SYSTEMATIC REVIEW

A blind spot? Confronting the stigma of hepatitis B virus (HBV) infection - A systematic review [version 1; referees: 1 approved with reservations]

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Abstract

Background: The Global Hepatitis Health Sector Strategy is aiming for the elimination of viral hepatitis as a public health threat by 2030. Successful diagnostic, treatment and preventive strategies can reduce incidence and morbidity; it is important to ensure that these interventions and services are not only available, but also accessible. Stigma, poverty, and lack of knowledge may present a substantial barrier, especially in resource limited settings. We therefore set out to assimilate evidence for the nature and impact of stigma on the lives of people with HBV infection and on the community, and to suggest ways to tackle stigma and discrimination.

Methods: We carried out a literature search in PubMed using the search terms ‘hepatitis B’, ‘stigma’ to identify relevant papers published between 2007 and 2017 (inclusive), with a particular focus on Africa.

Results: We identified a total of 34 articles, of which only one study was conducted in Africa. Lack of knowledge on HBV was consistently identified: there were misconceptions about HBV transmission among the public, healthcare workers (HCWs) provided inaccurate information to individuals diagnosed with HBV, and poor understanding resulted in lack of preventive precautions. Stigma negatively impacted on health behaviour such as help-seeking, screening, disclosure, prevention of transmission, and adherence to treatment.

Conclusion: Stigma is a potentially major barrier to the successful implementation of preventive, diagnostic and treatment strategies for HBV infection, and yet there is very limited recognition of the magnitude of this challenge, especially in Africa. There is a need for more research in this area, to
identify and evaluate interventions that can be used effectively to tackle stigma in HBV, and to inform collaborative efforts between policy makers, HCWs, traditional healers, religious leaders, charity organisations and support groups, to improve awareness and tackle stigma in HBV in Africa.

**Keywords**
hepatitis B virus, discrimination, stigma, barriers, ethics, funding, elimination, Africa

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- **Matthews PC:** Conceptualization, Investigation, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Hepatitis B virus (HBV) infection has been reported worldwide, with an estimated burden of 250 million cases, and has been associated with high mortality rates resulting from complications including cirrhosis and hepatocellular carcinoma (HCC)\(^1\). There are effective prevention and treatment strategies available, including vaccination and suppressive antiviral therapy, both of which also contribute to prevention of vertical transmission\(^2\). The Global Hepatitis Health Sector Strategy is aiming for the elimination of viral hepatitis as a public health threat by 2030\(^3\). However, there are important challenges still to be addressed including gaps in vaccine coverage\(^4\), limited access to diagnostic tests and treatment\(^1\) and lack of a curative therapy\(^2,4\). Stigma, poverty, and lack of knowledge add further to the challenge, especially in resource-limited settings\(^5\). There is a growing body of personal testimonies providing evidence of stigma associated with HBV\(^6\). However, there is a very limited literature to describe this, and more work is required to understand the nature and impact of stigma for individuals with HBV infection.

Individuals who are stigmatised as a result of illness or infection not only have to bear potential challenges to health, but may also be denied the opportunities that define quality of life such as education, employment, access to appropriate health care and interaction with a diverse cross-section of society\(^7\). Although many diseases are stigmatised, awareness of – and investigation into – stigma is better represented in some areas than others. In HIV, stigma has been shown to limit engagement with services including screening and prevention of mother to child transmission (PMTCT), and uptake of antiretroviral therapy\(^8\); in tuberculosis (TB) it has been shown to cause diagnostic delays and treatment non-compliance\(^2,3\), and in mental illness, stigma has been associated with delays in help-seeking, discontinuation of treatment, suboptimal therapeutic relationships, patient safety concerns, and poorer quality mental and physical care\(^4,14\).

Stereotypes and prejudice may stem from physical differences attributable to the condition, misconceptions associated with fear of contagion, and judgements about routes of transmission, all of which may be underpinned by lack of knowledge\(^7,15\). Beyond the physical manifestations and potential complications of an illness, stigma usually arises from lack of awareness, lack of education and lack of perception\(^20\). People living with HIV/AIDS, especially those displaying wasting syndrome and certain identifiable opportunistic infections are more prone to stigma compared to those who are asymptomatic\(^8\). HIV and TB may be stigmatised as a result of anxieties about spread of infection, and may also be regarded as a punishment for ‘irresponsible’ or ‘immoral’ behaviour\(^3,21,22\). People with mental illnesses may be considered ‘dangerous’ or provoke fear, may lose their autonomy, or be treated as ‘childlike’\(^2\). Understanding why society reacts in a particular way is one way to address stigma\(^8\), and could therefore help to guide approaches to tackling stigma in HBV.

