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TDF-3TC-DTG or TDF-3TC-EFV First Line Antiretroviral Therapy Protocols and Their Relation to Salivary Biochemical Constituents in HIV-1 Infected Patients in Yaoundé, Cameroon

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Abstract

Antiretroviral therapy (ART) has the potential to slow down the progression of Human Immunodeficiency Virus (HIV) infection, which is increasingly becoming a chronic disease. However, many studies reported that ART can lead to changes in the composition of biological fluids including saliva. Few studies have been conducted on the modification of the salivary biochemical composition of HIV-1 infected patients and to the best of our knowledge, very few, if none of such studies have been done in Cameroon. Thus, we sought to investigate the salivary biochemical composition of patients living with HIV and who are undergoing antiretroviral treatment. A comparative analytical cross-sectional study was conducted on 102 participants, 51 of whom were HIV-1 infected patients under treatment on ART and 51 HIV-seronegative healthy individuals. A salivary sample was taken from these patients and quantitative analysis was performed on some salivary constituents (sodium, potassium, phosphorus, chloride, albumin, alpha amylase and creatinine), and on some of salivary oxidative stress markers (malondihaldehyde, reduced glutathione and total antioxidant ability).

The results of our study showed statistically significant decrease ($p<0.05$) concentrations of salivary potassium, phosphorus, albumin and creatinine of HIV-1 infected patients on ART compared to HIV-seronegative subjects. We also found significantly ($p<0.05$) higher levels of sodium and reduced glutathione concentrations of HIV-1 infected patients on ART. In addition, salivary total antioxidant ability was significantly ($p<0.005$) higher in the saliva of men compared to that of women. Overall, our study showed an alteration of salivary biochemical composition in HIV-1 infected patients on first line antiretroviral treatment, which is impacted by the treatment combination, in particular TLD for alpha amylase and MDA; treatment duration for chlorides, albumin, GSH and total antioxidant ability; viral load for albumin and gender for total antioxidant ability, compared to HIV-1 seronegative subjects. Salivary malondihaldehyde concentration could be quantified in HIV-1 infected patients on TLD in order to ascertain this ART efficacy.

Keywords: Human immunodeficiency virus, ART, treatment duration, salivary composition

Introduction

Since the emergence of HIV/AIDS in 1981-1982[1], there has been no

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known treatment, among the huge range of those nowadays available, which could cure the disease. HIV infection remains a major public health concern. Globally, in 2021, about 38.4 million people were living with HIV. Among them 20.6 million of people were in sub-Saharan Africa. Of the 28 million of people who were accessing antiretroviral therapy worldwide, 16.2 million were in sub-Saharan Africa [2]. Thus, only 4.4 million of the 20.6 million people in sub-Saharan Africa were not on treatment and there is an urgent need to continue to manage all these people for their wellbeing. In Cameroon particularly, the overall HIV/AIDS prevalence rate is about 2.7% and about 78.5% of people living with HIV were on ART in 2021[3]. Several studies showed that ART alters the composition of body fluids [49].

Until mid-2018, ART combination consisted of two nucleoside reverse-transcriptase inhibitors (NRTIs) with a nonnucleoside reverse-transcriptase inhibitor (NNRTI), namely efavirenz, was the preferred first line ART recommended in the World Health Organization (WHO) guidelines for human immunodeficiency virus type 1 (HIV-1) infection for adult beside other first line ART [4]. The efavirenz-based reference regimen was then challenged by the landmark Study ING114467 (SINGLE) trial [5], which showed that a dolutegravir (an integrase inhibitor) based regimen had a more favorable profile with regard to sustained viral suppression and immunologic recovery than did the efavirenz-based regimen. Because dolutegravir has a high genetic barrier to resistance and is available in a fixed-dose combination and at low cost [6], it appears to be an ideal candidate for a universal first-line ART regimen and was introduced as a WHO preferred first-line treatment in 2018, but this recommendation was conditional [4].

It has been shown that the human immunodeficiency virus leads to a decrease in cellular immunity, thus allowing the development of opportunistic infections. These infections have serious repercussions on the body's tissues and organs. Among these infections, oral manifestations are early clinical signs of HIV infection [7]. However, the prevalence of these infections has been significantly reduced with ART, although the use of ART is sometimes accompanied by side effects and organ toxicity [8]. The aim of ART is to prevent the viral spread and to better restore the immune system. At the same time, ART reduces the oral pathological manifestations that can be observed in the salivary fluid, which is a biological fluid essential for the proper functioning of the oral cavity [9]. Saliva, a biological fluid secreted by the salivary glands, has been of great interest in recent years, especially in the diagnosis, monitoring and management of various pathologies. Its secretion is regulated by the autonomic nervous system, and its composition is complex, containing a large number of inorganic and organic compounds that can be identified and become biomarkers of general health [9]. It performs multiple functions namely: Mechanical, humidifying, lubricating, protective and digestive functions; and thus, quantitative and qualitative changes in its composition conditions these main roles. Saliva has specific advantages distinct from serum and it is often used as a diagnostic fluid [9].

