International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 6; Issue 7; July 2017; Page No. 4897-4902
DOI: http://dx.doi.org/10.24327/ijcar.2017.4902.0609

Research Article

VULNERABILITY OF PATIENTS LIVING WITH HIV / AIDS, WITH THE USE OF HAART OR NOT WHO DEVELOPED DIABETES MELLITUS, EVENING THE RISKS OF XEROSTOMY, CARIES AND PERIODONTIC DISEASES

Giovani E. M[1]., Noro-Filho G. A[2]., Caputo, B. V[3]., Georgevich Neto R[4] and Santos C. C[5]

[1]Master in Oral Pathology, Ph.D. in Integrated Clinic, Full Professor of Integrated Clinical Discipline and Patients with Special Needs, Professor of Master's and Ph.D. Program, Coordinator of CEAPE, Dentistry Course of the Faculty of Dentistry of Paulista University, FOUNIP, Sao Paulo, Brazil
[2,3,4,5] UNIP, Sao Paulo, SP, Member of Center for Studies and Special Service for Patients, Brazil

A R T I C L E I N F O

Article History:

Received 5th April, 2017
Received in revised form 20th May, 2017
Accepted 26th June, 2017
Published online 28th July, 2017

Key words:

HAART, HIV / Aids, Diabetes Mellitus

A B S T R A C T

With the advent of highly active antiretroviral therapy (HAART), a profound impact on the natural history of HIV infection has been observed. However, prolonged treatments with drug combinations are difficult to maintain due to poor adherence and toxic effects, generating undesirable side effects, which includes metabolic changes. Certain systemic diseases, such as Diabetes Mellitus, may occur, favoring the appearance, maintenance or exacerbation of diseases in the oral cavity. This study aimed to diagnose the risks of xerostomia, periodontal disease, caries and other oral and systemic diseases in patients living with HIV / AIDS, who developed diabetes mellitus (DM). Individuals of both genders were analyzed in all age groups, divided into three groups: Group I (control) - 70 patients, non-diabetic and HIV negative; Group II (control) - 70 patients living with diabetes mellitus and HIV negative; Group III - 70 patients living with HIV / AIDS and diagnosed with diabetes mellitus developed after initiation of HAART therapy. Measurements of salivary flow (salivary test), plaque index, presence of gingival bleeding, periodontal pocket and DMFT index were analyzed. Results: 60% of the patients in Group I presented normal levels and 20% presented intermediate and lower levels respectively, but when compared to Groups II and III, it is clear that there is an even greater decrease in patients with levels Group III (40%), with an increase in the intermediate and lower levels of Groups II and III. At salivary pH, Group I presented 74.3% of the patients with pH equal to 6.5; 20% at pH 7 and only 5.7% at pH 3.5, differing greatly from Groups II and III, where there is a much increased incidence at pH 7.0 (48.6% and 37.1% Groups 2 And 3 respectively). The ability to balance pH decreased gradually between Groups I, II and III at normal levels (54.3%, 51.4% and 45.7%), thus increasing the low levels among the same groups (5.7 %, 8.6% and 17.1%). For periodontal disease there is evidence of differences between groups ($P \leq 0.048$). It is concluded that patients who use HAART have important systemic and oral changes that should be taken into account in order to better recognize the process of metabolic performance of the drugs inserted in HAART.

INTRODUCTION

Background

Acquired Human Immunodeficiency Syndrome (AIDS) was described in 1981 in the United States, its etiologic agent being the Human Immunodeficiency Virus (HIV). Since the report of the first cases, an important change was observed in the demographic and epidemiological characteristics of the disease. Initially restricted to specific areas, then spreading globally becoming a pandemic. The World Health Organization (WHO) estimates that around 40 million people are infected with HIV worldwide. At the beginning of the epidemic the relationships between men who have sex with men (MSM) and injecting drug users (IDUs) were the main transmission routes of the disease, representing the so-called "risk groups". Currently, there is an increase in heterosexual transmission (HET), which is the main route of infection among women, resulting in an increase in infected children through vertical transmission. There is currently a large number of patients living with HIV / AIDS in the third age and young adolescents starting out sexually, no longer considered as "risk groups" but in the group of "risk behaviors and practices"(4).

