

# Protocol of Determining the Effect of Vimang® and Spirel® Supplementation in Aids Patients with Delayed Diagnosis of HIV: An Open Randomized Controlled Trial

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## Abstract

**Background:** Infection by Human immunodeficiency virus (VIH) constitutes a world health problem. The antiretroviral therapy accordingly recent WHO recommendation is proposed for all HIV seropositive individuals. Treatment optimization is encouraged due to certain risk of toxic adverse effects and resistance. The use of antioxidants has been indicated as a plausible option in these patients indeed pre or post exposition to antiretroviral treatment.

**Methods:** In an open randomized control trial, 170 aids delayed diagnosis patients whose received prescription of High active antiretroviral therapy (HAART) will selected to be covered under Hospital-IPK monitoring consults (Cuban Referral HIV/aids Research Centre). Patients will be randomised to receive 10 mL of Vimang® aqueous extract twice a day or Spirel® tablets (400 mg) three times a day or only HAART, but all groups will consume HAART during 12 months. The baseline assessment of the patients who meet the inclusion criteria includes doing some lab tests to determine the absolute count of CD4+ T lymphocyte, viral load, chemical, haematological and seven plasma redox indexes. Both, opportunistic infection and adverse reaction occurrence will be reported during the monthly visits in the first six months of the follow-up and at the end of the 12<sup>th</sup> month. For evaluating the effect of both products concomitant to antiretroviral all variables will be measured in the final follow-up session and compared with the baseline value. Also quality of life interview, physical activity and dietary questionnaires will be assessed at pre and post study period in the three groups.

**Keywords:** Antioxidant; Supplementation; HIV; Aids; CD4+ T Lymphocyte count; Randomized clinical trial

## Introduction

Acquired immune deficiency syndrome (aids) is currently a critical global problem and it continues to endorse health politics worldwide [1-3]. Although the expansive coverage of antiretroviral therapy (HAART) since 2003 [4,5], more than 30 million people were diagnosed with HIV in low and middle-income countries in 2010 [6] and of them only 36% with CD4+ T lymphocyte count  $\leq$  350 cells/mL received HAART in the same year [7].

The Cuban government offers free HAART to HIV and aids patients regularly since 2003 and up to 2013; reaching 97% of the adults who required it according global guidelines and 100% of children [8]. HAART toxic effects combined with the development of new strains of the virus and subsequently resistance to available drugs are frequently reported, especially in areas with acceptable coverage of the therapy. Those indicate that in addition to ART, other complementariness therapies are needed in this regard [9].

Several researches have reported that in a highly oxidative state (OS), meanly produced by chronic activation of immune system, the progress of HIV infection can be stimulated in the host [10]. Redox imbalance could mediate modulation and inflict activation of transcriptional signal, exerting specific cellular dynamic including apoptosis and tissues damage which in turn might conduce to dysfunction related or not to the pathology.

Therefore, treating the patients with antioxidants since initial phases of the disease is believed to be favourable and it is recommended by different authors.

According to the results of various studies, lower serum selenium (Se) levels, a micronutrient with antioxidant and immunoregulatory

properties [10-12], correlate with a smaller total number of CD4+ T lymphocyte, more advanced stages of infection and higher rates of mortality caused by HIV [13-15]. Diverse previous studies remark the effect of depleted antioxidant agent-like glutathione peroxides-resources (as a result of HIV infection) in promoting virus replication and CD4+ T lymphocyte count depletion [13,15-19]. During infection evolution, serum Se concentration diminishes gradually due to several factors including malabsorption caused by chronic infection, infectious diarrhea and HIV-related enteropathy, protein-calorie malnutrition and the inadequate intake of Se through diets [15,16,20]. Moreover, HIV possesses an enzyme, glutathione peroxidase-like structure which had selenoprotein in its molecular composition. Theoretically, virus replication contribute to the consumption of Se, influencing its availability in infected T cells, through the production of the abovementioned enzyme [17].

