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Probiotic Yogurt, What Effect on Inflammation and Oxidative Stress (Case of HIV Positive Patients on Antiretroviral Treatment)

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ABSTRACT

In a context of antiretroviral treatment with suppressed viral load, immune restoration does not seem proportional to this state of control of viral replication; we observe an immune hyperactivation, due to a translocation of intestinal bacteria and an almost permanent oxidative stress which keeps the patients in a vicious circle: chronic inflammation-oxidative stress. The purpose of this study was to assess the ability of probiotic yogurt to break this vicious cycle by reducing chronic inflammation parameters and increasing antioxidant enzyme activity over a follow-up period. 48 weeks since the inclusion. By simple 1:1 randomization, patients on antiretroviral therapy with efavirenz or lopinavir were additionally subjected to probiotic yogurt supplementation and then followed for 48 weeks and evaluated at baseline, at 24 weeks, and at 48 weeks by measuring the following markers: CD4, viral load, Hs CRP, soluble CD14, and soluble CD163 as well as Superoxide dismutase, Glutathione peroxidase, zinc, and 8-oxoguanine. The results confirm that HIV infection induces inflammation with a significant increase in sCD14, sCD163, and HsCRP; and degradation of the antioxidant protective system characterized by the decrease in the level of Superoxide dismuthase, gluthation peroxydase, and Zinc and an elevated level of 8-Oxoguanosine. At weeks 24 and 48, a significant reversal of all markers under the antiretroviral + yogurt arm. Zinc alone remained at a lower level than the reference. Thus, probiotic yogurt supplementation with antiretroviral therapy significantly reduces the level of inflammation, oxidative stress, and the risk of cancer.

KEYWORDS: HIV; Oxidative stress; Inflammation; Probiotic yogurt

ABBREVAITIONS: ROS: Reactive Species of the Oxygen; TA: Transcriptional Transactivator; Mn-SOD: Manganese Superoxide Dismuthase; PTD: Protein Transduction Domain; A: Adenosine; C: Cytosine; 8-oxo-G: 8-oxoguanine

INTRODUCTION

HIV infection increases the process of oxidative stress and antiretroviral combination therapy increases protein oxidation and pre-existing oxidative stress and induces an imbalance in cellular homeostasis due to excessive production of reactive species of the oxygen (ROS), from the deterioration of cellular antioxidant defenses; during HIV infection. It results in an enteropathy characterized by a pronounced loss of CD4+ lymphocytes, increased intestinal permeability and microbial translocation that promotes systemic immune activation implicated in disease progression [1], treatment response, non-AIDS comorbidities and molecular damage due to HIV-1[2] Transcriptional Transactivator (Tat) activity which influences the cellular redox state by two mechanisms; by decreasing the concentrations of antioxidants, in particular the collapse of the expression of manganese superoxide dismuthase (Mn-SOD) and that of the content of cellular glutathione (GSH) by down-regulating

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glutathione synthetase [3,4]. And/or by increasing oxidant levels. Additionally, Tat can induce ROS production in several cell types [5,6]. That also contains a protein transduction domain (PTD) that allows the protein to be secreted by HIV-1 infected cells and enter uninfected cells to regulate host gene expression [7,8] to cause diseases associated with AIDS such as Kaposi's sarcoma and HIV-associated dementia [8]. This sustained inflammatory/oxidative environment leads to a vicious circle, which can damage healthy neighboring epithelial and stromal cells and over a long period can lead to carcinogenesis via the production of nitrosative radicals, reactive oxygen intermediates and nitrogen, which can directly oxidize DNA or interfere with DNA repair mechanisms and which can react rapidly with proteins, carbohydrates and lipids, as well as derivative products and induce high disturbance from intracellular and intercellular homeostasis, to DNA mutation [9]. Which will be at the origin of an instability of the genome; whose finality is a cellular proliferation [10] and on the other hand of HO mainly generated in the vicinity of the nucleic acids, reacting with the bases by their oxidation especially with guanine due to its lower redox potential, it is the preferred target of oxygenated radicals which convert it into 8-oxoguanine (8-oxo-G) capable of pairing with adenosine (A) instead of cytosine (C), and thus inducing a conversion of GC bases into AT during DNA replication and the appearance of mutations [11]. Given its detrimental effect on overall immunity, several interventions aimed at preventing or blocking microbial translocation, are currently being investigated as new therapeutic agents for HIV/AIDS [12].

