VIEWPOINT

Unraveling the mechanisms of HIV-induced hearing loss

Jake Langlie[a], Rahul Mittal[a], Nathalie B. Bencie[a], Umakant Sharma[b], Sabita Roy[b] and Adrien A. Eshraghi[a,c,d,e]

AIDS 2022, **36**:1737–1740

Keywords: gut dysbiosis, highly active antiretroviral therapy, human immunodeficiency virus, inner ear, sensorineural hearing loss

The prevalence of hearing loss among HIV seropositive patients has been shown to be alarmingly high compared with the general population. Studies have reported that 24% [1] of children and 49% [2] of adults with HIV demonstrate clinically significant hearing loss. HIV can affect nearly any tissue in the body, including the sensory and supporting cells of the inner ear that can lead to hearing loss. Recent studies have demonstrated that there is over a two-fold increase in the prevalence of sensorineural hearing loss (SNHL) in HIV-infected individuals compared with uninfected control groups [3]. The clinical manifestations of auditory disorders in HIV-positive patients mirror those in the general population including tinnitus (26%), vertigo (25%), hearing loss (27.5%), otalgia (19%), and ear canal pruritus (38%) [4]. Currently, limited data exist regarding the underlying molecular mechanisms involved in HIV-induced hearing loss.

It has been proposed that HIV has a multifocal effect on auditory perception (Fig. 1). Studies have postulated that HIV infection may first lead to synaptic loss, followed by cochlear damage and central disease, as the virus induces local inflammation and degeneration of auditory structures (Fig. 1) [5]. It has thus been suggested that all individuals presenting with HIV infection should undergo assessment of hearing function by otoacoustic emission (OAE) testing, pure tone and speech audiometry, speech-in-noise tests, or auditory brainstem recording measurements [5].

There are several factors that need to be investigated in the interplay of HIV and SNHL. Recent studies have shown that HIV-infected individuals demonstrate high morbidity of chronic SNHL. The ototoxicity of HAART [6] and separating its effects from HIV-induced hearing loss has been superficially explored [7,8]. HIV-positive patients have been shown to have increasingly abnormal OAE in higher frequencies as the duration of HAART treatment increases [9]. Higher rates of complications, including chronic otitis media, were also observed to be more common in HAART-treated HIV-positive children compared with matched controls [10]. As HAART has been shown to be toxic to multiple organ systems, it is necessary to further explore the effects of the therapy on hearing outcomes. Although HAART therapy has been shown to influence SNHL [11], there is currently no literature differentiating hearing outcomes of patients who are on HAART therapy versus those that are not. Furthermore, there is limited data regarding the ototoxic effects of the various classes of HAART, including nucleosides, nucleoside analog reverse transcriptase inhibitors, nonnucleoside analog reverse transcriptase inhibitors, and protease inhibitors, and their individual effects on SNHL susceptibility. There is a need to identify which HAART medications may have ototoxic side effects and to

[a]Department of Otolaryngology, Hearing Research and Cochlear Implant Laboratory, [b]Department of Surgery, [c]Department of Neurological Surgery, University of Miami Miller School of Medicine, [d]Department of Biomedical Engineering, University of Miami, Coral Gables, and [e]Department of Pediatrics, University of Miami Miller School of Medicine, Miami, Florida, USA.

Correspondence to Adrien A. Eshraghi, MD, MSc, FACS, Department of Otolaryngology, Neurological Surgery, and Pediatrics, University of Miami-Miller School of Medicine, 1600 NW 10th Avenue, Miami, FL 33136, USA.

Tel: +1 305 243 8078; e-mail: aeshraghi@med.miami.edu

Received: 23 March 2022; revised: 8 June 2022; accepted: 22 June 2022.

