Study of hearing functions in individuals with HIV/AIDS submitted and not submitted to antiretroviral therapies

Estudo da função auditiva em indivíduos com HIV/AIDS submetidos e não submetidos à terapia antirretroviral

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ABSTRACT

Purpose: To characterize the audiologic manifestations in individuals with HIV/AIDS (Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome) submitted and not submitted to antiretroviral therapy. **Methods:** The audiologic evaluation was carried out in 28 individuals in Research Group I (RGI) with HIV/AIDS submitted to antiretroviral therapy; 24 individuals in Research Group II (RGII) with HIV/AIDS not submitted to antiretroviral therapy, and 45 healthy individuals in the Control Group (CG). The audiologic tests that comprised this study were: Conventional Pure Tone Audiometry, Speech Audiometry and High Frequency Audiometry. **Results:** There were differences between groups RGI and RGII regarding conventional audiologic evaluation and high frequency audiometry. There were higher thresholds for both Conventional and High Frequency Audiometries when compared with CG subjects, however without significant difference among RGI and RGII. **Conclusion:** Individuals with HIV/AIDS present more abnormal results in Conventional Pure Tone Audiometry and High Frequency Audiometry than healthy individuals (CG), which indicates impairment in the hearing system. Individuals with HIV/AIDS present more abnormal findings in High Frequency Audiometry when compared to Conventional Pure Tone Audiometry. There was no difference between individuals with HIV/AIDS submitted (RGI) and not submitted (RGII) to antiretroviral therapy regarding Conventional Pure Tone Audiometry and High Frequency Audiometry.

Keywords: Acquired immunodeficiency syndrome; HIV; Antiretroviral therapy, Highly active; Audiometry; Hearing loss

RESUMO

Objetivo: Caracterizar as manifestações audiológicas em indivíduos com HIV/AIDS (Vírus da Imunodeficiência Humana/Síndrome da Imunodeficiência Adquirida) submetidos e não submetidos à terapia antirretroviral. **Métodos:** A avaliação audiológica foi realizada em 28 indivíduos do Grupo Pesquisa I (GPI) com HIV/AIDS, submetidos à terapia antirretroviral; 24 indivíduos do Grupo Pesquisa II (GPII) com HIV/AIDS, não submetidos à terapia antirretroviral e 45 indivíduos saudáveis do Grupo Controle (GC). Os exames audiológicos que compuseram esta pesquisa foram: Audiometria Tonal Convencional, Logoaudiometria e Audiometria em Altas Frequências. **Resultados:** Houve diferença nos grupos GPI e GPII, para os resultados obtidos tanto na avaliação audiológica convencional, como na avaliação em altas frequências, observando-se limiares auditivos mais elevados quando comparados aos indivíduos do GC, porém sem diferença significativa entre GPI e GPII. **Conclusão:** Indivíduos com HIV/AIDS apresentam mais alteração na Audiometria Tonal Convencional e na Audiometria em Altas Frequências quando comparados a indivíduos saudáveis (GC) sugerindo comprometimento do sistema auditivo, sendo observada maior ocorrência de perda auditiva na Audiometria em Altas Frequências quando comparada à Audiometria Tonal Convencional nos grupos GPI e GPII. Não houve diferença entre indivíduos com HIV/AIDS submetidos (GPI) e não submetidos (GPII) à terapia antirretroviral para a Audiometria Tonal Convencional e Audiometria em Altas Frequências.

Descritores: Síndrome da imunodeficiência adquirida; HIV; Terapia anti-retroviral de alta atividade; Audiometria; Perda auditiva

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INTRODUCTION

Acquired immunodeficiency syndrome – AIDS – is caused by action of the Human Immunodeficiency Virus – HIV, which affects the immune system by infecting lymphocytes T4, responsible for cellular immunity, which multiply within it through CD4+ cells. HIV invades the body and destroys these cells, modifying the functioning of the immune system, causing weakening of body defenses and favoring the onset of a series of diseases named opportunistic infections.