ART remains the most effective treatment for HIV infection to date. Access to treatment continues to expand and almost all known people living with HIV in Cameroon are on ART [10]. However, the study of their effects combine to that of the virus on salivary biochemical composition is not yet well established in many countries around the world, especially in resource-limited settings where ART was late introduced. The study of patients on ART is therefore of paramount importance in a Cameroonian context where access to treatment continues to grow. Very few studies have been conducted on the salivary biochemical composition of these patients in Cameroon. Therefore, in the present study, we investigated the salivary composition of HIV-1 infected patients on ART as well as that of HIV-1 seronegative followed up at the Cité-verte District Hospital and at the Central Hospital of Yaoundé Cameroun, in order to find out the probable altered parameters which could serve as biomarkers among those considered.

Material and Methods

Ethical considerations

For ethical transparency, we asked and received research authorizations from the "Comité Régional d'Ethique de la Recherche pour la Santé Humaine du Centre (CRERSH-Ce)", ethical clearance number CE N° -2266-/CRERSHC/2021, and the authorization to collect the sample in the above mentioned hospitals before starting the work. The people recruited for the study participated voluntarily after signing an informed consent form, and were free to withdraw at any time from the study. During the study, the dignity of the participants as well as their anonymity were respected and protected. The data collected were kept secret and were not used for any other purpose unless for research.

Study site and timeline

This cross-sectional study was conducted between December 2021 and May 2022, at the care unit for patients living with HIV (UPEC) of the Cité-Verte district hospital, where we recruited patients undergoing ART and collected their salivary samples. The saliva of HIV seronegative patients was collected at the blood bank of the Yaoundé Central Hospital. All the various parameters were analyzed at the biochemistry laboratory of the Faculty of Medicine and Biomedical Sciences of Yaoundé I University.

Sampling

We collected saliva from people living with HIV-1 and who were on first-line antiretroviral treatment (ART), and

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from HIV seronegative people coming at the blood bank of the Yaoundé Central Hospital; The later were took as the control group after passing the medical screening stage and declared eligible to donate their blood. However, with the agreement of these participants and the health staff, we checked the results of the various confirmatory tests to reassure ourselves of the health status of these participants. They were then considered healthy. The sample size was calculated on the basis of HIV prevalence in Cameroon, using the formula: $n=Z^2.P(1-P)/m$. (where n= minimum sample size for meaningful results; Z= confidence level (for 95%, Z=1.96); P= estimated proportion of the population with the characteristic (2.7% in Cameroon); m: margin of error (5%).

This study therefore involved a total of 102 participants. We collected saliva samples using the method described by Hirtz et al. (2005) and Dawes (1972) [11]. Thus, each person who agreed to participate in the study was first asked to sign an informed consent form and to answer a questionnaire. Unstimulated saliva was collected in the morning, approximately 2 hours after breakfast. Participants should have brushed their teeth with a toothbrush without toothpaste or rinsed their mouth properly with clean water; 15 minutes before collection, participants were asked to rinse their mouth with distilled water. The saliva collected was total unstimulated saliva. Each participant was given a sterile box into which they were asked to put about 3 ml of saliva, avoiding clearing their throat. These sterile vials were placed directly into a cooler containing carbohydrate ice and taken to the laboratory. After collection, the samples were centrifuged at 3000g for 15 minutes to remove mucins and other debris still present in the saliva. The supernatant was collected, taking great care not to detach the pellet, and was kept in 1.5 ml Eppendorf tubes and stored at -20°C till the different parameters quantification. With the consent of the patients and the staff in charge, the patients' medical records were consulted to collect information such as treatment duration, viral load, $CD4^+$ T cells count, and any other information useful for our study.

Quantification of salivary biochemical parameters

The quantification of different biochemical parameters was performed using the UV-visible absorption spectrophotometer BIOBASE analyzer, Shandong, China. For the determination of alpha-amylase, albumin, creatinine and electrolytes (Sodium, Potassium, Phosphorus and Chloride) we used BIOLABO (France) and BIOREX (United Kingdom) assay kits. However, the determination of oxidative stress parameters was carried out with the appropriate reagents according to standard methods: Malondihaldehyde (Wilbur et *al.*, 1949), reduced glutathione (Ellman in 1959) and the total antioxidant ability (Benzie et al., 1996).

