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Effects of Antiretroviral Therapy to Changes in Salivary pH and Plaque Index on HIV/AIDS

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Abstract

Antiretroviral Therapy (ART) are used to eliminate the replication of the HIV virus so it does not continue into the AIDS phase, and prevent another infection that attacks the immune system and their complications. On the other hand, there are side effects ART which are found oral cavity lesions, like formation of white lesions on the lips and buccal mucosa accompanied by complaints of taste disorders, dry mouth, xerostomia, and a burning feeling in the mucosa of patients using Nevirapine, Zidovudine, and Lamivudine. This is caused by enlargement of the salivary glands so that it affects the rate of salivary flow. The purpose of this research is to examine the relationship between antiretroviral treatment of HIV / AIDS patients with plaque index and salivary pH, and the relationship between duration of antiretroviral treatment on these two variables. This study used an observational research method with a cross sectional design by directly observing 100 samples of HIV / AIDS patients using antiretroviral therapy. Data were analyzed using chi square test.
The research found that there was a relationship between antiretroviral treatment in HIV / AIDS patients with plaque index (p = 0.355) and salivary pH (p = 0.042), while analysis of the duration of antiretroviral treatment was less than 5 years and more than 5 years, there was no relationship with plaque index (p-0.726) and salivary pH (p = 0.102).

Keywords*:* antiretroviral, salivary pH, plaque index

Introduction

HIV (Human Immunodeficiency Virus) is a virus that attacks the human immune system, whereas AIDS (Acquired Immunodeficiency Syndrome) is an immune syndrome by HIV infection. The virus enters through the intermediaries of blood, semen and vaginal secretions. Most infections (75%) are caused by sexual relations.

HIV is a virus that causes AIDS which has a primary target cell in the form of T4 lymphocyte cells, and has a CD4 receptor. HIV infects in a way, the gp 120 HIV sheath protein will touch and bind CD4 receptor of the host cell, then there is viral replication, starting with the production of the same proviral RNA so that new virions will form, a new HIV virus ready to infect target cells that are targeted others, after leaving the host cell through budding [1].

After the experts discovered that AIDS was caused by HIV, various studies about drugs that could eliminate this virus began. The drug used in HIV virus therapy is antiretroviral therapy [1]. HIV sufferers need antiretrovirals (ARV) to suppress the amount of virus in the blood so it does not progress to the AIDS stage. The antiretroviral therapy aim is to maximize suppression of viral replication, to undetectable levels for as long as possible and also maintain and improve immune function, minimizing drug toxicity. Combination therapy can slow down the progression of the disease, improve survival, maintain immune and virological responses and inhibit the development of viral mutations thereby preventing drug resistance being used [2].

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ARV treatment also prevents opportunistic infections from occurring with various complications. One of them is Epstein Barr virus infection (EBV). HAART is useful in reducing the release of EBV in saliva of HIV / AIDS patients thereby indirectly reducing the risk of transmission of EBV [3]. So it is important for people with HIV / AIDS to adhere to ARV therapy to suppress the development of the virus so that they can live normally longer.

At present, a well-known antiretroviral drug administration technique is Highly Active Antiretroviral Therapy (HAART) which has brought revolutionary changes to the treatment and prognosis of HIV / AIDS. HAART is combination of antiretroviral regimen namely Reverse Transcriptase Inhibitors and Protease Inhibitors. This therapeutic strategy provides very significant results in reducing disability, the prevalence of some oral lesions and deaths caused by HIV infection. Therefore HAART can increase the life expectancy of HIV patients. Although the use of HAART can increase patient life expectancy, but the main problem that must be taken into consideration is the side effects of the use of this drug, especially the problems it causes in the oral cavity [4].

Adverse effects of ART in the oral cavity of people with HIV / AIDS began to be found. A case regarding the adverse effects of ART was reported by Moura, et al, namely the discovery of oral cavity lesions likely white plaques on the lips and buccal mucosa that have occurred more than one month accompanied by complaints of taste disorders, xerostomia, and a burning feeling in the mucosa of patients using Nevirapine, Zidovudine, and Lamivudine [4]. Predisposing factors to this occurrence are due to reduction of salivary antibodies and salivary flow rate, use of drugs containing sucrose, and an unbalanced diet that is high in carbohydrates but low in protein.

