**Protocol**

# Association of hearing loss in the patients with treated with lamivudine: a systematic review protocol

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## ABSTRACT

**Background:** Hearing loss has been reported with lamivudine therapy. The World Health Organization (WHO) international database of suspected adverse drug reactions (Vigibase) prioritised clinical review of lamivudine and hearing loss in 2015. This manuscript provides the details of research protocol for a systematic review of association of lamivudine with hearing loss.

**Methods:** English-language publications that assess hearing loss within patients who are receiving lamivudine therapy will be included. All study types like clinical trial designs, case-control study, cohort study, retrospective study, case-series or a case report will be included. Preclinical studies, studies enrolling patients with known differential diagnosis such as presbycusis etc will be excluded. Electronic databases (PubMed, Cochrane reviews, Embase and Google scholar), international clinical trials registry, clinicaltrials.gov and pharmaceutical company clinical study registries will be searched for key words related to lamivudine and hearing loss. After a thorough electronic/manual search of manuscript they will undergo a screening process and selected articles will be assessed for risk of bias using online ROBINS-I tool. We will explore outcomes as an observational systematic review.

**Conclusions:** This review will provide detailed benefit-risk analysis of lamivudine with respect to hearing loss in patients with chronic conditions such as Human immunodeficiency virus (HIV) and Hepatitis B virus (HBV) infection.

**Trial Registration:** PROSPERO registration number is CRD42018112205.0.001.

**Keywords:** Lamivudine, Hearing loss, Deafness, Systematic review, HIV, Hepatitis B

## INTRODUCTION

Lamivudine, a nucleoside reverse transcriptase inhibitor (a cytidine analogue) was approved for use in 1995 by the U.S. Food and Drug Administration (FDA) for human immunodeficiency virus (HIV) and for hepatitis B infection (HBV).[1,2] Soon after, the FDA approved the lamivudine/zidovudine combination, in 1997. Since then it is used as a backbone in combination therapy with other nucleoside or nucleotide reverse transcriptase inhibitors (NRTI or NtRTI), with medicines of other classes notably the non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease Inhibitors (PI).[3] Currently, three-drug combination is a standard of care and lamivudine is often used as an important component of highly active antiretroviral therapy (HAART) regimen in the treatment of HIV infection.[4,5]

Few *in-vitro* studies as well as some case studies have shown that, hearing loss of different types (conductive, neurosensory and mixed) in individuals affected by HIV and HBV infections may be associated with lamivudine treatment.[6-9] Due to the serious nature of HIV and HBV infection the health of non-vital sensory organs was given minimal consideration early on in the management of the disease. The drug-event combination of lamivudine and hearing loss was prioritized for further clinical review in a signal detection screening of VigiBase, the WHO international database of suspected adverse drug reactions (ADRs), in September 2015.[10] The screening focused on

drug-event combinations sensitive to reporting patterns in mainly Africa, Asia and Latin America and the Caribbean.

Lamivudine therapy is a chronic in patients with HIV or HBV and professionals in infectious disease, hearing health care and audiologists will be better informed about its benefit-risk profile over long-term treatment. While there are few observational studies available, there are no systematic reviews done in past for this aspect. Hence, the objective of this systematic review is to assess the relationship between lamivudine and hearing loss. The epidemiological features of patients included the type of hearing loss and possible dose-response relationship with lamivudine will also be assessed.

## METHODS

### Ethics and protocol registration

The study was reviewed and approved by the institutional ethics committee no. IEC/(II)/OUT/1260/18 on date 26 December 2018. The study protocol synopsis was first registered in the PROSPERO on 30th November 2018 (registration no. CRD42018112205) and an update was submitted on 23rd May 2020. The Appendix I provide the details of changes in the protocol. Any further change in the protocol will be notified to PROSPERO and Institutional Ethics Committee along with the details of date and changes implemented. The final publication of results will also summarise the changes done since the publication of the protocol. This manuscript is written as per the PRISMA-P guidelines (2015).[11,12] Further review will also be published according to PRISMA statement and other applicable guidelines or their updates.[13-15]