DOI:10.1097/QAD.0000000000003320

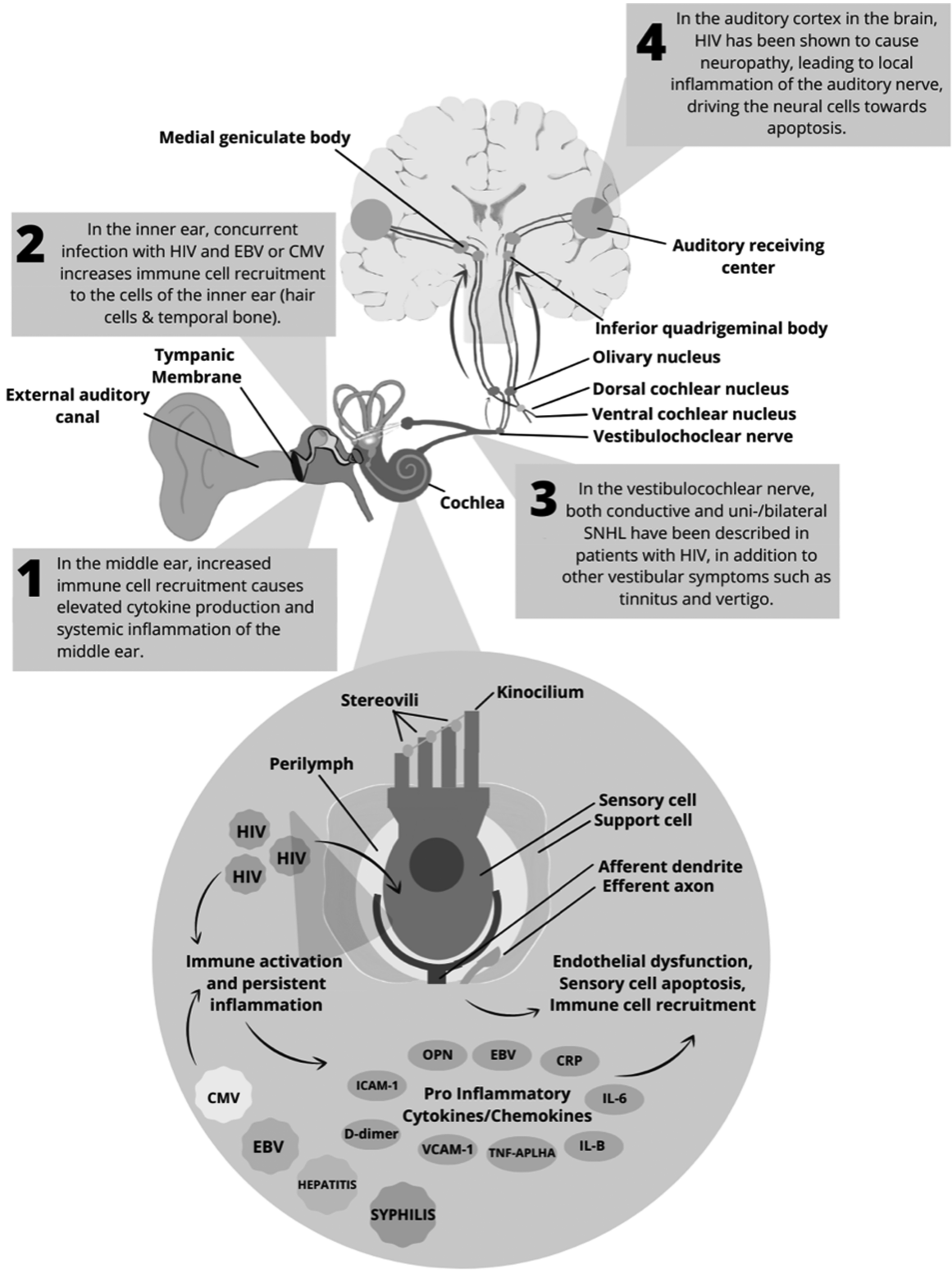

Fig. 1. Proposed mechanisms of HIV-induced sensorineural hearing loss: a schematic representation of HIV interaction with the auditory pathway leading to sensorineural hearing loss.

avoid those medications or reduce their dose in patients who are already suffering from mild to moderate hearing loss. Once identified, there is also a need to determine whether the duration of HAART use plays a role in SNHL.