Antiretroviral therapy also causes microbial changes in the mouth. Plaque is microbial accumulation on the tooth surface. From the accumulation of plaque on the tooth surface can cause various periodontal diseases with various causative factors including immunological reactions to the plaque accumulation [5].

Another case was also reported by Sari who found Stevens-Johnson Syndrome (SSJ) in a patient using combination antiretroviral drug therapy consisting of Duvival (Zidovudine 300 mg and Lamivudine 150 mg) and Neviral (Nevirapine 100 mg) twice a day [6].

Methode

This study uses an observational analytic method with cross sectional design that is by directly measuring the pH of saliva and checking the plaque index in 100 samples of HIV-AIDS patients taking anti-retroviral drugs. The research was carried out at Yayasan Peduli Kelompok Dukungan Sebaya (YPKDS) Makassar, Indonesia and was carried out in October 2019. Data retrieval lasted for 6 days. Saliva acidity or pH is measured using a pH meter. Salivary pH is said to be acidic if the value is <7 and said to be alkaline if the value is> 7. Meanwhile, if the value is 7, it means it is neutral. Plaque index was examined after the teeth were stained with disclosing solution. Plaque index score determination is measured using PHP Index. The measurement results obtained are processed and analyzed with the chi-square test.

Result

Table 1 : The relationship between drug use and drug type on Plaque Index

Duration of Use	Type of ARV	Plaque index			Total
		Good	Average	Poor	
Less than 5 years	Defural	10	2	0	12
	FCD	29	8	2	39
	HRV	3	1	0	4
	Nefiral	1	1	0	2
	V-Tripel	2	0	0	2
	Total	45	12	2	59

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More than 5 years	Defural	16	3	3	22
	FCD	7	1	1	9
	Nefiral	4	2	0	6
	V-Tripel	4	0	0	4
	Total	31	6	4	41
Total	Defural	26	5	3	34
	FCD	36	9	3	48
	HRV	3	1	0	4
	Nefiral	5	3	0	8
	V-Tripel	6	0	0	6
	Total	76	18	6	100

Table 1 shows that samples taking antiretroviral therapy were less than 5 years old, and had a good plaque index score of 45 people, a moderate score of 12 people and a poor score of 2 people. For the sample group that took antiretroviral therapy for less than 5 years, then the sample taking FCD antiretroviral therapy appeared to have the most good plaque index scores of 29 people, followed by Defural types of 10 people, HRV 3 people, Nefiral 1 people and V-triple 2 person. As for the moderate plaque index score, it was also found most in the samples taking FCD antiretroviral therapy, which were 8 people but there were no samples with moderate plaque index scores in the sample group consuming the V-triple type. Poor plaque index scores were only found in 2 samples who consumed FCD antiretroviral types for less than 5 years.

For the sample group who took antiretroviral therapy for more than 5 years, 31 samples were found with a good plaque index, 6 people with a moderate plaque index score and 4 people with a bad plaque index. The sample that consumed the type of antiretroviral Defural drug seen the most had a good plaque index score of 16 people, followed by 7 people FCD, and Nefiral and V-triple each 4 samples While the sample group that consumed the V-triple type did not find samples with moderate and bad plaque index. For the sample group consuming the type of antiretroviral drug FCD it was seen that each had 1 sample with a moderate and bad plaque index score. The sample group that consumed Nefiral showed 2 people who had a moderate plaque index and none who had a bad plaque index score.

Table 2. Relationship between Duration of Drug Use and Type of Drug on Saliva PH

Duration of Use	Type of ARV	Salivary pH		Total
		Acid	Neutral	
Less than 5 years	Defural	9	3	12
	FCD	26	13	39
	HRV	1	3	4
	Nefiral	1	1	2
	V-Tripel	1	1	2
	Total	38	21	59
More than 5 years	Defural	18	4	22
	FCD	8	1	9
	Nefiral	6	0	6
	V-Tripel	2	2	4
	Total	34	7	41

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Total	Defural	27	7	34
	FCD	34	14	48
	HRV	1	3	4
	Nefiral	7	1	8
	V-Tripel	3	3	6
	Total	72	28	100