### Study objectives

The primary objective of this systematic review is to review the association of hearing loss in patients treated with lamivudine. Secondary objectives include review of an association between various epidemiological/disease attributes; including, but not limited to age, gender, race, infection type (HIV or HBV or other), comorbid conditions and/or concomitant drugs in patients treated with lamivudine and hearing loss. Another secondary objective is to assess the possible relationship of confounding factors such as advancing age, poor socioeconomic stress, longstanding exposure to noise levels and concomitant ototoxic drugs given along with lamivudine to hearing loss etc. Also, additional secondary objectives include what is the type of hearing loss associated with lamivudine; whether it is reversible after lamivudine discontinuation and whether there is any dose-response relationship between lamivudine treatment on hearing loss.

### Statistical considerations and end points

In general, continuous variables including demographic data will be described by descriptive statistics (n, mean,

standard deviation (SD), median, minimum and maximum). Frequency counts and percentage of subjects will be provided for categorical data. "Missing" category will be presented wherever applicable to present the number of missing entries/subjects. Missing data will be kept as missing and no imputation will be done.

The primary endpoint will be prevalence of hearing loss reported in studies with the use of lamivudine. Hearing loss is defined as any complain of hearing loss by the patient or relatives, clinical diagnosis or audiometric or other audiological confirmation of any degree. Pre-existing hearing impairment of any cause will be excluded for the purpose of this analysis. For primary outcome measure a forest plot will be drawn to capture the prevalence of hearing loss along with the 95% confidence intervals for each study. A pooled estimate of the prevalence of hearing loss along with the 95% confidence will also be provided. The data will be pooled by using fixed-effects meta-analysis, in which the weight assigned from a given trial will be proportional to the amount of information provided by that trial. The robustness of this analysis will be explored in sensitivity analyses using the random effects method. The statistical heterogeneity will be tested by $I^2$ test. This test describes the percentage of variation across studies that is due to heterogeneity rather than due to chance. All p values will be two-sided and a p<0.05 will be considered to be significant. The forest plot will be prepared for the studies that report adverse events with the use of lamivudine.

Secondary end point includes association of epidemiological/disease conditions such as age, gender, race, infection type (HIV or HBV or other), comorbid conditions/concomitant drugs in patients treated with lamivudine and hearing loss. For this outcome measure a logistic regression model will be fitted to predict the association of the epidemiological/disease conditions with hearing loss in patients treated with lamivudine. Nature of hearing loss will be captured as sensorineural/conductive/ mixed HL and will be summarized by frequency and percentage. Reversible and irreversible HL after lamivudine discontinuation will be summarized by frequency and percentage. Median duration of lamivudine therapy before onset of HL will be estimated by using Kaplan-Meier estimates. Duration of lamivudine therapy before onset of HL will also be summarized descriptively. A listing will be presented for each subject for other concomitant medication and dose along with lamivudine use in patients reporting HL. A logistic regression model will be fitted to possible confounding factors such advancing age, poor socioeconomic stress, longstanding exposure to noise levels and concomitant ototoxic drugs given along with lamivudine. The model will have HL as the response variable. All analyses will be performed by using R software of version 4.0.2 or above.

The methodological characteristics of the studies which might potentially contribute to the heterogeneity in the results will be assessed for the risk of bias and details are

included in below section for the risk of bias assessment and details are included in the Appendix VI.