HBV is highly endemic in Africa, a continent that faces huge challenges in prevention, diagnosis and treatment\(^1\). The situation is further complicated by the substantial public health challenge of co-endemic HIV and HBV\(^21\). An understanding of the breadth and scope of stigma in HBV, especially in Africa, is an essential part of any strategy that seeks to tackle and eventually eliminate HBV infection as a public health problem. As the improvement of universal availability and accessibility of diagnostic, treatment and vaccination options are underway, it is important to ensure that products and services are not only available, but also accessible; people with HBV infection must be able to access education, clinical care, and support from their partners and families, healthcare workers, and members of their communities. Also, the WHO recommends HBV treatment in an environment that minimizes stigma and discrimination\(^20\).

We therefore set out to assimilate evidence for the nature and impact of stigma on the lives of people with HBV infection and on the community, to describe coping strategies employed by people with HBV, and to suggest ways to tackle stigma and discrimination.

Methods

Search strategy

In November-December 2017, we undertook a literature search in PubMed; our search strategy is detailed in Supplementary file 1. We carried out two searches: the first search focused on stigma in HBV in Africa; and a second search which was not limited to Africa. These searches yielded 50 and 879 articles, respectively. 49 articles were duplicates. On reviewing the titles and abstracts, 827 were excluded from search results as they were not on stigma or HBV. Full texts of 53 articles were reviewed and 19 were excluded (3 were reviews, 3 were reports, 1 was not available, and 12 did not report on stigma). A total of 34 articles were therefore downloaded in full (Supplementary file 3). From each publication, we extracted: citation, study design, sample size, study population, country, factors associated with stigma, impact of stigma on the lives of people with HBV, and proposed interventions to tackle stigma in the society. Data were curated using MS Excel software (Microsoft, Redmond, WA). Ethics approval was not required for this study.

Results

The full metadata generated from our literature search are available in Supplementary file 2.
Factors associated with creating or perpetuating stigma for individuals with HBV infection

Some of the common themes identified from literature that are associated with stigma and HBV are summarised in Table 1.

Lack of knowledge is a central theme in perpetuation of stigma. This applies to education among individuals with the infection, but also their families, society and health care workers (HCW). Failure of HCWs to provide adequate and accurate information may be a barrier to treatment, reduce the likelihood of disclosure to family, and contribute to fear, anxiety and depression which in turn negatively impact on coping strategies. Lack of knowledge may also be a reason why some HCWs are not themselves vaccinated against HBV and therefore are at an increased risk of acquiring HBV. A study carried out in Cameroon reported a HBV vaccination rate of only 12% among HCW, and a study in Nigeria reported a 25% prevalence of HBV infection among surgeons. Lack of awareness among policy makers negatively impacts on appropriate prioritisation, and this can be an important contributor to poor advocacy, inadequate allocation of resources and poor levels of education.

Given that HBV is not well understood in some communities, it may be considered a punishment or linked to ‘evil spirits’. Some individuals may therefore opt to seek assistance from traditional healers (THs) or faith leaders, seeking ‘purification’. Although THs and religious healers can have an important role in providing psychosocial support, there is also the potential for harm and/or delaying presentation to clinical care. A recent report showed that in Africa, HCC presents at a late stage, where effective treatment would be challenging for any healthcare system. Specialised training on HBV for THs and ministers of faith, and healthcare programs that work collaboratively with these groups, could be a valuable approach in some settings.

Although stigma has also been associated with old age and following of traditional values, this may primarily reflect lack of knowledge or exposure, while younger people tend to have more access to information, and are less defined by traditional values. However, this relationship is not consistent, as one study found an association between old age and decreased prejudice in HBV infection. It is important to pay special consideration to specific groups of people who might be most vulnerable to the effects of stigma when designing interventions.