The results of salivary pH measurements are shown in table 2, none of the sample groups that have salivary pH are basic (pH> 7). For the sample group that consumed antiretroviral therapy for less than 5 years, then the sample that consumed the type of FCD seemed to have the most samples with salivary pH <7 or acidic, as many as 26 people and 13 people were neutral pH (pH = 7). For samples that consumed Defural less than 5 years, it was seen to have an acidic pH of 9 people and 3 people of neutral pH. Meanwhile for HRV, Niferal and V-triple types, there were 1 sample each with acid or neutral salivary pH values. Meanwhile, for the sample group that consumed the type of antiretroviral Defural for more than 5 years, 18 people were found with salivary pH <7 (acidic pH) and only 4 people whose salivary pH was neutral (pH = 7).
Table 2 also shows that samples in the group that took antiretroviral therapy for more than 5 years, then the sample group that consumed the most types of Defural had salivary pH (pH <7), namely 18 people followed by FCD types of 8 people and for the type Nefiral and V-triple only 1 person each. While for the sample group with neutral pH (pH = 7), there were 4 samples that consumed Defural having saliva pH = 7. Furthermore, there were 1 people who consumed FCD who had neutral salivary pH and 2 people in the sample group who consumed the V-triple antriretroviral type.

Table 3 Chi square test the relationship between types of ARV with salivary PH and Plaque Index

Type of ARV	Variable	*P-Value*	Information
Defural	Salivary pH	0,638	No Significant
	Plaque index	0,407	No Significant
FCD	Salivary pH	0,186	No Significant
	Plaque index	0,679	No Significant
HRV	Salivary pH	-	Undefined*
	Plaque index	-	Undefined*
Nefiral	Salivary pH	0,043	Significant
	Plaque index	0,673	No Significant
V-Tripel	Salivary pH	1,0	No Significant
	Plaque index	-	Undefined*
Total	Salivary pH	0,042	Significant
	Plaque index	0,355	No Significant

Note: (*) the data is constant so it cannot be tested for chi square

Table 3 shows that the p-value of salivary pH variable 0.042 is less than 0.05. So it can be concluded that the type of Nefiral has a significant relationship with salivary pH variables. The overall total p-value of the salivary pH variable is 0.042 less than 0.05. So that we may conclude that overall the types of ARVs have a significant relationship to salivary pH variables. The overall total p-value of the plaque index variable is more than 0.05 which is 0.355. So it can be concluded that the whole type of ARV has no significant relationship to the plaque index variable.

Table 4 : Chi square test the relationship between duration of use with salivary PH and Plaque Index

Duration of Use	Variable	*P-Value*	Information

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Less than 5 years	Salivary pH	0,441	No Significant
	Plaque index	0,944	No Significant
More than 5 years	Salivary pH	0,208	No Significant
	Plaque index	0,697	No Significant
Total	Salivary pH	0,102	No Significant
	Plaque index	0,726	No Significant

Table 4 shows that the p-value of the salivary pH variable and plaque index is greater than 0.05, so it can be concluded that the duration of drug use of less than 5 years or more than 5 years has no significant or unrelated relationship to pH saliva and plaque index.

The p-value seen in the salivary pH variable was smaller in drug use for more than 5 years compared to drug use for less than 5 years. The plaque index variable p-value is smaller at a period of more than 5 years of use than a period of less than 5 years.

Discussion

HAART treatment is defined as a combination of several ARVs between Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and 1 Protease Inhibitor (PI) or a combination of 2 NNRTIs and Protease Inhibitors (PI) [7].

Saliva has an important role in oral hygiene and caries prevention including cleaning effects, buffering capacity, balance of demineralization and remineralization, antimicrobial effects and antibody production. HIV infiltration and proliferation of CD8 lymphocytes in the salivary gland together with HAART reduce the rate of salivary flow and result in changes in oral cavity organisms [8].

In this study, from 100 samples of HIV-AIDS patients in Yayasan Peduli Kelompok Dukungan Sebaya (YPKDS) Makassar examined 72 people found acid salivary pH and 28 neutral people. From the chi-square test, the pValue value of the ARV type variable to the salivary pH is 0.042, while the length of usage is the pValue value of 0.102. This value indicates that salivary pH has a significant relationship to the type of ARV drugs consumed by the sample, but does not show a significant correlation to the duration of consumption.

These results are in line with the study of Sandra Lopez, et.al, who compared two groups of AIDS patients treated with HAART and without HAART therapy in Mexico. The results showed that there were significant differences between the salivary flow rates of groups treated with HAART and those not treated with HAART. The group with HAART therapy decreased salivary flow rate compared to the group without HAART therapy. This shows that there is a relationship between antiretroviral therapy with hyposalivation and xerostomia. Apparently, antiretroviral therapy presents a potential risk in reducing salivary flow, and most importantly, this risk can increase depending on the duration of therapy. However, there is a clear relationship between salivary flow dysregulation and subjective variables, so further research should be undertaken with larger samples and control group sizes [9].

