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Original Article

Pharmacology Section

Relationship of Hearing Impairment in Patients with Lamivudine Therapy: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Lifelong Antiretroviral Therapy (ARVT) in patients with Human Immunodeficiency Virus (HIV) infection damages cochlea. Hearing Loss (HL) has been reported with lamivudine therapy in both HIV and/or Hepatitis B Virus (HBV) infections. Hence, the benefit of lamivudine therapy in individuals affected by these infections and risk of development of HL needs to be studied to make an adequate benefit-risk assessment.

Aim: To evaluate the relationship of hearing impairment in patients treated with lamivudine and diagnosed with either HIV or HBV infection.

Materials and Methods: The present study is a systematic review in which English-language publications that assessed HL in patients who are on lamivudine drug therapy were included. The types of studies included were: prospective studies, retrospective studies, case reports and case series. A comprehensive database search (PubMed, PubMed Central, Cochrane review, Google scholar and Embase) was conducted to identify the relevant literature published on HL and were searched for keywords related to lamivudine and HL- 'lamivudine and hearing loss', 'lamivudine and deafness', 'lamivudine and hypoacusis', 'lamivudine and hearing impairment' and 'lamivudine and ototoxicity' for searching the data. The publications were independently reviewed and assessed for study quality and the data (title, author, year of publication, study design, study setting, population characteristics) extraction was done.

Results: Out of 1,778 publications found at the initial stage, nine were included in the systematic review and quantitative meta-analysis. The majority (4/9) were cross-sectional studies. The prevalence of hearing impairment defined as per the protocol was 41% (total population 1,548). The I^2 statistic was used to test statistical heterogeneity, with values of >50% representing important heterogeneity, then a random-effects model was used to perform the meta-analysis. A subgroup analysis was performed for the age group ≤18 years and >18 years. All analyses were conducted using the R software version 4.1.0. It was found that most of the studies (8/9) suffered moderate-serious overall risk across all the domains of ROBINS-1 tool.

Conclusion: This study showed a positive association of HL with lamivudine in patients with HIV infection.

Keywords: Antiretroviral therapy, Benefit-risk assessment, Hearing impairment, Hepatitis B, Human immunodeficiency virus, Ototoxicity

INTRODUCTION

The HIV infection can present with Ear, Nose and Throat (ENT) diseases and approximately 80% of patients with HIV infection suffer from ENT diseases [1,2]. HIV-infection is a risk factor for HL and the magnitude increases with severity of the disease [3]. HL may be conductive or sensorineural and sensorineural HL in HIV patients may be due to direct neurotropic effect of HIV (neurotoxicity) [4-8].

ARVT seems to be associated with HL. Some studies have shown a diminished ability to hear in HIV positive patients compared with HIV negative controls [9-11]. Other causes of HL in HIV infected individuals may include chronic suppurative otitis media and aminoglycosides used in the treatment of tuberculosis which is a common opportunistic infection associated with HIV [12,13]. Nevertheless, no cause can be identified in almost 50% of HIV-infected people with hearing impairment [14]. There is possible association with HL in the central hearing system caused by direct action of the virus, which in many cases is shown by otoneurological signs and symptoms presented by the patients, such as HL, tinnitus and dizziness [15,16].

Lamivudine is a nucleoside reverse transcriptase inhibitor (a cytidine analogue). It is a component of Highly Active ARVT (HAART) treatment and is a part of HIV combination therapy [17,18]. Lamivudine is used in combination therapy as supportive treatment with other Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTI or NtRTI). It is also used with other classes of ARTs, the Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and Protease Inhibitors (PI) [19]. Apart from HIV treatment lamivudine is also used in the treatment of chronic hepatitis B.

The drug-event combination of lamivudine and HL was first detected in a signal detection screening of VigiBase, the World Health Organisation (WHO) international database of suspected Adverse Drug Reactions (ADRs), in September 2015 [20]. The potential for a drug-induced HL in patients with HIV and HBV infection treated with lamivudine therapy has been reported to be high [21-26]. The toxicity of lamivudine occurs due to the mitochondrial dysfunction as it decreases mitochondrial DNA (m-DNA) levels in various tissues, including the cochlear, via polymerase gamma (γ) inhibition [27-29].

Specialists in hearing healthcare and audiologists have an onus to notify other related healthcare professionals about this issue. The benefit of lamivudine therapy in individuals affected by HIV and HBV infections and risk of development of HL needs to be studied to make an adequate benefit-risk assessment. This systematic review and meta-analysis evaluated association of HL with lamivudine therapy in individuals affected by HIV and HBV infections.

