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Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection

Mbah P Okwen[1], **Savanna Reid**[2], **Basile Njei**[3], and **Lawrence Mbuagbaw**[1]

[1]Centre for the Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon

[2]Department of Epidemiology and Biostatistics, University of Nevada, Las Vegas, Henderson, Nevada, USA

[3]Section of Digestive Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Abstract

Background—Hepatitis B vaccine has been recommended for use in people living with HIV (PLHIV) mostly because of the similarities in routes of infection and their prevalence in the same geographic areas. PLHIV may not develop sero-protection after receiving standard hepatitis B vaccine due to their compromised immune status.

Objectives—To evaluate the efficacy of hepatitis B virus vaccine in PLHIV compared to placebo or no vaccine.

Search methods—We searched 6 English language databases in July 2012, and updated the search in June 2013 and August 2014. We searched the grey literature, conference proceedings, specialised web sites, and contacted experts in the field.

Selection criteria—Randomised controlled trials of hepatitis B vaccine compared to placebo or no vaccine, evaluating relevant outcomes of efficacy and safety.

Data collection and analysis—Two review authors independently sought and extracted data on study design, participants, hepatitis B infection, hepatitis B related morbidity and mortality,

Contact address: Mbah P Okwen, Centre for the Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon. okwenpatrick@yahoo.fr. okwenpatrick@yahoo.fr.

CONTRIBUTIONS OF AUTHORS

MPO conceived and wrote the first draft of the review, LM, SR and BN provided input for writing the review. MPO did the literature search in collaboration with search experts of the HIV/AIDS Review Group at South African Cochcrane Centre. Two co-authors (MPO, and LM) independently assessed trials for inclusion in the review; all the trials that were assessed as excluded were independently reviewed by MPO to ensure accuracy of exclusion. Selected trials were assessed by the two co-authors (MPO and LM), who independently assessed their quality (study design, randomised treatment allocation, and blinded assessment of outcome). MPO and LM designed the data extraction form. MPO and LM separately extracted data on pre-designed and tested extraction forms; LM independently verified all extracted data. MPO wrote to authors of various studies to obtain any supplementary information including data. MPO undertook statistical analysis and writing up of the review. All co-authors approved the final draft of the review.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We followed our published protocol.

anti-HBs immunogenicity and adverse effects related to vaccines from published articles or through correspondence with authors. Data were analysed qualitatively.

Main results—One double-blind randomised controlled trial with 26 participants who were on antiretroviral therapy (ART), comparing hepatitis B vaccine to placebo conducted in Spain met our eligibility criteria and was included in this review. The study ran for three years and participants were followed up on a monthly basis. The study reported adequate humoral response to vaccine at 12 months and no local or systematic side effects in both intervention and control groups. This humoral response was lost when the participants stopped taking ART. The sample size of the study was small and the study was conducted in a high income setting unlike the areas of highest burden of hepatitis B and HIV co-infections.

Authors' conclusions—The evidence from this study is insufficient to support any recommendations regarding the use of hepatitis B vaccine in PLHIV. Neither does this evidence demonstrate that hepatitis B vaccine is unsafe in PLHIV. Further randomised controlled trials in high prevalence areas are required to generate evidence on the long term efficacy and safety of hepatitis B vaccine in PLHIV with and without ART. Different regimens and routes of administration should also be explored.

Medical Subject Headings (MeSH)

*Vaccination Anti-HIV Agents [therapeutic use]; HIV Infections [*complications; drug therapy]; Hepatitis B [immunology*prevention & control]; Hepatitis B Vaccines [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans

PLAIN LANGUAGE SUMMARY

Hepatitis B virus vaccine for People Living With HIV/AIDS

Study Question—This review seeks to determine whether vaccine for hepatitis B virus is effective in protecting people who have HIV against hepatitis B virus infection. It also seeks to determine if the vaccine is safe in people living with HIV.

Background—Hepatitis B virus infection can be acquired through contact with body fluids of infected people. Hepatitis B virus infection manifests with fever, yellowness of the eyes, abdominal pain and fatigue, but it can also be without symptoms especially in long standing infections. It can cause a persisting infection which can lead to liver complications and death. Hepatitis B virus infection and HIV infection are common in poorer countries and in these countries vaccines are not readily available. People living with HIV may not respond well to hepatitis B virus infection because of the weak ability for their bodies to develop resistance.

Study Characteristics—Our search for eligible papers was updated in August 2014 and we found one trial with 26 adult participants in Spain. The study sought to test if hepatitis B virus vaccine was better than placebo in preventing PLHIV from getting hepatitis B.

Key Results—The single study in this review showed improved immunity against hepatitis B among people living with HIV and taking antiretroviral therapy at 12 months. This immunity was lost once they stopped taking antiretroviral therapy. No side-effects were reported.

