b therapy improves liver histology in HBeAg-positive CHB patients, with robust declines in both the necroinflammatory score (decrease of ≥ 2 points) and fibrosis score (decrease of ≥ 1 point) in liver biopsy specimens.[59] HBeAg-positive CHB patients with advanced fibrosis (Ishak fibrosis score, 4–6) exhibited a higher virological response (HBeAg seroconversion and HBV DNA < 10,000 copies/mL) (25% vs 12%) and an increased rate of improvement in liver fibrosis (66% vs 26%) than those without advanced fibrosis in response to PEG-IFN-α2b treatment.[60] A total of 218 treatment-naïve CHB patients with pretreatment biopsy-proven Ishak fibrosis scores of 2–4 were randomly assigned to the ETV treatment alone or PEG-IFN-α2a add-on groups. Both groups showed similar fibrosis regression at 78 weeks posttherapy (68% vs 56%). PEG-IFN-α2a add-on induced higher HBeAg and HBsAg loss/seroconversion rates.[61] This single-center observational study enrolled 54 patients with HBV-related compensated cirrhosis who received PEG-IFN-α2b therapy for 48 weeks. HBsAg levels were robustly reduced 48 weeks post-treatment [227.2 (12.36, 2535) IU/mL vs 1668 (446.2, 4842) IU/mL]. Three patients experienced HBsAg loss and two achieved HBsAg seroconversion. Liver stiffness measurement did not change remarkably in response to PEG-IFN-α2b treatment.[62] None of the patients experienced acute hepatic decompensation or progressed to end-stage liver disease during the observational period.[60–62] Because PEG-IFN-α treatment leads to a high rate of sustained off-therapy response, patients with HBV-related fibrosis or compensated cirrhosis should also be considered for PEG-IFN-α therapy to achieve not only fibrosis regression, but also functional cure.

HBV-Related HCC Patients

The relative risk of HCC in patients with chronic HBV-infected infection ranges from 14 to 223 compared with that in patients without HBV infection.[63] This risk is substantially elevated in HBV-related cirrhosis.[64] The incidence rates of HCC in Asia are 0.2, 0.6, and 3.7 per 100 person-years for IHC, CHB, and HBV-related cirrhosis, respectively.[65] China harbors 250,000 HBV-attributable cancers, accounting for 69% of cases worldwide.[66] The incidence of HCC exhibits an increasing trend from 2006 to 2030 among Chinese HBV-infected populations, using individual-based Markov models.[67] Risk factors for HCC development include age > 40 years, male sex, family history of HCC, high HBV DNA load, alcohol consumption, smoking, diabetes mellitus, obesity, and aflatoxin exposure.[4,68] The oncogenic mechanisms of HBV include the creation of liver inflammatory microenvironments through the induction of cytokine secretion and oxidative stress, abnormal expression of oncogenes and tumor suppressor genes via HBV integration into the host

genome, and HBsAg and HBx protein-mediated activation of carcinogenesis-associated signaling pathways.[69] Antiviral therapy is important for reducing the occurrence and recurrence of HBV-related HCC.

Patients with CHB receiving NAs therapy are at high risk of HCC development. The 5-year cumulative HCC incidence was 11.4% and 18.8% in patients with and non-CVR patients, respectively.[70] ETV and TDF have comparable efficacy in the prevention of HCC in patients with CHB, but the 5-year cumulative HCC incidence is still approximately 7%.[71–73] This is partly due to the evidence that NAs only slightly down-regulate HBV integration frequency and hepatocyte clone size even post 10 years of therapy.[74] PEG-IFN-α not only triggers natural killer cell function and restores the viral-specific $CD8^+$ T cell response to clear HBV-infected hepatocytes[75,76] but also strongly inhibits the transcriptional activity of integrated HBV DNA and cccDNA.[51] Thus, PEG-IFN-α therapy is associated with a lower incidence of HCC than NAs treatment in patients with chronic HBV infection.[77] The interim analysis of the PARADISE study revealed that the 2-year cumulative HCC incidence was 0% in NAs+PEG-IFN-α-treated CHB patients with an intermediate to high risk of HCC.[78] The 5-year cumulative incidence of HCC in CHB patients treated with PEG-IFN-α was 0% before and after propensity score matching compared to ETV therapy.[79] The cumulative incidence of HCC at 10 years was remarkably lower in the IFN-α/PEG-IFN-α treatment group than that in the NAs group (2.7% vs 8.0%).[80] The results of a retrospective study showed that the cumulative adverse outcome occurrence (decompensated cirrhosis, liver failure, HCC, liver transplantation, and death) at 10 years was significantly lower in the IFN-α/PEG-IFN-α treatment group (1.1%, 10/877) and the NAs group (11.9%, 44/370).[81] Importantly, a meta-analysis indicated that the pooled HCC incidence after HBsAg loss was 1.88%, which was reduced to 0.76% in patients with CHB without liver cirrhosis.[82]