With the advent and introduction of highly active antiretroviral therapy (HAART), known as highly potent antiretroviral therapy, there was a profound impact on the natural history of HIV infection. Thus, the use of therapeutic combinations containing drugs of the class of Protease Inhibitors (PI) promoted an important and sustained suppression in viral replication, increasing the survival and the quality of life of seropositive patients. However,

Corresponding author:* **Giovani E. M
Department of General Medicine, Saveetha Medical College Hospital, Chennai, Tamilnadu, India

prolonged treatments with drug combinations are difficult to maintain due to poor adherence and toxic effects, and are accompanied by some undesirable side effects, including metabolic changes. The onset of certain systemic diseases may favor the appearance, maintenance or exacerbation of diseases in the oral cavity. Diabetes Mellitus (DM) is a systemic disease that has repercussions on the oral cavity and has a prevalence rate and co-morbidity associated with HAART use in patients living with HIV / AIDS, immunosuppression, age, diet, hereditary factor and others. The oral manifestations in diabetics mentioned in the literature include periodontal disease, hyposalivation, xerostomia, candidiasis, oral burning, geographic tongue, fissured tongue, lichen planus, median rhomboid glossitis, volumetric enlargement of the salivary glands, ketone breath, traumatic ulcer and others. Individuals with diabetes are more susceptible to changes in the oral mucosa, and these changes are exacerbated when there is association with HIV immunosuppression.

LITERATURE REVISION

HAART is accompanied by undesirable adverse side effects, such as metabolic changes, such as dyslipidemia, insulin resistance, hyperglycemia and redistribution of body fat, which are risk factors for cardiovascular disease. All these changes are known as HIV Lipodystrophic Syndrome (SLHIV) (14; 5).

There is currently no consensus for the prevention or treatment of SLHIV, the cause of which remains unknown, however there is great concern in the scientific world regarding the side effects of IPs in what are called class effects, which are: lipodystrophy, hyperlipidemia, hyperglycemia and metabolic disorders Bone. (16; 20; 21; 6; 22).

Lipodystrophy consists of a change in the structure of the body, causing central fat with fat depletion in the limbs, being a disorder that occurs between 5-60% of the patients. It appears to occur with all PIs, but occasionally occurs in patients who do not use these drugs. Body changes of lipodystrophy and lipoatrophy may be associated with lipid disorders, insulin resistance and changes in bone metabolism (3, 12). With the occurrence of side effects, it is recommended never to reduce the dose, otherwise it will be ineffective. This applies to all IPs. (10; 18; 13, 14; 20; 21; 19; 22)

Hyperlipidemia consists of an increase in cholesterol and triglycerides, being observed around 50% of the patients, being a side effect sufficiently severe to require intervention, either by discontinuation of the drug or by the administration of treatment for hyperlipidemia. This occurs with all PIs, but it seems to occur more often with ritonavir. The long-term consequences are unknown, but there are potential for cardiovascular complications and pancreatitis (13, 14; 16; 21).

Hyperglycemia occurs in about 10% of patients with diabetes and the recommendation is to control glucose levels while maintaining PIs, however it may be necessary to discontinue treatment due to severe diabetes. (18; 13; 14; 6).

The administration of HAART has also been implicated as a risk factor in the occurrence of alterations in bone metabolism(9; 14; 1) but the risk of developing osteonecrosis was higher in patients with HIV infection than in those with HIV infection. Risk factors such as DM, use of corticosteroids, or a significant increase in the survival of patients receiving HAART who are much more likely to develop osteonecrosis, emphasizing the importance of recognizing and minimizing risk factors in the management of these Patients. (5).

Although the major focus on the relationship between AIDS and metabolic changes is on the side effects of HAART, earlier HAART studies have established that HIV itself determines a more unfavorable lipid profile, characteristically with hypertriglyceridemia and low HDL-cholesterol, and The lower the CD4 lymphocyte count, the higher the triglyceride level and the lower the HDL-cholesterol levels, but the pathophysiology of this association still needs to be elucidated. It is further understood the means by which HAART, specifically PIs, potentiate this lipid disorder and entails others associated with it, such as increased insulin resistance, diabetes mellitus, lipodystrophy, centripetal obesity and important bone metabolic disorders, such as adverse effects to Medium and long term(10; 11; 2).