Quality of Evidence—The quality of evidence was assessed as very low.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Hepatitis B vaccination compared to placebo for reducing morbidity and mortality in persons with HIV infection						
Patient or population: Persons with HIV infection **Settings: Spain** **Intervention: Hepatitis B vaccination compared to placebo**						
Outcomes	**Illustrative comparative risks*** **(95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Hepatitis B vaccination compared to placebo**				
Hepatitis B Virus infection - not measured	See comment	See comment	Not estimable	-	See comment	
Hepatitis B virus morbidity - not measured	See comment	See comment	Not estimable	-	See comment	
Hepatitis B virus related mortality - not measured	See comment	See comment	Not estimable	-	See comment	
All cause mortality - not measured	See comment	See comment	Not estimable	-	See comment	
Hepatitis B antibody titre (IgG) Follow-up:12 months	The median IgG titre in the control group was **2.14 (IQR 695.55) mIU/mL**	The median IgG titre in the intervention group was **321.00 (IQR 970.31) mIU/mL**	Not estimable	25 (1 study)	⊕◯◯◯ **very low***1,2*	Authors report " Statistically significant (P<0.05) difference between groups using the Mann-Whitney U-test for comparison."

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **IQR:** Interquartile range

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Randomisation and allocation concealment not described

[2] Small sample size and wide interquartile ranges.

BACKGROUND

Hepatitis B virus (HBV) infection affects about 2 billion people worldwide, with about 350 million people living with chronic infection. An estimated 600,000 persons die each year due to acute or chronic consequences of hepatitis B virus infection (WHO 2008). A total of 35.5 million people were living with Human Immunodeficiency Virus (HIV) in 2007, and 22.5 million of these were living in Sub Saharan Africa (UNAIDS 2013). Due to the shared routes of transmission, co-infection with HIV and HBV is common, ranging from 20% in high HBV endemic areas to 5% in areas of low endemicity (Lee 2008; Diop-Ndiaye 2008; Nyirenda 2008; Alter 2006). Immunosuppressed patients have been shown to have a reduced antibody response following HBV vaccination (Miller 2012; Siriaksorn 2006). They are also less likely to maintain high protective antibody levels compared to immunocompetent individuals (McQuillan 2010). Lack of adequate adjuvancy - an appropriate immune response - may explain the lack of vaccine immunogenicity in immunosuppressed individuals (Angel 2008). Adjuvants can be added to vaccines to boost the immune response. These Adjuvant Systems, when added to recombinant protein antigens, can be fundamental in developing effective prophylactic vaccines against complex pathogens, e.g. clostridium, HIV infection and mycobacterium and vaccines against complex diseases, e.g. malaria, HIV infection and tuberculosis, and for special target populations such as subjects with an impaired immune response, due to age or medication (Vandepapelière 2008).

Description of the condition

The hepatitis B virus attacks the liver and can cause chronic or acute infection. Infected individuals manifest symptoms that may last several weeks. These include fever, jaundice, fatigue, nausea, vomiting and abdominal pain. People who get HBV infection earlier in their lives are more likely to develop a chronic infection. Just like HIV, it is transmitted through contact with blood or other bodily fluids from an infected person (WHO 2008). Co-infection of HBV and HIV results in a greater morbidity and mortality. These patients may also present with higher rates of ART-related hepatotoxicity and poorer immunologic outcomes (BHIVA 2004; BHIVA 2010). There are close to 350 million HBV carriers worldwide (BHIVA 2004; BHIVA 2010).

Description of the intervention

HBV infection can be prevented with a 3 dose-vaccine which induces protective antibody levels in more than 95% of infants, children and young adults. Vaccination is considered the best method of prevention against hepatitis B virus and following complete immunisation,

an adequate response will develop immunogenicity levels of anti-HBS antibodies greater than 10 mIU/ml (Behairy 2009). Despite advances in ART therapy, only a minority of patients with chronic hepatitis B will have a sustained humoral response. Therefore, primary prevention through vaccination to increase herd immunity remains the main thrust in the control of HBV infection. Currently available hepatitis B vaccines are safe, have an efficacy of more than 95% and are effective against all HBV serotypes and genotypes (WHO 2011).

How the intervention might work

Immunogenic response to HBV vaccine may vary in people already infected with HIV, it may also vary when immunized persons get infected with HIV and may vary in those on ART compared to the ART-naive. However, HBV vaccination can significantly reduce infection with HBV and thus reduce the co-infectivity of HBV/HIV, by reducing the chances of people living with HIV (PLHIV) getting infected with the HBV virus.