Data analysis

The data statistical analysis was done using SPSS version 20.0. ANOVA tests allowed comparisons of groups' mean and the results were expressed in terms of means ± standard deviation. $p<0.05$ was set as significance level.

Results

The present study included 102 participants: 51 were HIV-1 infected individuals followed at the Cité-verte district hospital, and 51 were HIV-1 seronegative individuals recruited at the Yaoundé central hospital blood bank. Our sample was divided into subgroups according to sex, age, viral load, treatment duration and first line ART protocol.

Socio-demographics and clinical characteristics of participants included in the study.

In each group of 51 subjects, 37.25% were male and 62.75% were female while 66.67% were male and 33.33% were female in HIV-1 infected subjects group and HIV seronegative subjects group respectively (table 1). According to age, women were younger than men for all considered age ranges in HIV-1 infected as well as in seronegative subjects' groups (table1).

According to viral load, overall, patients' salivary samples were divided into three groups: sample of those whose viral load was less than 40 copies of viral RNA per ml (56.86%) including, the one of those whose viral load was greater than 40 copies of viral RNA per ml (9.80%), and those with undetermined viral load (33.33%). More women showed suppressed viral load than men (79.31% versus 20.69%). The subgroup of patients with undetermined viral load consisted of patients who had mostly been on treatment for less than a year and whose viral load had not yet been determined. According to treatment duration, overall, salivary samples were subdivided into three groups: the group of patients with less than 1 year of treatment duration (21.57%), the one between 1 to 5 years (54.90%), and that of more than 5 years (23.53%). According to the first line treatment protocol, since all the patients included were on first line, salivary samples were classified as those of HIV-1 infected patients on Tenofovir/Lamivudin/Dolutegravir (TLD) representing 84.31% of samples or Tenofovir/Lamivudin Efavirenz (TLE) representing 15.69% of samples. Women were more on treatment than men and no man was on TLE (Table 1).

Comparison of salivary biochemical parameters in HIV-1 infected and HIV-1 seronegative individuals.

Table 2 shows a significant decrease concentration of potassium (p=0.029), phosphorus (p=0.006), albumin (p=0.000), creatinine (p=0.003) and a significant increase concentration of sodium (p=0.000), and reduced glutathione (p=0.000) in HIV-1 infected patients as compared to HIV seronegative controls. (Table 2).

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Comparison of salivary biochemical parameters in HIV-1 infected and HIV seronegative individuals according to sex.

The comparison of salivary biochemical parameters in HIV-1 infected patients according to sex showed a statistically significant difference only for the total antioxidant ability (p=0.005). The latter was higher in men than in women. For the HIV seronegative subjects, potassium and albumin concentrations showed a statistically significant difference according to sex; men had higher potassium and albumin concentrations than women (Table 3).

Comparison of salivary biochemical parameters in HIV-1 infected individuals according to age

According to age, table IV shows a statistically significant difference in chloride ion concentration in PLHIV/ART. The 18 to 27 age range showed the highest concentrations, while 58 to 67 age range showed the lowest concentrations (Table 4).

Comparison of salivary biochemical parameters in HIV-1 infected individuals according to viral load

Table 5 shows only the albumin concentration with a statistically significant variation (p=0.006) according to viral load. The salivary albumin concentration in PLHIV/ART was higher in patients with undetermined viral load than in patients with a viral load of less than 40 copies per ml, and in patients with a load of more than 40 copies per ml.

Table 1: socio-demographics and clinical characteristics of participants included in the study

Characteristics	Male	Female	P value
PLHIV/ART n (%)	19(37.25)	32(62.75)	
Age: years (mean±SD)	46 ± 10	36 ± 8	0.001
Main age range: years	38 – 57	28 – 47	0.015
Seronegative subjects n (%)	34(66.67)	17(33.33)	
Age: years (mean±SD)	33 ± 9	31 ± 7	0.374
Main age range: years	18 – 37	18 – 27	0.634
Viral load of PLHIV/ART			
Mean viral load±SD;(cps/ml)	176±149	2311±3207	0.297
n	3	2	
Less than 40 copies/ml	06(20.69)	23(79.31)	
More than 40 copies/ml	03(60)	02(40)	0.019
Not determined	09(52.94)	08(47.06)	
Treatment Duration			
Less than 1 year n (%)	05(45.45)	06(54.55)	
1 -5 years n (%)	11(36.67)	19(63.33)	0.761
More than 5 years n (%)	03(30)	07(70)	
First line treatment ART			
TLD n (%)	19(44.19)	24(55.81)	0.019
TLE n (%)	-	08(100)	