Referring to the mechanism of toxicity of antiretroviral drugs, there are many factors to consider. Nucleoside Reverse Transcriptase PIs (NRTIs) and Inhibitors (NRTIs) can have negative effects on various organ systems, such as the liver, muscles, pancreas, bone, and central nervous system. Lipodystrophy and metabolic changes may be linked to hepatotoxicity and changes in the mechanisms of glucose metabolism. The effects of NRTIs on adipose cell differentiation, insulin sensitivity and cell survival have been widely observed. Abacavir (abc), didanosine (ddI), and lamivudine (3TC) - do not modify the functions of adipose cells, however, stavudine (d4T) and zidovudine (AZT) decrease the lipid content of cells. (13; 14; 20; 6)

Proposition

To diagnose the risks of xerostomia, periodontal disease, caries and other oral and systemic diseases in patients living with HIV / AIDS, who developed diabetes mellitus (DM) as an adverse effect of highly active antiretroviral therapy (HAART) or not.

MATERIAL AND METHODS

After approval by the Research Ethics Committee - CEP / ICS / UNIP 643/09, and the patients signed the Informed Consent Form, and with medical diagnosis of diabetes mellitus, individuals of both genders were analyzed in all The age groups, divided into 3 groups: Group I (control) - 70 patients not diabetes and HIV negative; Group II (control) - 70 patients living with diabetes mellitus and HIV negative; Group III - 70 patients living with HIV / AIDS and diagnosed with diabetes mellitus developed after initiation of HAART therapy.

For Group I, II and III, information regarding age, race, education level, general and oral manifestations was analyzed and collected, and also for Group III the probable means of HIV contamination, the count of lymphocytes T- CD4 viral load, and highly potent antiretroviral therapy (HAART) in use.

For the 3 groups were performed: salivary flow measurement (salivary test), plaque index, presence of gingival bleeding, periodontal pocket and the DMFT index. The salivary flow measurement of all patients was collected through saliva stimulated for 5 minutes, according to the salivary test method: DentoBuff® Kit (Inodon, Porto Alegre, RS, Brazil), analyzing the secretion velocity - salivary flow, The daily secretion of saliva buffer capacity, salivary pH. To obtain plaque index, plate evidence (erythrosine tablet) was applied, and the result was evaluated through the Ainamo and Bay Test, diagnosing the presence or absence of plaque in a binomial pattern (dichotomous counting). The visible plaque was marked "1", while on "plaque" it was marked "0", for the analysis of the CPO-D index, prophylaxis of the dental elements was performed and clinical examinations of the same with relative insulation and mirror, In a dry and well-lit environment, by means of artificial lighting, evaluating the presence of caries, missing and filled teeth, and bleeding index, verified by visible bleeding spots, up to 15 seconds after the probing, and the periodontal pocket using Periodontal probe of Willians from 1 to 10 mm under relative insulation with artificial lighting. The probe was introduced into the marginal gingiva region and inserted from each dental element, measuring its depth.

The collected data were first analyzed in a descriptive way. In this phase were obtained means, standard deviations and percentages. In a second step, inferential statistical analysis was performed regarding the data. Homogeneity tests and tests were used to compare means.

RESULTS

All samples have an equivalent number of patients and among them there are no significant statistical differences regarding gender, however, data related to skin color were not considered.

Table 1 shows the mean and standard deviation (SD) values of the variables: age, CPO, bleeding index and plaque index for the three groups. This table also shows the value of the descriptive level P of the ANOVA. The averages of the Age variable were compared two by two using the z-test. In Table 2 the descriptive levels associated to the three tests performed to compare the means of the Age variable can be found.

Table 1 Mean, standard deviation (S.D.) and descriptive level P

Variable	Group	Mean	S.D.	*P*
	1	41,1	10,2	-
Age	2	53,1	10,6	
	3	39,0	5,3	
	1	16,3	5,6	0,000
CPO	2	15,5	6,7	
	3	24,0	4,8	
	1	39,3	28,7	0,004
Bleending Rate	2	27,5	18,3	
	3	47,8	26,1	
	1	54,9	27,5	0,272
Plate Index	2	47,7	30,1	
	3	58,7	29,0	

Table 2 Descriptive level P of the tests of means comparisons of the variable Age.

Groups	*P*	Conclusion
1 e 2	0,000	Mean in Group2 >Mean in Group1
1 e 3	0,281	Mean in Group1 = Mean in Group 3
2 e 3	0,000	Mean inGroup 2 >Mean in Group 3

Note that only for the variable, plate index the means can be considered equal among the three groups (P = 0.272). For the variable Age we noticed that the mean in Group 2 is higher than the average in the other two groups. For the CPO and bleeding index variables, there is evidence that the means are not all equal ($P \leq 0.004$). Through the application of the technique of multiple comparisons (Tukey's method), we can conclude that:

- The mean CPO in Group 3 is higher than in Groups 1 and 2 and that in the latter two groups, the averages are equal;
- The average Bleeding Index of Group 3 is higher than in Group 2; The average Bleeding Index of Group 3 is equal to that of Group 1; The mean Bleeding Index of Group 2 is equal to that of Group 1.