Why it is important to do this review

This review seeks to answer whether vaccination against HBV for people with HIV will contribute to reducing morbidity and mortality, and improving quality of life. There are several studies suggesting different options for vaccination against HBV in immuno-compromised persons including PLHIV (ART initiation, double dosing-quantity and frequency, and the use of adjuvants); however, there is insufficient evidence on what to do with respect to HBV vaccination for PLHIV even though the people at risk of acquiring HIV are also at risk of acquiring HBV. In addition, with HIV infection there has been reported sub optimal immune response to vaccination (BHIVA 2004; BHIVA 2008; BHIVA 2010; McQuillan 2010). Some studies also suggest that lower levels of immunity would be achieved if they were vaccinated prior to ART. A review of the current evidence will therefore help to guide decision-making with respect to improved outcomes and highlight avenues for research.

OBJECTIVES

To assess the efficacy of HBV vaccination in preventing hepatitis B virus infection and its consequences among PLHIV.

METHODS

Criteria for considering studies for this review

Types of studies

- We considered randomised controlled trials of hepatitis B vaccination against no vaccine or placebo.

Types of participants—We considered trials with adults and children infected with HIV confirmed by ELISA (Enzyme Linked Immuno Sorbent Assay); irrespective of whether they are on ART or not. All stages of disease were included. Trials with PLHIV who were already infected with HBV were excluded from the study owing to the inability to determine

changes in serology. Trials with PLHIV whose HBV status was unknown were also be excluded from the study.

Types of interventions—We considered all vaccinations against HBV including the single dose regimens. We compared these interventions against placebo or no vaccination. Trials with individuals who did not complete the immunisations were excluded. We did not consider multidose regimens, the use of adjuvants and combination interventions.

Types of outcome measures

Primary outcomes

- Infection with HBV: For this outcome we intended to measure the incidence of HBV based on the presence of the HBV surface markers (HbSAg, HBcAg) and/or HBV nucleic acids in a cohort of PLHIV known to be previously not infected with HBV.
- Hepatitis B related morbidity: We intended to measure the proportions of individuals with HBV related morbidity over the time frames defined by the authors. We intended to include liver cirrhosis, hepatic failure and primary liver cell carcinomas.
- Hepatitis B related mortality: We intended to measure the proportions of individuals who died subsequent to liver failure.
- All cause mortality

Secondary outcomes

- Levels of immunogenicity following vaccination (anti-HBs antibodies greater than 10mIU/ml was considered adequate levels of immunogenicity following vaccination)
- Adverse effects related to HBV vaccine: We considered all the adverse events as reported by the authors.

Search methods for identification of studies

We worked with the Cochrane HIV/AIDS Review Group Trials Search coordinator to assist with the search and identify studies to be included in the review. We systematically developed a comprehensive and exhaustive search strategy which helped us to identify all relevant studies. We included all relevant studies without bias of language or publication status (published, unpublished, in press or in progress). Study authors were contacted when the information in the retrieved manuscripts was incomplete or unclear.

Electronic searches—We searched the following electronic databases and conference proceedings:

1. The Cochrane Central Register of Controlled Trials (1981-August 2014) and the Cochrane Hepato-Biliary Group ControlledTrials Register (1981-August 2014) via the Cochrane Library (CLIB)

2. MEDLINE via PubMed (1981-August 2014)
3. EMBASE (1981-August 2014)
4. The WHO International Clinical Trials Registry Platform (1981-August 2014)
5. Clinicaltrials.gov (1981-August 2014)
6. AEGIS (AIDS Education Global Information System) which includes the following conferences:
    i. British HIV/AIDS Association, 2001–2009
    ii. Conference on Retroviruses and Opportunistic Infections (CROI), 1994–2008
    iii. European AIDS Society Conference, 2001 and 2003
    iv. International AIDS Society, AIDS 1994–2008
    v. International AIDS Society, Conference on HIV Pathogenesis, Treatment and Prevention (IAS), 2001–2009
    vi. US National HIV Prevention Conference, 1999, 2003, and 2005

We searched for relevant studies from 1981 to August 2014. This timeline corresponds to the identification of the first case of HIV in the United States and also the time when the first recombinant Hepatitis B vaccine was produced. The search strategy included text terms such as Vaccination, immunisation, hepatitis B Virus, Hepatitis B Virus Vaccination, Hepatitis B Virus Immunisation, Human Immunodeficiency Virus, HIV, HBV, Engerix B, Recombivax HB, Elovac B, Genevac B, Shanvac B used in various combinations.

Searching other resources—We performed a handsearch of relevant reference lists of all pertinent reviews and studies found. We also contacted experts, authors, pharmaceutical industries and research organizations in the field for unpublished and on going studies.