The aim of this study was to evaluate firstly the effect of probiotic yogurt supplementation on inflammation of the intestinal wall and oxidative stress on the course of the disease and secondly the antigenotoxic, antimutagenic and anticarcinogenic properties of probiotic yogurt. In response to damage caused by inflammation and oxidative stress in people living with HIV on antiretroviral therapy.

METHODS

A simple 1:1 randomization, selecting 229 HIV-positive patients on ART, of whom only 178 were elected and included in the study due to 141 on Bras Efavirens (68 on ART and 73 on ART+probiotic yogurt) and 37 on LPV/r (18 on ART and 19 on ART+probiotic yogurt) combined with Tenofovir (TDF) and Lamuvidine (3TC), according to the following criteria: written informed consent, age ≥ 18 years old, patient on antiretroviral treatment for more than six months, Meet the criteria following, negative pregnancy test at the screening visit (♀of childbearing age) and the non-inclusion criteria are defined as follows: presence of grade 4 laboratory abnormalities at the screening visit, ALT or AST > 3X the limit above normal, Hemoglobin < 8.5 g% (♀), <9.0 g % (♂), estimated creatinine clearance < 50ml/min, according to the Cockcroft-Gault formula suspicion of TBC on chest X-ray . And followed for 48 weeks.

The parameters of interest were as follows: the rate of CD4 (facs count), sCD14 (Enzo life science), sCD163 (Avisera Biosciences) (Hypersensitive CRP (Enzo life science), Glutathione peroxidase (Randox), sulfoxide dismutase (Randox), Zinc (Randox), viral load (CAPCTM Roche) and 8-oxoguanine level (Competitive ELISA from StressMarq Biosciences kit). The data collected at inclusion; in weeks 24 and 48 were analyzed using Epi Info software version 7.2.2.2, and Excel 2.

RESULTS AND DISCUSSION

The CD4 count follow-up results during randomization show that a significant difference in variation between the two arms, ART + Yogurt significantly improved the CD4 count, i.e. an increase of 92.7% and 396.6% respectively under supplementation in probiotic yoghurt and EFV (p=0.00206) and LPV (p=0.00278) against 43.6% and 46.5% respectively in EFV and LPV only. The CD4 count results obtained with ART alone are far lower than those obtained with ART and probiotic yogurt supplementation, which is confirmed by Irvine SL et al who found in their study that the introduction of probiotic yogurt, made by local women in a low-income community in Tanzania, was significantly associated with an increase in CD4 count in consumers living with HIV [13], the same observation was made by Anukam [14] in his study on Yogurt containing probiotics Lactobacillus rhamnosus GR-1 and L. reuteri RC-14 which helped treat cases of moderate diarrhea and increase CD4 count in HIV/AIDS patients (Figure 1).