PLHIV/ART: People Living with HIV on ART; n: Sample size; SD: standard deviation; TLD: Tenofovir/Lamivudin/Dolutegravir; TLE: Tenofovir/Lamivudin Efavirenz

Table 2: Overall comparison of salivary biochemical parameters between PLHIV/ART and HIV seronegative people

	PLHIV/ART	HIV-1 Seronegative	p value
Sodium (mmol/l)	1,43±0,05	1,34±0,11	0,000*
Potassium (mmol/l)	16,54±6,79	19,89±8,39	0,029*
Phosphorus (mmol/l)	2,98±0,95	3,56±1,12	0,006*
Chlorides (mmol/l)	25,44±11,26	23,97±5,09	0,396
Alpha amylase (UI/l)	63,14±15,58	59,32±17,24	0,243
Albumin (µmol/l)	276,48±7,81	287,43±6,03	0,000*
Creatinine (µmol/l)	13,99±12,05	21,92±13,83	0,003*
Glutathione (µmol/l)	2,36±0,45	0,81±0,22	0,000*
MDA (µmol/l)	0,32±0,19	0,37±0,19	0,114
Total Antioxidant ability(µmol/l)	165,10±66,19	170,20±65,53	0,697

Values are means ± SD. * statistically significant

Comparison of salivary biochemical parameters in HIV-1 infected individuals according to treatment duration.

Globally, table 6 shows a statistically significant difference in chloride ions, albumin and glutathione concentrations according to treatment duration. There was a statistically significant decrease in chloride ions, albumin and GSH as the treatment duration increased. (Table 6). Furthermore, table 7 shows a decreased in salivary albumin, reduced glutathione and malondialdehyde according to treatment duration on TLD while for the treatment duration on TLE, total antioxidant ability significantly decreased for less than 1 and for 1 to 5 years of treatment, but significantly increased for more than five years of treatment.

Comparison of salivary biochemical parameters in HIV-1 infected individuals according to first line ART combination.

Table 8 shows that Alpha amylase activity is significantly higher in patients' saliva on TLD treatment protocol (Tenofovir/Lamivudin/Dolutegravir) as compared to that of patients on TLE (Tenofovir/Lamivudin/Effavirenz). It also shows salivary malondialdehyde level significantly higher in patients on TLE as compared to that of patients on TLD (Table 8).

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Table 3: Comparison of salivary biochemical parameters according to gender.

Sexe	Na	K	P	Cl	α-amylase (UI/l)	albumin (µmol/l)	Creatinine (µmol/l)	GSH (µmol/l)	MDA (µmol/l)	CAT (µmol/l)
PLHIV/ART										
M	1,45±0,04	16,26±6,64	66,18±17,2	25,33±11,17	276,58±8,2	17,58±15,74	2,44±0,43	0,31±0,16	4,90±1,55	197,89±62,5
F	1,43±0,05	16,13±7,82	62,41±16,4	25,51±11,48	276,43±7,7	11,86±8,83	2,32±0,4	0,32±0,22	3,60±1,52	145,62±61,2
p-value	**0,197**	**0,951**	**0,766**	**0,957**	**0,439**	**0,948**	**0,102**	**0,372**	**0,906**	**0,005***
HIV seronegative subjects										
M	1,34±0,11	21,58±8,37	3,47±1,15	24,30±4,73	58,57±17,19	288,74±4,61	23,44±14,4	0,80±0,2	0,37±0,16	180±73,73
F	1,33±0,11	15,92±7,44	3,44±1,47	23,24±5,91	60,98±17,80	284,58±7,78	18,60±12,16	0,83±0,25	0,39±0,24	148±35,75
P value	**0,889**	**0,025***	**0,936**	**0,936**	**0,648**	**0,021***	**0,250**	**0,669**	**0,794**	**0,115**

Table 4: Comparison of salivary biochemical parameters in HIV-1 infected individuals according to age