Stigma affects various aspects of everyday lives of people with HBV infection (Table 2). Similar to mental disorders and HIV/AIDS, stigma in HBV can negatively impact on health behaviour such as help-seeking, screening, disclosure, prevention of transmission, access and adherence to treatment, and poorer quality mental and physical care.

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Table 1. Factors underpinning stigma in HBV infection, identified from a literature review.

<table>
<thead>
<tr>
<th>Lack of knowledge or awareness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of knowledge among the public was represented by:</td>
</tr>
<tr>
<td>1. Misconceptions that HBV can be transmitted through sharing of utensils, via food or eating together;</td>
</tr>
<tr>
<td>2. Beliefs that HBV is a genetic trait;</td>
</tr>
<tr>
<td>3. Lack of awareness that HBV could be transmitted sexually;</td>
</tr>
<tr>
<td>4. Representation of HBV as a consequence of bad behaviour, or perception of individuals with HBV as ‘bad’ people;</td>
</tr>
</tbody>
</table>

Lack of knowledge among healthcare workers (HCWs) was represented by:

- Lacking or inaccurate information provided by HCWs regarding HBV diagnosis or treatment;
- Provision of inappropriate reassurance, or overemphasisation of potential complications;
- Poor understanding among HCWs regarding appropriate laboratory testing to diagnose HBV infection;

Lack of knowledge among individuals with HBV was represented by:

- Lack of necessary precautions for prevention of transmission;
- Difficulty processing information about the infection, leading to anxiety or depression;
- Pursuit of traditional or religious interventions reflecting the belief that infection may be caused by evil spirits.

Other factors associated with stigma

Stigma in HBV has been associated with:

- Extremes of age (in some cases this is evident in older age and in other reports, in younger age groups);
- People strongly defined by traditional values;
- Lower education levels;
- People who have not themselves been screened or vaccinated against HBV.

Among HCWs, hesitance to provide care to individuals with HBV infection was noted among:

- Those who had not come across or offered healthcare to an individual with HBV infection;
- Those who perceived an infection risk to themselves or had low individual confidence in protecting themselves.
Coping strategies and interventions for HBV stigma

Coping strategies that have been described for HBV are listed (Table 3). Depending on the coping strategies used, not everyone experiencing stigma will necessarily suffer emotional distress or have diminished well-being as a consequence. In HIV, avoidant coping strategies such as denial have been associated with higher levels of depression whereas acceptance of the diagnosis, associated with personal control and self-efficacy, is associated with reduced levels of depression. Among patients with schizophrenia, the ability to use positive coping strategies was associated with reduced self-stigma. Further studies are needed to explore coping strategies used to deal with HBV stigma, to explore the choice of coping strategy, and to determine outcomes.

As well as individual coping strategies, a variety of other interventions have been proposed to tackle stigma (Table 3). In many cases, attitudes may improve after realising that infection can be prevented and managed therapeutically. This is in line with a report from the WHO about mental illness, highlighting that stigma can be combated through educational messages representing conditions as illnesses that respond to specific treatment.

Counselling can provide several benefits, alleviating anxiety associated with a new diagnosis, as well as providing an opportunity to share factual information regarding treatment, prevention, self-care and overall well-being.
Despite the limited evidence from Africa, the data we have gathered reflect consistent themes in stigma and discrimination affecting individuals with chronic viral hepatitis infection. These may have a wide-reaching influence on physical health (for example inhibiting interaction with clinical services and reducing treatment adherence), psychological well-being (through increasing isolation, anxiety and depression), and interactions with family and the wider society (by limiting relationships, social interactions and employment opportunities). Recognising, understanding and tackling the issue of this stigma in African populations could be a valuable tool to improve population health and to underpin advances towards elimination strategies proposed for the year 2030.

Limitations and caveats
There are very few data to inform this discussion: we identified only two studies on stigma from Africa and three other studies included African participants in North America, Australia and in UK. Although we did a robust search of the peer-reviewed scientific literature, there may be other sources that are not captured by this scientific style of approach. Most studies had very small sample sizes and some were opportunistic in recruiting participants, thus limiting generalisability of the findings. We have therefore also drawn on the literature for HIV, TB and mental illness.