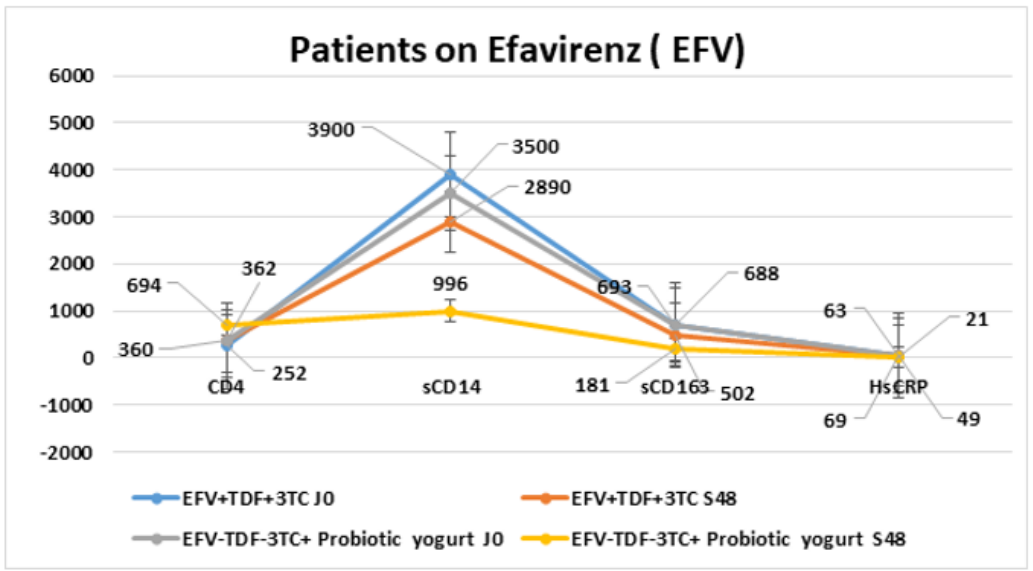

Figure 1: Variation in immunological parameters and inflammation in patients on Effavirens arms with or without probiotic yogurt supplementation.

A high level of macrophage activation markers, such as sCD163, sCD14 and Hs-CRP was observed in patients at baseline in this study. This persistence of high value of the sCD14 level was also observed by Macatangay et al. [15] who, having noted among the participants of his study who had started antiretroviral therapy during the first six months of HIV infection, elevated levels of sCD14 and CRP and remained similar to levels seen before antiretroviral therapy, suggesting that immune damage occurring during the initial phases of infection persists despite short-term virologic suppression. similarly, the level of sCD163, a mono-macrophage activation marker remained at high proportions in patients on antiretroviral treatment, which agrees with the assertion of Castley et al. [16] who state that HIV status was associated to a significant increase in the expression of CD64, CD143 and CD163 on CD16 + monocytes, regardless of the virological response to anti-HIV treatment.

This observation is also that of Burdo [17] and who observed that the sCD163 level was high in the plasma of people suffering from chronic HIV infection (>1 year in duration), compared to HIV in people - seronegative. And under effective antiretroviral therapy, the sCD163 level decreased in parallel with the level of HIV-RNA viral load without equaling the level of HIV-negative subjects, suggesting the presence of residual monocyte/macrophage activation, even with viral loads plasma levels below the detection limit. Ticona et al. [18] evaluating biomarkers of inflammation during suppressive antiretroviral therapy, found that before antiretroviral therapy, soluble CD163 concentrations were higher and remained higher after 24 months of suppressive therapy. 48 weeks later, a modest reduction was observed in patients on ART only. Indeed, Sereti et al. [19] also observed that sCD14 levels decreased during antiretroviral treatment but remained elevated compared to HIV-uninfected participants.

In addition to their persistence under ART, sCD14 and sCD163 are predictive markers of disease progression according to Generoso et al. [20] who established that high plasma levels of sCD163 are correlated with the progression of the disease and the cell activation and that initiation of antiretroviral therapy normalizes sCD163 levels and may alleviate HIV-related morbidity and improve long-term outcomes. Similarly, Negi N et al noted in their findings that elevated sCD14, Endo Cab and LPS IgM levels in HIV-1 infected individuals are strong predictors of disease progression and could be considered as candidate biomarkers for disease surveillance [21]. Thus, the activation of monocytes/macrophages (sCD14 and sCD163) could play a role in the pathogenesis of HIV and constitute a target for intervention.

After intervention with ART + probiotic yogurt, the rate of sCD163 and sCD14 decreased significantly. Indeed, under probiotic yogurt and ART, our results show a significant decrease in the level of sCD14 and Pei et al. [22] affirm it by their observation on the consumption of yogurt after nine weeks showed that, the ΔAUC ratios of the LY ratios /SCD14 of YO and YN were less than half that of the control groups (P=0.0093). Overweight and obese subjects found that the group with the healthiest eating behaviors (lower consumption of sweets and sugary drinks, and higher consumption of fruits, but also yogurts and soups) had the inflammatory markers the lowest (sCD14).

