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Clinical and Immunological Beneficial Effects of Phyto V7 Consumption by HIV-1 Seropositive Individuals

Wernik J. R.[1]*; Borkow G.[2]; Goldman W. F.[2]; Elias, A. C.[3]

[1]Facultad de Medicina, UDELAR, Montevideo, Uruguay;

[2]Immune Nutrition Incorp., Rehovot, Israel;

[3]Facultad de Bioquímica, Química y Farmacia, Universidad Nacional de Tucumán, San Miguel de Tucumán, Tucumán 4000, Argentina

*Corresponding author: Dr. Ruben J. Wernik Oliva, MD, ruben@redisis.info; Mar de Ajo y Secco García, El Bosque, Ciudad de la Costa. Canelones, Uruguay. Tel: 00 (598) 94 117 420.

Abstract

Phytochemicals (PHT) are a large group of biologically active plant chemicals that may have positive effects on human health such as immune system stimulation, down regulation of inflammatory responses, radical scavenging activities, cell repair function, and antibacterial and antiviral activity. In this proof of principle 6 months study, the effects of supplementing a PHT mix, Phyto V7, to HIV-1 seropositive individuals and AIDS patients were examined. Individuals with CD4+ T-cells below 350 counts/mm^3 were assigned to one of the following treatments: CG1 - no treatment, CG2 - only highly active antiretroviral treatment (HAART), TG1 - only Phyto V7, and TG2- both Phyto V7 and HAART. After 3 months of treatment there were approximately (-)1%, 1%, 2% and 4% increase in the mean weight of the CG1, CG2, TG1 and TG2 groups, respectively. The tendency for the body mass index (BMI) was similar. The CD4+ counts increased by 13%, 39%, 53% and 35%, respectively. Similar trends were noted after 6 months with 2%, 79%, 53% and 69% increases in the CD4+ counts, respectively. There was a significant reduction in viremia only in groups receiving HAART. Overall better results were obtained in the group of patients receiving both HAART and Phyto V7, in which the mean weight increased by 5.7% and the CD4+ T-cell counts increased by 69% after 6 months. This study indicates that providing Phyto V7 to HIV-1 seropositive individuals and AIDS patients, receiving or not receiving HAART, improves their physical wellbeing and CD4+ counts, enabling them to cope better with the viral infection.

Running Title:

Effect of phytochemicals on HIV-1 Patients

Keywords:

Phytochemicals, HIV-1, AIDS, CD4+ T-Cells, HAART

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Introduction

HIV infection and AIDS are endemic in many malnourished populations. A balanced nourishing diet is fundamental for healthiness and survival for all individuals, including for HIV-infected individuals. Tuberculosis and diarrhea, which occur in many HIV infected individuals, cause by themselves appetite loss, atrophy and weight loss. In HIV-infected individuals, the body energy requirements are higher than in non-HIV infected individuals(1-5). Following HIV infection, before and after the onset of AIDS, including in AIDS patients receiving highly active antiretroviral treatment (HAART), the energy requirements needed to preserve the body weight increase by 20% to 30%(6-8). In view of the above, the World Health Organization has recommended the inclusion of micronutrients (MMN) administration in any treatment protocol for HIV-infected individuals at any stage of their disease, including during pregnancy and lactation and for children(6).

Almost in all randomized controlled trials that studied the effects of MMN supplementation found increased CD4+ T-cell counts or reduced mortality in the group of HIV-infected persons receiving MMN as compared to the HIV-infected persons receiving placebo(9-15). Different MMN interventions have been evaluated in the various trials conducted and the conclusion from all these studies is that MMN supplementation confers clear clinical benefits to HIV-infected individuals, including to pregnant women and their offspring, regardless of their clinical stage and use of Antiretroviral Therapy (ART)(15).

Phytochemicals, chemical compounds that occur naturally in plants, serve as micronutrients. Importantly, some phytochemicals also have additional important beneficial properties, as demonstrated in several clinical studies. For example, some phytochemicals possess radical scavenging activities(16) some stimulate nonspecific immunity(17) some down regulate inflammatory diseases(18) and some have anti-hepatotoxic, anti-lithic, anti-hypertensive, and anti-hepatitis properties(19). Interestingly, some phytochemicals demonstrate potent anti-HIV *in vitro* activity, especially against the HIV-1 protease and integrase, and against gp41 acting as entry inhibitors (16,19-28).

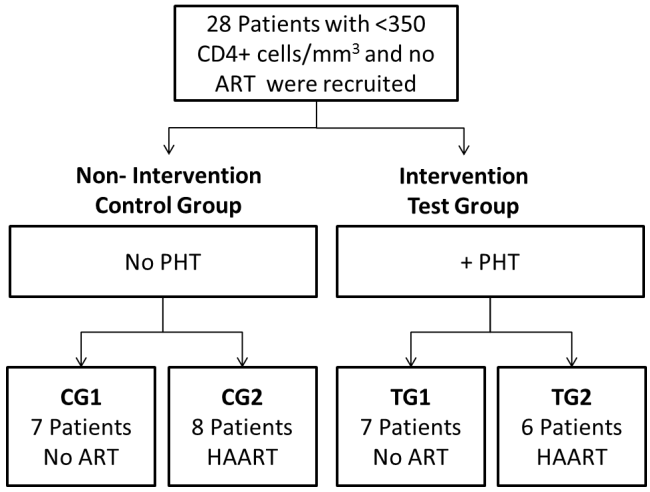
Phyto V7 is a specific mix of phytochemicals that has been found to have immune-stimulating properties. This was demonstrated in two separate studies. In the first one, administration of Phyto V7 to chicks vaccinated against Newcastle Disease Virus resulted in enhanced humoral immune responses against the virus (29). In the second study, administration of Phyto V7 to women, infected with Human Papilloma Virus (HPV) and with preneoplastic cervical lesions, resulted in enhanced cervical in situ cellular immune responses and increased clearance of HPV(30).