It is known that subjects with HIV/AIDS may present several infections and impairments associated with hearing as characteristic symptoms of the disease.

Studies in the literature have shown that the progression of AIDS may impair the Central Nervous System (CNS) and modify the auditory system both in its peripheral and central portions, justifying the investigation of the auditory pathways as a whole[1-5].

In the past, AIDS used to be described as an acute disease; it is currently considered by the World Health Organization (WHO) as a chronic disease, owing to major advances that have been achieved in its treatment, primarily as of 1996 with the use of highly active antiretroviral therapy - HAART[6].

Even though medications are necessary and essential to many patients, providing significant improvements and increase in survival[7], there are reports in the literature that discuss their adverse effects[8,9].

The involvement of the inner ear, resulting from the action of HIV virus, is mentioned in studies with AIDS patients[10-14], which also applies to auditory disorders resulting from use of antiretroviral treatment and ototoxic medication[9,15-21], which may lead to sensorineural hearing loss and, consequently, irreversible inner ear damage.

In addition to research studies showing that HIV/AIDS and the treatment medication may affect the hearing system, there are other studies that have suggested that subjects with HIV/AIDS would be more affected by hearing disorders than those without HIV/AIDS, and subjects taking medication would have more hearing disorders than untreated subjects.

Therefore, the objective of the present study was to characterized audiologic manifestations of subjects with HIV/AIDS submitted or not submitted to antiretroviral therapy.

METHODS

This study was developed at the Laboratory of Audiology Investigation in Auditory Evoked Potential, Course of Speech Therapy and Audiology, Department of Physical Therapy, Speech Therapy and Audiology and Occupational Therapy, Medical School, Universidade de São Paulo (FMUSP).

The research study was carried out in the city of Santos and involved two different municipal units: SECRAIDS – Section, AIDS Reference Center, coordinated by Santos Municipal Health Department, which enabled the selection of subjects contaminated with HIV; and SEVREST (Section of Occupational Health Surveillance and Reference), coordinated by Santos Municipal Health Department, which provided the site and the equipment for the tests.

The project was submitted to the Research Ethics Committee (CAPPesq), FMUSP, and was approved under protocol number 389/10.

The sample comprised 97 subjects aged 18 to 50 years, divided into three different groups: Research Group I (RGI), formed by 28 HIV-positive subjects, submitted to treatment with antiretroviral medication; Research Group II (RGII) formed by 24 HIV-positive subjects not submitted to treatment with antiretroviral therapy, and Control Group (CG) formed by 45 healthy subjects, with no auditory complaints and HIV-negative status as self-reported in the history.

After having signed the Free Informed Consent Term, we collected data about patient history, through anamnesis, asking about auditory complaints and diseases that could impair patients' hearing.

The next step included the following procedures for data collection: Meatoscopy, Conventional Pure Tone Audiometry (CPTA), Speech Reception Threshold (SRT), Percentage Index of Speech Recognition (PISR) and High Frequency Audiometry (HFA). The devices used were: Otoscope Heine®; audiometer Amplaid®, model A321, with headsets TDH 49P for conventional audiologic assessment and headsets HDA 200 for high frequency audiometry. SRT was carried out to confirm the results obtained from CPTA, and it was not statistically analyzed.

The adopted normal range criteria for each procedure are described below:

- Conventional Pure Tone Audiometry (CPTA): Airway auditory thresholds below or equal to 25 dB HL for frequencies 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz[22].
- High Frequency Audiometry (HFA): Normal range was defined based on mean values obtained by the CG in the study, considering one standard deviation above these values as the normal cut-off value (Chart 1).

Based on the defined criteria, the tests that did not present results within the normal range described above were considered abnormal and the subject was classified as having a disorder when at least one ear had such deviant results.

In the CPTA, abnormal results were classified as conductive, sensorineural or mixed loss[23], comparing the airway and bone auditory thresholds (presence or air-bone gap).