As for the Hypersensitive CRP level: on inclusion, its values were high as noted by Borato et al. [23] who observed a significantly high level of Hs-CRP in the group on ART, which indicates a factor predictive of cardiovascular events in HIV-positive patients; same observation made by Muswe et al. [24]; Kozić Dokmanović et al. [25]; Hattab et al. [26] studying the impact of various antiretroviral therapy regimens on markers of immune activation and inflammation, found that HS-CRP and sCD14 levels remained stable and no difference was found between LPV/r and EFV As in our study of probiotic yoghurt supplementation with ART, Naomi Trupper [27] measured in HIV-positive patients after consumption on ART and extra virgin olive oil, HsCRP at lower concentration levels due to the effect of the concentration of hydroxytyrosol, a powerful antioxidant found in olives possessing antiviral and anti-inflammatory properties and acts as a microbicide and reduces the transmission of HIV and reduces HIV transmission (Figure 2-4).

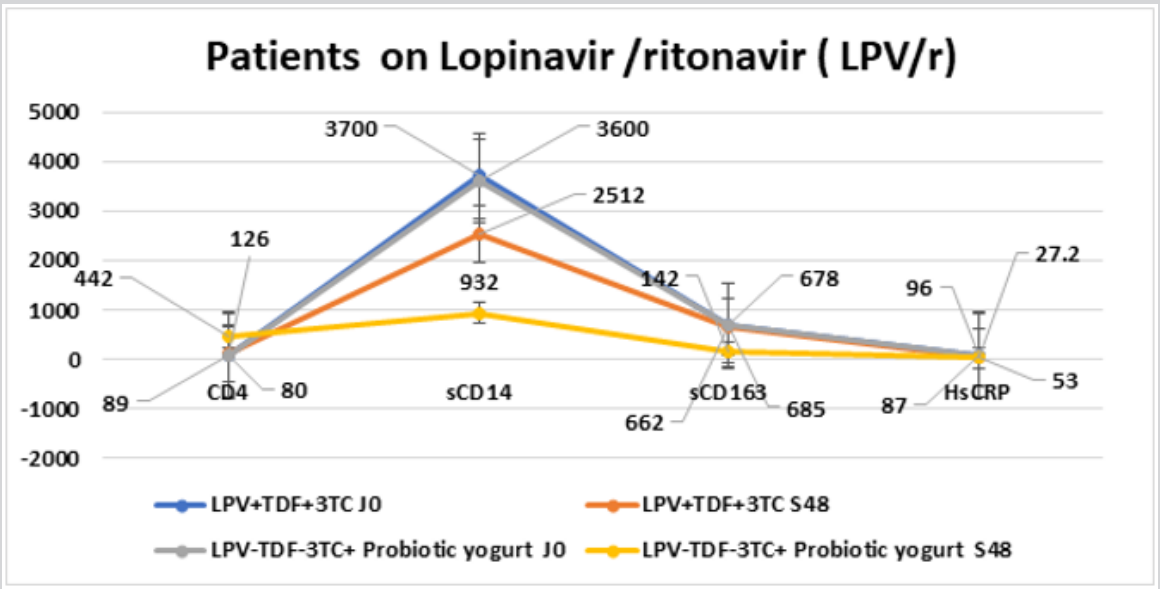

Figure 2: Variation of immunological parameters and inflammation of patients on Lopinavir arm with or without probiotic yogurt supplementation.