MATERIALS AND METHODS

The present systematic review and meta-analysis was approved by local Institutional Ethics Committee (IEC) (approval no. EC/OA-170/2018) and a waiver of consent of the participants and exemption from review was obtained from IEC, as the researchers have analysed the data freely available in public domain. Study protocol synopsis was first registered in the PROSPERO (registration no. CRD42018112205). The study duration was 11 months and it was

conducted between November 2020 and September 2021. The researchers have published the protocol of this systematic review in the year 2020 in International Journal of Clinical Trials [30].

Literature search strategy: The researchers have searched PubMed, PubMed Central, Cochrane review, Google scholar and Embase for the search strategy of relevant publications. They also searched the regulatory websites and textbooks and hand-searched journals, the pharmaceutical company and authors were contacted to get some relevant information on the topic. The 'key words' used by the authors for the search were 'lamivudine and deafness', 'lamivudine and hypoacusis', 'lamivudine and hearing loss', 'lamivudine and hearing impairment' and 'lamivudine and ototoxicity'. All glossary terms and text words for lamivudine and for HL were identified. The terms for each concept were combined with OR and the sets of each concept so combined, were combined with AND.

Inclusion criteria: The researchers included publications involving patients with HIV, postexposure prophylaxis of HIV and HBV infection of any age and both gender who received lamivudine therapy. No filters to limit the period of publication were put, and only the English language publications were included, and independently reviewed. All study types prospective studies, retrospective studies, case reports and case series were included in the review.

Exclusion criteria: Preclinical or animal model studies, grey literature (dissertation/thesis or conference abstracts), studies enrolling patients with either known other causes of HL such as ototoxic drugs (aminoglycosides) or other symptoms suggestive of alternative diagnosis {Herpes zoster oticus (Ramsay Hunt syndrome)}, known case of presbycusis (age-related), known case of hereditary HL, known case of Meniere's disease, known case of acute/chronic infections of ear for example; chronic suppurative otitis media and presence of other symptoms such as vertigo, purulent discharge, dizziness, tinnitus etc., which is suggestive of alternate pathology were excluded from the review.

Data Extraction and Quality Assessment

The selected studies were assessed for quality and the following data were recorded-title, author, country of origin, year of publication, journal of publication, study type and design, study setting, population characteristics, details of lamivudine therapy, any adverse events due to lamivudine, sample size, total duration of study and study outcomes.

A standard data extraction form was developed in Microsoft Excel. Two reviewers (MNB & KKJ) independently assessed the title and abstracts of the records identified from literature searches. Full text article was accessed to determine whether the study could be included in the analysis. MNB and KKJ categorised the abstract and title search as definite, potentially relevant or not relevant for data extraction. Assessment done by KKJ was validated by MNB and vice-a-versa. This was followed by further screening of potentially full text records. Any disagreement was resolved by mutual consensus.

Documentation of studies that were found to be relevant was done by MNB. Duplicate records were searched and removed. Duplicate records were eliminated by checking- author names, study number, inclusion/exclusion criteria, geography, sponsor details etc., before its inclusion in final analysis.

Full-text articles shortlisted for inclusion were procured and data extraction process was done. Standardised data collection form was 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 HL 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 co-morbid conditions as well as concomitant medications (MNB and KKJ). Again, MNB and KKJ extracted the data in duplicate and any disagreement was resolved by mutual agreement.

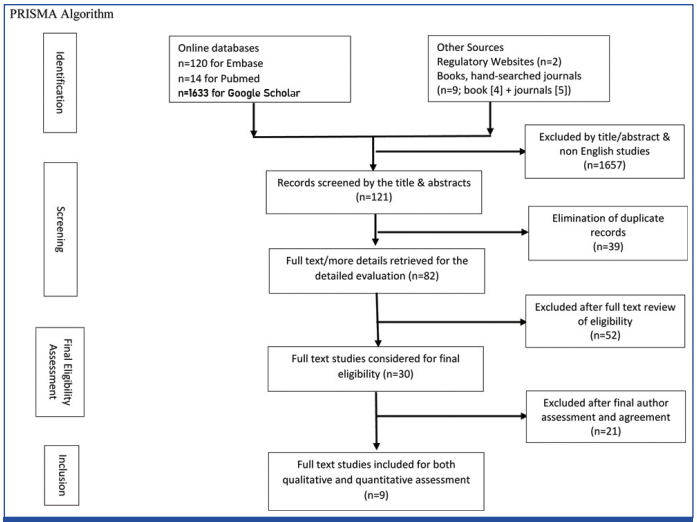
Assessment of bias: Publication bias was assessed with the help of ROBINS-1 [31] tool for the non randomised studies.