In the current study we studied the clinical and immunological effects of the administration of Phyto V7 on HIV-1 seropositive individuals and AIDS patients, in order to determine if this phytochemical complex may be an important nutritional component to be given to these populations.

Experimental Procedure

This was a prospective, controlled clinical trial designed to determine the effect of Phyto V7 supplementation on HIV-1 disease progression in HIV-infected individuals receiving or not receiving HAART. It consisted of an Intervention Test Group and a Non Intervention Control Group (Figure 1). The Test Group received Phyto V7 and was divided into 2 subgroups: with and without HAART. The Control Group did not receive Phyto V7 and was also divided into 2 subgroups: with and without HAART.

Figure 1. Trial Groups



Material and Methods

Enrollment took place between December 2009 and February 2010 in Hospital de Clínicas, Universidad Nacional de Córdoba, city of Cordoba, Argentina. Clinical interview, anthropometric and hematological analysis were performed prior to enrollment. Only diagnosed HIV -1 seropositive patients with less than 350 CD4+ T-cells per mm³, who had never received ART, were enrolled. Individuals with co-current infections or positive to hepatitis antibodies were excluded. Written informed consent was obtained from all study participants after explaining the trial aims and specifics in detail. Randomization to each of the detailed groups above was guided by the expressed will of the patient. A total of 28 patients were enrolled and divided into 4 groups as detailed in Figure 1: Control Group 1 (CG1; no Phyto V7, no ART); Control Group 2 (CG2; no Phyto V7, HAART); Test Group 1 (TG1; Phyto V7, no ART); and Test Group 2 (TG2; Phyto V7, HAART). The mean and age range, sex, weight and other characteristics of the enrolled patients per group are detailed in Table 1. The concomitant infections and HAART regimens of each of the patients are detailed in Table 2. In the Test Groups 1 and 2, the patients were requested to consume 2 tablets of Phyto V7 every 8 hours daily for the duration of the trial. Each Phyto V7 tablet contained 760 mg of the following phytochemicals: flavonols (Kaempferol, Quercetin), flavones (Apigenin, Luteolin), hydroxy-cinnamic acids (ferrulic acid), carotenoids (Lutein, Lycopene, Beta carotenne) andorganosulfur compounds, all from vegetal origin(31). Cross-sectional clinical and laboratory studies were conducted every 3 months. The CD4 lymphocyte count was measured by conventional flow cytometry. Plasma HIV-1 RNA was measured using an ultraquantitative polymerase chain reaction assay with a lower limit of quantification of 50 copies/mL.

Statistical Analysis

The Statistical Analysis Plan included the group mean, median and range analysis. The standard deviation (SD <10 and> 90) was performed by comparing the mobility of indicators in each case with longitudinal monitoring, average and increased by cuttings. For n = 28, validation sample was subjected to Yates Chi Square, giving a confidence interval of 95% (CI = 95) with a value α = 0.05, P = 0.2432. The delta % change in the weight or BMI of the patients after 3 and 6 months was calculated using the following equation [(Weight or BMI at 3 or 6 months/Weight or BMI at baseline) x100]-100. A Paired T-test was used to compare the means before and after treatment within groups. A Student T-test and/or a Mann-Whitney Rank Sum Test was used to compare between the changes in the weight, BMI and CD4+ T-cell counts between the groups. ANOVA of Kruskal & Wallis analyses and Conover post-test were used to compare the patient's characteristics at the onset of the trial. SigmaPlot 12.0 software was used to conduct the above statistical tests.

Results

Table 1. Characteristics of Patients at the Beginning of the Trial

	CG1	CG2	TG1	TG2.
Number	7	8	7	6
Sex (Male/Female)	6/1	5/3	5/2	5/1
Age (mean±SD) male	33±8	37±8	31±7	43±10
Age (mean±SD) female	54	42±9	28±3	46
Age (range) male	26-44	29-49	22-39	33-57
Age (range) female	54	33-51	25-30	46
BMI male	22±1	22±1	24±2	21±3
BMI female	21	22±2	22±0.2	23
CDC Classification	A2 all	A2 all	A2-6, A3-1	A2-5, C2-1
CD4 cells/mm^3(mean±SD)	295±32	271±42	276±38	233±74
CD4 cells/mm^3 (range)	237-336	203-350	175-329	93-298
Ln Viral load (mean±SD)	10.11±1.22	10.59±0.7	10.78±0.96	10.35±1.99

Table 2. Phyto V7, HAART Regimen and Concomitant Infections of Patients at the Beginning of the Trial

Patient #	Group	Phyto V7	HAART Regimen	Concomitant infections
1	CG1	None	None	Asymptomatic
2	CG1	None	None	Asymptomatic
3	CG1	None	None	Candidiasis
4	CG1	None	None	Asymptomatic
5	CG1	None	None	Microsporidium
6	CG1	None	None	Asymptomatic
7	CG1	None	None	Asymptomatic
8	CG2	None	Lamivudine/Zidovudine/Efavirenz	Asymptomatic
9	CG2	None	Lamivudine/Abacabir/Efavirenz	Tuberculosis
10	CG2	None	Lamivudine/Zidovudine/Nevirapine	Asymptomatic
11	CG2	None	Lamivudine/Zidovudine/Nevirapine	Asymptomatic
12	CG2	None	Abacabir/Tenofovir/Nevirapine	Asymptomatic
13	CG2	None	Lamivudine/Zidovudine/Nevirapine	Asymptomatic
14	CG2	None	Lamivudine/Zidovudine/Nevirapine	Pneumocystis Jiroveci
15	CG2	None	Abacabir/Tenofovir/Nevirapine	Asymptomatic
16	TG1	Yes	None	Asymptomatic
17	TG1	Yes	None	Asymptomatic
18	TG1	Yes	None	Asymptomatic
19	TG1	Yes	None	Asymptomatic
20	TG1	Yes	None	Tuberculosis
21	TG1	Yes	None	Asymptomatic
22	TG1	Yes	None	Asymptomatic
23	TG2	Yes	Lamivudine/Zidovudine/Nevirapine	Asymptomatic
24	TG2	Yes	Lamivudine/Didanosine/Nevirapine	Asymptomatic
25	TG2	Yes	Lamivudine/Zidovudine/Efavirenz	Epigastric distress
26	TG2	Yes	Abacabir/Tenofovir/Nevirapine	Asymptomatic
27	TG2	Yes	Abacabir/Tenofovir/Nevirapine	Candidiasis
28	TG2	Yes	Lamivudine/Zidovudine/Nevirapine	Asymptomatic