IFN-α/PEG-IFN-α can be considered as a therapeutic option for HBV-related HCC patients without contraindications.[4] IFN-α/PEG-IFN-α monotherapy or in combination with NAs therapy prevents recurrence and improves overall survival (OS) in HBV-related HCC patients after hepatectomy or ablation.[83–89] IFN-α therapy after TACE can effectively inhibit HBV replication, improve liver function, enhance cellular immune response, reduce HCC recurrence, and improve survival in HBV-related HCC patients.[90–93] IFN-α/PEG-IFN-α treatment was well-tolerated in patients with HBV-related HCC. IFN-α/PEG-IFN-α-based adjuvant therapy can improve the disease-free survival, recurrence-free survival, and OS in patients with HBV-related HCC after curative treatment.[94–96]

Patients with HBV and HIV-1 Co-Infection

Both HBV and HIV-1 are blood-borne viruses that share similar routes of transmission, including unprotected sexual intercourse, contaminated blood product exposure, or mother-to-child transmission. The prevalence of HBV infection is 8.4–11.1% in people living with HIV-1 worldwide, among whom 26.8% are HBeAg-positive.[97,98] A nationwide retrospective observational cohort study with data from the China National Free Antiretroviral Treatment Program from 2010 to 2011 showed that 2958 (8.7%) participants had HBV and HIV-1 comorbidity.[99]

There is a complicated interaction between HBV and HIV-1 that influences the clinical outcomes of co-infection. Chronic HBV infection is associated with an increased risk of HIV-1 progression to acquired immunodeficiency syndrome (AIDS) or death.[100] Chronic HBV/HIV-1 co-infected patients have significantly lower $CD4^+$ T cell counts at highly active antiretroviral therapy (HAART) initiation than HIV-1 mono-infected patients [278 (146, 410) cells/mm^3 vs 350 (243, 471) cells/mm^3].[100] A notably faster rate of elevation in $CD4^+$ T cell count was found in HBV/HIV-1 co-infection during the period between 4 and 12 years, reaching comparable $CD4^+$ T cell counts to HIV-1 monoinfection.[100] HIV-1 RNA and HIV-1 p24 antigen can be detected in parenchymal and non-parenchymal liver cells,[101] and HIV-1 DNA persists in the hepatocytes of people living with HBV/HIV-1 co-infection on HAART.[102] HIV-1 infection not only promotes liver inflammation through microbial translocation (increased lipopolysaccharide and soluble CD14 levels) and chemokine-induced recruitment of active T cells into the liver in HBV comorbidity conditions[103] but also exacerbates HBV-induced liver fibrogenesis via positive feedback between hypoxia-inducible factor-1α and transforming growth factor-β1 in hepatic stellate cells.[104] The progression of chronic HBV infection to cirrhosis, liver failure, and HCC is greater in people living with HBV/HIV-1 co-infection.[105,106]

Patients with HBV/HIV-1 coinfection are recommended to be treated with drugs that suppress the two viruses simultaneously, inducing two drugs with anti-HBV activity to avoid the development of drug resistance to NAs.[4] The ALLIANCE trial revealed that both bictegravir/emtricitabine/TAF and dolutegravir/emtrictabine/TDF are effective

therapeutic strategies for adults with HBV/HIV-1 co-infection who are starting antiviral treatment.[107] Interestingly, effective HAART therapy can achieve a high rate of HBV functional cure in HBV/HIV-1 co-infected patients based on the clinical trials in China[108–111] and all over the world.[112–115] The HBV functional cure rate reached 10–30% in all enrolled patients with HBV/HIV-1 co-infection in response to HAART therapy without PEG-IFN-α treatment despite HBeAg status.[108,110,111,114,115] The factors associated with HBV functional cure in HBV/HIV-1 co-infection include rapid restoration of $CD4^+$ T cell count,[108,113,115] low serum soluble programmed death-1 (PD-1),[110] baseline HBV DNA,[110,113] HBV RNA,[114] and baseline and reduction of HBsAg and HBeAg levels during treatment.[108,111]