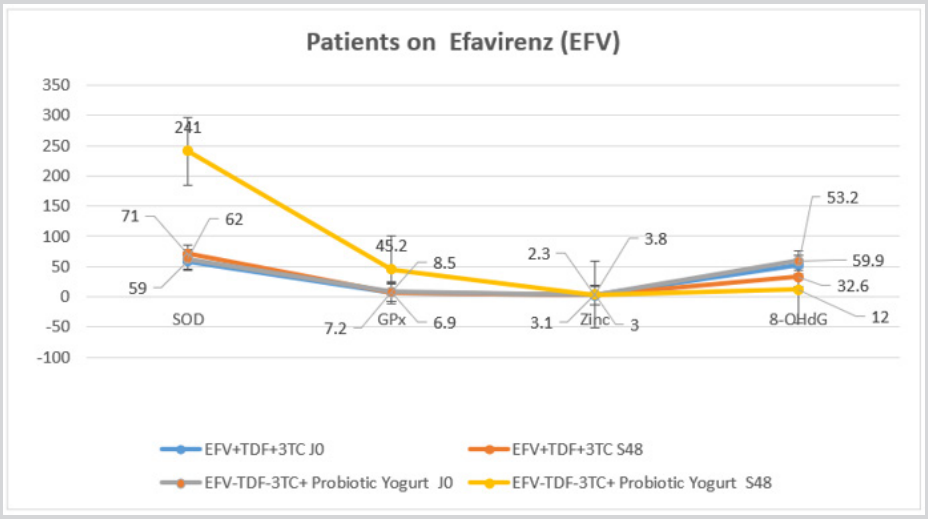

Figure 3: Variation in immunological parameters and inflammation in patients on Effavirens arms with or without probiotic yogurt supplementation.

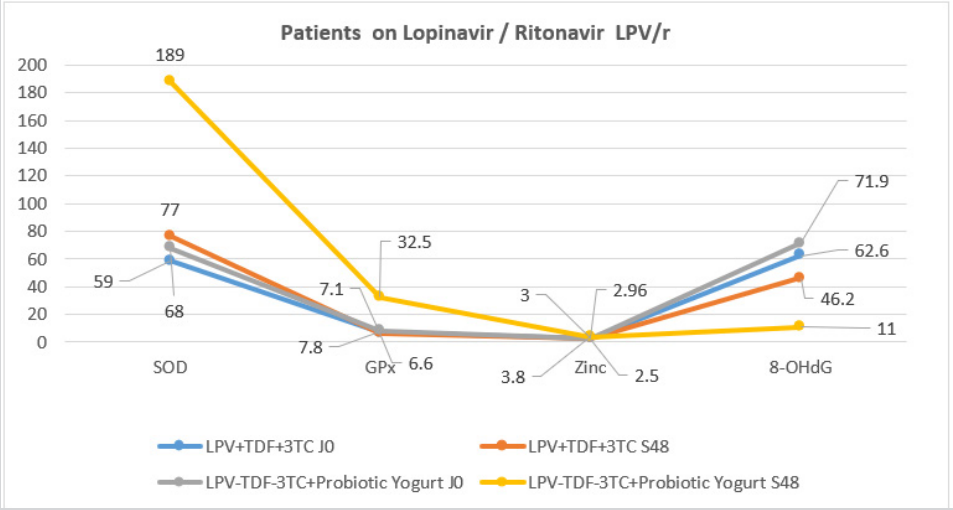

Figure 4: Variation in oxidative stress parameters of patients on Efavirenz arms with or without probiotic yogurt supplementation.

Inflammation during HIV infection contributes to the development of cancer, primarily by causing oxidative stress and DNA damage. And thus, disrupting the enzymatic and non-enzymatic antioxidant defense system, in our study, we observe a decrease in the activity of Superoxide dismutase and Glutathione peroxidase as well as a decrease in the rate of Zinc. There was no significant change in this situation on ART and very significant on ART with probiotic yogurt supplementation