Patients with HIV have been found to have a high rate of concurrent infection with cytomegalovirus (CMV), Epstein–Barr virus (EBV), syphilis [12,13], and human papillomavirus (HPV) due to the immunodeficiency

induced by HIV, making the host more susceptible to infections. This has also been demonstrated in patients with multidrug-resistant and extensively drug-resistant tuberculosis [14,15], wherein the HIV-positive cohort experienced greater hearing loss (70%) than the HIV-negative (42%) cohort following aminoglycoside treatment. As EBV and CMV are known causes of SNHL [16], we predict that those coinfected with HIV will fare worse. Concurrent infection with other organisms will increase immune cell recruitment to the cells of the inner ear, including hair cells [17] and temporal bone cells (Fig. 1) [18]. It has been hypothesized that HIV-associated deafness involves infiltration and malfunction, leading to premature death, of the supportive cells and hair cells of the cochlea [19].

HIV has a neurotropic nature and can preferentially spread to the cochlear nerve and semicircular canals [19,20]. HIV infection of the auditory nerve [5] has been hypothesized as a mechanism of hearing loss. HIV has been shown to cause neuropathy, resulting in local inflammation of the auditory nerve, which drives neural cell apoptosis. In addition, HIV infection induces profound alterations in the gastrointestinal microbiome composition leading to gut dysbiosis. This gut dysbiosis has been hypothesized to be further exacerbated with HAART therapy. It is reasonable to speculate that the inflammatory mediators generated during gut dysbiosis, which are released into the bloodstream, enter the cochlea by enhancing the permeability of the blood labyrinth barrier. These inflammatory mediators can induce damage to the cochlear sensory cells leading to SNHL. There is a need to determine the role of gut dysbiosis in HIV-induced SNHL that will pave the way for developing novel microbiome-mediated therapies.

Intriguingly, HIV may preferentially infect certain parts of the cochlea over others in patients with chronic SNHL. In a large study of 278 HIV-positive patients, individuals had worse hearing at lower frequencies and had significant differences in tympanometry compared with HIV-negative controls [2]. Low-frequency hearing loss was confirmed in the middle-aged population, wherein typically only high-frequency hearing loss should be expected [21]. However, additional studies have shown both low-frequency pure tone average (250, 500, 1000, and 2000 Hz) and high-frequency pure tone average (3000, 4000, 6000, and 8000 Hz) are significantly affected in patients who are HIV-positive when compared with HIV-matched controls. Although it appears that HIV may preferentially affect basal regions of the cochlea, corresponding to high-frequency hearing, there is a need to refine the disease of HIV infection in the inner ear [21].

Apart from chronic SNHL, HIV has been found to be a presenting diagnosis for patients experiencing sudden sensorineural hearing loss (SSHL) [22]. HIV infection was demonstrated as a predictor of increased prevalence of SSHL by 2.17-fold over a matched control group among patients aged 18–35 years [3]. This incidence was even higher among a male-only cohort. The interplay of sex and age, and their influence on SSHL, remains to be explored.

Current research has indicated that during early stages of inner ear development, developmental markers, including SOX2, FGFR3, and CDKN1B, are more susceptible to being affected by viruses [23]. Abnormalities in the expression and function of these key developmental markers influence hair cell, supporting cell, and cochlear development. Although these markers have been identified, there is a need to further understand the effects of HIV on these molecules and mechanisms underlying inner ear cell development, cochlear dysfunction, and accelerated HIV-mediated SNHL.

Proximal to the inner ear, HIV has been shown to have effects on auditory-neurophysiological functions, demonstrating that speech-evoked frequency-following response, an objective measure of auditory function, has weaker responses among HIV-positive patients [24]. This corresponds to decreased speech perception among HIV-positive patients. Beyond speech perception, cognitive, language, and central auditory dysfunction have been identified at an increased prevalence in individuals with HIV [25]. A large cohort study demonstrated four distinct cognitive change phenotypes that revealed declines in HIV-positive patients, including verbal fluency, executive function, learning and recall, and motor function [26]. However, the underlying mechanisms leading to this higher-level dysfunction are limited at a clinical level and relatively unknown at a molecular level. One clinical manifestation of this may be a higher prevalence of seizures [27] in HIV-positive children presenting with severe hearing loss. This suggests that the effects of HIV extend beyond the auditory nerve and into the cortical regions of the brain.