Observing salivary flow data, 60% of the patients in Group I presented normal levels and 20% presented intermediate and lower levels respectively, however, when compared to Groups II and III, it is clear that there is an even greater decrease In patients with normal Group III levels (40%), with an increase in the intermediate and lower levels of Groups II and III, as shown in table 3.

Table 3 Distribution of joint frequencies between variables Salivary flow and Group (in parentheses are the percentages obtained per line).

	SalivarFlow			
Group	**Low**	**Intermediate**	**Normal**	**Total**
1	14 (20,0)	14 (20,0)	42 (60,0)	70 (100,0)
2	10 (14,3)	24 (34,3)	36 (51,4)	70 (100,0)
3	12 (17,1)	30 (42,9)	28 (40,0)	70 (100,0)
Total	36 (17,1)	68 (32,4)	106 (50,5)	210 (100,0)
P = 0,329				

Regarding salivary pH, Group I presented 74.3% of the patients with pH equal to 6.5; 20% at pH 7 and only 5.7% at pH 3.5, differing significantly from Groups II and III, where there is a much increased incidence at pH 7.0 (48.6% and 37.1% Groups 2 And 3 respectively), as shown in table 4.

Table 4 Distribution of joint frequencies between Sal salivary and Group variables (in parentheses are the percentages obtained per line).

	Ph salivar			
Group	**3,5**	**6,5**	**7,0**	**Total**
1	4 (5,7)	52 (74,3)	14 (20,0)	70 (100,0)
2	6 (8,6)	30 (42,9)	34 (48,6)	70 (100,0)
3	14 (20,0)	30 (42,9)	26 (37,1)	70 (100,0)
Total	24 (11,4)	112 (53,3)	74 (35,2)	210 (100,0)
P = 0,018				

The ability to balance the ph decreased gradually between Groups I, II and III at normal levels (54.3%, 51.4% and 45.7%), thus increasing the low levels among the same groups (5.7 %, 8.6% and 17.1%), according to table 5.

For the variable periodontal disease, we observed that all groups present high percentages of P1 and P2, but Group III was the group that presented the highest P3 indices, differing

greatly from Groups I and II, however, Group II, Shows an increase of P3 in relation to Group I, showing the periodontal vulnerability in patients with Diabetes Melitus and more exacerbated changes in Group III where there is HIV-associated Diabetes Melitus (Table 6).

Table 5 Distribution of joint frequencies between the variables Ability to balance ph and Group (in brackets are the percentages obtained per line).

	Abilityto balance ph			
Group	**Low**	**Intermediate**	**Normal**	**Total**
1	4 (5,7)	28 (40,0)	38 (54,3)	70 (100,0)
2	6 (8,6)	28 (40,0)	36 (51,4)	70 (100,0)
3	12 (17,1)	26 (37,1)	32 (45,7)	70 (100,0)
Total	22 (10,5)	82 (39,1)	106 (50,5)	210 (100,0)
P = 0,613				

Table 6 Distribution of joint frequencies between the variables Periodontal disease and Group (in parentheses are the percentages obtained per line).

Group	P1	P2	P3	Total
1	36 (51,4)	32 (45,7)	2 (2,9)	70 (100,0)
2	40 (57,1)	26 (37,1)	4 (5,7)	70 (100,0)
3	30 (44,1)	26 (38,2)	12 (17,7)	70 (100,0)
Total	106 (51,0)	84 (40,4)	18 (8,7)	210 (100,0)
P = 0,212				

Table 7 presents the descriptive levels (P) of chi-square homogeneity tests to compare the presences of systemic diseases Hypertension, Cardiopathy and Hyperlipidemia / Cholesterolemia among the three groups. The presences of no systemic disease were also compared and the descriptive level of the test is shown in Table 7. The following results were found:

For the three diseases and for the absence of all diseases there is evidence of differences between groups ($P \leq 0.048$);

Hypertension: the percentage of presence of hypertension in Group 1 is lower than in the other two groups; In Groups 2 and 3 these percentages are the same Cardiopathy: the percentage of presence of Group 2 Cardiopathy is equal to that of Group 3; The percentage of presence of Cardiopathy of Group 1 is equal to that of Group 3; The percentage of presence of Group 1 Heart Disease is lower than that of Group 2 Hyperlipidemia / Cholesterolemia: the percentage of presence of Hyperlipidemia / Cholesterolemia in Group 3 is higher than in the other two groups; In Groups 1 and 2 these percentages are the same.