Age ranges (years)	**18-27**	**28-37**	**38-47**	**48-57**	**58-67**	p-value
Sodium (mmol/l)	1,42±0,05	1,41±0,06	1,45±0,04	1,44±0,05	1,44±0,03	0,246
Potassium (mmol/l)	14,63±6,60	15,69±8,36	17,60±6,92	14,61±6,78	17,48±6,50	0,831
Phosphorus (mmol/l)	3,04±0,74	2,67±1,31	3,21±1,11	2,22±0,92	1,94±0,71	0,151
Chlorides (mmol/l)	35,69±10,67	24,94±11,12	21,47±8,97	31,24±12,60	17,51±6,47	0,029*
A-amylase (UI/l)	66,15±25,95	68,37±15,77	62,71±16,49	56,67±15,45	63,64±0,15	0,565
Albumin (µmol/l)	283,49±6,84	278,08±6,77	274,47±8,07	274,22±8,24	275,08±7,63	0,147
Creatinine (µmol/l)	7,08±4,49	13,32±8,24	17,11±16,61	14,82±10,83	7,87±0,68	0,459
GSH (µmol/l)	2,50±0,40	2,39±0,42	2,29±0,56	2,45±0,37	2,21±0,00	0,797
MDA (µmol/l)	0,31±0,08	0,32±0,19	0,33±0,24	0,35±0,16	0,19±0,17	0,832
CAT (µmol/l)	140±42,43	168,75±65,71	144,44±67,41	200±56,57	206,67±92,38	0,183

CAT: total antioxidant capacity; * The result is statistically significant. Values are means ± SD

Table 5: Comparison of salivary biochemical parameters in HIV-1 infected individuals according to viral load

Viral load	Na	K	P	Cl	α-amylase (UI/l)	Albumin (µmol/l)	Creatinine (µmol/l)	GSH (µmol/l)	MDA (µmol/l)	CAT (µmol/l)
<40	1,43±0,05	16,72±7,31	2,73±1,09	23,73±11,03	61,95±16,73	275,41±7,41	13,61±9,82	2,31±0,51	0,28±0,19	153,10±58,7
>40	1,42±0,03	15,40±9,06	2,33±0,96	19,14±8,47	66,47±14,83	268,94±6,04	12,04±5,86	2,35±0,33	0,36±0,22	184±74,03
ND	1,45±0,06	15,21±6,79	2,97±1,31	30,22±11,09	66,21±17,41	280,52±6,97	15,20±16,5	2,47±0,36	0,37±0,19	180±75,83
P	0,249	0,778	0,530	0,068	0,664	0,006*	0,853	0,523	0,341	0,336

Na, K, P, Cl (sodium, potassium, phosphorus and chloride respectively in mmol/l), ND: not determined; viral loads unit is the number of viral RNA copies/ml. Values are means ± SD * The result is statistically significant, p: p-value

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Table 6: Comparison of salivary biochemical parameters in HIV-1 infected individuals according to treatment duration

Treatment duration (Years)	Na	K	P	Cl	Alpha amylase (UI/l)	Albumin (µmol/l)	Creatinine (µmol/l)	GSH (µmol/l)	MDA (µmol/l)	CAT (µmol/l)
<1	1,44±0,05	17,91±8,62	3,22±1,30	31,83±12,39	72,56±20,47	282,83±5,53	18,77±20,04	2,67±0,37	0,37±0,16	156,36±61,2
1 to 5	1,42±0,06	14,71±6,72	2,67±1	25,13±10,95	60,05±13,44	275,33±7,68	13,53±9,08	2,26±0,40	0,31±0,21	167,33±63,6
>5	1,45±0,03	17,71±7,04	2,66±1,33	19,36±7,47	65,47±18,48	273,67±7,47	11,11±8,07	2,33±0,52	0,31±0,20	168±83,90
P	0,273	0,328	0,378	0,036*	0,094	0,007*	0,305	0,033*	0,633	0,889

Na, K, P, Cl (sodium, potassium, phosphorus and chloride respectively in mmol/l), Values are means ± SD * The result is statistically significant, p: p-value

Table 7: Comparison of salivary biochemical parameters in HIV-1 infected individuals according to duration on each first line ART

First line ART	Treatment duration (Years)	Number of patients	Na	K	P	Cl	α-amylase (UI/l)	Albumin (µmol/l)	Creatinine (µmol/l)	GSH (µmol/l)	MDA (µmol/l)	CAT (µmol/l)
TLD	<1	10	14,459	1,71,606	32,374	3,18,477	7,25,343	28,37,038	2,04,140	26,470	0,3910	154
	1 to 5	24	14,249	1,51,386	27,362	2,55,469	6,18,250	27,43,843	1,32,750	22,058	0,2644	18,66,666
	>5	9	1,43,503	1,69,263	25,181	1,91,557	6,56,786	27,41,181	98,333	22,875	0,2350	14,88,888
	P value		0,286	0,671	0,355	0,061	0,142	0,004*	0,177	0,029*	0,019*	0,152
TLE	<1	1	13,993	2,54,464	30,596	3,16,992	3,17,800	27,40,596	23,600	29,411	0,1923	180
	1 to 5	6	14,154	1,46,795	21,401	2,34,543	5,29,666	27,62,180	1,44,750	25,735	0,4700	90
	>5	1	15,067	2,41,851	47,264	2,12,114	6,35,600	27,98,504	1,29,800	22,058	0,8333	340
	P value		0,367	0,463	0,158	0,669	0,473	0,840	0,213	0,487	0,490	0,003*