In the context of children, it has been shown that hearing loss is more common in HIV-negative exposed and HIV-positive children when compared with matched controls, although later presentation was correlated with an increased risk of hearing loss in HIV-positive children [28]. As the ability to hear is one of the most important factors in normal brain and speech development, there is an urgent need for improved identification, treatment, and screening tools for HIV-infected children. Hearing loss is commonly misidentified by caregivers, so children presenting with frequent ear drainage, ear infection, low BMI, or severely progressed HIV should receive frequent assessments and auditory function evaluations [1,29].

There are key questions that need to be addressed in determining the correlation between HIV and SNHL. Specifically, do $CD4^+$ levels, an objective marker of HIV

infection, predict outcomes of patients with SNHL? This easily attainable measure can help predict adherence to HAART therapy regimens as well as the chronicity and extent of HIV replication. One study showed that otological and auditory symptoms are more common in patients with HIV, especially toward the advanced stages of HIV disease progression [4].

With the advancement of HAART therapy and the transition of HIV from an acute to a chronic disease, there is an urgent need to identify the mechanisms and interplay between HIV and SNHL. Future prospective studies with large cohorts of HIV-infected patients are needed to determine when hearing loss starts and the effect of HAART in further worsening of HIV-induced SNHL. As we identify the molecular mechanisms that underlie HIV-induced SNHL, we will be able to more accurately and readily identify patients who are at an increased risk for HIV-mediated SNHL, which will lead to early interventions and, hence, better clinical outcomes.

Acknowledgements

The authors are grateful to Dr Valerie Gramling for critically reading the manuscript. No funding was received for the present study.

Jake Langlie and Rahul Mittal contributed equally to this work.

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflicts of interest

There are no conflicts of interest.