Characteristics of Trial Participants at Recruitment

Twenty eight patients were recruited to the study and assigned into 4 groups as detailed in Figure 1, according to the patients expressed will. According to the CDC Classification System for HIV infection, 26 patients were classified A2 patients, one A3 and one with more severe symptoms as C2 (Table 1). The concomitant infections and HAART regimens for each group are also detailed in Table 2. The overall patient's characteristics were similar between all 4 groups at enrollment. These included physical characteristics such as the age, weight, Body Mass Index (BMI) and height of the patients, and similar CDC classification (most patients were A2), viremia and CD4+ T-cell counts. Data points were collected from all patients for baseline, 3 and 6 months.

Patient's Physical Status

After 3 months from the commencement of the Trial it became clear that there were obvious differences between the physical wellbeing of the patients in the different groups. This was especially noticeable in the increase in the weight of the patients (Table 3). While in the CG1 there was a mean decrease in the weight of the patients of 1%, and in the CG2 patients there was a slight 1% non-significant increase in the weight of the patients as compared to the CG1, in the TG1and TG2 groups, there was a 2% and 4% statistically significant increases in the mean weights of the patients as compared to the reference CG1 (Figure 2a). The differences in the weight changes were even more noticeable at 6 months, especially in the TG2 group (Figures 2b and 2c). Very similar results were obtained with the Body Mass Indexes (Figure 3). In Control Group 1, that did not receive any treatment, there were no improvement in the CDC classification of the Patients at 3 and 6 months after the commencement of the Trial. In Control Group 2 that received ART only, in 0/8 and 5/8 of the patients improvements in their CDC classifications occurred at 3 and 6 months, respectively. In Test Group

Table 3. Mean, median and SDs of weights and BMI at 3 and 6 months of treatment

		Months	CG1	CG2	TG1	TG2
Weight	Mean	0	65	70.37	69.43	67.67
		3	64.27	70.76	70.54	70
		6	64.24	71.27	70.8	71.55
	Median	0	65	68.5	67	64
		3	65.4	69	67.3	67.5
		6	65	69.3	67.7	71.5
	SDs	0	5.38	9.53	10.2	12.1
		3	5.86	9.76	10.39	11.49
		6	6.37	10.2	10.39	11.14
BMI	Mean	0	21.69	22.3	22.86	21.44
		3	21.45	22.42	23.23	22.18
		6	21.43	22.57	23.32	22.68
	Median	0	21.72	22.56	21.97	21.39
		3	22.04	22.74	22.4	21.9
		6	22.1	22.82	22.51	22.87
	SDs	0	1.15	1.43	1.73	2.43
		3	1.41	1.51	1.82	2.11
		6	1.52	1.63	1.81	2