### Eligibility criteria of studies

Essentially there are no limitations imposed with respect to geography, study design or publication date. Studies enrolling patients with HIV, post-exposure prophylaxis of HIV and HBV infection of any age and both gender who are receiving lamivudine therapy will be included. This being a non-comparative systematic review, no comparator arm will be included. However, only English language studies will be included. Unpublished studies if available will also be included. Duplicate reports of the same study or preclinical or animal model studies will be excluded. Grey literature such as dissertation/thesis topics or conference abstracts will be excluded. Also, studies enrolling patients with either known other cause of hearing loss or other symptoms suggestive of alternative diagnosis such known case of *Herpes zoster oticus* (Ramsay Hunt syndrome), known case of presbycusis (age related hearing loss), known case of hereditary hearing loss, known case of Meniere's disease, known case of acute/chronic infections of ear example: chronic suppurative otitis media and presence of other symptoms such as vertigo, purulent discharge, dizziness, tinnitus etc. which is suggestive of alternate pathology will be excluded. Also, studies with patients with taking known ototoxic drugs example: aminoglycosides will be excluded.

### Search strategy

The 'key words' that will be used for the search are 'lamivudine and hearing loss', 'lamivudine and deafness', 'lamivudine and hypoacuosis', 'lamivudine and hearing impairment' and 'lamivudine and ototoxicity'. All thesaurus terms and text words for Lamivudine and for hearing loss will be identified. The terms for each concept will be combined with OR. And the sets of each concept so combined, will be combined with AND.

A draft search strategy for PubMed is presented as follows: Lamivudine (tw), 3TC (tw), Epivir (tw), BCH 189 (tw), GR109714X (tw), "2',3' Dideoxy 3' thiacytidine"(tw), #1 OR #2 OR #3 OR #4 OR #5 OR #6, Hearing (tw), Auditory (tw), Deaf* (tw), Hypoacusis (tw), #8 OR #9 OR #10 OR #11 and #7 AND #12.

### Information sources

MB is the guarantor. KJ drafted this manuscript. All authors contributed to the development of the manuscript. Vasumathi Sriganesh of Qmed Knowledge foundation provided the search strategy and librarian assistance for literature search of PubMed, Cochrane reviews, and Google scholar. Embase will be searched by KJ. International clinical trials registry, clinicaltrials.gov (for any recently completed or ongoing studies) registry will be searched (KJ). Pharmaceutical company websites for registries of clinical studies will also be searched (KJ). We

will also contact the authors of publications to assess for any ongoing / unpublished work (MB). Key regulatory agency websites will also be searched [MB]. Books and some select journals will be hand-searched (MB). We will also search PROSPERO for any such similar ongoing or recently completed systematic review (MB).

### Study records & data management

This section elucidates how study records will be identified and selected (Figure 1). Authors MB & KJ will independently assess the title and abstracts of the records identified from the literature searches. Full text article will be accessed to determine whether study can be included in the analysis, or if abstract is not available, or if there is any uncertainty about its inclusion or duplication is suspected. MB and KJ will categorize the abstract and title search as definite, potentially relevant or not relevant for data extraction. Assessment done by KJ will be validated by MB and vice-a-versa with the help of screening questionnaire (Appendix II). This will be followed by further screening of potentially full text records. Any disagreement will be resolved by mutual consensus. Documentation of studies that were found to be relevant will be done by MB. Duplicate records will be searched and removed. We will assess duplicate records of a study by checking various details such as author names, study number, inclusion/exclusion criteria, geography, sponsor details etc. before its inclusion in final analysis.

Full-text articles shortlisted for inclusion will be procured and data extraction process will begin. Standardized data collection form (Appendix III) will be used to extract the following data items from the studies that were included; primary author, country of origin, patient demographics, diagnosis of patients, lamivudine dosage, association of hearing loss with lamivudine therapy, length of lamivudine therapy and follow up for treatment, outcomes with lamivudine therapy and any other adverse events with lamivudine therapy and information related to causality assessment (dechallenge, rechallenge) and comorbid conditions as well as concomitant medications (MB and KJ). Again, MB & KJ will extract the data in duplicate and any disagreement will be resolved by mutual agreement.