STATISTICAL ANALYSIS

A descriptive data synthesis method was used. The researchers analysed the results of those studies which were methodologically more robust. The results were then further tabulated in a way that demonstrated the methodological robustness of each study. The narrative written by the lead researcher was then checked independently by two researchers, with feedback and comments. Any disagreements were resolved by consensus. For meta-analysis R software version 4.1.0 was used and the I^2 statistics was used to test statistical heterogeneity among the studies.

RESULTS

Search results: The initial search strategy yielded 1778 publications from the online database, regulatory websites and book and hand-searched journals. The pharmaceutical company and author contact did not yield any new searches. After reviewing the titles/abstract and language search 1657 publications were excluded. Out of the remaining 121 publications, the duplicate records were eliminated, and 82 publications were left. After the full-text review for eligibility, 52 publications were rejected. Thus, 30 publications were finally found to be eligible and the full texts were retrieved. After the agreement and discussion between the two authors, 21 publications were excluded, and nine were included in the systematic review and meta-analysis. This is represented in PRISMA flow diagram [Table/Fig-1].

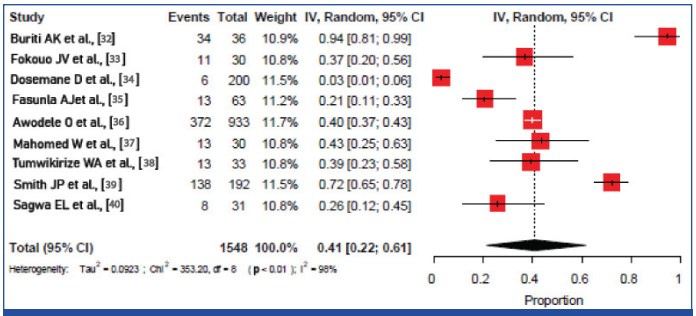


[Table/Fig-1]: PRISMA algorithm.

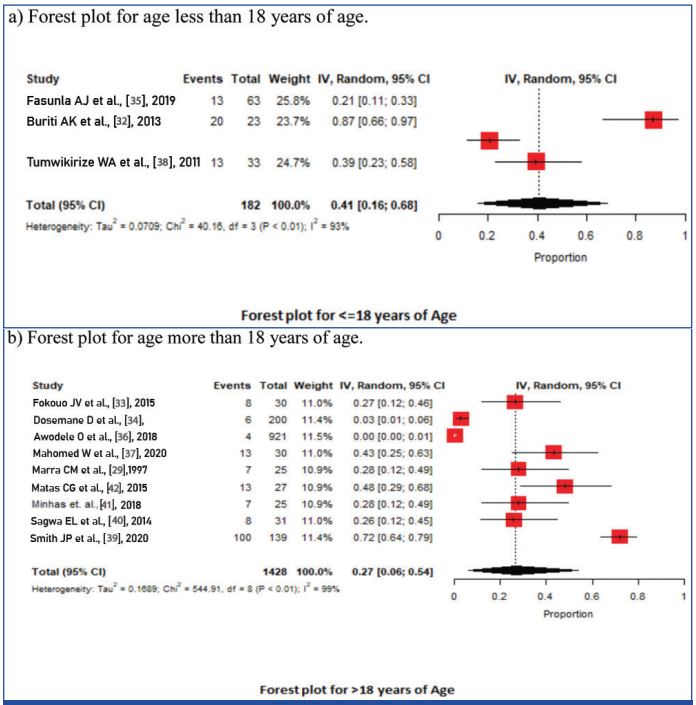
Overall prevalence of hearing impairment: In the nine articles, 1548 patients of HIV infection were there, and were started on lamivudine therapy. There were no studies in which patients were infected with hepatitis B and were on lamivudine therapy. The age range of the patients was 35-45 years, and there were 604 (39%) males. The duration of lamivudine therapy ranged from 6-15 months.

The prevalence of hearing impairment, defined as per the protocol, was 41%. To test statistical heterogeneity the I^2 statistic was used, with values of >50% representing important heterogeneity, and a random-effects model was used to perform the meta-analysis [Table/Fig-2] [32-40]. A subgroup analysis was performed for the age group ≤18 years and >18 years [Table/Fig-3] [29,32-42]. The R software version 4.1.0 was used for this analysis.

