

## Original Research Article

# The duration of antiretrovirals administration and hearing impairment in HIV-infected patients

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## ABSTRACT

**Background:** Antiretrovirals (ARV) treatment in HIV has a role in preventing HIV transmission, because ARV drugs have a mechanism of action to prevent viral replication which gradually reduces the amount of virus in the blood. Nucleoside analogue reverse transcriptase inhibitors (NRTIs) are a type of ARV that has side effects of hearing impairment. This research was purposed to determine the relationship between the duration of ARV administration with hearing impairment HIV-infected patients.

**Methods:** We used a cross-sectional design in HIV patients aged 19-59 years who were undergoing ARV treatment at Dr. Kariadi Semarang. We identified 91 patients whose complaints of hearing impairment (tinnitus and/or hearing loss) obtained from the history. We analyzed the data with the chi-square test, fisher's exact and yate correlation.

**Results:** There were 91 respondents who received ARVs. Male 62 people (68.1%) female 29 people (31.9%), the youngest was 19 years old, the oldest was 52 years old, mean age was 34.8 years+ 8.04. The duration of ARV administration was not associated with tinnitus ( $p=0.385$ ), hearing loss ( $p=0.344$ ), and hearing impairment ( $p=0.454$ ).

**Conclusions:** The duration of ARV administration was not associated with tinnitus, hearing loss, hearing impairment.

**Keywords:** Human immunodeficiency virus, Antiretroviral, Hearing impairment

## INTRODUCTION

Human immunodeficiency virus (HIV) has been identified as the cause of AIDS.<sup>1</sup> HIV is a neurotropic and lymphotropic virus that primarily affects T-helper (CD4) lymphocytes, producing cells that suppress immune responses and decrease the number of T4 lymphocytes (low CD4).<sup>2</sup> The data from the directorate general of P2P of the ministry of health of the republic of Indonesia in 2017 the number of HIV infection cases increased every year, cumulative data from 2005 to December 2017 was obtained HIV infections of 280,623 people. The number of infections in central Java in 2017

was 22,292 meanwhile in Dr. Kariadi hospital was 2019, 778 adults and 78 children.<sup>3</sup>

Antiretrovirals (ARVs) is used for HIV therapy. ARV treatment is proven to have a significant role in preventing HIV transmission through a mechanism of action to prevent viral replication which gradually reduces the amount of virus in the blood. ARV drugs fall into three main groups: nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors. The NRTI causes hearing impairment through mitochondrial DNA toxicity.<sup>4</sup>

The audiometric features of HIV infected patients who took ARVs show worse results on pure tone audiometry with a frequency of 4000 Hz to 8000 Hz than those who did not take ARVs.<sup>5</sup> A study about the relationship between the duration of ARV administration and hearing impairment has not been carried out.

The aim of this study was to determine the association between the duration of ARV administration and hearing impairment (tinnitus and/or hearing loss) in HIV-infected patients.

## METHODS

This study used a cross-sectional method which been taken place at Dr. Kariadi central hospital Semarang from March to April 2020. We identified the 91 HIV-infected patients who received ARV aged 19-59 years as the samples. We grouped HIV treatment into two group that is ARV treatments with zidovudine, lamivudine, efavirenz and tenofovir, lamivudine, efavirenz as prescribed by internal medicine colleagues. Duration of treatment was classified as <4 years and ≥4 years. We divided ages into two groups of young adults (19 to <35 years) and adults (≥35 to 59 years). We collected tinnitus and hearing loss data after receiving ARV from a questionnaire via google form. We excluded the samples whos' with a history of tinnitus, hearing impairment before receiving ARVs, exposed to ototoxic drugs, exposed to noise, history of diabetes mellitus, hypertension, and produced discharge from the ear. We collected the data from google form that had been filled by the respondent. We were getting this research approval by the research ethics commission Dr. Kariadi Semarang. We analysed the data using the chi-square test, Fisher's Exact, and Yates correction and  $p < 0.05$  was considered significant.

## RESULTS

A total samples of this study were 91 whose mean age was 34, 8 years±8.04, the youngest was 19 years old, the oldest was 52 years old.

Table 1 shows 16 patients with hearing loss complaints (17.6%), consisting of 10 (62.5%) tinnitus complaints, 3 (18.8%) complaints of hearing loss and those who complained of tinnitus and hearing loss: 3 ( 18.7%).

Table 2 shows the results, HIV patients who received ARV <4 years who complained of tinnitus: 7 people (70%) and did not complain of tinnitus: 48 people (59.3%). Patients who received ARV ≥4 years who complained of tinnitus: 3 (30%) and who did not complain of tinnitus: 33 people (40.7%).