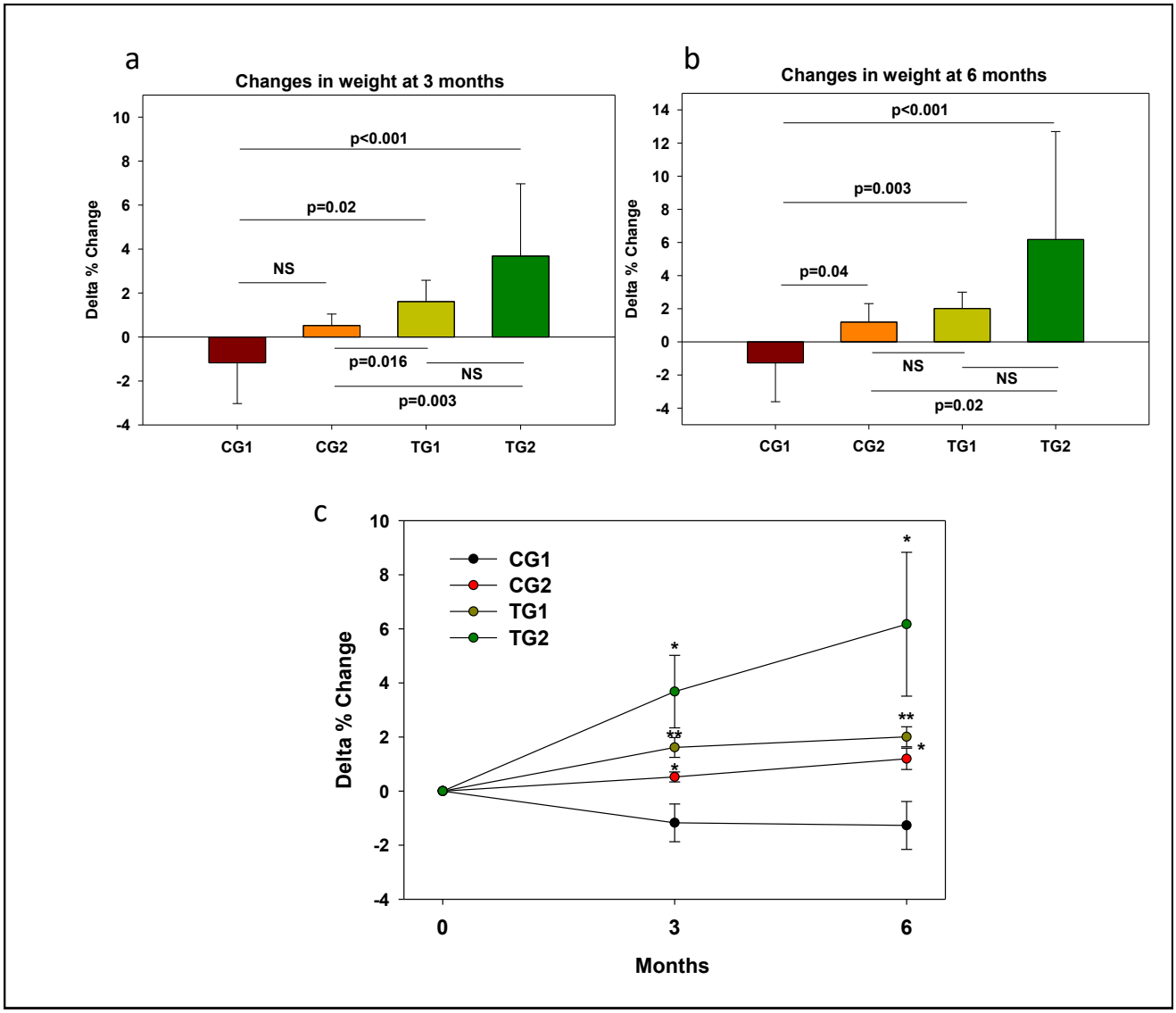
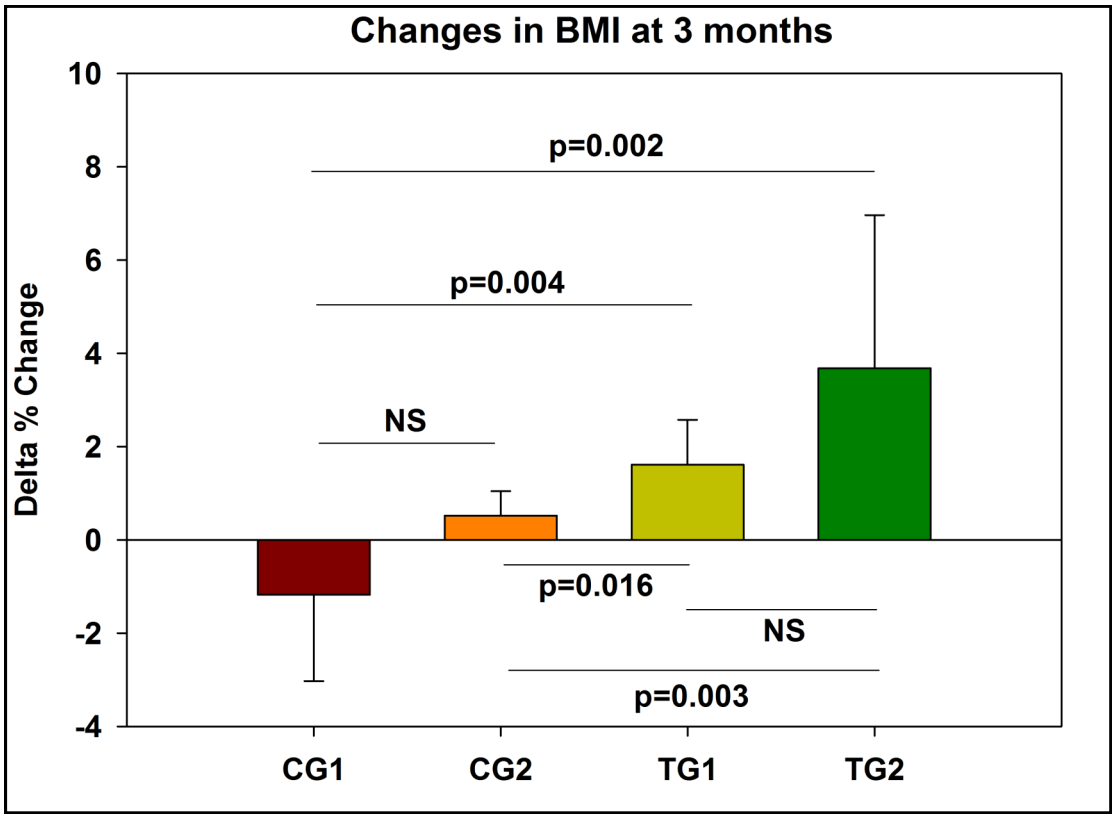


Figure 2. Changes in the patients weight from baseline at 3 and 6 months of the commencement of the Trial. In (a) and (b) the means and standard deviations are shown. In (c) the median and standard errors are shown. * p<0.05; ** p<0.01 per group as compared to time 0.