Preceding researches conducted in different countries have been reported OS associated to HIV infection evolution and to antiretroviral treatment also. Delmas-Beavieux chose 52 HIV positive patients

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randomly and supplied them with Se and beta carotene supplements and placebo daily for 12 months. They failed to report any improvement in CD4+ T Lymphocyte count, as for the placebo group. However, glutathione levels-an antioxidant factor were significantly higher, whereas malondialdehyde levels-an indicator of lipid peroxidation were significantly lower in both treated groups. Diverse but limited antioxidant supplementation trials were conducted in HIV groups [16].

Also Korean red ginseng (KRG) was used combined to HAART analysing the CD4+ T lymphocyte count, viral load, and resistance mutations to HAART in 46 individuals. The study population was divided into two groups: specifically, a group treated with a combination of HAART plus KRG (23 patients) and a group treated with HAART only (23 patients). The annual increase in CD4+ T lymphocyte count in the combination group was significantly higher than that in the group treated with HAART alone ( $P < 0.05$ ). High-level resistance mutations were significantly lower in the combination group than in the group treated with HAART alone. The data support the clinical utility of KRG intake during HAART therapy [18].

Considering the results of these studies regarding the beneficial effects of antioxidant supplementation in HIV+ /aids patients other contributions in special national options are necessary.

Vimang® is a natural product which contains a defined mixture of polyphenols, triterpenes, phytosterols, fatty acids and microelements including Se. It is prepared as an aqueous extract of the mango (*Mangifera indica* L) stem bark (EMSB) of selected varieties. EMSB pre-clinical assays documented antioxidant, analgesic and anti-inflammatory potentialities [21,22].

Vimang® has a powerful *in vitro* scavenger activity of hydroxyl radicals and hypochlorous acid and acts as an iron chelator. EMSB has shown to have a significant inhibitory effect on the peroxidation in brain and DNA damage by bleomycin or copper phenanthroline systems in rat model [23]. It protected mice biomolecules against 12-O-tetradecanoylphorbol-13-acetate-induced oxidation and peritoneal macrophage activation [24], reduced ischemia-induced neuronal loss and oxidative damage in the gerbil brain [25], and prevented liver injury associated with ischemia/reperfusion in rats [26], demonstrating its high antioxidant capacity.

Spirel® is composed by spiruline platensis algae, a cyanobacteria exerting biological effect in relation to its components. Many algae and also cyanobacteria are rich in the compound phycocyanobilin (PhyCB), a chromophore that, as a component of the holoprotein phycocyanin, benefits the affected condition of reduced energy. PhyCB is a biliverdin derivative which is converted by the ubiquitously expressed enzyme biliverdin reductase to phycocyanorubin in mammalian cells, a compound similar structurally to bilirubin, a potent inhibitor of NADPH oxidase [27].

Phycocyanin or spiruline administered orally exerts anti-inflammatory effect in rodents which suggests that PhyCB ingested can be sufficiently well absorbed to provide important systemic antioxidant activity. PhyCB's homolog biliverdin is likewise effective when administered orally [27].

There are some syndromes induced in animal models in which spiruline demonstrated protective effectiveness included adjuvant arthritis, doxorubicin-induced cardiomyopathy, and nephropathy mediated by cisplatin and cyclosporine; it is unlikely to be coincidental that activation of NADPH oxidase has been shown to be a key mediator of each of these syndromes [28].

## Aim

Determining the effect of Vimang® and Spirel® supplementation in HIV delayed diagnosis patients treated with antiretroviral combinations.

## Objectives

Determining the effects of Vimang® and Spirel® supplementation in aids patients with delayed diagnosis of HIV analyzing the following parameters:

- CD4+ T lymphocyte count
- redox indexes
- rate of developing opportunistic infections
- quality of life

## Study Population

From among 20000 HIV+/aids patients covered under the Cuban health program for HIV/AIDS, one hundred seventy HIV delayed diagnosis individuals eligible to receiving HAART will be selected and attending in the Hospital of Institute of Tropical Medicine Pedro Kouri (IPK). IPK, located in Havana is working under the supervision of Ministry of health of Cuba. It offers free services such as paraclinical and clinical treatment and consultation to HIV positive individuals as well as others at risk of developing HIV or any other sexually transmitted disease.