At first, the statistical analysis was performed by quantitative data assessment, calculating descriptive measures (mean, median, standard deviation) by ear, frequency and group, using Friedman test to compare right ear (RE) and left ear (LE) by frequency and group, as well as Kruskal-Wallis test to compare the three groups. The level of significance was equal to 5% and

Chart 1. Cut-off values for normal range in high frequencies (in dB HL), by age range, according to the control group of the study

Age range	9 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz	18 kHz	20 kHz
18-29 years	9.6	8.8	10.8	7.4	6.7	7.0	16.3	24.1
30-39 years	16.3	15.7	15.5	16.7	19.8	34.7	37.9	38.3
>40 years	20.4	21.0	24.5	27.1	28.8	37.4	36.5	38.3

all significant values were marked with an asterisk.

Following, qualitative data analysis was made by comparing the normal and abnormal results found in each group and among the groups (chi-square statistical test for homogeneity), describing the types of abnormal results observed for each assessment.

RESULTS

Conventional Pure Tone Audiometry (CPTA)

In the comparison among groups CG, RGI and RGII for auditory thresholds in frequencies 250, 500, 2000, 3000, 6000 and 8000 Hz (Table 1), we considered the mean between RE and LE, given that the results obtained for both ears did not present any difference in distribution.

We have observed that in frequencies 250, 2000, 6000 and 8000 Hz hearing thresholds were significantly higher in groups with HIV/AIDS when compared to the CG, and in the comparison with groups RGI and RGII there was significant difference with the CG for frequencies 250, 6000 and 8000 Hz (250 Hz: CG x RGI p=0.04, CG x RGII p=0.04; 6000 Hz: CG x RGI p=0.002, CG x RGII p=0.019; 8000 Hz: CG x RGI p=0.005, CG x RGII p=0.026). In frequency 2000 Hz, only RGII presented differences when compared to CG (p=0.008).

When auditory thresholds obtained for both ears for frequencies 1000 and 4000 Hz presented differences in distributions, the comparisons between the three groups were made separately for RE and LE. In 1000 Hz in the RE, there was no difference in the comparison between the groups (p=0.208), given that this difference was present in the LE (p=0.003), with lower auditory thresholds in the CG when compared to groups RGI and RGII (p=0.021 and p=0.002 respectively), but there was no difference between groups with HIV/AIDS (p=0.275). In 4000 Hz, there was difference in the comparison between the groups, both for RE and LE (p=0.003 and p=0.031, respectively), showing lower auditory thresholds for CG when compared to RGI (RE: p=0.001; LE: p=0.007).

In the distribution of the occurrence of normal and abnormal CPTA results, the authors have noticed that subjects with HIV/AIDS (RGI and RGII) presented more disorders than subjects in the CG (Table 2).

Upon comparing the groups two by two, there were no differences between normal and abnormal results in the groups with HIV/AIDS submitted or not to antiretroviral therapy (p>0.999), but the results were significant when compared to CG (RGI: p=0.007 and RGII: p=0.004).

Concerning types of disorders found by CPTA, the authors

Table 1. Descriptive statistics for variable CPTA by frequency and group

Frequency	Group	Mean	Median	Standard deviation	p-value (among groups)
250 Hz	CG	11.78	12.50	4.15	0.044*
	RGI	14.46	15.00	5.37	
	RGII	14.17	13.75	4.40	
500 Hz	CG	10.22	10.0	3.69	0.119
	RGI	12.05	12.5	4.81	
	RGII	12.60	11.25	5.19	
2000 Hz	CG	6.44	5.00	5.73	0.032*
	RGI	8.66	8.75	6.99	
	RGII	9.17	8.75	4.34	
3000 Hz	CG	8.44	7.50	5.44	0.067
	RGI	10.27	8.75	6.71	
	RGII	11.35	11.25	5.05	
6000 Hz	CG	9.22	7.50	5.25	0.004*
	RGI	14.91	13.75	8.88	
	RGII	14.38	12.50	9.22	
8000 Hz	CG	8.10	7.50	5.36	0.008*
	RGI	13.75	11.25	9.61	
	RGII	13.75	10.00	10.91	