Table 7 Descriptive levels (P) of chi-square tests of homogeneity.

SystemicDisease P	*P*
Hypertension	0,000
Cardiopathy	0,048
Hiperlipidemia/Cholesterolemia	0,000
None	0,000

When we consider the variables included in systemic diseases, what stands out are the indices referring to arterial hypertension, presence of heart disease, hyperlipideremia / cholesterolemia and absence of systemic disease.

Regarding arterial hypertension, the data obtained between Groups II and III differ greatly from the data obtained in Group I, which shows that, because the patient has diabetes mellitus, this would be the factor that causes this difference between the Groups, However, when we look at the data on heart disease and hyperlipideremia / cholesterolemia, the data are more comprehensive, since, the greater percentage of patients already proven to be cardiopathy belong to Group II, however, they already have the diagnosis and the appropriate treatment, presenting themselves under Medical / therapeutic control that make these rates relatively low for hyperlipideremia / cholesterolemia findings. However, Group III presents percentages lower than 20% of heart disease, but hyperlipideremia / cholesterolemia rates are much higher, almost 50%, making them a high risk group for the development of coronary and cardiological diseases, demonstrating that patients in use Of HAART, are more likely to develop heart disease.

For the variable no systemic disease, the results show that patients in Groups II and III have similar systemic diseases that they already had with statistically greater differences than the patients in Group I, thus demonstrating the health vulnerability to which both patients are subjected. Only diabetic patients such as patients who associate diabetes and HIV / AIDS.

Table 8 shows the descriptive levels (P) of chi-square homogeneity tests to compare the presences of mouthwashes and erythematous candidiasis among the three groups. The presences of no oral disease were also compared and the descriptive level of the test. The following results were found:

- For both diseases there is no evidence of differences between the groups ($P \geq 0.050$);
- For the absence of all diseases there is evidence of differences between groups ($P = 0.009$);
- None: the percentage of presence of any disease in Group 1 is higher than in the other two groups; In Groups 2 and 3 these percentages are the same.

Table 8 Descriptive levels (P) of chi-square tests of homogeneity.

Systemicdisease	*P*
Flyffytongue	0,057
ErythematousCandidiasis	0,058
None	0,009

Another characteristic observed is the correlation between no systemic disease and no oral disease. The data demonstrate that as well as the chances of increasing the incidence of other systemic diseases in Groups II and III when compared to Group I, this also affects the oral cavity, increasing the chances of patients developing oral diseases in Groups II and III is statistically Higher than the indices presented by Group I that have the highest indices of any oral disease.

The analysis of the variables only for the HIV group, in relation to the viral load, revealed that 25.7% of the patients in the HIV group had the result undetectable. The standard deviation of the Viral Load variable is very large (more than twice the value of Mean), that is, the values of the variable Viral Load have a great variability around the mean. In this case, the median represents the data set better than the mean, that is, it is verified that 50% of the 26 observations have values less than or equal to 2900.

As for the CD4 variable, it was observed that the majority of the patients (48.6%) presented from 200 to 499 cells. Regarding the exposure category of most patients was HET (57.1%).

Table 9 Mean and standard deviation (S.P.) of the variable Viral charge.

Variable	No.ofpatients	Mean	S.P.	Medium
ViralCharge *	52	11140	26186	2900

* Undetectable result was removed from the analysis.

Table 10 Frequency distribution of the CD4 variable

CD4	No. ofpatients	%
1 a 199 cel.	22	31,4
200 a 499 cel.	34	48,6
500 ou mais cel.	14	20,0
Total	70	100,0

DISCUSSION

Acquired Human Immunodeficiency Syndrome (AIDS) is characterized by the severe attack of the immune system by the Human Immunodeficiency Virus (HIV), weakening the organism, and can generate an enormous susceptibility of infections, neoplasias and comorbidities that can lead the individual to death, However, this process has been improved due to the introduction of Highly Active Antiretroviral Therapy (HAART), which provides better and longer survival of these patients. HAART, however, is accompanied by a number of undesirable side effects, such as HIV Lipodystrophy Syndrome (SLHIV), which to date has no consensus for prevention or treatment (14; 20; 6; 22; 5).