Figure 3(a)



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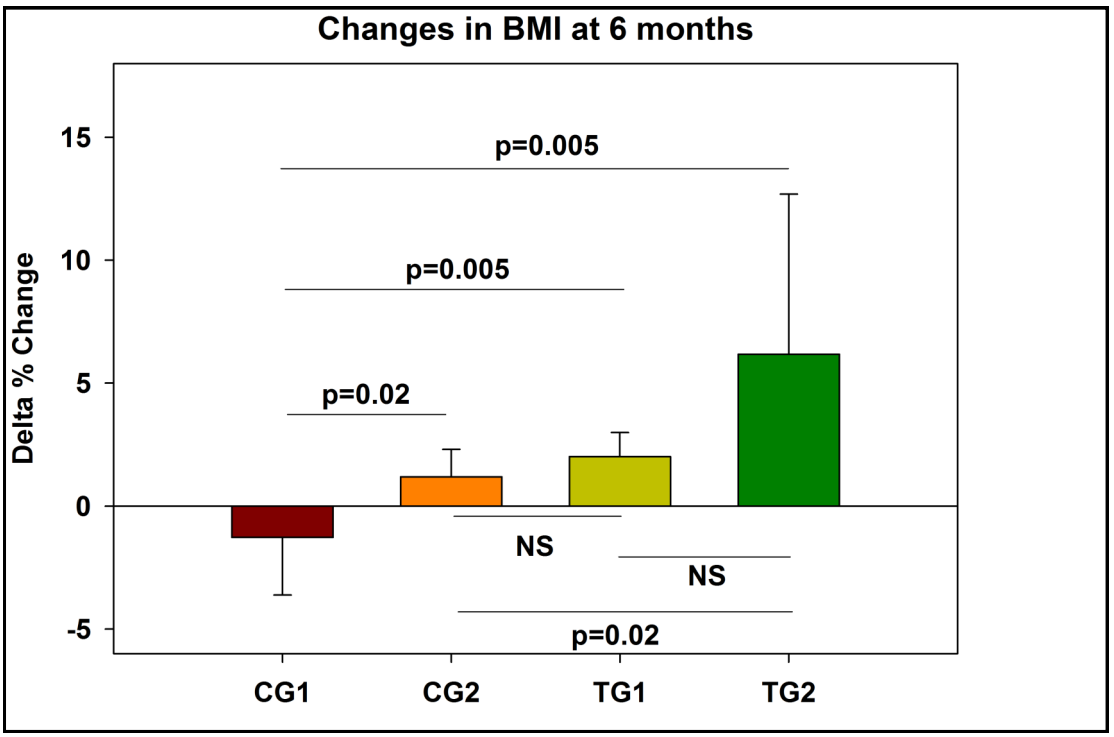


Figure 3(c)

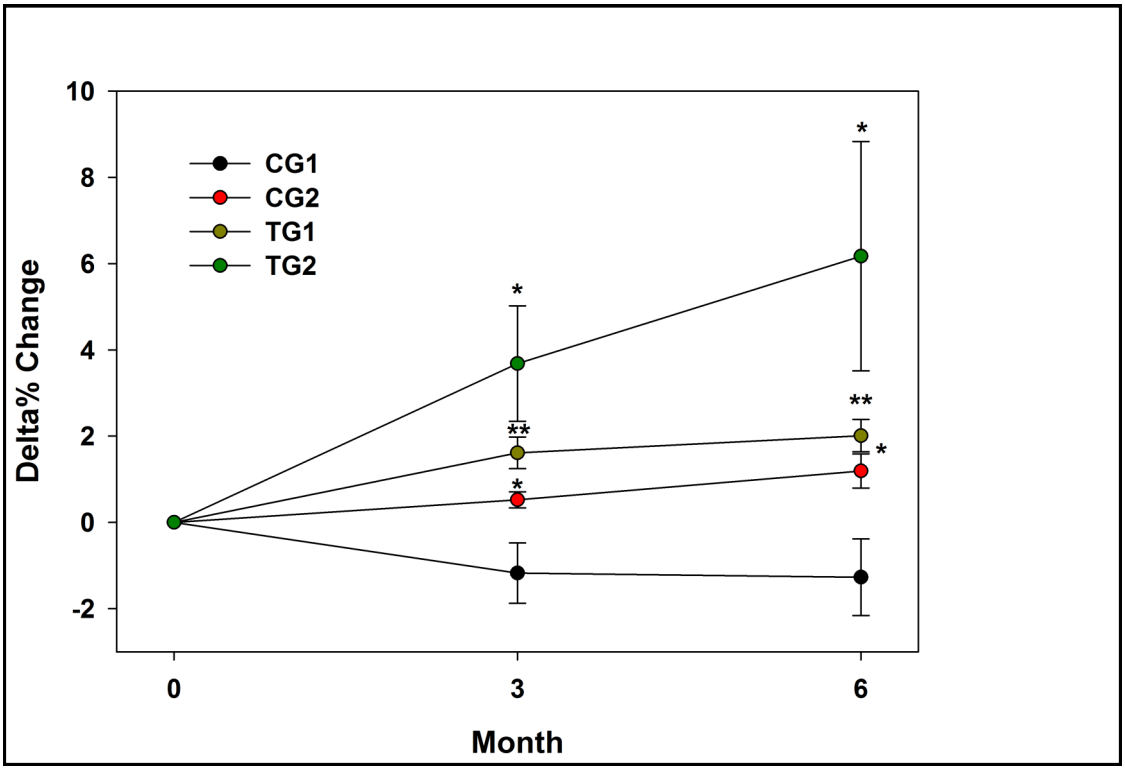


Figure 3. Changes in the patients BMI from baseline at 3 and 6 months of the commencement of the Trial. In (a) and (b) the means and standard deviations are shown. In (c) the median and standard errors are shown. * $p<0.05$; ** $p<0.01$ per group as compared to time 0.

1 that received PHT only, in 2/7 and 3/7 of the patients improvements in their CDC classification occurred at 3 and 6 months, respectively. In Test Group 2 that received ART and PHT, in 2/6 and 4/6 of the patients, improvements in their CDC classification occurred at 3 and 6 months, respectively.