Data collection and analysis

Selection of studies—Two authors (MPO and LM) critically appraised all the identified citations independently to establish the possible relevance of the articles for inclusion or exclusion and also to ensure they met the pre-specified criteria for the review. Agreement was estimated using the Kappa statistic (Viera 2005). We reviewed studies for relevance based on type of study, trial participants, trials interventions, and outcome measures using a pre-tested study eligibility form. We resolved any disagreement by discussion or by contacting an independent author for arbitration (SR/BN). Full text for potentially relevant manuscripts were obtained and screened. We gave reasons for excluding potentially relevant trials in a table of excluded studies (Excluded studies). Multiple results for the same study were investigated for inclusion or exclusion following pre-specified criteria. The reviewers were not blinded to authors, journals or titles.

Data extraction and management—We developed and tested a data extraction form tailored to the review question and covering the review outcomes. We used the agreed upon

data extraction form to extract data. Each author extracted data independently thereafter, authors verified each others extraction to arrive at a consensus. We included in our extraction, comprehensive information about each study such as:

- Source of data (study ID, report ID, review author ID, citation and contact detail)
- eligibility (confirm if paper is eligible for review or not and specify reason for exclusion)
- Populations and settings (number of participants, setting, geographical location, diagnostic criteria, age, sex, co-morbidity, ethnicity and date of publication)
- Methods (study design, total study duration, sequence generation, allocation sequence concealment, blinding, follow up and other concerns of bias)
- Interventions (total number of interventions, specific interventions, intervention details, and integrity of intervention)
- Outcomes (outcomes and time points - collected and reported, outcome definition, unit of measurement and scales)
- Results (number of participants allocated to each intervention or control group, - sample size, missing participants, summary of data, sub group analysis)
- Miscellaneous (funding source, key conclusions of study authors, correspondences, comments from authors and review authors)

In the event of multiple reports for same studies, we came to a consensus on how to handle the data before decision on a data collation strategy. We handled disagreements by discussion.

Assessment of risk of bias in included studies—The risk of bias was assessed independently by two review authors using the following key criteria:

1. Sequence generation: how the allocation sequence was generated and whether it was adequate.
2. Allocation concealment: how the allocation sequence was concealed and whether it was adequate.
3. Blinding of participants, personnel, and outcome assessors.
4. The description of the completeness of outcome data for each main outcome.
5. Selective outcome reporting. We verified that all expected and relevant outcomes were reported.
6. Other potential threats of reliability

We assessed the risk of bias of the trials and classified them as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2008).

Assessment of the quality of the body of evidence—We assessed the quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE; Guyatt 2008) tool. The quality rating across studies has four levels: high, moderate, low and very low.

Measures of treatment effect—We planned to analyse data using Review Manager (Revman 2008) for statistical analysis. The standard methods of the Cochrane HIV/AIDS Review Group were used to synthesize data (Higgins 2008). We planned to calculate the median and interquartile range (IQR) or means and standard deviations (SD) for quantitative variables and numbers and percentages for categorical variables, alongside 95 % confidence intervals.

Unit of analysis issues—No cluster RCTs were included in this review.

Dealing with missing data—We contacted authors for missing data. In case we did not get a response from an author, we considered that incomplete outcome data had been adequately addressed if 85% or more of the participants were included in the analysis, or if less than 85% were included but adequate steps were taken to ensure or demonstrate that this did not interfere with the outcomes. In cases where the above was not clear, we planned to perform an intention-to-treat analysis.

Assessment of heterogeneity—We planned to first assess studies for methodological and clinical heterogeneity. If studies were comparable enough to combine, a meta-analysis was to be performed and statistical heterogeneity assessed. A random effects meta-analysis would have been performed if there was statistical heterogeneity.

We also planned to explore possible sources of heterogeneity in this review which included type of HBV vaccine used (plasma derived vaccine or recombinant HBV vaccine, use of adjuvants or not; ART medication being taken; threshold for detection of viral nucleic acids, drug dosage, and study design).

The impact of any statistical heterogeneity would have been quantified using the I^2 statistic (Higgins 2008). Where we were not able to combine data, we provided a narrative report.

Assessment of reporting biases—Publication bias was not assessed because minimal criteria for assessing publication bias were not met (Ioannidis 2007).

Data synthesis—We planned to carry out statistical analysis using the Review Manager software (Revman 2008), using fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: that is, where trials were examining the same intervention, and the populations and methods of trials were judged sufficiently similar. In case there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or in case substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary in case an average treatment effect across trials was considered clinically meaningful.

Subgroup analysis and investigation of heterogeneity—If there was heterogeneity and the data were available we planned to explore this by looking at the following subgroups: age (children/adolescents/adults), sex (male/female), medication (drugs like Tenofovir, Lamuvudine and Emcitrabine are also potent against HBV (Levy 2006)), type of vaccine (protein derived vaccines/recombinant DNA; DNA), ethnicity or race (Black/Caucasian/Hispanic etc.), HIV disease stage and study design.