In his study Saravani et.all (2013) examined the dental health status of 119 HIV positive people, also finding that ARVs were considered a risk factor that played an important role in decreasing the level of salivary flow and enlarged salivary glands in HIV-positive patients. It was also observed that most ARVs had higher sugar concentrations and some in syrup form had below critical pH values, which made the oral cavity vulnerable to dental caries, tooth loss, and increased DMFT index [10].

The acidic pH of saliva as happened in 72 samples that we examined according to Olive et.al (1998) can be a result of Protease Inhibitors (PI) in ARVs that cause abnormal fat accumulation and the occurrence of parotid lipomatosis, thus causing enlargement of salivary glands and decrease salivary flow [11].

However, on one hand Voelker et al. (2013) found that there was a significant correlation between smoking, decreased salivary pH and its buffering ability, with an increased risk of caries, but according to Voelker, there is

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no effect of smoking to accumulation of Streptococcus mutans in the mouth of HIV patients treated with antiretroviral therapy [12].

Contrary to Voelker's study, Lopez-Verdin et.al (2013) in her study stated that no significant impact use of Protease Inhibitors in ARVs on salivary dysfunction in patients taking ART. This study shows that complaints of xerostomia patients do not always show decreased salivary gland function [9].

As mentioned by Olive, et al. The acidic atmosphere of salivary pH due to HAART consumption is influenced by decreased salivary flow causing xerostomia. This can be overcome by maintaining oral lubrication (such as drinking plenty of water), avoiding local irritants, acidic drinks or food, alcohol, or drugs that can make the situation worse. (such as anticholinergic drugs) and avoid environments where humidity is lacking. Patients with complaints of dry mouth and xerostomia can be helped by using products such as chewing gum or chewing fruit. If it is not resolved, the use of artificial saliva can be considered. However, further study is needed on the use of topical salivary stimulation products to increase the flow of saliva.

Routine dental examinations at least every six months, plaque control and avoiding snacks containing sugar, or using special non-detergent toothpaste are also recommended to overcome the complaints of dry mouth [13].

Next we conducted an index plaque examination of 100 samples of HIV-AIDS patients at Yayasan Peduli Kelompok Dukungan Sebaya (YPKDS) Makassar, and analyzed its relationship to the type and duration of antiretroviral therapy. Of the 100 samples examined, 76 were found to have good plaque scores while only 6 were bad. The results of statistical analysis with the chi-square test did not show a significant relationship between ARV therapy with the sample plaque index value.

This is in line with research conducted by John et.al, 2013 in an infectious disease clinic in South Africa. The study was conducted by examining 4 clinical indexes in the form of gingival index, plaque index, pocket depth and gingival attachment to 120 samples aged 17-55 years with HIV-AIDS. The study showed that there was no significant correlation between the use of ARV drugs with the four clinical index values. This study states the value of the index plaque itself is not directly affected by the consumption of ARVs due to behavioral factors and habits of individuals in caring for their dental health, such as the habit of brushing teeth, the use of interdental aids, periodic visits to the dentist as well as education and motivation. In this study smoking samples (n = 60) mentioned a significant relationship to index plaques, pockets and gingival attachment but were not related to index gingival values [5].

Another study by Saravani et.all (2016) conducted on 119 HIV positive patients treated with ARVs at Medical Sciences, Zahedan University, Iran showed the same thing as previous studies that found no correlation between oralhygiene with received ARV therapy. This can be caused by subjective factors such as oral hygiene habits, nutrition, access to dental health services as well as training and prevention programs provided to these patients while in care. Besides that it was mentioned, there is a positive correlation between the use of dental health services with employment status and insurance ownership, because for those who have jobs it is more likely to get access to regular dental check-up services [10].

From our study of 100 HIV-AIDS samples receiving ARV therapy at Yayasan Peduli Kelompok Dukungan Sebaya (YPKDS) Makassar, Indonesia, no significant relationship was found between the plaque index value and the received ARV therapy, both in terms of the type of ARV and duration of use. The health education and motivation programs conducted by the Caring Support Group Foundation every month have a positive contribution so that the fostered residents have the awareness to have a healthy lifestyle, including brushing twice a day. Fostered residents have access to designated health facilities to carry out special health services to them including dental health services at puskesmas and hospitals. Mentoring programs, both motivation and counseling conducted by fellow inmates, also have a positive influence on them.