TLD: Tenofofovir/Lamivudin/Dolutegravir; TLE: Tenofofovir/Lamivudin/ Efavirenz. Na, K, P, Cl (sodium, potassium, phosphorus and chloride respectively in mmol/l), Values are means ± SD * The result is statistically significant.

Table 8: Comparison of salivary biochemical parameters in HIV-1 infected individuals according to first line ART combination

First line ART	Na	K	P	Cl	α-Amylase (UI/l)	Albumin (µmol/l)	Creatinine (µmol/l)	GSH (µmol/l)	MDA (µmol/l)	CAT (µmol/l)
TLD	1,44±0,05	15,87±6,89	2,81±1,13	25,67±11,81	66,08±15,64	276,50±8,15	14,21±12,89	2,33±0,45	0,29±0,14	171,16±59,1
TLE	1,42±0,06	17,21±9,14	2,58±1,28	24,20±8,12	51,64±17,39	276,40±6,11	12,77±6,25	2,57±0,39	0,48±0,35	132,5±94,4
P value	0,541	0,633	0,610	0,738	0,022*	0,976	0,760	0,153	0,009*	0,131

TLD: Tenofofovir/Lamivudin/Dolutegravir; TLE: Tenofofovir/Lamivudin/ Efavirenz. Na, K, P, Cl (sodium, potassium, phosphorus and chloride respectively in mmol/l), Values are means ± SD * The result is statistically significant.

Discussion

Saliva is a major part of the oral immune system. It represents an exocrine secretion consisting of mostly (99%) of water, in addition to a variety of electrolytes (sodium, potassium, calcium, chlorine, magnesium, bicarbonate, phosphate) and proteins (enzymes, immunoglobulins, mucosal glycoproteins, traces of albumin, some polypeptides and oligopeptides). Salivary composition varies from person to person depending on the oral environment. Age and gender are also major determinants of the salivary composition. Antiretroviral treatment (ART) provides effective and sustained inhibition of viral replication, resulting in recovery of the immune system. In a study by Shahar et al. (2008), the salivary composition of HIV-infected patients was altered, but returned to normal in patients on ART [12].

However, other studies have shown that antiretroviral therapy can cause adverse effects on saliva biochemical composition. A study by Kamei et al. (2018) demonstrated the alteration in salivary composition in HIV-infected patients under highly active antiretroviral therapy (HAART) [13]. In the present study, the salivary concentration of Sodium, Potassium, Phosphorus, Chlorine, both in HIV-1 infected on treatment and HIV-seronegative patients were within the reference range found in other studies on healthy participants. According to Devoize et al. (2010), total unstimulated saliva contains sodium (1.5 mmol/l), potassium

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(24 mmol/l), chlorine (22 mmol/l), inorganic phosphate (6 mmol/l) [14], but Fenoll-Palomares et al. (2004) obtained the following range value of biochemical markers in a total unstimulated saliva, sodium (3 -29 mmol/l), potassium (3.4 - 36.6 mmol/l), phosphorus (1.35 - 13.15 mmol/l) and chlorine (0 - 27 mmol/l) [15]. The values obtained in our study were within these ranges, demonstrating the effectiveness of the ART treatments which restored the immune system and not affects functions of the organism.

Human saliva contains a large number of proteins and peptides that are easily accessible and may serve as a potential source of biomarkers to monitor changes that occur under pathological conditions. The value of saliva as a biological fluid for the detection of diagnostic and prognostic biomarkers has become increasingly well established. The salivary electrolytes include sodium, potassium, chloride, calcium, phosphorus. The electrolytes play an important role in the buffering action of the saliva in oral cavity. We observed significant changes in some of these salivary biochemical parameters in the studied groups (PLHIV/ART and HIV-seronegative). Regarding electrolytes, there was a significantly lower concentration of potassium and phosphorus in PLHIV/ART as compared to those of HIV seronegative subjects while the salivary concentration of sodium and chloride was higher in PLHIV/ART. This variation might be due to HIV infection or a combined effect of treatment and HIV infection. These results are similar to that of Mahajan et al. in 2021, who observed a statistically significant difference in the concentrations of electrolytes including sodium, potassium and chloride, in HIV-1 infected individuals with and without ART [16]. On the contrary, Johan et al., 2005, in a comparative study of salivary composition in HIV-1 infected patients on and off ART, suggested that highly active ART does not quantitatively alter salivary composition [17].