Future aspiration and challenges
Studies looking at stigma may benefit from a mixed method study design, providing stronger evidence and increasing generalisability of the findings. It is important to carry out research on stigma with the aim of demonstrating its burden and its effects, while also considering how to establish and evaluate interventions that tackle stigma within communities. We identified only one study that evaluated the effectiveness of stigma reduction programmes among Asians in USA. More studies like this are needed in Africa as they will also help to deploy resources in the most appropriate and effective ways.

Table 3. Coping strategies and other interventions that have been used to tackle stigma in HBV, identified from a literature review.

<table>
<thead>
<tr>
<th>Coping strategies for individuals with HBV infection</th>
<th>Coping strategies associated with negative influence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Seeking words of encouragement and prayers from spiritual leaders or family members;</td>
<td>• Establishing culturally appropriate public education or awareness programmes that promote surveillance and treatment;</td>
</tr>
<tr>
<td>• Lifestyle modification, such as reduced intake of alcohol and fatty foods;</td>
<td>• Providing specialised training about HBV infection, which may be designed to target people living with HBV, HCWs, THs, and the wider public;</td>
</tr>
<tr>
<td>• Reaching out for support from family members and friends;</td>
<td>• Training of policy makers and healthcare professionals on the urgency of tackling HBV, and on prevention, diagnosis and treatment;</td>
</tr>
<tr>
<td>• Use of support groups;</td>
<td>• Training of healthcare workers to provide pre- and post-test counselling;</td>
</tr>
<tr>
<td>• Note that certain coping strategies may also result in negative influences, such as avoiding disclosure, disengagement from seeking active treatment, and emotional responses including grief, denial, anger and aggression.</td>
<td></td>
</tr>
</tbody>
</table>

There are several strategies that have been used to raise awareness of HIV/AIDS which could be applied to HBV. Dissemination of factual information through use of radio, television, posters, pamphlets and drama has been widely used to diminish stigma towards HIV in resource limited settings. Multiple educational sessions can also be an effective way of increasing awareness and therefore reducing stigma, as participants have the opportunity to reflect on the concepts learnt in the previous sessions. Another successful method for training HCWs is perspective-taking and empathy: participation is associated with increased willingness to treat people with certain illnesses, decreased stigma and increased awareness of confidentiality among healthcare workers. These approaches could be used to tackle HBV stigma among HCWs and community members.

On-line support groups provide a platform for people living with HBV to share their experiences, and charities can be influential in raising awareness, and promoting important health messages. The internet is widely used as a tool for sharing experiences, and as such can raise awareness of stigma, as well as uniting individuals and communities as a support network. It is important for HCWs to introduce newly diagnosed individuals to these avenues to help people living with HBV. Importantly, more charities and support groups that are well suited for people with HBV infection in Africa are needed.

Discussion
Despite the limited evidence from Africa, the data we have gathered reflect consistent themes in stigma and discrimination.
In addition to raising awareness among individuals with HBV infection, the general public and HCWs, enhanced communication with policy makers is also crucial. Despite the high burden of HBV in low and middle-income countries, there is limited infrastructure to support diagnosis and treatment, and disproportionately little international research funding for HBV compared to other infectious diseases.

Conclusion

Stigma is a potentially major barrier to the successful implementation of preventive, diagnostic and treatment strategies for HBV infection, and yet there is very limited recognition of the magnitude of this challenge, especially in Africa. Lack of knowledge among policymakers, HCWs, the general public and patients is a potent driver of stigma. Stigma in turn, negatively impacts health behaviour such as help-seeking, screening, disclosure, prevention of transmission and adherence to treatment. Establishing education programmes and awareness campaigns is crucial. There is also a pressing need for more research in this area, to identify and evaluate interventions that can be used effectively to tackle stigma in HBV, and for collaborative efforts between policy makers, HCWs, traditional healers, religious leaders, charity organisations and support groups, to improve awareness and tackle stigma in HBV in Africa.

Data availability

All data underlying the results are available as part of the article and supplementary files, and no additional source data are required.

Competing interests

No competing interests were disclosed.