## Rationale Issues and Significance

Vimang® and Spirel® are Cuban products registered by Institute of Nutrition and Hygiene of Food as nutritional supplements and produced by LABIOFAM and commercialized by GENIX. Vimang® has a sanitarian register number: PN-409/14 since 2014 and the commercial formulation are aqueous solutions in dark bottle of 500 mL with total content of 25g Gallic acid per L. Spirel® has a sanitarian register number: 5R-097/96-I since 2012 and the commercial formulation is a tablet with 400 mg of platensis spiruline, a plastic flask had 100 tablets. Doses recommended by physicians were in accordance with previously doses used in others applications and also considering established posology by manufacture.

The methodology adopted includes the determination of a set of validated and normalized variables and indexes in involved laboratories and also could be related to the possible effect of supplements prescribed.

The significance of the research could be the evaluation of possible beneficial effect and safety of antioxidant supplementation with two natural products concomitant to antiretroviral therapy in aids patients with delayed diagnosis of HIV. The results of the present study will allow for a better clarification of possible regulatory effects of natural antioxidant and might elucidates the potential underlying mechanism through redox indexes.

## Recruitment

Subjects of the study consist of individuals who manifested opportunistic infection previously to confirm serological HIV infection through Western blotting test and they were classified as delayed diagnosis. One hundred seventy eligible patients meeting the inclusion criteria will be recruited and the others will be excluded (Table 1). A detailed written explanation of the study process, researchers' names and institutions, possible benefits and potential adverse effects of the interventions will be explained to the participants and additional

information should be provided upon request. Informed participants will be asked to sign a written informed consent. After baseline assessment achievement and signing the informed consent, all patients will be randomized based on age, gender, HIV infection and aids by permuted block randomization with 4 numbers block into three groups. One group will receive Spirel®, the other will receive Vimang®, both groups in concomitant manner to antiretroviral therapy and the third group will not receive any supplements only antiretroviral drugs. All groups will be treated and followed during one year (Figure 1).

### Sample Size

According to literature revision there was no preliminary study evaluating the Spirel®, or Vimang® supplementation effect on selected indexes included on trial in HIV infection; therefore the sample size were calculated according to a previous work reported which consider 1 µmol/mL difference of malondialdehyde concentrations, 1 µmol/mL reduction of glutathione concentrations and 150 cel mm<sup>3</sup> of CD4 T lymphocyte count difference between interventions and control group (29, 30). To detect this difference with 80% power and an α- error of 5%, a total of 45 individuals are needed. Allowing for 10% drop – out over 12 months of intervention, the total sample size required for the study is 50 individuals.

### Baseline Assessments

At the initial visit all participants will required to complete a questionnaire on their demographic information, HIV transmission way and the number of opportunistic infections during one year prior to the study. A comprehensive physical exam will be performed, a complete medical history will be appointed and specific lab tests will be executed by the trial clinician in turn (Table 2). All participants will be instructed to take their usual diet and physical activity during

| Inclusion Criteria                                                                                                                                                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Age 30 to 60 years.</li> <li>• Confirmed HIV-1 infection with western blotting test.</li> <li>• Signing an informed written consent.</li> <li>• Without HAART treatment.</li> <li>• With opportunist disease associated to HIV diagnostic.</li> </ul>                                                                                                    |
| Exclusion criteria                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>• Pregnancy.</li> <li>• Consumption of any other antioxidant supplements except for those under investigation in the present study.</li> <li>• History of chronic diseases like diabetes, hypertension, arthritis and others.</li> <li>• Active Hepatitis B or Hepatitis C infection.</li> <li>• Suffer any malignancy like lymphoma or others.</li> </ul> |

**Table 1:** Inclusion and exclusion criteria.

| General and life style                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Age</li> <li>• Gender</li> <li>• Infection incidence</li> <li>• History of smoking, alcohol consumption and other kinds of addiction (oral, inhalation)</li> <li>• Dietary assessment and physical activity questionnaire</li> <li>• Rout of infection transmission (History of unsafe sex, using illegal intravenous drugs, consumption of blood products, mother to child transmission)</li> </ul> |
| Comprehensive physical examination, medical and drug history                                                                                                                                                                                                                                                                                                                                                                                  |
| Lab tests                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>• Complete blood count-differentiation</li> <li>• Erythrocyte sedimentation rate</li> <li>• Liver function test (SGOT, SGPT, ALP)</li> <li>• Anti HBs Ab</li> <li>• Anti HCV Ab</li> <li>• Absolute CD4 + T lymphocyte count</li> <li>• Viral Load</li> </ul>                                                                                                                                          |

**Table 2:** Baseline parameters.

intervention period. Follow- up procedure will be done by bimonthly questionnaire application that will be included in individual clinical history of patients.