In the present study, we also found a significant decrease in salivary albumin concentrations in PLHIV/ART as compared to that of HIV seronegative controls. This could be due to the effect of HIV and ART. The increased salivary total protein in HIV seronegative patients could be attributed to the increase in basement membrane permeability, allowing easy and increased passage of serum proteins into the whole saliva via salivary gland and gingival crevices [18]. Other studies demonstrated the increase of serum albumin of HIV infected patients under ART compared to ART naïve patients [19] or on HIV seronegative patients compared to HIV infected patients [20]. In their study, Shahar et al. reported that salivary albumin concentration was significantly altered in HIV-infected individuals, but returned to normal after highly active antiretroviral treatment [12]. This emphasizes the role of potent drugs like TLD combination in HIV-infected patients care however in 2021, Mahajan et al, in their study, noted the alteration of salivary composition in HIV-infected individuals with and without treatment [16].

The present study also shows a significantly higher albumin level in patients with undetermined viral load as compared to that of patients with viral load of less than 40 copies per ml and that of subjects with a viral load of more than 40 copies/ml; the latter was lower than that of patients with a viral load of less than 40 copies per ml. This shows that HIV infection can affect salivary albumin levels. According to Rajashekar & Rao in 2021, the values of albumin and $CD4^+$ T cells counts were found to have a strong positive correlation amongst them [21]. These results are in agreement with those obtained in our study, as the pattern of results for both $CD4^+$ T cells count and viral load are usually related; wen viral load is going down, $CD4^+$ T cells count will be going up. However, our results are not in agreement with those of Mellanen et al. in 2001 following a study of the salivary composition of HIV-infected patients, where they reported that albumin levels were significantly higher in the asymptomatic phase and in the complex phase of AIDS [22].

Creatinine is a waste product of metabolism primarily excreted by the kidneys. All creatinine is excreted without reabsorption; as such, its levels in blood are used as an index of kidney function [23]. Creatinine, a muscle creatine metabolite, shows a blood level that depends on gender, age, body weight, nutrition, physical activity and muscle mass. Creatinine is the most commonly used marker in clinical practice. Its clearance is mostly useful for renal function evaluation. Salivary level of creatinine has been shown to reflect its blood level and it has been shown that salivary creatinine increases in chronic kidney disease and can be used as diagnostic biomarker [24, 25]. Our study showed a statistically significant difference in creatinine levels between the two studied groups. The salivary creatinine concentration was higher in the HIV seronegative group. The elevated levels of salivary creatinine and urea observed in patients with HIV ART group are reflections of the blood levels which can be correlate with kidney function. Creatinine is mainly eliminated by the kidneys. Thus it's salivary and serum concentration depends, on the capacity of kidney elimination and could be associated with the effectiveness of the treatment. Kalayjian et al. suggested that highly active antiretroviral therapy would be beneficial for both preserving and improving renal function in HIV-infected patients [26]. Another study by Atta et al. found that kidney survival was significantly better in the treated group [27]. On the contrary, Kaba et al. found that combination ART did not impact the renal function [28].

Salivary alpha amylase has been characterized as a biomarker of psychosocial stress [29,30,31,32,33]; considering the fact that most of HIV-infected patients are under HIV associated neurocognitive disorders condition [34], considering the social discrimination and their state of mind due to the disease, their salivary alpha amylase activity

could increase as compare to HIV seronegative subjects. On the contrary, our study showed no significant difference in alpha-amylase activity between the two groups.

This result is in agreement with a study done by Oliveira et al. in 2020, who reported that alpha-amylase activity was not impaired in HIV-1 infected patients [35]. However, the salivary amylase activity is therefore not influenced by HIV infection, but rather by the first line ART combination, TLD may increase its activity as compare to TLE (66,08±15,64 versus 51,64±17,39, p = 0,022). This could be due either to the biological oxidative stress or to the effect of TLD on sympathetic nervous system activity [36,37,38.39,40, 41] or to a pronounced psychosocial stress in these TLD treated patients.