PEG-IFN-α has also been administered for HBV/HIV-1 coinfection. PEG-IFN-α2a+ribavirin therapy for 24 weeks induced complete cure of HBV and hepatitis D virus (HDV) with HBsAg loss, appearance of anti-HBs, and negativity for HBV DNA and HDV RNA in a patient co-infected with HBV and hepatitis C virus (HCV)/HDV/HIV-1.[116] In a Phase I clinical trial, five HBV/HIV-1 co-infected patients received PEG-IFN-α2a monotherapy, and the other five patients received PEG-IFN-α2a plus delayed-initiation TDF (beginning on week 18 of IFN therapy). Most patients present with decreased HBV DNA load and improved necroinflammatory and fibrosis scores post-therapy.[117] Administration of 48-week PEG-IFN-α2a to ongoing HAART induced HBeAg loss in 20% of patients with HBV/HIV-1 co-infection, but did not significantly increase HBeAg seroconversion or HBsAg loss.[118] Importantly, patients with HBV/HIV-1 co-infection experience a decreased $CD4^+$ T cell count while preserving or increasing their $CD4^+$ T cell percentage, as previously described in HCV/HIV-1 co-infected patients receiving PEG-IFN-α2a therapy.[119,120] In our opinion, a personalized course of PEG-IFN-α2 for ongoing HAART therapy may be more suitable and likely to achieve an HBV functional cure in HBV/HIV-1 co-infected individuals with viral suppression (negative for HIV-1 RNA and HBV DNA), high $CD4^+$ T cell counts (>350 cells/mm^3), and low HBsAg levels (< 1500 IU/mL).

Pediatric Chronic HBV Infection

Globally, more than 6.3 million children under 5 years of age are chronically infected with HBV, and the pooled average prevalence of HBsAg among children under 5 years of age is 0.9%.[121] The global age-standardized incidence of hepatitis B in children and adolescents decreases from 1385.20 per 100,000 in 1990 to 418.48 per 100,000 in 2021, with an annual average percentage change of −3.76%.[122] In China, the HBsAg prevalence at 1–4 years of age has reduced from 9.67% in 1992 to 0.30% in 2020.[123]

Antiviral strategies for children with chronic HBV infection should be comprehensively evaluated based on HBV DNA load, serum alanine aminotransferase (ALT) levels, HBsAg and HBeAg levels, liver inflammation/fibrosis based on imaging examinations (ultrasonography, computed tomography, or magnetic resonance imaging), or liver biopsy.[124] Antiviral therapy should be initiated immediately in children with CHB or advanced liver disease, despite the HBeAg status.[4,124] Importantly, age at treatment initiation is one of the most pivotal predictors of functional cure,[125–127] even in children with mother-to-child transmitted hepatitis B.[128] The HBsAg loss rate is more than 60% in patients aged 1–3 years and 40% in those aged 3–7 years, but the functional cure rate is robustly reduced to 1.64% at 12–16 years of age.[126,129] Thus, children with chronic HBV infection should be considered as early as possible to achieve functional cure.

IFN-α is recommended for children aged ≥ 1 year, whereas PEG-IFN-α2a is recommended for children aged ≥ 3 years.[124] IFN-α treatment for an average of 21 weeks induced HBsAg loss and seroconversion in 22.2% (4/18) of the children.[130] Moreover, 52-week of PEG-IFN-α2a monotherapy for CHB children (age 2–16 years) resulted in HBsAg clearance and seroconversion rates of 48.1% and 47.1%, respectively.[131] More than 90% of children achieving functional cure retained a sustained response during the 104-week followed-up.[131] Furthermore, a meta-analysis showed that IFN-α combined with NAs (eg TAF[132] or lamivudine[133]) therapy is more effective than IFN-α monotherapy in viral inhibition and serological response in children.[134] Importantly, IFN-α/PEG-IFN-α also induces a high rate of HBsAg loss in chronically HBV-infected children in the immune-tolerant or gray zone phase. IFN-α-based therapy leads to a cumulative functional cure rate of 56.3% (18/32) in chronically HBV-infected children with high-level viremia and normal or mildly elevated ALT levels after 36 months.[135] Data from the Sprout Project showed an overall HBsAg rate of 48.2% after 24 months of PEG-IFN-α2b treatment in HBeAg-positive ALT-normal children and adolescents.[136] Notably, 61.5% of

children developed detectable anti-HBs prior to HBsAg clearance.[136] Thus, children with detectable serum HBV DNA could be treated with IFN-α (age ≥ 1 year) or PEG-IFN-α (age ≥ 3 years) to achieve a functional cure as early as possible.