### Risk of bias in individual studies

Risk of bias across the studies will be assessed using the approach outlined by Jadad score for randomized controlled studies (Appendix IV).[xvi] We will also follow ROBINS – I tool to assess the risk of non-randomised studies as recommended by Cochrane Review of systemic interventions, version 6.0; accessing the online version.[17,18] Based on ROBINS – I tool, the overall risk of bias of a study will be categorized as 'Low', 'Moderate', 'Serious' or 'Critical' risk of bias. Such risk assessment will be documented for every included study.[19] The tool can be accessed at www.riskofbias.info after following few simple steps (see details of ROBINS – I tool in Appendix V). KJ & MB will assess ROBINS-1 tool

individually and then match it for the consensus of outcome. Appendix VI will provide details of risk bias

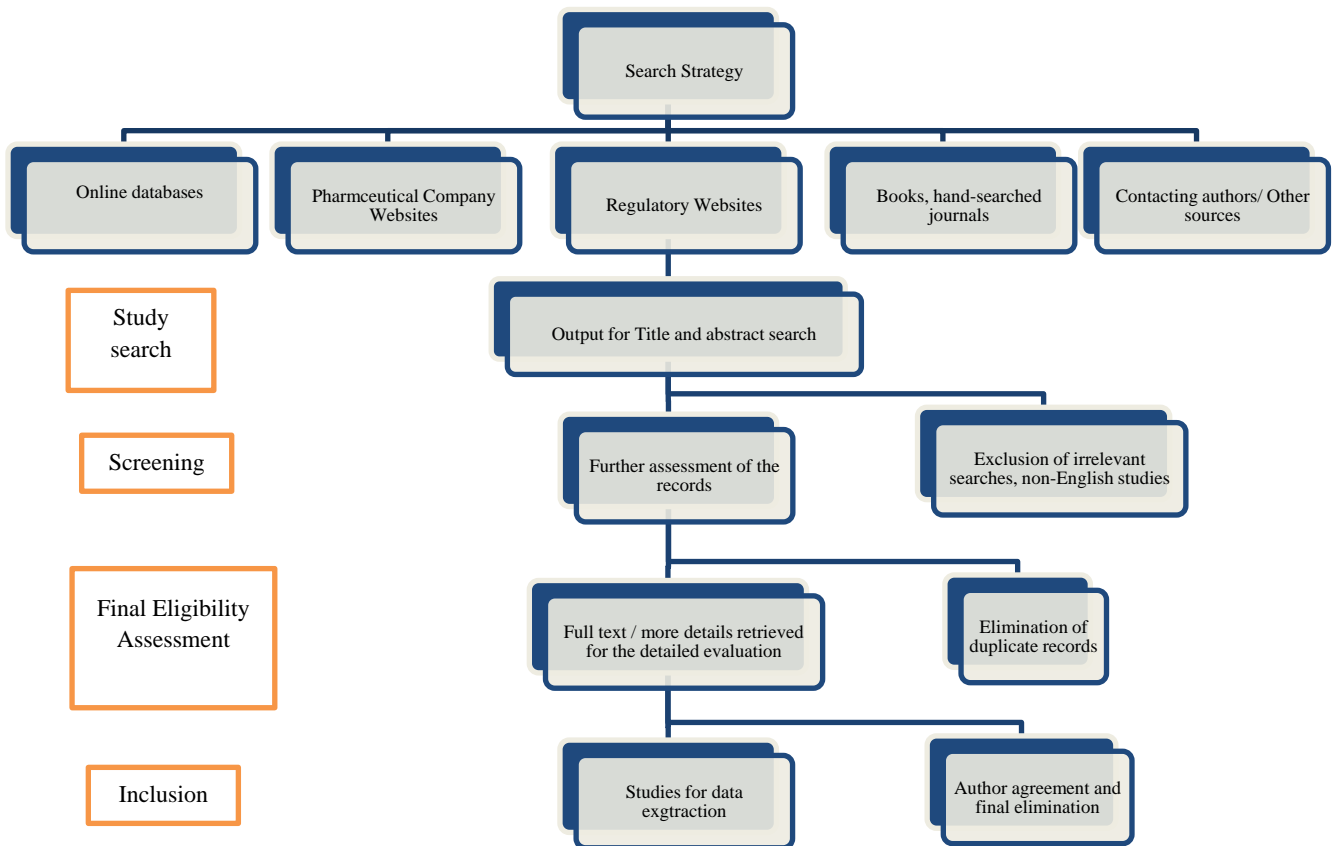assessment outcome for all included studies using ROBINS – I tool.