Under ART, the activation of SOD remained relatively low under ART compared to inclusion (EFV p=0.803, LVP p=0.712), this is also what Quaye et al. [18] also notice in Ghana in HIV-infected patients that SOD activity was significantly reduced in antiretroviral treatment naïve compared to those on antiretroviral treatment and the control group and Similarly, Suresh et al. [29] evaluating, the total antioxidant capacity and a new early biochemical marker of oxidative stress in HIV-infected individuals, found a significant drop in vitamin E, vitamin C and SOD levels and finally, Makinde et al. [30] who after vitamin A supplementation in HIV-positive people on ART, the SOD level in his series remained low. In addition, our results demonstrate that antiretroviral treatment associated with probiotic yogurt supplementation improves SOD activity and restores defense activity against oxidative stress (EFV + Yogurt p = 0.0006; LPV + Yogurt p = 0.0025),

The evaluation of Glutathione peroxidase activity remains low in patients on ART, which improves significantly on ART and probiotic yogurt. Indeed, Look et al. [31] also noticed by evaluating the various antioxidant markers in people living with HIV that stages I to III of HIV disease are characterized by significant alterations in the antioxidant defenses provided by selenium, GSH-Px, SH groups and GSH. This is also confirmed by Ogunro et al. [32] who, studying the correlation between the concentration of Selenium and Glutathione peroxidase, found that selenium and glutathione peroxidase are reduced to scavenger antioxidants, and that their concentration decreases significantly with evolution of the disease and this is exactly what was observed by Wanatabe et al. [33] who concluded that HIV infection was associated with an increase in oxidative stress and seems to affect the protective activity of Glutathione Peroxidase. While Stephensen et al. [34] insist on the relationship between the activity of Glutathione peroxidase and good nutrition because in their conclusion, they specify that the activity of GPX

seems to have been induced by the oxidative stress associated with the infection by HIV and antiretroviral therapy. Thus, young, well-nourished individuals may mount a compensatory antioxidant response to HIV infection; this is our observation by carrying out probiotic yogurt supplementation in participants on ART (EFV + Yogurt p = 0.006; LPV + Yogurt p = 0.00501).

The Zinc level remains low in our series throughout 48 weeks of follow-up under ART or under ART supplemented with Probiotic Yogurt. Shivakoti et al. [35] in their study observed that despite increasing micronutrient concentrations, the prevalence of individual deficiencies remained virtually unchanged after 48 weeks of antiretroviral therapy and observed no improvement in micronutrient deficiency on antiretroviral therapy alone. And in Iran, Khalili et al. [36] also noticed that the serum concentrations of zinc and selenium in subjects infected with the human immunodeficiency virus were significantly lower compared to healthy people. In addition, it is known that low zinc levels and chronic inflammation are common in people infected with the human immunodeficiency virus (HIV); [37] and that zinc deficiency can promote systemic inflammation [38]. This is confirmed by Mburu et al. [39] in a study in Kenyan adults living with HIV showing that the plasma zinc level was lower in those who had inflammation. Similarly, Osuna-Padilla et al. [40] found frequent deficiencies in serum zinc concentration in HIV-positive treated individuals (Table 1).

Table 1: Prevalence of metabolic syndrome and DNA damage among groups.

	EFV-TDF-3TC				EFV-TDF-3TC+Yaourt Probiotique			Viral Load (VL)		CD4 Week 48
	Inclusion		Week 48		Inclusion		Week 48			
	Patients with 8-OH-dG ≤ 16ng/ml	Patients with 8-OH-dG > 16ng/ml	Patients with 8-OH-dG ≤ 16ng/ml	Patients with 8-OH-dG > 16ng/ml	OR	Chi	Value	CV±SD (log copies) Inclusion	Week 48	
EFV-TDF-3TC	10	58 (85.29%)	15	37 (71.15%)	2.35 (0.95-5.78)	3.57	0.058	2,17 (0–4,6)	TND	362
EFV-TDF-3TC+probiotic yogurt	17	56(76.71%)	66	1(1.49%)	217.41 (28.04-85.49)	81.89	0	3,21 (0–5,2)	TND	695
LPV/r-TDF-3TC	2	16(88.88%)	5	5(50%)	8(1.16-57.72)	5.18	0.022	2,17 (0–4,6)	TND	126
LPV/R-TDF-3TC+probiotic yogurt	2	17(89.47%)	16	0(0%)	Ind	28,48	0			442