* Significant values (p<0.005) - Kruskal Wallis test

Note: CPTA = Conventional Pure Tone Audiometry; CG = Control Group; RGI = Research Group I; RGII = Research Group II

Table 2. Distribution of the occurrence of normal and abnormal results in CPTA in groups CG, RGI and RGII

Pure tone audiometry	Group							
	CG		RGI		RGII		Total	
	n	%	n	%	n	%	n	%
Normal	45	100	23	82.14	19	79.17	87	89.69
Abnormal	0	0	5	17.86	5	20.83	10	10.31
Total	45	100	28	100	24	100	97	100

Chi-square test for homogeneity (p=0.008)

Note: CPTA = Conventional Pure Tone Audiometry; CG = Control Group; RGI = Research Group I; RGII = Research Group II

have observed greater occurrence of sensorineural hearing loss. In the RGI, three subjects had unilateral sensorineural hearing loss and two had bilateral loss. In the RGII, two subjects had unilateral sensorineural hearing loss, two had bilateral sensorineural loss and one had unilateral conductive hearing loss.

High Frequency Audiometry (HFA)

In the comparison among groups CG, RGI and RGII for auditory thresholds (frequencies 9, 10, 11.2, 12.5, 14, 16 and 18 kHz) by HFA (Table 3), we considered the mean between RE and LE, given that the results obtained for both ears did not present any difference.

It was observed that in frequencies 10, 11.2, 12.5, 14 and 18 kHz auditory thresholds were significantly higher in HIV/AIDS groups when compared to the CG, and in two by two group comparison only RGI presented difference compared to CG in 14 and 18 kHz (p=0.008 and p=0.003, respectively) and in 10 and 11.2 kHz, only RGII presented difference when compared to CG (p=0.007 and p=0.001, respectively).

When auditory thresholds obtained for both ears for frequency 20 kHz in HFA presented differences in distributions, the comparisons between the three groups were made separately for RE and LE. There was difference in the comparison between the groups, both for RE and LE (p=0.049 and p=0.05, respectively), showing lower auditory thresholds for CG when compared to RGI (RE: p=0.016; LE: p=0.018).

In the distribution of the occurrence of normal and abnormal results obtained by HFA, it was observed that in subjects with HIV/AIDS there were more disorders than in subjects in the CG (Table 4).

In the comparison between the groups, there were no differences in normal and abnormal results obtained for subjects with HIV/AIDS submitted and not submitted to antiretroviral therapy

Table 3. Descriptive statistics for variable HFA by frequency and group

Frequency	Group	Mean	Median	Standard deviation	p-value
9 kHz	CG	9.00	7.50	6.75	0.098
	RGI	14.20	8.75	13.59	
	RGII	14.90	12.50	12.46	
10 kHz	CG	7.00	7.50	7.81	0.029*
	RGI	12.32	7.50	16.09	
	RGII	15.00	11.25	13.51	
11.2 kHz	CG	8.89	10.00	8.13	0.004*
	RGI	16.88	11.25	18.44	
	RGII	19.38	15.00	14.13	
12.5 kHZ	CG	8.00	7.50	9.53	0.003*
	RGI	20.45	11.25	22.89	
	RGII	20.52	13.75	18.55	
14 kHZ	CG	6.56	5.00	12.24	0.018*
	RGI	23.48	13.75	25.64	
	RGII	18.33	12.50	21.95	
16 kHZ	CG	12.33	15.0	17.98	0.054
	RGI	25.36	25.0	20.28	
	RGII	20.10	20.0	23.10	
18 kHZ	CG	18.56	20.00	16.21	0.015*
	RGI	30.09	30.00	11.17	
	RGII	22.71	26.25	19.35	