Grant information

JM is funded by a Leverhulme Mandela Rhodes Scholarship. PCM is funded by the Wellcome Trust (grant ref. 110110).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary material

Supplementary file 1: Details of search strategy used to identify studies on stigma in Hepatitis B virus (HBV) infection, from PubMed database. The terms in each row were combined by Boolean operator ‘OR’, the columns were combined by Boolean term ‘AND’. We carried out two searches: the first search focused on stigma in HBV in Africa - we combined all the columns in search strategy (#1 AND #2 AND #3); a second search was not limited to Africa – for this we only combined columns (#1 AND #3).

Click here to access the data.

Supplementary file 2: Full details of 34 studies identified by a systematic literature search of stigma in Hepatitis B virus (HBV) infection published between 2005 and 2017.

Click here to access the data.

Supplementary file 3. Flow diagram illustrating identification and inclusion of studies for a systematic review of stigma in Hepatitis B virus (HBV) infection, based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria.

Click here to access the data.

References

5. Hepatitis B Foundation. Reference Source
Open Peer Review

Current Referee Status: ?

Version 1

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Summary: The article presents findings from a systematic review on HBV stigma. The authors recognize the large burden of HBV globally and the potential for stigma to hamper prevention, diagnosis and treatment. They unpack the lack of knowledge underpinning the stigmatization of HBV as well as some factors associated with stigmatization of HBV. They also present findings on how HBV stigma impacts health care, familial and social relationships, employment, mental health, and behavior. The authors also describe strategies individuals use to cope with or manage HBV stigma and interventions to address HPV stigma. Finally, the authors conclude by identifying gaps in the literature, particularly a paucity of research conducted in Africa, and provide guidance for future research.

Specific Comments to explain ratings:

With respect to rating for Question 1 (partly): The rationale for the paper is clear, however the objectives of this paper are less clear. We are uncertain what the word assimilate means with respect to the literature. Did the authors mean to use this term? If so, it may be helpful to explain it further. As well, it’s unclear if the authors are going to abstract suggestions to address stigma and discrimination from the included articles or if they are going to use their findings to provide suggestions, drawing on literature from other stigmatized conditions. It is also unclear from the results section, and in particular the literature included in the tables, if this literature review is restricted to HBV stigma, or also includes HIV and mental health stigma (in which case the review is not extensive enough). The supplementary material showing the search strategy indicates it is restricted to HBV stigma, yet the results section suggests otherwise. The paper would be strengthened by a clearer statement of the objectives and then ensuring that those objectives are adhered to throughout.

With respect to rating for Question 2 (partly): The authors do not include their specific inclusion/exclusion criteria, which relates to the point above with respect to the mixing of what looks like included literature from the search, with other literature from HIV and Mental Health in the results section. It is also unclear how “factors associated with stigma,” “impact of stigma on the lives of people with HBV,” and “proposed interventions to tackle stigma in the society” were systematically captured. There is one article included in the data abstraction supplementary file (Cochrane et al 2016 1) for which “not/applicable” is listed for all of the data abstraction categories related to stigma. It is unclear why this article is included.

More detail is needed on the process of reviewing and selecting which abstracts went to full review and
then which articles were included. Was this done by one person? Two people who then compared results with a third as tie breaker in cases of disagreement? This information will help the reader assess the strength of the review.

A standard figure showing the two searches graphically would be helpful for the reader (how many initial abstracts, how many of those went to full review and then how many of those were included).

**With respect to rating for Question 4 (partly):** The manuscript would benefit from the authors including a discussion on risk of bias in their process and review. They do not mention bias or describe any methods used for assessing risk of bias of individual included studies. Other limitations that need to be mentioned include that many of the findings presented in the results section come from a single article (e.g. in most of the tables, each point often only has one reference attached to it, and in some cases not even a reference from the search itself).

**Other comments:**

**Abstract:** The authors state that only one study was conducted in Africa, while in the limitations it states that two studies were conducted in Africa.

**Overall language comment:** Please do not use HIV/AIDS, it is considered stigmatizing. UNAIDS language guidelines recommend using HIV, HIV and AIDS, or HIV or AIDS, depending on the context. Using HIV/AIDS implies HIV=AIDS and that one cannot live a long, healthy and productive life with HIV.