Side Effects and Barriers to Adherence

The clinical utility of PEG-IFN-α is influenced by inherent side effects and patient adherence challenges. The common and systemic side effects of PEG-IFN-α include flu-like symptoms, hematological abmormalities (commonly presented as leukocytopenia and thrombocytopenia), and metabolic and endocrine effects [commonly presented as weight loss, thyroid dysfunction (hypo- or hyperthyroidism), and mood disturbances (anxiety, depression)]. The organ-specific and severe side effects of PEG-IFN-α include hepatic flare, dermatological and autoimmune reactions, as well as pulmonary and cardiovascular effects (interstitial pneumonia and arrhythmias). Although excessive or prolonged ALT increase the risk of hepatic decompensation in patients with advanced fibrosis or compensated cirrhosis,[137] a single-center cohort study in compensated cirrhotic patients receiving PEG-IFN-α2b reported ALT elevation but no progression to end-stage liver diseases,[62] suggesting careful monitoring of liver function allowed for safe administration in patients with liver cirrhosis. Combination of PEG-IFN-α and NAs does not substantially increase the incidence or severity of side effects.

Adherence to Peg-IFN-α is critical for achieving functional cure, but multiple patient-, treatment-, and healthcare-related barriers reduce adherence rates, particularly in special populations. The patient-related barriers include lack of awareness of therapeutic goals and psychosocial factors. The main treatment-related barriers are injection route and frequency and side effects burden. The healthcare-related barriers consist of monitoring burden and cost and accessibility. The strategies to mitigate side effects and improve adherence include proactive side effect management, patient education and counseling, simplified monitoring schedules as well as financial assistance programs.

PEG-IFN-α-based therapy is effective for functional cure in special CHB populations, but its utility is constrained by manageable yet impactful side effects and adherence barriers. Common side effects are generally tolerable with monitoring and proactive management, while severe adverse events are rare but require careful patient selection. Adherence barriers can be mitigated through patient education, supportive care, and healthcare system improvements. A balanced approach that integrates efficacy data with safety and adherence considerations is essential for optimizing PEG-IFN-α usage in clinical practice.

Unaddressed Factors

The underlying basis for the effectiveness of PEG-IFN-α remains unelaborated due to limitations in existing clinical data and study designs, particularly the roles of population-related factors (eg ethnicity, host genetic variations) and viral genotypes in specific geographic regions. Firstly, ethnic differences in immune system function (eg innate immune activation, T-cell responsiveness) may directly influence the mechanism of PEG-IFN-α action. For example, Sub-Saharan African population with HBV/HIV-1 co-infection had higher baseline immune activation than East Asian populations,[112] which may alter PEG-IFN-α-induced immune restoration and thus treatment efficacy. The early treatment with IFN-α at age of 1–3 years achieves more than 60% HBsAg loss,[125–131] but most data are derived from Chinese pediatric cohorts. It remains unclear whether this high response rate is replicable in other ethnic groups (eg African, Caucasian children) who may have distinct immune maturation patterns. Secondly, host genetic polymorphisms, especially in genes regulating IFN signaling pathway or innate immunity, are critical determinants of IFN-α response in CHB population. For instance, polymorphisms in bone marrow stromal antigen 2 (BST2), an IFN-stimulated gene, predicted PEG-IFN-α response. The BST2 rs_9576 GG genotype was associated with higher HBeAg seroconversion and HBV DNA suppression.[138] However, few studies focused on the genetic factors contribution to PEG-IFN-α efficacy in special populations. For example, PEG-IFN-α reduced HCC recurrence by inhibiting integrated HBV DNA transcription and enhancing immune cell function,[51,75,76] but it is unknown whether polymorphism in tumor protein 53, which regulates tumor immune surveillance,[139,140] influences the ability of PEG-IFN-α to prevent HCC recurrence. Thirdly, HBV genotypes (A–J) exhibit distinct geographic distributions and differ in biological characteristics, which may impact PEG-IFN-α efficacy. HBV genotype A was independently associated with HBsAg loss in HBeAg-negative CHB patients with PEG-IFN-α combined with NAs therapy.[141] Addressing the above gaps through multiethnic, genetically informed, and genotype-