* Significant values (p<0.005) - Kruskal Wallis test

Note: HFA = High Frequency Audiometry; CG = Control Group; RGI = Research Group I; RGII = Research Group II

Table 4. Distribution of the occurrence of normal and abnormal results in HFA in groups CG, RGI and RGII

High Frequency Audiometry	Group							
	CG		RGI		RGII		Total	
	n	%	n	%	n	%	n	%
Normal	45	100	10	35.71	4	16.67	59	60.82
Abnormal	0	0	18	64.29	20	83.33	38	39.18
Total	45	100	28	100	24	100	97	100

Chi-square test for homogeneity (p<0.001)

Note: HFA = High Frequency Audiometry; CG = Control Group; RGI = Research Group I; RGII = Research Group II

(p=0.209). The proportion of subjects with normal result was higher in the CG (p<0.001), whereas in groups RGI and RGII there was higher proportion of abnormal results (p=0.001).

Subjects with HIV/AIDS were also assessed concerning distribution of normal and abnormal results in CPTA and HFA (Table 5), and the authors have observed differences in the comparison of the tests (p<0.001), given that HFA had higher occurrence of abnormal results (73.08%) when compared to CPTA (19.23%).

Table 5. Comparison of the results obtained from CPTA and HFA in groups RGI and RGII

Results	CPTA		HFA		Total	
	n	%	n	%	n	%
Normal	42	80.77	14	26.92	56	53.85
Abnormal	10	19.23	38	73.08	48	46.15
Total	52	100	52	100	104	100

Chi-square test for homogeneity (p<0.001)

Groups were assessed together, except for Control Group, whose results were normal for CPTA and HFA

Note: CPTA = Conventional Pure Tone Audiometry; HFA = High Frequency Audiometry; RGI = Research Group I; RGII = Research Group II

DISCUSSION

Manifestations of HIV/AIDS in the auditory system are reported in studies that have shown the affection of both the peripheral and the central portions. It is important to emphasize that the existing abnormalities may occur due to the action of the virus upon the body, the immunosuppression and presence of opportunistic infections, as well as the action of antiretroviral medication and potentially ototoxic medication[5,9-21,24].

The specialized literature has shown widely diversified results concerning the occurrence of hearing loss in the population with HIV/AIDS. Some studies refer that approximately 21 to 49% of the subjects with HIV/AIDS may present hearing loss[1,9-12,21].

The findings presented in our study have shown that for CPTA the results were less expressive than in previously described studies, but the presence of HIV seems to have interfered in the results, as there was higher occurrence of abnormal results in groups when RGI and RGII when compared to CG (Table 2).

We have observed the occurrence of hearing loss in 17.86 in RGI and in 20.83 in RGII. For RGI, out of five subjects with CPTA abnormality, the sensorineural hearing loss was present in 100% of the cases (60% unilateral and 40% bilateral affection). In RGII, out of the five subjects with abnormal results in the CPTA, 80% presented sensorineural hearing loss (50% unilateral and 50% bilateral) and 20% had conductive hearing loss (unilateral).

Many different studies in the literature refer that the most frequently observed type of hearing loss in HIV/AIDS adults is sensorineural[5,14,21,24], followed by conductive hearing loss[21], and that the impairment is normally bilateral and progressive[2,9,15].

Concerning middle ear impairment, and consequently, presence of conductive or mixed hearing loss, some studies report that this impairment would result from immunosuppression, which favors the presence of opportunistic infections[25].

In the present study, the authors have noticed higher occurrence of sensorineural hearing loss compared to conductive loss in the CPTA, demonstrating the inner ear impairment in this population. The obtained results confirmed one study in which the author, to characterize the results of audiologic assessment in children and adults with HIV/AIDS, observed higher occurrence of conductive hearing loss in children (92.9% of the cases), whereas in the adult population there was higher occurrence of sensorineural hearing loss (44.4% of the cases)[26].