**Methods:** See comment above on explanation for rating for Question 2.

**Results:** The results section would be strengthened by presenting only the results of the search in the results section and keeping discussion (and inclusion of non-HBV stigma literature) to the discussion section. The results section often seems more like a discussion section and it is sometimes difficult to tell what findings are coming from the HBV stigma literature review, versus what are coming from other articles not included in the review (e.g. some of the findings presented in tables are from HIV, mental health or general stigma literature), or are views/conclusion the authors have drawn. For example, in the 4th paragraph of the “Factors associated with creating or perpetuating stigma for individuals with HBV Infection” section, the authors hypothesize about why a certain trend is observed. As well, the “coping strategies and interventions for HBV stigma” section is almost entirely a discussion of coping strategies that have been used to tackle stigma in other fields or interventions that have been used to address stigma related to diseases other than HBV. While pertinent, this information probably belongs in the discussion section.

The results section would benefit from a clearer organizational structure and ensuring only results from the HBV literature are included. For example,

- “Factors associated with creating or perpetuating stigma for individuals with HBV Infection"
  - It seems the first section is trying to unpack factors driving or causing stigma and factors associated with higher levels of stigma. However, this section also includes some behavioral impacts, such as pursuing traditional or religious intervention at the individual level, which could be considered “impact on access to care”
  - At the health care level, providing inaccurate information and the provision of inappropriate reassurance or over emphasis of potential complications seem to be the result of lack of knowledge, rather than evidence of lack of knowledge, that could be considered “impact on access to care” or “impact on quality of care.”
  - The text notes stigma among policy makers can be problematic, but this isn’t supported by evidence in the table.
Table 1: Unclear if these factors are actually coming from the HBV literature or not, given the inclusion of HIV articles in the table that from the supplementary material describing the literature search, were not included. For example references 40, 41.

Table 2:

1. The “Impact on mental health” section of the table seems to have some redundant items, particularly around guilt and shame

2. The “Impact on social behavior” section of the table seems to largely encompass manifestations of stigma, but not necessarily social behaviors. It is unclear what is meant by “suffer feelings of “passivity” because of lack of treatment, or cost of treatment, which results in missing…”

3. The “relationship with education/knowledge” section seems to almost entirely overlap with the previous table, highlighting factors associated with stigma. However, it is interesting to highlight that stigma may drive lack of knowledge just as lack of knowledge may drive stigma. However, this might be better said in the text.

4. All references to articles that were not part of the actual HBV stigma review should be removed. This includes references 40, 41, 57,58, 59. The articles should instead be referred to in the discussion section if the authors feel they are important to discuss around a key result.

Coping strategies and interventions for HBV stigma

Table 3

1. The title “Coping strategies associated with negative influence” is unclear. It seems like this bullet is for interventions.

2. All references that are not coming directly from the review need to be removed. Specifically, #’s 40,48, 57, 58, 70

The table included in the supplementary material showing the articles should be included within the body of the article in a reduced format, given it is central to the review process.

Discussion: The discussion section paragraph reads more like a conclusion paragraph, while there is much discussion embedded in the results section. Moving the discussion from the results into the discussion section will strengthen both the results and discussions section and also make clearer to the reader what is emanating directly from the review of the HBV literature versus what the authors are supplementing from other fields, because of the sparse HBV stigma literature. The discussion section could be expanded by discussing what the gaps are that were found—and then using the literature from other fields to suggest how those gaps might be filled etc.

Limitations: In addition to comments above to Q.4, it would be appropriate to discuss the strength of findings/quality of included articles. Was any rating of the quality of articles conducted? We also find the statement at the end of the limitations section that literature from HIV, TB and mental illness was drawn on, because of the limitations of the literature found to be confusing. The fact that this was done, muddies
the methods and results sections. If the literature review is only focused on HBV stigma, no matter how scarce the literature is, only this literature should be drawn on/presented in the results section. Other literature can/should be discussed in the discussion section. This is conflating of the results coming from the search itself, with ‘supplementary’ literature from other fields in the result section is problematic. Please move all discussion of other literature not coming from the literature search on HBV to the discussion section.

Conclusions: The conclusions state stigma may disrupt adherence, however, adherence to treatment is not discussed in the results. However, hampered adherence is listed as an impact of stigma in the abstraction table for the Huang et al 20162 article.

References

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.