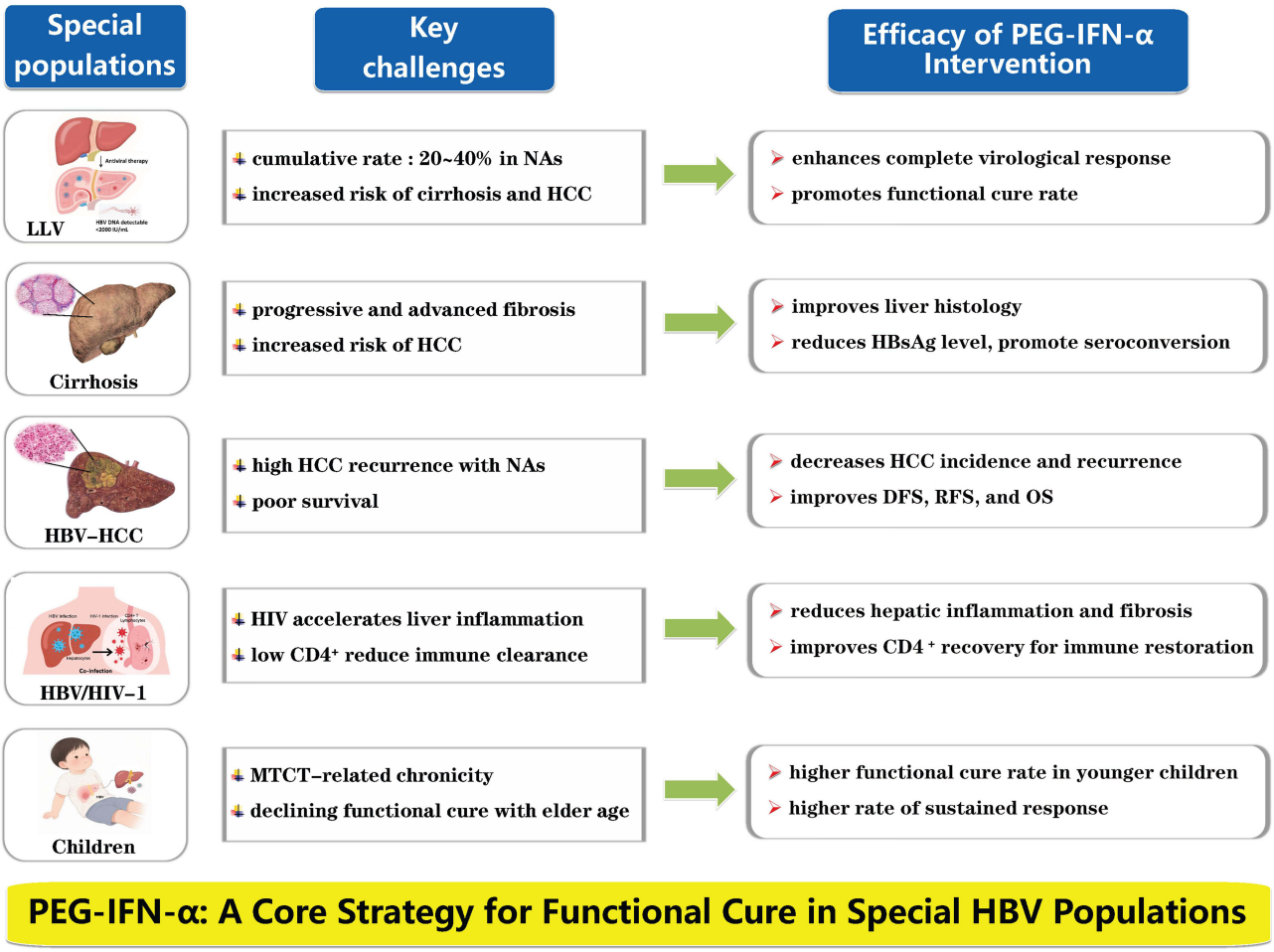

Figure 1 The key challenges and efficacy of pegylated interferon-α intervention for special populations with chronic hepatitis B virus infection.
Abbreviations: PEG-IFN-α, pegylated interferon-α; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HIV-1, human immunodeficiency virus-1; HCC, hepatocellular carcinoma; LLV, low-level viremia; NAs, nucleos(t)ide analogs; DFS, disease-free survival; RFS, recurrence-free survival; OS, overall survival; MTCT, mother-to-child transmission.

stratified research will not only deepen mechanistic understanding but also enable precise, personalized treatment strategies.

Conclusion and Prospection

In conclusion, PEG-IFN-α demonstrated consistent efficacy and safety in special HBV populations, laying the foundation for a functional cure and supporting clinical decision-making for HBV management (Figure 1). While PEG-IFN-α remains a cornerstone for functional cure in special populations with chronic HBV infection, emerging therapies are needed with synergistic potential to overcome current limitations (eg residual cccDNA, HBV integration, and suboptimal immune restoration). Integrating PEG-IFN-α with novel therapeutic strategies, such as small interfering RNA, Toll-like receptor agonists, and antisense oligonucleotides,[142] will target multiple HBV life cycles and address unmet needs, leading to the 2030 HBV elimination goal being closer to reality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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