References

1. Hrapcak S, Kuper H, Bartlett P, Devendra A, Makawa A, Kim M, *et al*. **Hearing loss in HIV-infected children in Lilongwe.** *Malawi PLoS One* 2016; **11**:e0161421.
2. Luque AE, Orlando MS, Leong U-C, Allen PD, Guido JJ, Yang H, *et al*. **Hearing function in patients living with HIV/AIDS.** *Ear Hear* 2014; **35**:e282.
3. Lin C, Lin S-W, Weng S-F, Lin Y-S. **Increased risk of sudden sensorineural hearing loss in patients with human immunodeficiency virus aged 18 to 35 years: a population-based cohort study.** *JAMA Otolaryngol Head Neck Surg* 2013; **139**:251–255.
4. Van der Westhuizen Y, Swanepoel DW, Heinze B, Hofmeyr LM. **Auditory and otological manifestations in adults with HIV/AIDS.** *Int J Audiol* 2013; **52**:37–43.
5. De Jong MA, Luder A, Gross M. **Main aspects of peripheral and central hearing system involvement in unexplained HIV-related hearing complaints.** *Front Neurol* 2019; **10**:845.
6. Fokouo JVF, Vokwely JEE, Noubiap JJN, Nouthe BE, Zafack J, Ngom ESM, *et al*. **Effect of HIV infection and highly active antiretroviral therapy on hearing function: a prospective case-control study from Cameroon.** *JAMA Otolaryngol Head Neck Surg* 2015; **141**:436–441.
7. Assuiti LFC, de Melo Lanzoni GM, dos Santos FC, Erdmann AL, Meirelles BHS. **Hearing loss in people with HIV/AIDS and associated factors: an integrative review.** *Braz J Otorhinolaryngol* 2013; **79**:248–255.
8. Makau S, Ongulo B, Mugwe P. **The pattern of hearing disorders in HIV positive patients on antiretrovirals at Kenyatta National Hospital.** *East Afr Med J* 2010; **87**:425–429.
9. Swathi V, Raju SS, Tejaswini L, Praveen KB, Veenapani M, Manjunath S. **Effect of antiretroviral therapy (ART) on hearing in HIV positive patients.** *J Evol Med Dent Sci* 2016; **5**:2528–2531.
10. Smith AF, Ianacone DC, Ensink RJ, Melaku A, Casselbrant ML, Isaacson G. **Prevalence of hearing-loss among HAART-treated children in the Horn of Africa.** *Int J Pediatr Otorhinolaryngol* 2017; **98**:166–170.
11. Marra CM, Wechkin HA, Longstreth W, Rees TS, Syapin CL, Gates GA. **Hearing loss and antiretroviral therapy in patients infected with HIV-1.** *Arch Neurol* 1997; **54**:407–410.
12. Pasricha JM, Read TR, Street AC. **Otosyphilis: a cause of hearing loss in adults with HIV.** *Med J Aust* 2010; **193**:421–422.
13. Song JJ, Lee H-M, Chae SW, Hwang SJ. **Bilateral otosyphilis in a patient with HIV infection.** *Eur Arch Otorhinolaryngol* 2005; **262**:972–974.
14. Harris T, Bardien S, Schaaf HS, Petersen L, De Jong G, Fagan JJ. **Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients.** *S Afr Med J* 2012; **102**:363–366.
15. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. **Hearing loss in patients on treatment for drug-resistant tuberculosis.** *Eur Respir J* 2012; **40**:1277–1286.
16. Maple PA. **Cytomegalovirus and Epstein–Barr virus associations with neurological diseases and the need for vaccine development.** *Vaccines* 2020; **8**:35.
17. Pappas DG Jr, Lim J, Hillman D. **Ultrastructural findings in the cochlea of AIDS cases.** *Am J Otol* 1994; **15**:456–465.
18. Chandrasekhar SS, Siverls V, Sekhar H. **Histopathologic and ultrastructural changes in the temporal bones of HIV-infected human adults.** *Am J Otol* 1992; **13**:207–214.
19. Roland JT, Alexiades G, Jackman AH, Hillman D, Shapiro W. **Cochlear implantation in human immunodeficiency virus–infected patients.** *Otol Neurotol* 2003; **24**:892–895.
20. Edkins O, Harris T, Fagan JJ, Edkins O. **ENT manifestations of HIV in clinical practice.** *ENT MASTERCLASS* 2011; **4**:123.
21. Torre P, Hoffman HJ, Springer G, Cox C, Young MA, Margolick JB, *et al*. **Hearing loss among HIV-seropositive and HIV-seronegative men and women.** *JAMA Otolaryngol Head Neck Surg* 2015; **141**:202–210.
22. Timon C, Walsh M. **Sudden sensorineural hearing loss as a presentation of HIV infection.** *J Laryngol Otol* 1989; **103**:1071–1072.
23. Karimi-Boroujeni M, Zahedi-Amiri A, Coombs KM. **Embryonic origins of virus-induced hearing loss: overview of molecular etiology.** *Viruses* 2021; **13**:71.
24. White-Schwoch T, Magohe AK, Fellows AM, Rieke CC, Vilarello B, Nicol T, *et al*. **Auditory neurophysiology reveals central nervous system dysfunction in HIV-infected individuals.** *Clin Neurophysiol* 2020; **131**:1827–1832.
25. Kallail KJ, Downs D, Scherz J, Sweet D, Zackula RE. **Prevalence of communication disorders in HIV-infected adults.** *J Int Assoc Provid AIDS Care* 2014; **13**:8–11.
26. Dastgheyb RM, Sacktor N, Franklin D, Letendre S, Marcotte T, Heaton R, *et al*. **Cognitive trajectory phenotypes in human immunodeficiency virus infected patients.** *J Acquir Immune Defic Syndr* 2019; **82**:61–70.
27. Chao CK, Czechowicz JA, Messner AH, Alarcón J, Kolevic Roca L, Larragan Rodriguez MM, *et al*. **High prevalence of hearing impairment in HIV-infected Peruvian children.** *Otolaryngol Head Neck Surg* 2012; **146**:259–265.
28. Torre P III, Zeldow B, Hoffman HJ, Buchanan A, Siberry GK, Rice M, *et al*. **Hearing loss in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents.** *Pediatr Infect Dis J* 2012; **31**:835–841.
29. Phanguphangu M, Ross AJ. **Clinical utility of smartphone-based audiometry for early hearing loss detection in HIV-positive children: a feasibility study.** *Afr J Prim Healthcare Fam Med* 2021; **13**:e1–e4.