### Dietary assessment

Dietary intake is assessed by a three-day 24-h dietary recall questionnaire (including a weekend day) apply at baseline, each 2 months and at the end of one year of supplementation.

### Physical activity

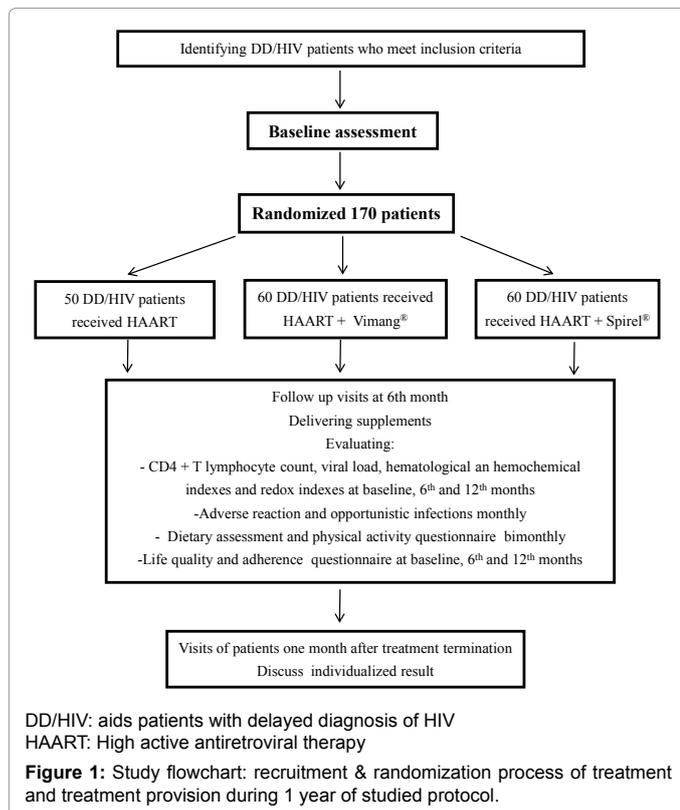
Physical activity is measured using the short form of international physical activity questionnaire (IPAQ). This face-to-face questionnaire includes the information about three specific types of activity that are walking, moderate-intensity activities and vigorous-intensity activities in a comprehensive set of domains including: leisure time physical activity, domestic and gardening (yard) activities, work-related physical activity and transport-related physical activity. The analysis is based on the total time spent on physical activity in the previous week (metabolic equivalent / minute).

### Biochemistry measurements

After an overnight fasting (10-12 hours) at 8:30 – 9:30 a.m. in the morning venous blood samples (20.0 mL) will be collected. Some haematological and immunological indexes will be assayed. The remaining blood is put into a dry tube for serum extraction and after analysed for biochemical profile characterization. Sera are transferred into clean microtubes in aliquots for determine proposed schedule of indexes measurement.

### Intervention

This open randomized control trial has three arms including two supplemented groups and one non-supplemented group. There will be a treatment period of 12 months and supplements consist of: Spirel®