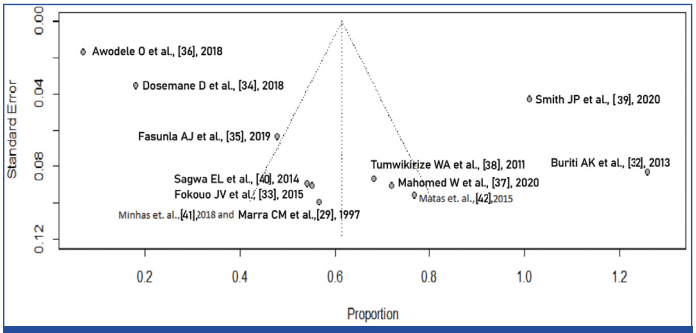
Publication bias was checked by using a funnel plot [Table/Fig-4]. In case of no publication bias, the data should form a roughly symmetrical, upside-down funnel. For the plot above, there are three studies which do not really fall as at the top (Dosemane D et al., Awodele O et al., and Smith JP et al.,) [34,36,39]. This indicates a possibility of publication bias in the studies included. There were not too many studies which could provide us the required information



[Table/Fig-2]: Forest plot for estimation of Hearing Loss (HL) prevalence when treated with Lamivudine [32-40].



[Table/Fig-3]: Forest plot by age for estimation of Hearing Loss (HL) prevalence when treated with Lamivudine [29,32-42].



[Table/Fig-4]: Funnel plot for all the studies included in the analyses [29,32-42].

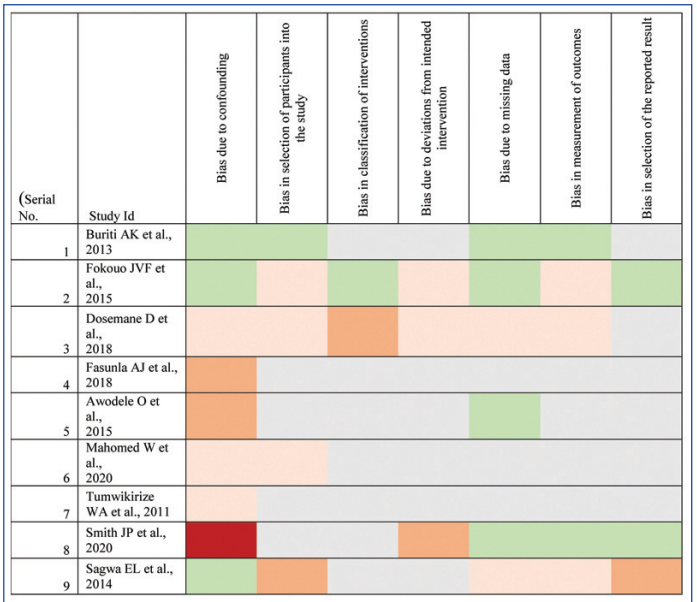
and therefore authors included the above mentioned three studies in the current meta-analysis. Other three studies Buriti AK et al., Fasunla AJ et al., and Sagwa EL et al., does not fall under the funnel plot [31,36,41]. This means there was no publication bias in these studies. The nature of bias here means publication or reporting bias which applies to all forms of results dissemination. This will not impact the outcome of the present study.

Secondary endpoints: There was no quantitative data available for the meta-analysis of secondary endpoints related to correlation of HL to various epidemiological features like age, gender, concomitant medications/treatment.

Assessment of the bias: None of the studies were randomised controlled trials. The [Table/Fig-6] reports the ROBINS-1 assessment about the risk of bias in various studies into seven domains (three domains are preintervention and intervention domains; bias due confounding, in selection of participants in study and in classification of interventions; four domains are postintervention domains: bias due to deviations from intended intervention, due to missing data, in measurement of outcomes and in the selection of the reported result). Author judgement and supporting data for the judgement (wherever possible) have been reported. It can be noted that most of the studies suffered moderate-serious overall risk across all the domains of ROBINS-1 tool. Particularly, retrospectives studies suffered more risk of bias as compared to prospective case-controlled studies. The data extraction details and risk of bias are tabulated in [Table/Fig-5,6] [31,33,34,36-41].