Viremia

The patients in all 4 groups had similar significant high viral loads with no statistically significant differences in the group mean viremia at the beginning of the Trial (Table 1). As depicted in Figure 4 and detailed in Table 4, the mean viral load in the Control Group 1 that did not receive ART or PHT did not change significantly over the 6 months Trial. Similarly, there were no changes in the Test Group 1 that received PHT but did not receive ART. In contrast, the mean viral load in the patients of the Control Group 2, who received ART, was below detectable levels already after 3 months of treatment and remained below detectable levels also at 6 months of treatment. In the test Group 2, which received both ART and PHT, there was a reduction in the viral load below detectable levels at 3 months in all patients but one. After changing the antiretroviral medication to this patient, from the 3rd month of the commencement of the Trial and onward, his viral load was reduced to undetectable levels. Also in this group of patients no viral load was detected at 6 months.

CD4+ T-cell Counts

As depicted in Figure 5 and detailed in Table 4, no significant changes in CD4+ T-cell counts occurred in all

Figure 4. Viral loads at baseline and after 3 and 6 months after the commencement of the Trial.

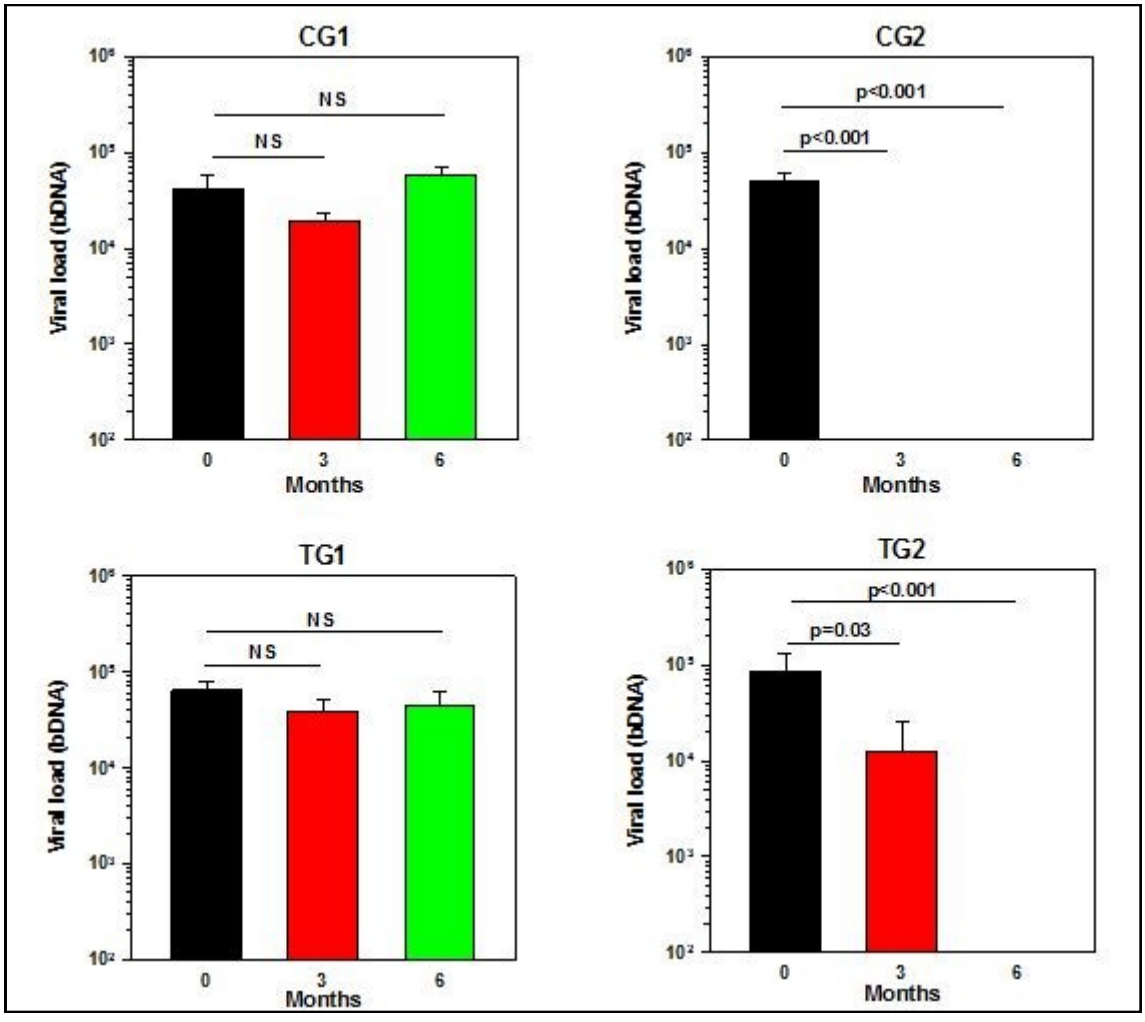


Table 4 – Mean, median and SDs of viremia and CD4+ T-cell counts at 3 and 6 months of treatment

		Months	CG1	CG2	TG1	TG2
Viremia (ln)	Mean	0	10.11	10.59	10.78	10.35
		3	9.79	3.91*	9.58	5.34
		6	10.77	3.91	9.47	3.91
	Median	0	10.16	10.42	11.16	10.84
		3	9.78	3.91	10.52	3.91
		6	11.04	3.91	10.04	3.91
	SDs	0	1.22	0.7	0.96	1.99
		3	0.44	0.0	2.58	3.19
		6	0.81	0.0	2.64	0.0
CD4+ T-cells	Mean	0	295	271	276	233
		3	335	378	424	315
		6	300	485	428	394
	Median	0	297	266	274	255
		3	351	377	434	330
		6	328	495	401	402
	SDs	0	32.2	42.2	38.5	73.7
		3	68	107.6	172.5	173.6
		6	75.5	141.1	119.1	170.8