Conclussion

There is a relationship between antiretroviral treatment in HIV / AIDS patients with salivary acidity, namely salivary pH (0.042). While the duration of antiretroviral treatment in people with HIV / AIDS is not related to plaque index or salivary pH.

Reference

[1] S. R. Flint, A. Tappuni, J. Leigh, A.-M. Schmidt-Westhausen, and L. MacPhail, "(B3) Markers of immunodeficiency and mechanisms of HAART therapy on oral lesions," *Adv. Dent. Res.*, vol. 19, no. 1, pp.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 10877 - 10883
Received 05 March 2021; Accepted 01 April 2021.

146–151, 2006.

[2] W. Panel, Merino, “Panel on antiretroviral therapy and medical management of HIV-infected children.. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2012. AIDSinfo. nih. gov/guidelines.” 2016.

[3] Y. Yan *et al.*, “Evaluation of Epstein-Barr Virus Salivary Shedding in HIV / AIDS Patients and HAART Use: A Retrospective Cohort Study,” *Virol. Sin.*, vol. 33, no. 3, pp. 227–233, 2018.

[4] M. D. Moura, M. I. Senna, D. F. Madureira, L. M. Fonseca, and R. A. Mesquita, “Oral adverse effects due to the use of Nevirapine.,” *J. Contemp. Dent. Pract.*, vol. 9, no. 1, pp. 84–90, 2008.

[5] C. N. John, L. X. Stephen, and C. W. J. Africa, “Is human immunodeficiency virus (HIV) stage an independent risk factor for altering the periodontal status of HIV-positive patients? A South African study,” *BMC Oral Health*, vol. 13, no. 1, p. 69, 2013.

[6] S. G. P. Sari L M, “Manifestasi Sindroma Stevens-Johnson Akibat Obat Antiretroviral Nevirapine Pada Pasien Acquired Immunodeficiency Syndrome (AIDS). Dentika Dental Journal. 2006; 11(2): 171-6.,” *Dentika Dent. J.*, vol. 11, no. 2, 2006.

[7] I. D. Miziara and R. Weber, “Oral lesions as predictors of highly active antiretroviral therapy failure in Brazilian HIV-infected children,” *J. oral Pathol. Med.*, vol. 37, no. 2, pp. 99–106, 2008.

[8] J. C. Cavasin Filho and É. M. Giovani, “Xerostomy, dental caries and periodontal disease in HIV+ patients,” *Brazilian J. Infect. Dis.*, vol. 13, no. 1, pp. 13–17, 2009.

[9] S. López-Verdín, J. Andrade-Villanueva, A. L. Zamora-Perez, R. Bologna-Molina, J. J. Cervantes-Cabrera, and N. Molina-Frechero, “Differences in salivary flow level, xerostomia, and flavor alteration in Mexican HIV patients who did or did not receive antiretroviral therapy,” *AIDS Res. Treat.*, vol. 2013, 2013.

[10] S. Saravani, T. N. Zehi, H. Kadeh, and S. Mir, “Dental health status of HIV-positive patients and related variables in Southeast Iran,” *Int. J. high risk Behav. Addict.*, vol. 5, no. 2, 2016.

[11] A. Olive, A. Salavert, M. Manriques, B. Clotet, and A. Moragas, “Parotid lipomatosis in HIV positive patients: a new clinical disorder associated with protease inhibitors,” *Ann. Rheum. Dis.*, vol. 57, no. 12, p. 749, 1998.

[12] M. A. Voelker, M. Simmer-Beck, M. Cole, E. Keeven, and D. Tira, “Preliminary findings on the correlation of saliva pH, buffering capacity, flow, consistency and Streptococcus mutans in relation to cigarette smoking,” *Am. Dent. Hyg. Assoc.*, vol. 87, no. 1, pp. 30–37, 2013.

[13] I. Nizamuddin, P. Koulen, and C. P. McArthur, “Contribution of HIV infection, AIDS, and antiretroviral therapy to exocrine pathogenesis in salivary and lacrimal glands,” *Int. J. Mol. Sci.*, vol. 19, no. 9, p. 2747, 2018.