Table 3 shows HIV patients who received ARV <4 years old who complained of hearing loss: 1 person (33.3%) and who did not complain of hearing loss: 54 people (61.4%). Patients who received ARV ≥4 years and

complained about hearing loss: 2 people (66.7%) and 34 people who did not complain about hearing loss (38.6%).

**Table 1: Data distribution.**

Variable	Total	Percentage (%)
<b>Sex</b>		
Male	62	68.1
Female	29	31.9
<b>Age (year)</b>		
19-<35	45	49.5
35-59	46	50.5
<b>Duration of treatment (year)</b>		
<4	55	60.4
≥4	36	39.6
<b>ARV treatment</b>		
Lamivudine-Zidovudin-Efavirenz	26	28.6
Lamivudin-Tenofovir-Efavirenz	65	71.4
Hearing impairment	16	17.6
Tinnitus	10	62.5
Hearing loss	3	18.8
Tinnitus and hearing loss	3	18.7
No hearing impairment	75	82.4

**Table 2: The relationship between the duration of ARV administration and tinnitus.**

Variable	Tinnitus				P
	Yes		No		
	N	%	N	%	
Duration of ARV treatment (year)					0.385 <sup>‡</sup>
<4	7	70	48	59.3	
≥4	3	30	33	40.7	
Total	10	100	81	100	

Note: \*significant ( $p < 0.05$ ), <sup>‡</sup> Fisher's exact

**Table 3: The relationship between the duration of ARV administration and hearing loss.**

Variable	Hearing loss				P
	Yes		No		
	N	%	N	%	
Duration of ARV treatment (year)					0.344 <sup>£</sup>
<4	1	33.3	54	61.4	
≥4	2	66.7	34	38.6	
Total	3	100	88	100	

Note: \*significant ( $p < 0.05$ ), <sup>‡</sup> Fisher's exact

Table 3 shows HIV patients who received ARV <4 years old who complained of hearing loss: 1 person (33.3%) and who did not complain of hearing loss: 54 people (61.4%). Patients who received ARV ≥4 years and complained about hearing loss: 2 people (66.7%) and 34 people who did not complain about hearing loss (38.6%).

Table 4 shows HIV patients who received ARV <4 years old who complained of tinnitus and hearing loss: 3 people

(100%) and who did not complain of tinnitus and hearing loss: 52 people (53.2%). Patients who received ARV  $\geq 4$  years and complained of tinnitus and hearing loss: none (0%) and who did not complain of tinnitus and hearing loss: 36 people (34.8%).

**Table 4. Duration of ARV administration with tinnitus and hearing loss.**

Variable	Tinnitus and hearing loss				P
	Yes		No		
	N	%	N	%	
Duration of ARV treatment (year)					0.410 <sup>€</sup>
<4	3	100	52	53.2	
≥4	0	0	36	34.8	
Total	3	100	75	100	

Note: \* significant ( $p < 0.05$ ), <sup>€</sup> Yates correction

**Table 5: Duration of ARV with hearing impairment.**

Variable	Hearing impairment				P
	Yes		No		
	N	%	N	%	
Duration of ARV treatment (year)					0.454 <sup>¥</sup>
<4	11	68.8	44	58.7	
≥4	5	31.3	31	41.3	
Total	16	100	75	100	

Note: \*significant ( $p < 0.05$ ), <sup>¥</sup> person chi-square

Table 5 shows HIV patients who received ARV <4 years who complained of hearing loss: 11 people (68.8%) and who did not complain of hearing loss: 44 people (58.7%). Patients who received ARV  $\geq 4$  years and complained of hearing loss: 5 people (31.3%) and those who did not complain of hearing loss: 31 people 41.3%).

**Table 6: ARV treatment, age, and sex with hearing loss.**

Variable	Hearing impairment				P RP
	Yes		No		
	N	%	N	%	
ARV treatment					
Lamivudine- Zidovudin- Efavirenz	4	25	22	29.3	0.494 <sup>£</sup>
Lamivudin- Tenofovir- Efavirenz	12	75	53	70.7	0.803
Age (year)					
19-<35	12	75	33	44	0.023 <sup>¥</sup>
35-59	4	25	42	56	3.818
Sex					
Male	10	62.5	52	69.3	0.594 <sup>¥</sup>
Female	6	37.5	23	30.7	0.737
Total	16	100	75	100	

Note: \*significant ( $p < 0.05$ ), <sup>¥</sup> Pearson chi square, <sup>£</sup> Fisher's exact.