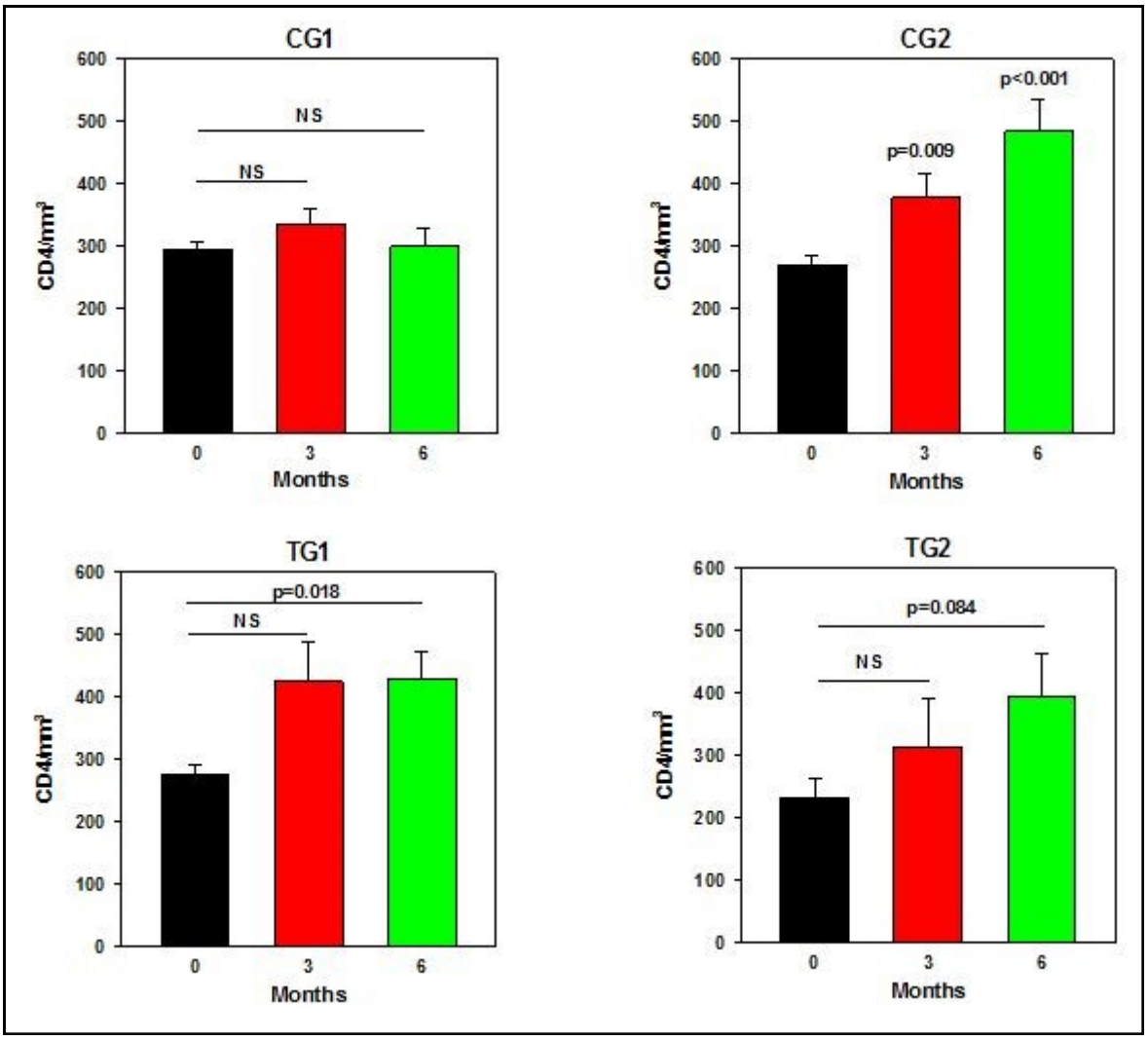
*Lower limit of viral load detection (equivalent to 50bDNA copies)

patients that belonged to the Control Group 1 during the 6 months trial. In the Control Group 2 that received ART there was a statistically significant increase from baseline in the CD4+ T-cell counts at 3 months (39%; p=0.02), which further increased at 6 months (79%; p<0.001). Impressively, also in the Test Group 1, who did not take any ART but only PHT, there was a significant increase of ~53% in the CD4+ T-cell counts at 3 and 6 months of treatment (p<0.05). Similar trend was noted in Test Group 2, who received both ART and PTH with 35% and 69% of increase in the mean CD4+ T-cell counts at 3 and 6 months, although in this group no statistical significance was reached (p=0.06).

Discussion

This study demonstrates that the oral administration of a phytochemical complex (Phyto V7) is beneficial to HIV-1 seropositive individuals and AIDS patients, whether receiving antiretroviral therapy or not. There were quantitative improvements in the patients receiving Phyto V7 in their weight, BMI and CD4+ T-cell counts. While there was a mean decrease in the weight and BMI of the patients that did not receive any treatment during the trial, in the patients that received only Phyto V7 there was a significant increase in the weight and BMI both after 3 and 6 months of the study. Interestingly, in the patients that received only ARV treatment, there was a statistical significant increase in weight and BMI only after 6 months of treatment, as compared to the patients that did not receive any treatment. The most notorious increases in weight and BMI were noted in the patients that received both ARV treatment and Phyto V7. Meaningfully, there was a clear statistical difference

Figure 5. CD4 counts at baseline and after 3 and 6 monthsafter the commencement of the Trial.



between the increase in weight and BMI in those patients that received ARV treatment only and those that received the ARV and also the phytochemicals both at 3 and 6 months (Figures 2 and 3), indicating the significant contribution of the phytochemicals to the well -being of the patients. Outstandingly, there was also clear improvement in the CD4+ T-cell counts of the group of patients that received Phyto V7 only as compared to those that did not receive any treatment (Figure 5), which was similar to the increase in CD4+ T-cell counts that occurred in the group of patients that received antiretroviral treatment only. The medical improvement in the patients receiving Phyto V7 was very noticeable according to the treating doctor's impression and the patient's feedback (appetite, reduction of diarrhea). While it has been reported that some phytochemicals possess potent anti-HIV in vitro activity (16,19-28), apparently their beneficial effects cannot be explained by their direct activity on the virus, as there were no decreases in viremia in the patients that received the phytochemicals only. The results of this study are in accordance with the dramatic improvement in the physical status of a small cohort of 9 terminal AIDS patients following 45 days of administration of Phyto V7(32) and with the significant improvement in the well-being of 199 HIV-1 infected individuals, who were not undergoing antiretroviral treatment and were recruited as part of the Uruguay National Program of AIDS, which received only a daily administration of Phyto V7 for a period of 90 consecutive days(31).