Our study also showed statistically higher concentration of reduced glutathione in PLHIV/ART saliva as compare to that of HIV seronegative control subjects. This could be due to the body's own defense mechanism, which needs to continuously produce preventive antioxidants, including glutathione, to fight against free radicals' generation due the virus. During infection, HIV infection and ART increase oxidative stress process in the body [20]; thus, these antioxidants are produced to neutralize free radicals generated during oxidative stress and to protect the body from associated damages. A study published by Kamei et al. in 2018 showed significantly increased glutathione peroxidase and superoxide dismutase activities, which are preventive antioxidants enzymes in HIV-1 infected patients on ART. Their result is at odds with the elevation of reduced glutathione concentration observed in our study, as an increase in glutathione peroxidase activity would result in a reduction in reduced glutathione concentration. However, we found a statistically significant difference of total antioxidant ability in HIV-1 infected individuals salivary according to sex which was higher in men than in women. This difference was not seen in HIV seronegative individuals, suggesting that HIV-infection inhibits certain antioxidant hormones (estrogens) in women. In 2003, Sculley et al. found a similar result in a study of saliva composition where total antioxidant ability was significantly lower in women than in men [42]. Furthermore, a study by Brumelli et al. in 2014 on blood plasma showed that women had a high oxidative status, although the antioxidant role of estrogens is well known [25].

The study also showed a significant decrease in chloride and albumin levels with increasing treatment duration. Also, the level of saliva's reduced glutathione concentration was significantly higher in patients who had been on treatment for less than 1 year, compared to those who had been on treatment for more than 1 year. This suggests that long-term antiretroviral therapy may cause alterations in saliva chloride, albumin and reduced glutathione levels. In fact, Inductivo et al. in 2008 reported that long-term administration of ART potentially induces hepatotoxicity and can thus alters albumin synthesis [44]. This was the case for HIV-1 infected patients on TLD combination therapy according to treatment duration (table VII); in addition, these patients on TLD also showed a decrease in MDA concentration according to treatment duration, suggesting TLD efficacy.

However, Serpa et al. found an increase in albumin concentration with increasing ART duration in HIV-1 infected patients [45] but it should be noted that they analyzed patients only at 6 months and 12 months after initiation of treatment. Also, the patients enrolled in their study were more at advanced disease stages. It should also be noted that for HIV infected patients under TLE combination protocol, we did not have significant result in term of treatment duration unless for total antioxidant ability which seems to increase with treatment duration. This could be due to the body response to an increase generation of reactive oxygen species due to viral replication.

Concerning first line antiretroviral therapies' effects on salivary biochemical parameters, our study revealed that HIV infected patients on TLD showed decrease salivary malondialdehyde concentration and increase salivary alpha amylase activity as compared to those of HIV-1 infected patients on TLE. This reduction of salivary malondialdehyde concentration could be due to the high genetic barrier of Dolutegravir in TLD which help in reducing viral replication and consequently to fight against lipid peroxidation by free radicals. On the contrary, Efavirenz, a low barrier genetic drug in TLE [6], had been reported to result in a number of adverse effects, including neurodegenerative disorders, lipid alterations and generation of reactive oxygen species which are the leading cause of lipid peroxidation [46]. This is the case of studies conducted by Obaghwarhievwo and Edagha et al. who respectively showed significantly elevated MDA levels and brain antioxidant alteration in Wistar rats following efavirenz administration and [47, 48,]. The salivary alpha amylase increased activity could be due to TLD effects on sympathetic nervous system activity [40,41] or or to psychosocial stress.

Conclusion and Recommendation

The salivary composition of some biochemical parameters of HIV-1 infected patients on ART is altered compared to that of healthy subjects; this alteration is impacted by the treatment combination, in particular TLD for alpha amylase and MDA; treatment duration for chlorides, albumin, GSH and total antioxidant ability; viral load for albumin and gender for total antioxidant ability. Salivary MDA concentration could be quantified in HIV-1 infected patients on TLD in order to have an idea on their treatment outcome.

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Study limitations

Our study did not include HIV-1 infected naïve patients in order to understand salivary biochemical parameters' variation due to the only virus itself, this is due to the WHO "test and treat" policy which explain the scarcity of HIV-1 infected naïve patients for such purpose. We did not also include patients on second and third line therapy because almost all the patients we received at the "Cité-Verte district hospital" were on first line ART; this would have given added value to better understand effects of drugs on salivary biochemical parameters' variation, added to the small number of subjects in our study; by increasing our sample size and by extending the analysis to other biological parameters and fluids like urine or blood, to other ART classes, more knowledge could be acquired about ART and biological fluids biomarkers variation.

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