8-OHdG, an interesting marker of oxidative stress, expressing a higher risk of eventually developing cancer [41], is at a high level in all patients on inclusion in our study, and after evaluating the effects of antiretroviral therapy alone or in supplementation with probiotic yoghurt, table 1 shows us that not all the patients had an 8-OHdG value above the reference threshold. We see this while: Under EFV-TDF-3TC 85.29% of patients have an 8-OHdG level above the reference threshold on inclusion compared to 71.15% 48 after weeks of follow-up with p=0.58. While under EFV-TDF-3TC + Probiotic Yogurt, only 1.49% of patients had their plasma 8-OHdG level above the threshold against 76.71% at inclusion with p<<<< 0.00, an OR 217.41 (28.04- 685.49) and Pearson's chi-square 81.89.

Under LPV/r-TDF-3TC 888.88% of patients have an 8-OHdG level above the reference threshold on inclusion compared to 50% 48 after weeks of follow-up with p=0.022. While under LPV/r-TDF-3TC+Probiotic Yogurt, only 0% of patients have their plasma 8-OHdG level above the threshold against 89.47% at inclusion with p<<<<0.00 with indeterminate OR and Chi Pearson's square of 27.83.

From the above, it should be noted that patients without antiretroviral therapy run a significant risk of developing cancer, given the high level of 8-OHdG, this increase is the consequence not only of direct effects of ROS, generally attributed to high concentrations at the site of damage, include DNA strand breaks, point mutations, aberrant DNA cross-linking, and mutations in proto-oncogenes and tumor suppressor genes, thereby promoting neoplastic transformation [42,43], but also because chronic inflammation is induced by biological, chemical and physical factors and is in turn associated with an increased risk of several human cancers [44]. Because indeed during inflammation, mast cells and leukocytes are recruited to the site of damage, leading to a "respiratory burst" due to increased oxygen uptake, and thus increased release and accumulation of ROS at the site of damage [42,45]. Thus, chronic inflammation, such as HIV infection, acts as a "secret killer" for diseases such as cancer [46].

Indeed, studies have observed that immediate initiation of antiretroviral significantly reduces cancer risk and still others, including Lesley S et al have found that viral suppression under long-term antiretroviral therapy may contribute to cancer prevention [47] , as well as Robert Dubrow's team studying the associations of the number of CD4 + T lymphocytes, the viral load of HIV-1 RNA and antiretroviral treatment with the risk of Kaposi's sarcoma in people infected with HIV in the United States and Canada, found a very significant relationship between the measurement of viral load, that of CD4 and the risk of Sarcoma Kaposi and this without any evidence of anti-sarcoma activity of Kaposi directly from ART, regardless of CD4 count and viral load, and after close adjustment the team did not detect an independent association between ART use and the risk of Sarcoma Kaposi [48], same observation made by Semeere et al. [49] as well as Franceschi et al. [50] who also found that the incidence of Kaposi's sarcoma fell sharply during the first months after the initiation of multi therapy, Although having made the same observation, Dittmer et al. [51] found that although the incidence of Kaposi's sarcoma has been reduced in developed countries

since the introduction of highly active antiretroviral treatment, its incidence is still markedly increased in HIV-infected patients in resource-rich areas of the world and is a major complication in HIV-infected people in sub-Saharan Africa. These observations confirm our results obtained in patients on antiretroviral therapy. In this group, we observed a decrease in the number of patients with 8-OHdG above the threshold remained fairly represented despite the improvement in the CD4 count and the suppression of the viral load. Indeed, in the Democratic Republic of Congo, all lines include Nucleotide Analogues essentially Nucleotide Inhibitors of Reverse Transcriptase either TDF+3TC+EFV or AZT/TDF+3TC+LPV/r depending on whether one is on the first line or the second line [52]. Nucleoside Analogs are used in the treatment of cancer and viral infections, they inhibit viral genome replication, but at high concentrations they induce a DNA damage response in cells [53,54]. This response is linked to the mobilization of the cellular DNA repair system to eliminate Nucleoside Analogs, which are incorporated into the host genomic DNA. Nucleoside Analogs also affect telomerase activity and induce the production of Oxygen Sulfide Radicals, leading to further DNA damage. Cells with a compromised DNA damage response are expected to display an increased level of DNA damage resulting from inefficient DNA repair of lesions produced by Nucleoside Analogs [55].