Although it is clear that the use of HAART has led to the prevalence of HIV infection, being beneficial for both individual and population levels. Recent work by Nansseu and Bigna (2017) (15) also questions whether we are able to deal with the consequences of large-scale HAART implementation. Whether adequate medications to control the adverse effects of HAART will be accessible to HIV-infected patients who develop adverse effects related to HAART.

The major concern in the scientific world is related, among others, to the side effects caused by Protease Inhibitors (PIs) regarding class effects, constituted by lipodystrophy, hyperlipideremia, hyperglycemia and alterations in bone metabolism, which make up the SLHIV itself (16; 21; 22)

These effects, caused by the medium and long-term administration of PIs, result in central fat, insulin resistance, altered bone metabolism, increased cholesterol and triglyceride levels, and may lead to an association of comorbidities such as diabetes mellitus, To heart disease, pancreatitis, arterial hypertension, centripetal obesity, osteonecrosis, and others (18; 13; 14; 21; 13; 6; 19; 5).

The monitoring of the organic conditions of each patient should be performed frequently to avoid serious complications that may evade the medical control and, therefore, to evaluate the risks of maintaining or suspending the use of these drugs (18; 13; 14; 21; 13; 6; 19; 5).

Although the post-HAART era has brought many and undeniable benefits to patients, it is necessary to identify the broad mechanism of action of these drugs in the medium and long term, so that it can prevent or even reach a means of controlling adverse effects Related to it, knowing that specifically PIs culminate in these metabolic changes that can have irreversible consequences and that to the present moment, there is no consensus as to the appearance of the changes and as little as possible to prevent or control them without, however, Need to stop taking the drug. Once these issues have been solved, adequate treatment can be achieved and this will surely contribute to prevent, reduce or control the comorbidities related to them, further improving the quality of life and reducing the chances of morbidity of these patients (10; 11; 13; 14; 20; 2; 6; 5).

This study clearly demonstrated that Group III, that is, the group formed by HIV positive patients under HAART, has different characteristics when compared to Groups I and II, formed by non-diabetic and HIV negative patients and patients living with diabetes, But with HIV negative respectively. Among them, we observed a considerable decrease in salivary flow, acid buccal pH, a representative increase in the low levels of buffer capacity and higher P3 indexes of periodontal disease, with significant statistical differences, where we concluded that there are considerable alterations in the organic metabolism of Group III patients with significant repercussions on oral health. These data are important in order to establish adequate dental therapy, where the possibility of drug intervention is eminent, but common sense, caution and, above all, scientific basis should be used in the practical handling of the dental treatment itself. Criterion and reasoned when the need for invasive or prophylactic-invasive interventions where the use of systemic adjuvant medication becomes indispensable.

All Group III patients became diabetic after the introduction of HAART, which concluded that HAART alone is already a risk factor for obtaining comorbidities as demonstrated in the present study, so we conclude that because The patient living with diabetes mellitus already makes it prone to severe periodontal disease, however, HAART exacerbates this whole process as shown in Chart 6, with statistically significant differences.

In the same way, we observed that for data obtained regarding systemic manifestations such as hypertension and hyperlipidermia / cholesterolemia there is a direct correlation with the increased risk and propensity for such signs in Group III patients under HAART use when compared to the other groups, demonstrating Vulnerability to coronary heart disease, pancreatitis, and all other comorbidities related to altered arterial hypertension and elevated cholesterol.

CONCLUSION

Among the analyzed variables, it is concluded that patients who use HAART have important systemic and oral changes that must be taken into account in order to better recognize the process of metabolic performance of drugs inserted in antiretroviral therapy in an attempt to recognize and to disclose its mechanism of action in order to minimize or eradicate symptoms, which may lead to more severe organic consequences or the need to discontinue therapy, which could lead to therapeutic failure or loss of adherence.

Thus, it is evident that the attention given to patients under HAART should be doubled, observing it in a comprehensive and cautious way in oral and systemic treatment, emphasizing the importance of specialized and multidisciplinary care, with

frequent monitoring of all the intrinsic variables included in this study, emphasizing the clinical and laboratory monitoring that dentists who care for these patients should take into account to minimize undesirable consequences that can irreversibly alter situations that may lead to the impossibility or failure of therapy for HIV of these patients.

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