Table 6 shows that HIV patients who received Lamivudine-Zidovudin-Efavirenz and those who received Lamivudin-Tenofovir-Efavirenz were more likely to not complain of hearing loss. HIV patients aged 19 to <35 years who complained of hearing loss: 12 people (75%) and who did not complain of hearing loss: 33 people (44%), patients who received ARV aged  $\geq 35$  to 59 years who complained of hearing loss: 4 people (25%) and those who did not complain of hearing loss: 42 people (55%). There is a significant relationship between age and hearing loss complaints ( $p < 0.05$ ). Male HIV patients who complained of hearing loss: 10 people (62.5%) and who did not complain of hearing loss: 52 people (69.3%). Female HIV patients and complained of hearing loss: 6 people (37.5%) and those who did not complain of hearing loss: 23 people (30.7%).

## DISCUSSION

The results of this study showed that gender was not associated with hearing loss. This is consistent with Fokou IVF et al's study about the effects of HIV infection and ARV therapy on hearing function, the study concluded that there was no significant difference between gender with hearing loss.<sup>6</sup>

Tinnitus complaints in this study mostly occurred in respondents who received ARV <4 years. There was no significant association between the duration of ARV with complaints of tinnitus ( $p = 0.385$ ; RP: 1.604, 95% CI: 0.386 to 6.658). The results of this study were consistent with those reported in Matas CG et al's study which showed no significant difference between HIV patients who received ARVs and those did not. (tinnitus was occurred on 61% samples of those who did not receive ARVs and 89% of those who received ARVs). The most common symptoms found in HIV patients receiving ARVs were hearing loss in 52% of cases, tinnitus (44%) and dizziness (33%).<sup>5</sup> The symptoms in HIV patients who did not receive ARVs were dizziness (61% of cases), tinnitus (39%) and sensation of full in ears (33%). The etiological factors associated with hearing loss may be due to the direct viral invasion of the hearing system structures, opportunistic infections in people with HIV and/or using ARV drugs (lamivudine, zidovudin, tenofovir, efavirenz) which are ototoxic.<sup>5</sup>

The results of this study found 3 respondents (3.3%) got symptoms of hearing loss, most of them got ARV treatment  $\geq 4$  years. Eighty-eight (96.7%) subjects did not complain about hearing loss. There was no significant association between duration of antiretroviral administration with the occurrence of hearing loss in HIV-infected patients ( $p = 0.344$ , RP: 0.315, 95% CI: 0.027-3.606). This might be the ototoxicity of the ARVs into the inner ear (the cochlear mitochondrial DNA) damaged the high frequency (>4000-12,000 Hz) so that did not affect or interfere speech frequency (500-400Hz) then the complaints of hearing loss had not been felt. These results were the same as Minhas et al study which

reported that subjects experienced an increasing the threshold of hearing at high frequencies (4 and 8 KHz) in both ears. None of the subjects experienced symptoms in otology for 6 months of observation. Seven subjects had sensory neural hearing loss in one or both ears at 0 and 6 months followed-up. This observation did not show a significant difference.<sup>7</sup>

In this study, age factor affected hearing loss in HIV-infected patients who received ARVs ( $p=0.023$ ). Patients in the group 19 to <35 years old had a three times higher risk of developing hearing loss (RP: 3.818). The synergistic relationship between the use of NRTIs and a strong noise exposure resulted in a hearing loss than noise exposure without any previous NRTI drug administration. NRTI drug interactions and noise consistently cause harmful effects on cellular mitochondrial activity.<sup>6</sup>

The results of this study showed the group of young adults (19-<35 years) was associated with increased complaints of hearing impairment, especially tinnitus ( $p=0.023$ ). This was the possibility that patients who received ARV in young adults were more susceptible to hearing impairment when accompanied by daily behaviour related to noise exposure, for example, behaviour using personal listening device (PLD) and other noise exposure which was associated with increased damage to cochlear cellular activity.<sup>8</sup>

### Limitations

This research cannot be carried out directly to assess the hearing loss status due to the COVID-19 pandemic so it was replaced with a google form which only assessed complaints. Tinnitus and hearing loss caused by abnormalities in the outer ear and middle ear cannot be excluded because otoscopy and audio tympanometry were not be performed.

### CONCLUSION

The duration of ARV administration was not associated with hearing loss in HIV-infected patients. It is necessary to do further research on the relationship of hearing loss in HIV-infected patients who receive ARV by performing ear examinations and audio tympanometry examinations.

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