capsules which contain 400 mg, the trial clinician will explain the use of capsules three times a day, preferentially one hour before meals and Vimang<sup>®</sup> bottles of aqueous extract with 25 g/L refers to Gallic acid, the trial clinician will explain the use of 10 mL of Vimang<sup>®</sup> aqueous extract twice a day, one hour before meals. Then, there will be 5 monthly visits at the end of 1<sup>st</sup>, 3<sup>rd</sup>, 5<sup>th</sup>, 9<sup>th</sup> and 11<sup>th</sup> months of study. During every monthly and follow up visit, the physician in turn will complete a brief history of the previous month, focusing on opportunistic infection incidence and occurrence of toxicity. A goal directed physical examination based on the taken history will be performed to evaluate the two subjects mentioned above. Physical examination will also include weight, height and blood pressure measurement. Determination of absolute count of CD4+ T lymphocyte and viral load will be repeated every 6 months at 6<sup>th</sup> and 12<sup>th</sup> visits in order to evaluate the trend of CD4+ T lymphocyte and viral load modification. The indexes values at baseline and that of each measure will be compared to determine whether could be any significant changes. Values of haematological and haemochemical indexes will also be measured in the visits.

This study will be open, implying that both participants and the conductors of the trial (individuals providing drugs to patients, those performing physical examinations and taking histories in addition to those in charge of performing lab tests) will be aware whether each patient is receiving Vimang<sup>®</sup>, or Spirel<sup>®</sup> or none.

### Measures of Compliance

The patients will be asked to bring the unused capsules back in the next monthly visit to determine their drug taking compliance. It will be determined as the proportion of unused capsules related to the total number of the capsules for each one antioxidant supplement or antiretroviral. Unused capsules number refers to capsule which were not taken by patients in the time schedule.

### Statistical Analysis

All analysis will be performed using SPSS software (Version 17, SPSS Inc., Chicago, IL, USA). Normality of data will be tested with the Kolmogorov-Smirnov test. A two-sided P value less than 0.05 was considered statistically significant.

### Conclusions

This is the first trial to investigate the effects of Vimang<sup>®</sup> and Spirel<sup>®</sup> supplementation concomitant to HAART on HIV patients. The authors hope that this study helps clarifying the effectiveness of these products modifying in different but beneficial mode on redox indexes; CD4+ T lymphocyte count, opportunistic infections and quality of life in patients with HIV delayed diagnosis.

### Ethics

The participants will be informed about the purpose and possible hazards of the trial and they will be free to leave the study at any time. Written informed consent is obtained from all of the participants before enrolling. The study is approved by ethics committee of Institute of Tropical Medicine Pedro Kouri in Havana Cuba (Project number 12-13-09). This trial has also been approved and registered at Cuban Ministry of Health (code: 131094).

### Effect Assessment

#### CD4+T lymphocytes count

The absolute count of peripheral blood CD4+ T lymphocytes is measured by flow cytometry method.

### Opportunistic infections

All infectious diseases and malignancies detected in immune compromised individuals like HIV infected individuals and are rare with normal immune system function and are clinically or par clinically diagnosed. In our study, these would be HSV infection, mycobacterial infections, Hairy leukoplakia, oral candidiasis, recurrent bacterial pneumonia, Kaposi's sarcoma and cervical cancer.

### Redox plasmatic indexes

Validated analytical techniques for redox diagnosis in humans according to international recommendations and reference values established in a healthy supposedly population. The methodology included spectrophotometer determination of biomolecules damage biomarkers (malondialdehyde, hydroperoxides and advanced oxidation protein products), antioxidant enzymes (superoxide dismutase, and catalase), total antioxidant status (ferric reducing ability of plasma) and non-enzymatic antioxidants (reduced glutathione) in plasma [29,30].

### Quality of life

The administration of the Spanish-language version of the Medical Outcomes Study (MOS) HIV Health Survey Questionnaire [31] to 170 patients recruited for the trials. MOS questionnaire were adapted from the version used in Mexico [32] to which one word were replaced with another of equivalent meaning.

### Trial Status

The trial was first designed and started at 2015. The study and subject recruitment is on-going. Accordingly randomization recruitment 75 patients were included, supplemented and followed during at least 8 months however biochemical assays and data analysis is still incomplete. Others patients will include since classification as delayed diagnosed were obtained and inclusion criteria are accomplished. The indexes and execution tasks are complimented as well as pre-consider, adherence to both antiretroviral and supplements are evaluated and also quality of life questionnaires. Final results are projected to December 2017.

### Trial Registration

This trial has been registered as associated project of MINSAP, code 131094.

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