**Figure 1: Selection process of studies.**

## CONCLUSION

This review will provide detailed benefit-risk analysis of lamivudine with respect to hearing loss in patients with chronic conditions such as HIV and HBV infection. This might help infectious disease expert or audiologists regarding the long-term impact of lamivudine on hearing. While causality can't be ascertained in this review, further treatment and follow up strategies of patients can be better advised. It will also highlight the gaps in the current evidence and provide direction for future research.

## ACKNOWLEDGMENTS

## REFERENCES

1. Lamivudine (Epivir) US FDA label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020564s37_020596s036lbl.pdf. Accessed on 24 April, 2020.
2. Lamivudine (Epivir HBV) US FDA label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021003s015,021004s015lbl.pdf. Accessed on 24 April, 2020.
3. Bankaitis AE, Schountz T. HIV-related ototoxicity. In: Seminars in Hearing. Thieme Medical Publishers, Inc. 1998;19(2):155-63.
4. Kohan D, Rothstein SG, Cohen N. Otologic disease in patients with acquired immunodeficiency syndrome. Ann Otol Rhinol Laryngol. 1988; 97(6):636-40.

5. Michaels L, Soucek S, Liang J. The ear in the acquired immunodeficiency syndrome: I. Temporal bone histopathologic study. Am J Otol. 1994; 15(4):515-22.

6. Thein P, Kalinec PM, Park C, Kalinec F. In vitro assessment of antiretroviral drugs demonstrates potential for ototoxicity. Hear Res. 2014;310:27-35.

7. Araújo ES, Zucki F, Corteletti LC, Lopes AC, Feniman MR, Alvarenga KF et al Reversible bilateral ototoxicity in a patient with chronic hepatitis B during peginterferon alpha-2a treatment. Indian J Pharmacol. 2015;47(1):121-2.

8. Campanini A, Marani M, Mastroianni A, Cancellieri C, Vicini C. Human immunodeficiency virus infection: personal experience in changes in head and neck manifestations due to recent antiretroviral therapies. Acta Otorhinolaryngol Ital. 2005;25:30-5.

9. Eda AS, Zucki F, Corteletti LC, Lopes AC, Feniman MR, Alvarenga Kde F. Hearing loss and acquired immune deficiency syndrome: systematic review. J Soc Bras Fonoaudiol. 2012;24(2):188-92.

10. WHO Pharmaceuticals newsletter. 2018;(3). http://apps.who.int/medicinedocs/documents/s23169 en/s23169en.pdf. Accessed on 12 April, 2020.

11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A (deceased), Petticrew M, et al. On the behalf of PRISMA-P Group. Preferred reporting items for systematic review andmeta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647.

12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberti A (deceased), Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4. 2015;1.

13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.

14. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. BMJ. 2009;339:b2535.

15. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008-12.

16. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary?. Controlled Clinical Trials. 2017;(1):1-12.

17. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0. Cochrane. 2019. Available at: www.training.cochrane.org/handbook. Accessed on 10 March, 2020.

18. Sterne JAC, Hernan M, Reeves BC, Savovic J, Berkman ND, Viswanathan M et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

19. ROBINS-1 tool. 2016. Available at: https://www.riskofbias.info/welcome/home/current-version-of-robins-i/robins-i-tool-2016. Accessed on 21 April, 2020.

20. No authors listed. Halpern HS, Douglas MJ (editors). Appendix: Jadad Scale for Reporting Randomized Controlled Trials Blackwell Publishing Ltd; 2005: 237-238.