The HAART regimens used in this trial were based on the recommended Argentinian Ministry of Health guidelines at the time the trial was conducted. Those regimens as well as other HAART regimens, when taken with good compliance, can effectively reduce the viral loads to undetectable levels and significantly improve prognosis and well-being of the patients, as indeed was the case in the group of patients in this study that only received the antiretroviral therapy. However, HAART may cause also significant adverse effects, such as lipodystrophy, dyslipidaemia, cardiovascular complications, central and peripheral nervous system disturbances and insulin resistance(33-36). HAART may be very problematic to certain populations, such as pregnant women and children(37,38). The large number of pills needed for HAART also leads to significant problems of compliance and development of resistant virus(39). HAART is not implemented in many resource-limited regions where the AIDS epidemic is rampant due to its high cost. Furthermore, the spectrum of adverse effects related to HAART in developing countries may be even more deleterious and hard to treat because of the high prevalence of conditions such as anemia, malnutrition, and tuberculosis and frequent initial presentation with advanced HIV disease(40). Taken together, there is a rational for postponing the administration of HAART to HIV-1 infected patients as much as possible, but not too late before the CD4+ T-cell counts are too low (41).

As indicated in this study, in patients that did not receive antiretroviral treatment, the administration of Phyto V7 resulted in an increase in their CD4+ T-cell counts, weight and BMI, indicating that supplementation of this phytochemical mix may improve the capacity of HIV-1 infected individuals to cope with the viral infection and potentially delaying the need to treat them with HAART, postponing the potential complications associated with HAART treatment.

HAART treatment taken with good compliance in most cases results in viremia suppression, immune reconstitution, and reduction in incidence and severity of opportunistic diseases and death(42). Similar results were obtained in this study. However, in many HIV-1 infected individuals and AIDS patients undergoing HAART treatment, there is no reconstitution of their immune system, and the CD4+ T-cell counts do not increase even if full plasma viral load suppression is achieved(43). This may be further exasperated in AIDS/ tuberculosis patients, AIDS patients that already suffer from opportunistic infections, or are co-infected with other parasites, such as helminthes or other viral infections, as is the case in many African countries. It would be very significant if in these individuals the supplementation with phytochemicals would increase their CD4+ T-cell counts. This would be a much simpler associated safe treatment than immune therapies being explored today like cytokine therapies, therapeutic immunization, monoclonal antibodies, immune-modulating drugs, nanotechnology-based approaches and radio immune therapy (44,45).

What are the mechanisms by which the phytochemicals benefit HIV-1 seropositive and AIDS patients is not yet clear and should be elucidated. While it has been reported that some phytochemicals possess potent anti-HIV in vitro activity(16,19-28), apparently their beneficial effects cannot be explained by their direct activity on the virus, as there were no decreases in viremia in the patients that received the phytochemicals only (Figure 4). In the HAART and PHT co-treatment group (TG2), when looking at the mean viremia of the group (Fig. 4), the impression that PHT counteracts the effect of HAART could be reached. However, as explained in the Results section, in the TG2 group there were 6 individuals, all of which had high viral loads at the onset of the trial. Following the HAART treatment and PHT co-treatment in 5 out of the 6 patients, no viral load was detected at the 3 months period (less than ln

3.9, i.e. less than 50 viral RNA copies/ml). Unfortunately, in one individual the viremia remained very high (62685 viral RNA copies/ml) at 3 months examination. It turned out that this particular patient had a resistant virus and only after changing the antiretroviral medication, from the 3rd month of the commencement of the Trial and onward, the HAART treatment was efficacious. This indicates that the PHT co -treatment does not interfere with antiviral activity of HARRT therapy.

Part of their positive effect can be explained as serving as micronutrients, having radical scavenging activities (16), stimulating nonspecific immunity(17), and by down regulating inflammatory responses(18). Importantly, administration of Phyto V7 to 33 women infected with Human Papilloma Virus (HPV) and with preneoplastic cervical lesions, resulted in enhanced cervical in situ cellular immune responses and increased clearance of HPV(30). Additionally, enhancement of antibody titers against Newcastle Disease Virus occurred in vaccinated chicks following administration of Phyto V7(29), further supporting the notion that Phyto V7 has immune-stimulatory properties.

Additional studies should be performed to support the notion that supplementation of phytochemicals to HIV-1 infected patients is beneficial, and to elucidate their mechanism of action. This should be done with larger cohorts of HIV-1 infected individuals and AIDS patients. In the current study only patients with less than 350 CD4+ T-cells per mm^3 were recruited. Future studies should examine individuals with significantly higher CD4+ T-cell counts not receiving HAART as well as individuals with very low CD4 T-cell counts receiving or not receiving HAART. Future studies should also include patients receiving just multiple micronutrients supplementation (MMN) and compare them with patients receiving just phytochemicals. If proven the significant added value of phytochemicals over MMN, current recommendations, like the UN requested of inclusion of MMN for treatment of HIV carriers and AIDS patients at any stage of their disease, should be revised to include phytochemicals.

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