S. No.	Author particulars	Country and year of publication	Study type
1	Buriti AK et al., [32]	Brazil; 2013	Cross-sectional study
2	Fokouo JV et al., [33]	Cameroon; 2015	Prospective case-control study
3	Dosemane D et al., [34]	India; 2018	Cross-sectional study
4	Fasunla AJ et al., [35]	Nigeria; 2019	Cross-sectional study
5	Awodele O et al., [36]	Nigeria; 2018	Observational Study
6	Mahomed W et al., [37]	South Africa; 2020	Cross-sectional study
7	Tumwikirize WA et al., [38]	Uganda; 2011	Longitudinal observational study
8	Smith JP et al., [39]	South Africa; 2020	Prospective observational study
9	Sagwa EL et al., [40]	Namibia; 2014	Retrospective observational cohort study

[Table/Fig-5]: Data extraction items for the included studies [32-40].



[Table/Fig-6]: Assessment of risk of bias in included studies ROBINS-1.

DISCUSSION

This systematic review and meta-analysis aimed to review the association of HL in patients treated with lamivudine, and suffering from either HIV or HBV infection. There was an association between HL and lamivudine, when the latter is used in individuals affected by HIV infections. Out of the nine publications included in this systematic review and meta-analysis, four were cross-sectional studies, three were observational studies and one study each was a prospective case control and a retrospective cohort study. ROBINS-1 assessment about the risk of bias of various studies was used as all of the studies were observational in nature. Most of the studies suffered moderate-serious overall risk across all the domains of ROBINS-1 tool.

A study conducted by Buriti AK et al., found that lamivudine was the most prescribed (94.4%) medication in children who developed HL due to ARVT [32]. Fokouo JV et al., found that HIV positive patients had a poorer hearing on Pure-Tone Audiometry (PTA) than that of HIV negative patients [33]. In India, reduced hearing in HIV positive patients on ARVTs was reported by Dosemane D et al., [34].

Although, conductive HL is the principal type of HL in HIV infection (Matas CG et al., and Molyneux EM et al.,) [13,43], sensorineural HL was predominant in the study conducted by Fasunla AJ et al., in Nigeria [35]. A study by Awodele O et al., reported that Zidovudine/lamivudine/nevirapine combination reported more suspected ADRs among ARVTs [36]. Mahomed W et al., have found that higher incidence of hearing impairment in adults with HIV compared to those without HIV [37].

Tumwikirize WA et al., have found suspected ADRs with combination of stavudine, lamivudine and nevirapine [38]. The study by Smith JP et al., found no difference in HL due to HIV infection, but they found that a large proportion of patients developed HL of any grade and severe hearing impairment who received ARVTs along with MDR-TB treatment [39]. Sagwa EL et al., found the occurrence of moderate-to-severe ADRs commonly during Drug Resistant Tuberculosis (DR-TB) treatment. They found these ADRs to occur more likely to happen and to continue in HIV co-infected patients than those without HIV infection [40].

This systematic review and meta-analysis add evidence to the recent 2020 recommendation of the National Coordinating Centre-Pharmacovigilance Program of India (NCC- PvPI) of IPC, Ghaziabad, India, in its Subject Expert Committee (SEC- antimicrobial and antiviral drugs) that HL should be incorporated in the package insert of lamivudine [44].

Strengths of this systematic review include a comprehensive search strategy that permitted for the documentation of published studies on HL in HIV positive individuals.

Limitation(s)

The present study was limited by the the fact that only observational studies were found, and no randomised controlled trials could be marked.

CONCLUSION(S)

This systematic review and meta-analysis showed a relationship between HL and lamivudine in patients with HIV infection. In this study, authors were not able to evaluate more details about the lamivudine therapy (dose, duration of therapy, etc.,) as they were not mentioned in the studies which were analysed. Authors recommend further research like randomised controlled trials is needed to understand more about the association of HL in patients infected with HIV and HBV infections and on lamivudine therapy.

Further details like lamivudine daily dose and duration of treatment, concomitant medications, and whether the treatment was discontinued/continued after the development of ADR was not mentioned in most of the studies which were analysed. Also, the details of other co-morbid conditions and the treatment given for them were not mentioned in most of the studies which were analysed. The information on investigations done like audiogram, auditory brain stem response, Computerised Tomography (CT) scan, Magnetic Resonance Imaging (MRI) scan was not available in the studies which were analysed. The information on patient/relative reported HL, tretament of HL and causality assessment of ADR was not available.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 30, 2022
- Manual Googling: Jun 15, 2022
- iThenticate Software: Jun 18, 2022 (14%)

ETYMOLOGY: Author Origin

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