Under Antiretroviral treatment with probiotic yoghurt supplementation, we observe almost all of our patients a significant reduction in the cancer risk marker 8OHdG compared to the initial values and this reduction remains below the acceptable threshold. This reflects an anti-mutagenic or anti-carcinogenic effect of probiotic yoghurt [56,57] whose propaedeutics were suspected by Biffi et al. [58] in their study on the antiproliferative effect of fermented milk on the growth of a human breast cancer cell line, they speculated that the presence of an ex novo soluble compound produced by lactic acid bacteria during milk fermentation or microbial transformation of certain milk components into a biologically active form would be responsible for growth inhibition induced by all fermented milks. This is how Dos Reis et al. [59], in their study on the review of the mechanisms of probiotic actions in the prevention of colorectal cancer, probiotic yogurt acts by the change in the composition and metabolic activity of the microbiota, the fixation of carcinogenic compounds present in the intestinal lumen and their degradation, production of compounds with anti-carcinogenic activity, immunomodulation, improvement of the intestinal barrier, changes in the physiology of the host, inhibition of cell proliferation and induction of apoptosis in cancer cells". Kahouli et al. [60] add that selected probiotic bacteria and their metabolites have been used to promote cell differentiation and reduce DNA damage. These are mainly *Streptococcus thermophilus* and *Lactobacillus delbruckii* subsp. bulgaricus, a bacterial combination that actively reduces the risk of colorectal cancer was correlated with increased yogurt consumption (especially in humans); [61-63]. This bacterial protocooperation between *Streptococcus thermophilus* and *Lactobacillus delbruckii* subsp. Bulgaricus allows the synthesis of bioactive peptides such as sphingolipids have anti-carcinogenic and antimicrobial properties and bioactive peptides have antioxidant, anti-oxidant and anti-inflammatory properties [64] and these properties depend, not only, on micro -organisms present in these foods, but, much more of the proto- cooperation between *Streptococcus thermophilus* and *Lactobacillus delbrukeckii* ssp. Bulgaricus which relies on exchanges of metabolites that accelerate acidification during yogurt fermentation [65] and induce other beneficial actions exerted by yogurt cultures, unrelated to lactose digestion including intestinal immune modulation [66,67] as well as improving the vitamin B profile in adults [68,69] and finally maintaining the integrity of the intestinal barrier [70].

CONCLUSION

Inflammation and oxidative stress induced by HIV infection are two major problems that prevent optimal evolution of patients on antiretroviral treatment. They maintain a low CD4 level, a very remarkable increase in inflammation biomarkers (sCD14, sCD163 and HsCRP) and permanent oxidative stress due to the collapse of the main defense enzymes of the antioxidant system (Superoxide dismutase and Glutathione peroxidase) anise than the Zinc cofactor, the deficiency of which also maintains systemic inflammation. And HIV during tat-stimulated replication induces DNA damage not only in lymphocytes, but also in nearby cells, once accumulated in the cells and once the repair mechanisms are obsolete, it induces a mutation by change of bases likely to start a neoplastic process, evaluated by the assay of 8-OHdG which is a major marker of DNA damage Supplementation with probiotic yogurt with Lactobacillus acidophilus and streptococcus bulgaricus improved the CD4 level and that of the enzymes of the antioxidant system, a significant reduction in the biomarkers of inflammation and the level of 8-OHdG thus presaging a significant reduction in the risk occurrence of cancers, regardless of the therapeutic line. Only the Zinc concentration remained at subnormal values regardless of the intervention.

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