# APPENDIX

## Appendix I: Details of changes in the protocol.

| S. no. | Protocol Version no. | Date of Change | Details of key changes | Rationale / other comments |
|---|---|---|---|---|
| 1 | 1.1 | 20th April 2018 | Not applicable – first draft | |
| 2 | 1.2 | 17th December 2018 | Objectives and end-points were updated.<br><br>**Primary objective**<br>To review the association of hearing loss in patients treated with lamivudine<br><br>**Secondary objectives**<br>• To review the association of hearing loss in lamivudine treated patients suffering from HIV infection<br>• To review association of hearing loss in lamivudine treated patients suffering from HBV infection<br><br>Editorial changes in the overall protocol. | |
| 3 | 1.3 | | Update in inclusion criteria to include paediatric patient: from ' ' to 'Study population - patients with HIV, post-exposure prophylaxis and hepatitis B virus infection of any age and both gender who are receiving lamivudine therapy' Other editorial changes and formatting were done. | |
| 4 | 1.4 | 21st March 2020 | Further updates in the study inclusion criteria:<br>• English language as well as non-English studies will be included. Non-English studies will be translated to English with the help of Google-translate online too.<br>• Study design – clinical trials, case-control study, cohort study, retrospective study, case-series or a case report will be included. | The intent was to do a broad search as much as possible. However, non-English articles were removed later due to non-reliable translation with Google Translate. |
| 5 | 1.5 | 20th April 2020 | Details of literature search strategy was included as a separate appendix. Key word for literature search were updated: ' ', 'lamivudine and hearing loss', 'lamivudine and deafness', 'lamivudine and hypoacuosis', 'lamivudine and hearing impairment' and 'lamivudine and ototoxicity'. Numerous editorial changes were done, figure for study selection process was updated & author contributions were updated. | This update has been notified to EC and PROSPERO |

### Appendix II: Screening questionnaire to assess the inclusion of studies.

Literature searched will be captured and assessed in following format by each author (MB & KJ). Below is an example of a literature record (authors, titles, citation included along with author's assessment about the relevance of article as a last column). Any disagreement about the potential relevance of the article to include will be resolved by mutual consensus.

| Study title | Screening questions | | | Review of abstract & title: whether article is relevant for inclusion : definitely relevant / potentially relevant / not relevant | | | Review of full text: Whether article is relevant for inclusion: definitely relevant / not relevant | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Question | Yes/ no | | Author 1 decision | Author 2 decision | Consensus | Author 1 decision | Author 2 decision | Consensus |
| **Mukhametshina E., Gavrilov P. Tuberculous meningoencephalitis in patient with HIV-infection QJM (2019) 112:12 (932-933). Date of Publication: 1 Dec 2019** | Are patients receiving lamivudine treatment? | | | | | | | | |
| | Whether hearing loss is one of the reported outcomes? | | | | | | | | |
| | Whether the language of study is English? | | | | | | | | |
| | Whether all the study participants are humans? | | | | | | | | |
| | Whether this is a duplicate publication? | | | | | | | | |
| | Whether there are any other symptoms suggestive of alternative aetiology? | | | | | | | | |
| | Whether patient is suffering from any of pre-existing condition associated with hearing loss? | | | | | | | | |

Key: Answer to all inclusion questions (first 4 questions to be bold) should be 'Yes' and answer to all the exclusion questions (last 3 to be italics) should be 'No' to make a final decision as definitely relevant or not included. At times since abstract and title screening may not answer all the questions, a third category of potentially relevant has been added before making a final decision.

**Appendix III: Data extraction items for the included studies.**

Once the studies are selected data will be collected in a following format. While the tables are split below for ease of formatting, there will be a single Microsoft excel spreadsheet for all below details.