Upon comparing the subjects with HIV/AIDS submitted and not submitted to antiretroviral therapy, the data observed in the present study showed that there were no differences in occurrence of hearing loss in these two groups, confirming the results of some specific studies in the area[14,19,20], and disagreeing with other studies that correlated the use of antiretroviral medication with higher occurrence of hearing impairment[5,9,15-18,21].

Considering the data found in the present study, we could observe that sensorineural hearing loss was associated with the presence of HIV virus and its adverse effects in the infected subject, in agreement with other studies published in the literature[10-12,14,24,25].

The results of the present study are in disagreement with some other studies that have observed patients submitted or not to antiretroviral treatment and found higher occurrence of conductive hearing loss in the group submitted to treatment (30.8%) when compared to the group without treatment (20%),

whose finding was justified by the fact that those who take medication are normally subjects with longer duration of infection and more marked immunosuppression[26].

HFA is a test that has shown great potential for hearing loss early detection because the basal cochlear region, where the hair cells can be found, is the first to be affected by auditory abnormalities caused by endogenous and exogenous factors, enabling the anticipation of potential CPTA affections[27,28].

Auditory monitoring of subjects that take ototoxic medication using HFA has provided early evidence about the maximum limit dose that may cause hearing loss, leading to ototoxicity prevention and reduction of severity.

In the present study, the results found for HFA in subjects with HIV/AIDS were more expressive when compared to those obtained by CPTA (Table 5). In the comparison of groups RGI and RGII with the CG (Table 4) there was significant difference ($p<0.001$), and RGI had 64.29% of abnormal results, followed by 83.33% of abnormal results in RGII for HFA.

These findings confirm different studies in the literature that have shown the presence of significant impairment in HFA[9,21,26]. In a study that assessed 25 subjects with HIV, it was found that 88% of the cases had abnormal HFA results[21]. Investigating the hearing of 56 subjects with HIV/AIDS, some authors found 90.2 % of HFA abnormal results, with prevalence of 84.2 % in the group not submitted to medication and 95.5 % in the group submitted to antiretroviral therapy, emphasizing that HFA can be considered a more sensitive procedure for early identification of hearing loss in this population[9], and that it should also be used for auditory monitoring.

The expressive values of hearing impairment found by HFA in our study confirm the previously mentioned studies and emphasize the importance of carrying out HFA as a clinical routine test in subjects with HIV/AIDS, proving to be an important and efficient procedure for early diagnosis of hearing loss, taking into account that CPTA could have failed to detect such losses at early stage.

In the present study, it was not possible to correlate the effects of antiretroviral therapy with the performed behavioral audiologic assessments. Even though some authors have not excluded or correlated the effect of medication on hearing impairment[19,20], others have demonstrated significant differences among subjects with HIV/AIDS submitted or not to antiretroviral therapy, especially detected by HFA[9,21,26]. It is important to point out that this difference between these two groups (submitted or not to antiretroviral therapy) might not have been detected owing to the fact that HIV virus affects the peripheral auditory system earlier, causing opportunistic infections, as described by some studies[10-12,14,25], which means that the auditory impairments are also detected in subjects who have not started using the medication yet.

As a result of the progression of research studies of the auditory system in subjects with HIV/AIDS and HFA, science will enable all patients to be monitored, avoiding major auditory damage and even using such monitoring to adjust or even replace the medication. There is still a lot to learn from this disease and hearing impairments are only a small part of the myriad of affections resulting from acquired immunodeficiency syndrome.

CONCLUSION

In view of the results, we can conclude that subjects with HIV/AIDS present more audiologic affections than healthy subjects, suggesting the impairment of the hearing system. HFA presented higher occurrence of hearing loss when compared to CPTA. In the present study, it was not possible to observe any differences concerning the results of CPTA and HFA among subjects with HIV/AIDS submitted or not to antiretroviral therapy.

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