Sensitivity analysis—A sensitivity analysis was planned to evaluate how robust our findings were for different study designs, type of vaccine used, and type of ART.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search—With the assistance of the Cochrane HIV/AIDS group trial search coordinator, we conducted a search on July 26, 2012 and updated on June 12, 2013 and again in August 2014. A total of 959 records were identified, after sorting and removal of 68 duplicate titles, a total of 894 titles were left (Figure 1). After review of titles and abstracts, 44 titles were short listed for further critical appraisal of full text. Only 1 paper met our inclusion criteria. (Castro 2009). All disagreements were resolved by discussion. Thirty-three (33) papers were also identified as on-going trials. Studies were included based on design, types of participants, interventions and outcomes measured. There were no studies for which it was necessary to contact the authors. A kappa score was calculated for screening between the two reviewers (MPO and LM) and suggested good strength of agreement; Kappa= 0.62, 95% CI 0.53,0.71; $p<0.001$ (Viera 2005).

Included studies—The single study we included (Castro 2009) was a single site prospective, double-blind randomised placebo controlled trial, conducted in Spain between April 2003 to June 2006. This trial included men who have sex with men (MSM), heterosexuals, injection drug users, male and female participants (n=26). THe participants were all living with HIV and receiving ART. They were randomised into two arms with one arm receiving recombinant Hepatitis B Virus vaccine (Engerix B by SmithKline Beecham) and the other hand receiving a placebo of normal saline. At the twelfth month, ART was interrupted for six months. This study did not report on any of the outcomes of interest, but rather on viral load, genotypic mutations, different T cell subsets, and HIV-1-specific immune responses. A second publication from the same study (Gonzalez 2010) reported on IgG titres.

Excluded studies—We excluded 43 studies some of which were non-randomised (Abzug 2009; Alaei 2003; Bailey 2008; Carne 1987; Horster 2010; Kalinowska-Nowak 2007; Koblin 1999; Lao-Araya 2011; Loke 1990; Paitoonpong 2008; Sellar 2009; Thaithumyanon 2002; Wilson 2001; Wursthorn 2011), not in PLHIV (Altuntas 2011; Mehta 2010; Mehta 2010a; Miller 1989; Odaka 1988; Pasricha 2005; Thompson 1998) testing adjuvants to hepatitis B vaccine (Cooper 2005a; Cooper 2008; Overton 2010; Overton 2011; Sasaki

2003; Sayad 2012); testing modalities of administering hepatitis B vaccine (Bunupuradah 2011; de Vries-Sluijs 2011; Flynn 2011; Fonseca 2005; Hwang 2010; Launay 2011; McQuillan 2010) vaccines targeting other conditions (Johnson 1999; Kintu 2013; Launay 2011a). See Characteristics of excluded studies.

Risk of bias in included studies

We used the Cochrane Collaboration tool for assessing risk of bias (Higgins 2008) in this study. See: Methodological quality summary and graph (Figure 2; Figure 3). The risk of bias tables were filled independently by MPO and LM.

Allocation—It was unclear how sequence of randomisation was generated and if there was allocation concealment.

Blinding—The study participants and personnel were blinded, it was however unclear if outcome assessors were blinded.

Incomplete outcome data—There was complete outcome data reported in the trial.

Selective reporting—All planned outcomes were reported.

Other potential sources of bias—There were no other potential sources of bias

Effects of interventions

See: **Summary of findings for the main comparison** Hepatitis B vaccination compared to placebo for reducing morbidity and mortality in persons with HIV infection

See Summary of findings for the main comparison

Vaccination with Hepatitis B vaccine was associated with higher IgG titres (Median 321.00; interquartile range [IQR] 970.31) compared to the control group (median 2.14; IQR 695.55), up to 12 months ($p<0.05$, Mann-Whitney U-test). At the 18 month IgG titres dropped in both the intervention (median 87.57; IQR 969.11) and control groups (median 15.28; IQR 707.70). There were no adverse events in either arm.

DISCUSSION

Summary of main results

One RCT, published in two papers, was included in this review. (Castro 2009; Gonzalez 2010). Hepatitis B vaccine increased antibody titres to protective levels over the short term (one year). This protection was not sustained in the absence of ART. No adverse events were noted. Other outcomes such as hepatitis B infection, morbidity and mortality due to hepatitis B were not addressed.