### i. Details of study

| S. no./ trial registration number | Title/ Reference | Author details | Country of origin | Year of publication | Journal | Study methodology |
|---|---|---|---|---|---|---|
| | | | | | | |

### ii. Details of intervention (lamivudine dose, duration etc. details)

| Patient details | Diagnosis as HIV/ Hepatitis B infection and on lamivudine therapy | Lamivudine dosage | Lamivudine start date and stop date (duration of treatment) | Other adverse events with lamivudine therapy (Yes/ No)[if yes list of the ADRs] | Whether lamivudine discontinued or continued after the development of ADR |
|---|---|---|---|---|---|
| | | | | | |

### iii. Details of concomitant medications

| S. no. | Concomitant medication/s | Daily Dosage | Duration of treatment | Whether treatment was discontinued or continued after the development of ADR |
|---|---|---|---|---|
| | | | | |

### iv. Details of comorbid conditions.

| S. no. | Comorbid conditions | Duration (months/years) | Treatment given | Whether controlled or NOT |
|---|---|---|---|---|
| | | | | |

### v. Assessment of outcomes.

| Audiogram finding | CT scan finding | MRI finding | Auditory brainstem response | Patient / relative reported HL (Yes/No) | Treatment for HL | Authors assessment of Lamivudine Causality |
|---|---|---|---|---|---|---|
| | | | | | | |

**Appendix IV: Jadad score outcome for reporting risk of bias using for randomized controlled studies.**

| Study citation | Item | Maximum Points | Key for scoring | Author Judgement | Sub-score | Total score |
|---|---|---|---|---|---|---|
| | Randomization | 2 | 1. 1 point if randomization is mentioned<br>2. 1 additional point if the method of randomization is appropriate.<br>3. Deduct 1 point if the method of randomization is inappropriate (minimum 0) | | | |
| | Blinding | 2 | 1. 1 point if blinding is mentioned<br>2. 1 additional point if the method of blinding is appropriate<br>3. Deduct 1 point if the method of blinding is inappropriate (minimum 0) | | | |
| | Withdrawal and dropouts (an account of all patients) | 1 | The fate of all patients in the trial is known. If there are no data the reason is stated | | | |

## Appendix V: ROBINS – 1 tool for the assessment of risk of bias: Table A (protocol stage).

Authors will create a tabular summary to provide risk of bias assessment for each included study. The proposed format will be derived from ROBINS – I tool. As an example, currently we have completed the ROBINS-I tool (Stage I): At protocol stage of Table A. The risk of bias in non-randomized studies – of interventions (ROBINS-I) assessment tool which is as below –

**Table A: The risk of bias in non-randomized studies – of interventions (ROBINS-I) assessment tool**

The ROBINS-I tool is reproduced from riskofbias.info with the permission of the authors. The tool should not be modified for use.

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

| Participants | Patients HIV or HBV infection or HIV post-exposure prophylaxis |
|---|---|
| Experimental intervention | Lamivudine |
| Comparator | Those without lamivudine treatment |
| Outcomes | Hearing loss is defined as any complain of hearing loss by the patient or relatives, clinical diagnosis or audiometric or other audiological confirmation of any degree. |

List the confounding domains relevant to all or most studies

1. Age – higher age is positively correlated with hearing loss / presbycusis.
2. Occupational hazard - exposure to chronic high sound / noise levels
3. Low socioeconomic status – associated with poor ear health and increase in hearing impairment
4. Presence of CV conditions / higher BMI – a possibility of atherosclerosis of arteries affecting inner ear may lead to hearing loss
5. Herpes zoster oticus (Ramsay Hunt syndrome) or other middle ear aetiopathogenesis such as chronic suppurative otitis media.

List co-interventions that could be different between intervention groups and that could impact on outcomes

1. Aminoglycosides
2. Diuretics like forsemide, ethacrynic acid and bumatenide
3. Cancer chemotherapeutic agents such as cisplatin, carboplatin and vincristine
4. Aspirin and salicylates
5. Quinine
6. Heavy metal poisoning with mercury and lead

## Appendix VI: Outcome of study bias assessment.

This will be elaborately done as per the ROBINS-1 tool & will be summarized as below:

| Study citation | Quality of the study | Bias | Confounding factor | Authors judgement | Support for judgement |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |