

Review

Patient acceptability of, and attitudes towards, hepatitis B cure research – A scoping review and identification of knowledge gaps

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ABSTRACT

Functional cure, defined as durable loss of hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA suppression off therapy, is an increasingly important goal in the treatment of chronic hepatitis B. Although novel treatments aimed at achieving functional cure are being developed and tested in clinical trials, it is important to assess the perspectives of people living with HBV towards these potential treatments and their participation in HBV functional cure research. We have performed a scoping review that revealed that there is limited knowledge regarding patient perspectives of HBV functional cure research and then identified gaps in knowledge for further investigation. Our work highlights the need for further studies in patient perspectives in HBV functional cure research.

1. Introduction

The global burden of chronic hepatitis B virus (HBV) infection is estimated to be almost 300 million people, resulting in approximately 800,000 deaths per year.^{1,2} Current antiviral medications effectively decrease HBV DNA as well as liver fibrosis and disease progression,² yet treatment can be associated with toxicity, pill fatigue, stigma, and high costs. However, these treatments rarely achieve HBV functional cure,^{3,4} which is defined as hepatitis B surface antigen (HBsAg) loss (with or without anti-HBs seroconversion) and sustained HBV DNA suppression off treatment.^{5–8} However, functional cure is an important goal since it is associated with improved clinical outcomes, including decreased risk for hepatocellular carcinoma, over HBV DNA suppression alone.^{2,9,10} In contrast, to date, the goal of eradication cure for HBV, defined as the elimination of all viral proteins and genomes such that there would be no risk for relapse of the infection remains out of reach.^{11,12} The primary hurdle for eradication cure is overcoming integration of HBV DNA into the host genome and the stable intranuclear covalently closed circular DNA (cccDNA), which is the template for producing all viral RNAs.^{6,12–14} Thus, functional cure has also been established as an endpoint in clinical trials, treatment goals, and a threshold at which treatment discontinuation can be considered.^{4,5,15}

Although some new strategies to achieve functional cure include oral medications, other strategies involve injected or infusion medications with significant adverse event profiles. Further, clinical trials often include frequent study visits and blood sampling to monitor pharmacokinetics, unknown safety profiles and treatment response, and liver sampling (biopsy or fine needle aspiration). To determine whether newer strategies lead to functional cure, discontinuation of antiviral therapy after treatment completion in people who achieve HBsAg loss on treatment is required to determine if the loss is durable. Given these considerations, there is surprisingly little information about patient preferences regarding their willingness to participate in research involving various HBV cure strategies.^{10,16–19} Given that current HBV therapy with oral antiviral therapy is highly effective in HBV virologic suppression as well as mitigation of most, though not all, adverse clinical outcomes,² these experimental strategies must also be weighed against currently available well-tolerated antiviral therapy. In this scoping review, we outline the current landscape of perspectives of persons living with HBV (PLWHBV) on HBV cure research. We then identify possible areas for future research.

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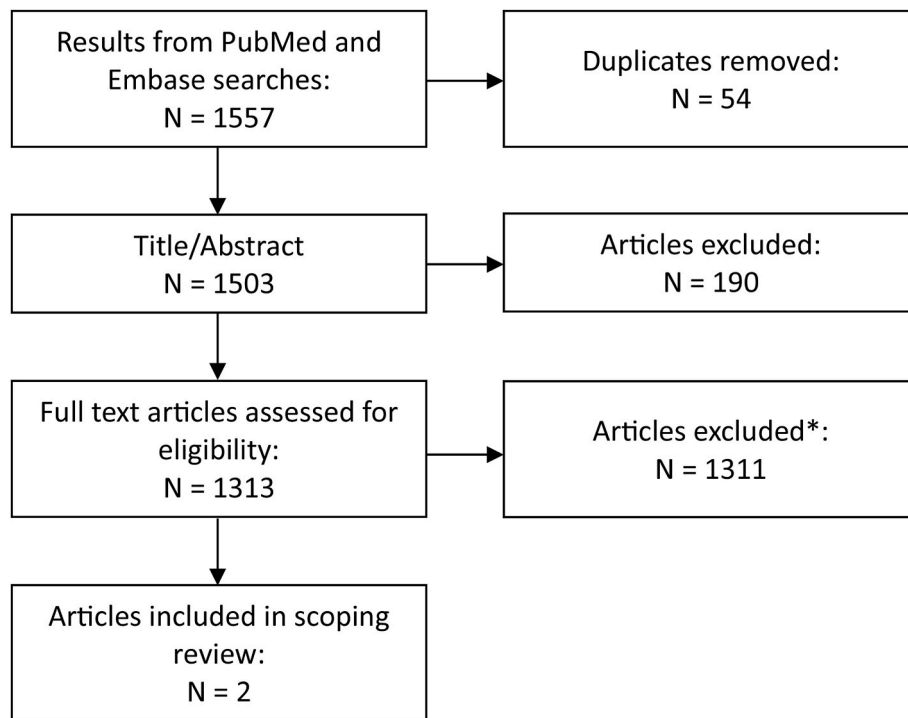


Fig. 1. Study selection flow chart.

Table 1
Summary of scoping review included articles.

| Author | Article Type | Study | Attitudes of PLWHBV |
|-------------------------|-------------------|---|--|
| Freeland ²⁰ | Original Research | 19 PLWHBV in the United States | Main drivers of participant decision/acceptability for HBV functional cure: high efficacy, therapy regimen, safety, and number of physician visits Functional cure improvements positively correlated with probability of choosing a treatment alternative |
| Hardstock ²¹ | Original Research | 130 PLWHBV in Germany attending outpatient gastroenterologists and hepatologists, and eligible hospital departments | Majority of participants felt positively about functional cure Most participants were wary of side effects (wanted low side effects), and high efficacy Some participants expressed importance of representation in HBV clinical studies, as well as accessibility and affordability |

2. Methods

2.1. Review questions and objective

Our primary objective was to understand the acceptability of, and attitudes towards, HBV cure research among PLWHBV by reviewing existing literature on questions around patient acceptability, feasibility,

patient-reported outcomes, and HBV novel therapeutics with a future goal of guiding socio-behavioral research that could help inform a multi-disciplinary HBV cure research agenda.

3. Methods

We performed a search of Medline and Embase specific to PLWHBV and their attitudes, perspectives, and willingness towards HBV cure research (Fig. 1). Our initial search yielded 366 articles. To ensure that all potential articles were included, we expanded our search criteria and identified a total of 1557 articles. Of those, 1313 papers remained after removing duplicates and articles without full text. The full search strategy is available in Supplementary Text 1. We excluded abstracts and any papers that did not include HBV cure research perspectives of PLWHBV. Full articles published between January 1980 and March 2023 written in English were assessed by two authors (N.Z.M and D.B.) who independently reviewed each paper to determine eligibility. Data from the eligible articles include attitudes of PLWHBV towards HBV cure and HBV cure research, as well as authorship information, article type, and cohort (Table 1).

4. Results

Our search yielded two articles that are included in this review (Table 1).

Freeland et al. conducted qualitative interviews with 19 PLWHBV in the United States regarding HBV functional cure treatment preferences.²⁰ The majority of interviewees desired a functional cure, though they expressed wariness about side effects. Specifically, 79% were currently on treatment, and did not want the functional cure therapies to lead to more side effects than they currently had. Their preferred functional cure would be highly efficacious and have minimal side effects. Their preferred modality was either a daily pill or an injection that was long-acting so that they would only need to come into clinic once every few months. Some participants also expressed the importance of gender and racial representation in HBV clinical research, and that accessibility and affordability of future treatments post-trial were also

crucial considerations.

Hardstock et al. performed a discrete choice experiment (DCE) in Germany with 130 participants at 30 sites that assessed the preferences of PLWHBV regarding hypothetical HBV functional cure regimens.²¹ In the DCE design, participants were given several scenarios where the levels of the attributes in each scenario varied in efficacy, number of days with side effects, travel distance to doctor, frequency of doctor visits, and mode of delivery. The main drivers of acceptability in terms of relative importance were high efficacy (57%), therapy regimen (17%), safety (12%), and number of physician visits (11%). Highly efficacious treatment was preferred (utility 1.46 $p < 0.001$); as was an oral regimen when compared to electroporation (EP, the practice of temporarily opening pores in cell membranes such that DNA may be introduced into the cell) plus tablets (utility 0.430, $p < 0.001$). EP plus tablets compared to subcutaneous (SC) injection plus tablets did not show a statistically significant difference in preference (utility 0.459, $p = 0.06$). Patients preferred fewer physician visits (utility 0.29, $p < 0.001$) and no days per month with side effects compared to 3 days per month (utility 0.18, $p = 0.013$). A latent class analysis distributed the participants into three main classes: Class 1 (46% of participants) placed the highest importance on efficacy; class 2 (36%) had a more equal distribution of importance among frequency of required physician visits, safety profile, and efficacy; and class 3 (18%) placed the most importance on route of treatment administration. Bivariate analyses revealed that previous experience with side effects was associated with class 2 grouping, and older age was associated with class 3 placement.

These investigations found that the efficacy of HBV functional cure regimens is paramount for PLWHBV, though some are willing to do whatever it takes to achieve functional cure, regardless of side effects.^{20,21} PLWHBV were also concerned about safety and the risk of side effects in functional cure, with high efficacy and low side effects highly preferred.

5. Discussion

As the HBV research field turns its focus towards cure it will be critical to assess the perspectives of patients who could eventually benefit from these novel interventions. The most important finding from our scoping review is the paucity of data regarding patient perspectives on HBV cure and novel therapeutics research. Further, this scoping review has identified several gaps in knowledge that will be critical to address as the field strives towards HBV functional cure. In the two published papers included in this scoping review, we found that efficacy of HBV functional cure regimens is paramount, and patients are concerned about safety and the risk of side effects.^{20,21} One of the considerations in HBV cure that these papers reveal is that PLWHBV placed high value on functional cure particularly if it is effective and includes minimal risk of adverse events and side effects, so developing new therapies that match or improve upon this minimal side effect profile will be challenging. Oral regimens as well as reduced physician visits may be preferred.²¹ Nevertheless, both studies were conducted in high-income countries (United States and Germany) that have low HBV endemicity; thus, further studies that include people from diverse populations in areas with higher HBV endemicity will be important to either reinforce or dispute these findings and to discover unanswered questions regarding PLWHBV's attitudes towards HBV cure research. Developing a framework for these investigations may be facilitated by building on what has been learned regarding HCV and HIV cure research, where the current literature on patient attitudes towards cure research, clinical trials, novel therapeutics, and treatment is more robust.^{22–32}

Patient perspectives are crucial to developing HBV cure research strategies and protocols.^{33–36} However, studies of PLWHBV regarding their acceptability of, and attitudes towards, HBV cure research are currently limited and, to our knowledge, only include the two papers presented in this scoping review. Although we did not include conference abstracts in our search methodology, we are aware of one that

Table 2
Future research questions.

| Questions of interest |
|--|
| What is the acceptability of conducting clinical HBV cure research for persons living with hepatitis B (PLWHBV)? |
| What are the attitudes towards and acceptability of various potential HBV cure research strategies for PLWHBV? |
| What are the attitudes towards and acceptability of side effects in HBV cure research in PLWHBV? |
| What is the acceptability towards liver biopsy or fine needle aspirations in developing an HBV cure? |
| What are the attitudes toward HBV treatment interruptions in PLWHBV? |
| Are PLWHBV concerned about cost effectiveness in HBV cure research? |
| Are PLWHBV concerned about fairness and equity in HBV cure research? |
| Are PLWHBV concerned about scalability of interventions to resource-limited settings? |
| What would be the target product profile for globally scalable HBV cure? |

reported that the majority of PLWHBV felt positively about functional cure once the concept was defined.³⁷ Related work has focused on the perspectives of PLWHBV on current treatments and care as well as barriers to treatment,^{38–46} which may be helpful in developing studies regarding the acceptability of HBV cure research in PLWHBV.

In light of the findings of this scoping review we have identified several research questions currently unanswered by the literature (see Table 2). Our research questions primarily target research and treatment strategies as well as equity and scalability, which we believe are critical to appreciate the attitudes of PLWHBV regarding HBV cure research. It will be important for investigators and stakeholders to explore these questions in order to develop effective clinical trials for HBV cure. Understanding the attitudes of PLWHBV towards HBV cure research, and their involvement in developing this research, are both critical to developing equitable, effective, and scalable HBV cure research studies.

6. Limitations

Our search yielded a limited number of papers that specifically included the perspectives of PLWHBV regarding HBV functional cure that we could include despite using wide search criteria. In addition, they were from high income settings and in a US/European cultural context.

7. Conclusions

The dearth of person-centered research on acceptability of, and attitudes towards, HBV cure research calls for urgent investment in this area, particularly in areas of high HBV endemicity. Understanding perspectives of PLWHBV will be critical to informing a multi-disciplinary HBV cure research agenda and developing translatable HBV cure discoveries for those who need them most, particularly in low- and medium-income settings.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JS: Oxford University Press and Georgetown University Press (academic book royalties); Merck KGaA and IQVIA (consulting fees, support to attend ethics advisory board meeting); Biogen (consulting fees); Merck (participation on a Data Safety Monitoring Board or Advisory Board); Aspen Neurosciences, Inc (consulting fees and stock options)

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Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jve.2023.100354>.

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