Overall completeness and applicability of evidence

There is insufficient evidence to draw firm conclusions about the effects of hepatitis B vaccine in preventing hepatitis B infection, morbidity or mortality in PLHIV. This one trial,

conducted in Spain may not be generalisable to other regions of the world with higher diseases burdens of HIV and hepatitis B. The number of participants (26) were too few and the follow-up time was short (18 months). In addition, this trial did not cover important hepatitis B related outcomes. The participants in this trial received other vaccinations (hepatitis A, rubella, *S. pneumoniae, C. tetani, C. diphtheriae*) and it is unclear how they may interact with the hepatitis B vaccine. However, the declines in IgG titres following the interruption of ART would suggest that ART naive subjects would be an important subgroup to investigate, given that other studies suggest the PLHIV may respond poorly to hepatitis B vaccine, and sero-protection may be better in ART-experienced patients than in ART-naive patients (Miller 2012; Siriaksorn 2006).

Quality of the evidence

Overall we grade the evidence quality as very low (Guyatt 2008). See Summary of findings for the main comparison.

Potential biases in the review process

We minimised selection bias for in this review by using an exhaustive search strategy to identify studies, and also by including studies in all languages, unpublished and published. Titles were independently appraised and selected by two authors and differences were resolved through discussion. We searched journal electronic databases, conference databases and prospective trials registries. We contacted experts in vaccinology, hepatology and HIV whenever the need arose. We contacted authors of eligible titles to confirm that data outcomes were eligible for the review. It is unlikely that important studies were missed considering the rigorous process in study search and selection.

Agreements and disagreements with other studies or reviews

We found no other reviews on the efficacy of hepatitis B vaccine for PLHIV.

AUTHORS' CONCLUSIONS

Implications for practice

There is presently insufficient evidence comment on the use of hepatitis B Vaccine for PLHIV. Current BHIVA (BHIVA 2010) and WHO (WHO 2011) guidelines recommend vaccination using current Hepatitis B vaccines regimens. Associations, organisations, governments and health ministries considering implementing Hepatitis B vaccine for PLHIV should consider exploring and documenting the outcomes in PLHIV who receive hepatitis B vaccination.

Implications for research

Larger long term trials are needed in HIV/hepatitis B endemic regions that include adults and children who are ART-experienced and ART-naive. These trial should focus of outcomes that measure control of hepatitis B infection like infection rates, mortality rates and changes in morbidity in addition to direct measures of immunity (antibody titres). It is also worthwhile to explore the incremental cost of hepatitis B vaccine in this population. There is

also a need to explore the most efficacious regimens (dosage and timing) and modalities (with or without adjuvants) of immunisation.

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Dr Lawrence Mbuagbaw provided mentorship to Dr Okwen P Mbah.

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DATA AND ANALYSES

This review has no analyses

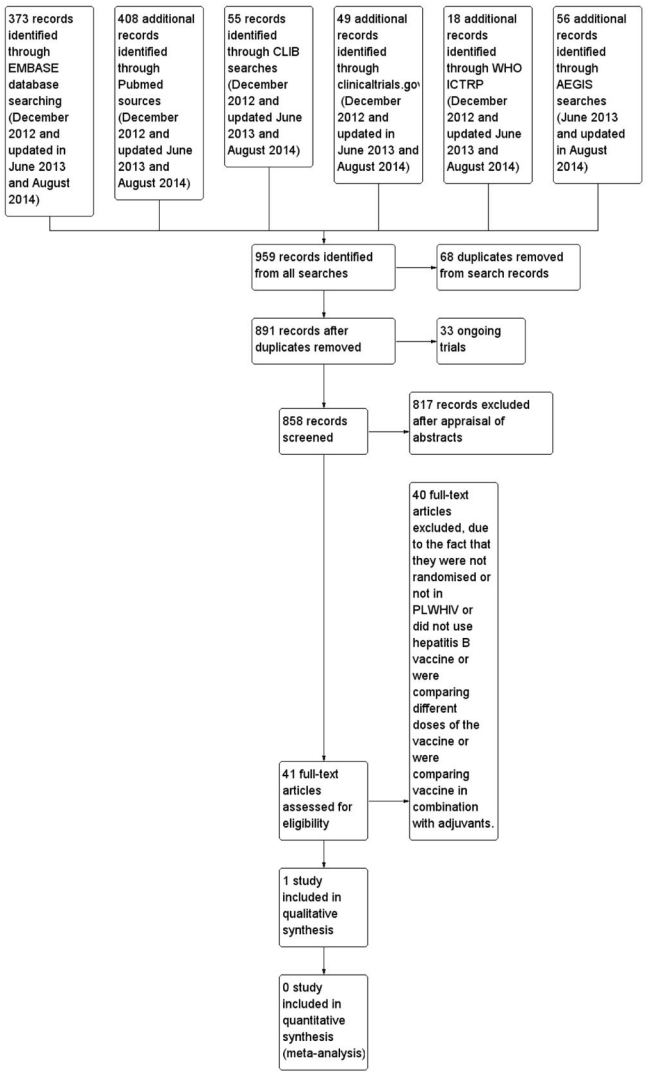

Figure 1.
Hepatitis B Vaccine for People Living With HIV/AIDS PRISMA Study flow diagram.

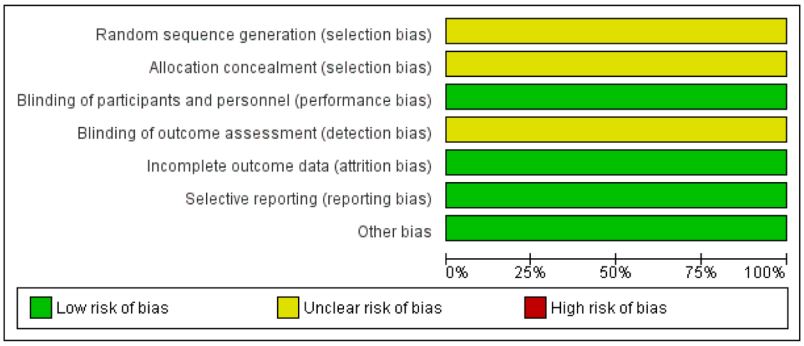

Figure 2.

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

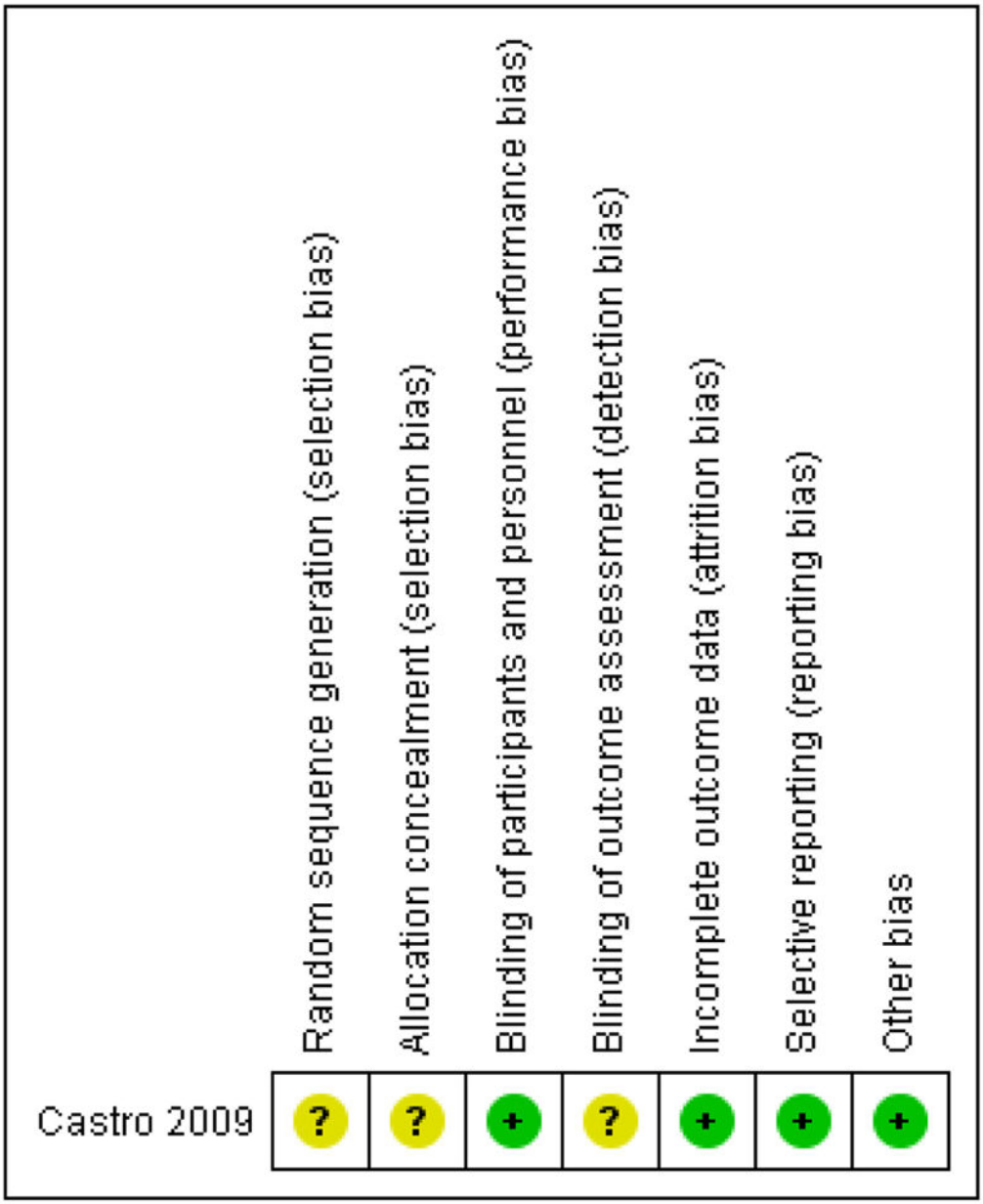

Figure 3.
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table 1

Characteristics of included studies *[ordered by study ID]*

Castro 2009		
Methods	Single site prospective double blind randomised controlled trial done in Spain	
Participants	26 people living with HIV (PLHIV); 13 in each arm. All participants were on ART and did not have HBV infection prior to study	
Interventions	4 doses of Hepatitis B Vaccine (Engerix B by SmithKline Beecham which is an antigenic stimuli vaccine) compared against placebo. Many other vaccination interventions were added to Hep B Vaccine (See notes). The vaccine administrator is not mentioned in the paper 0.5ml of vaccine or placebo was administered at 0, 1, 2 and 6 weeks and efficacy measured at monthly intervals for 18 months ART was interrupted in both intervention and control groups at 12 months	
Outcomes	Viral load CD4 Count Progression to AIDS IgG titres	
Notes	**1** IgG titres reported in secondary publication **2** Multiple immunisations: "The vaccination program included 15 antigenic stimuli with 7 different usually recommended vaccines against 10 different agents (Fig. 1): hepatitis B (Engerix B, Smithkline Beecham SA; months 0, 1, 2, and 6), hepatitis A (Havrix 1440, Smithkline Beecham SA; months 4 and 10), influenza (2003–2004 WHO recommended vaccine [A=New Caledonia=20=99 (H1N1), A=Moscow=10=99 (H3N2), and B=Hong Kong=330= 2001]; month 1), pneumococcal (Pneumo 23, Aventis Pasteur MSD SA; month 2), varicella (Varilrix, Smithkline Beecham SA; months 4 and 6), measles-mumps-rubella (Priorix, Smithkline Beecham SA; month 8), and tetanus-diphtheria (Ditanrix Adult, Smithkline Beecham SA; month 10). The placebo group received the same doses of placebo (0.5 ml of saline solution) at the same months."	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation is not mentioned in the paper
Allocation concealment (selection bias)	Unclear risk	Allocation concealment is not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessor is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are accounted for
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported
Other bias	Low risk	Funding was private and public

Table 2

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abzug 2009	Not a randomised trial
Alaei 2003	Not a randomised trial
Altuntas 2011	Participants were not PLHIV
Bailey 2008	Not a randomised trial
Bunupuradah 2011	Intervention was route of vaccine administration
Carne 1987	Not a randomised trial
Cooper 2005a	Intervention was for adjuvants to hepatitis B vaccine
Cooper 2008	Intervention was for adjuvants to hepatitis B vaccine
Cornejo-Juarez 2006	Study is assessing dose of hepatitis B vaccine
Cunningham 2010	Participants were not PLHIV
de Vries-Sluijs 2011	Intervention was different doses of hepatitis B vaccine
Flynn 2011	Intervention was different doses of hepatitis B vaccine
Fonseca 2005	Intervention was different doses of hepatitis B vaccine
Horster 2010	Not a randomised trial
Hwang 2010	Intervention was different regimens of hepatitis B vaccine
Johnson 1999	Study used mycobacterium vaccine as intervention and hepatitis B vaccine was a control
Kalinowska-Nowak 2007	Not a randomised trial
Kintu 2013	Intervention was HIV vaccine
Koblin 1999	Not a randomised trial
Lao-Araya 2011	Not a randomised trial
Launay 2011	Intervention was different doses of Hepatitis B vaccine
Launay 2011a	Intervention was for H1N1 influenza
Loke 1990	Not a randomised trial
McQuillan 2010	Intervention was different doses of Hepatitis B vaccine
Mehta 2010	Participants were not PLHIV
Mehta 2010a	Participants were not PLHIV
Miller 1989	Participants were not PLHIV
Odaka 1988	Participants were not PLHIV
Overton 2010	Intervention was for adjuvants to hepatitis B vaccine
Overton 2011	Intervention was for adjuvants to hepatitis B vaccine
Paitoonpong 2008	Not a randomised trial
Pasricha 2005	Participants were not PLHIV
Pasricha 2006	Participants were not PLHIV
Ristola 2004	Intervention was different doses of Hepatitis B vaccine
Sasaki 2003	Intervention was for adjuvants to hepatitis B vaccine
Sayad 2012	Intervention was for adjuvants to hepatitis B vaccine
Sellar 2009	Not a randomised trial

Study	Reason for exclusion
Thaithumyanon 2002	Not a randomised trial
Thompson 1998	Participants were not PLHIV
Wilson 2001	Not a randomised trial
Wursthorn 2011	Not a randomised trial