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Long Term Outcomes of Anti-retroviral Treatment vs. Additional Nutritional Supplementation for HIV Patients

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by

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Abstract

The purpose of this systematic literature review is not to determine the best treatment for human immunodeficiency virus HIV but to analyze additional supplementation that can prolong the progression of the disease process. Zinc, vitamin A, D, and E will be evaluated additionally with the antiretroviral treatment ART. The cost of an ART Regimen can be very expensive and challenging for patients to afford. The goal is to find an acceptable option to complement ART with a sensible cost to prolong disease progression and minimize additional costs of health care. With the advances of ART, more and more patients can be managed by their primary care provider. This brings us to the importance of this literature review. The trials are randomized, longitudinal, observational, and placebo-controlled with randomized studies. All the studies were published within the last ten years. In this review, CD4 and viral load will be just a few of the markers that will be measured. Participants will range by gender, age, health status, and location. The data shows that the introduction of multivitamin supplementation has increased CD4 values and decreased viral loads. More studies need to be conducted, including many more vitamins in for a more definitive conclusion.

Keywords: HIV, HIV treatment, HIV antiretroviral resistance, zinc and HIV, Vitamin A and HIV, vitamin E & HIV, in vitamin D and HIV.

Introduction

In the United States, approximately 1.2 million people have been diagnosed with the human immunodeficiency virus (HIV). With the HIV population trending up yearly, care is becoming more efficient. Antiretroviral medications are increasing longevity and, primary care providers can manage the continuity of care in the clinic. This review will use the terms antiretroviral therapy ART and highly active antiretroviral therapy HAART interchangeably. This is due to the progression and efficiency of antiretroviral drugs. As this happened, the "highly active" portion began to drop off the classification. Many times, HIV patients are referred out to infectious disease for the management of treatment modalities. This action is still the recommended course of action with complex patients or an acute change in viral load. A harsh regimen of antiretroviral medications compounds these patients. The addition of nutritional support could help the longevity of their immune system to fight off any opportunistic infections. Nutritional support can take many forms, special diets, multi-vitamin, and specific vitamin supplementation.

Statement of the Problem

Patients diagnosed with HIV can develop acquired immunodeficiency syndrome (AIDS) if left untreated sooner than those who started antiretroviral medication with early detection and diagnosis. In addition, they may need to be treated for other comorbidities such as hepatitis, HIV-associated neurocognitive disorder, heart disease, diabetes, mental health issues, renal disorders, or chronic inflammation. The dangerous progression of HIV is categorized in stages based on the viral load and CD4 levels; stage one with CD4 cell counts >1,500, stage two CD4 cell counts 750-1,499, and stage three < 750 and becomes severely ill (Tsibris, n.d.). In the last stage (stage 3), the patient is diagnosed with AIDS, making them more susceptible to

opportunistic infections due to an immunocompromised state. It is hypothesized that the patient at all stages will have better protection from opportunistic infections with additional nutritional support.

Research Question

In adults over 40 diagnosed with HIV, does the addition of nutritional support (vitamins) with antiretroviral medication help the longevity more than the standard care of antiretroviral medication?

Methods

A comprehensive literature review was completed using databases such as Clinical Key, PubMed, and DynaMed. The keywords used-were HIV, HIV treatment failure, HIV antiretroviral resistance, Zinc and HIV, Vitamin A & HIV, Vitamin E and HIV, and Vitamin D and HIV. This led to further filtering search results to articles published within the last ten years. The search total resulted in approximately 50,000 articles. The results were further narrowed down by defining the adult population, vitamin-specific topics and eliminate nonhuman trials. The studies included were systematic reviews, peer-reviewed articles, and longitudinal studies. Many articles met the criteria. The studies were then review and chosen based on supplements used, and correlation to this topic. The ten studies that were chosen and included in this scholarly project looked at outcomes of standard anti-viral therapy and the possible benefits of additional nutritional supplementation.

Literature Review

The literature review shows that anti-retro viral treatment will be the mainstay treatment modality for the prophylactic or direct treatment with the goal for viral loads to be undetectable with a high level of CD4 cells. The treatment with antiretroviral medications can affect the serum levels of many essential nutrients contributing to a negative outcome related to the patient's health. With supplementation of these nutrients through diet and oral dosing, the patient can benefit from other immune benefits to increase overall health and well-being. This scholarly project will select a few vitamins that play an important role in immunity to discuss in detail.

Theme 1: Standard treatment for HIV

Human Immunodeficiency Virus HIV is a retrovirus that was introduced to the world around 1920 in Africa (Tsibris, n.d.). HIV has spread worldwide, infecting approximately 38 million people, of which 3.7 million are in the United States. According to the CDC the standard recommendation is to test all pregnant women, adults 15-65, and anyone with-risk behaviors (Tsibris, n.d.). The Centers of Disease Control and Prevention (CDC) recommends a 3-step test algorithm containing a confirmatory nucleic acid amplification test and two immunoassays. The standard treatment once diagnosed is 1-2 nucleoside reverse transcriptase inhibitors (NRTI) and an integrase strand transfer inhibitor (INSTI) congruent with treatment for pre-exposure prophylaxis (PrEP). Currently, two drugs are approved for PrEP use: Truvada and Discovy (Tsibris, n.d.). Postexposure prophylaxis will be given for a 28-day course and should include tenofovir plus emtricitabine and raltegravir or doleuegravir (Tsibris, n.d.). Antiretroviral therapy (ART) can also decrease transmission during pregnancy from mother to fetus. After treatment has begun, CD4 cell counts, and viral loads will be monitored routinely. CD4 levels need to stay above 500, if not it will increase the chance of opportunistic infections. If less than 200, it can be

diagnosed as Acquired Immunodeficiency Syndrome AIDS (Tsibris, n.d.). Monitoring these levels will define staging 0-4 for HIV progression. Lower CD4 levels expose patients to an increased risk from opportunistic infections, the leading cause of morbidity in HIV patients. Tuberculosis, Pneumocystis jiroveci pneumonia PJP, toxoplasmosis, and mycobacterium avium are just a few of the bacteria that can exacerbate an HIV diagnosis (Tsibris, n.d.).

INSIGHT START

The INSIGHT START Study Group is a randomized longitudinal trial to determine the risks and benefits of starting antiretroviral therapy in asymptomatic patients with HIV, who have a CD4 count of more than 350 cells per cubic millimeter. The study had 4685 patients who were followed for the mean of three years, with a median of 2.8 years, and 23 percent of patients were followed for more than four years (Lundgren et al., 2015). Four percent or 93 patients had no contact for data in at least ten months. The participants were at least 18 years old, had not started ART, and previous diagnosis of AIDS. 51.2% of the participants were above the age of 35. Patients were assigned treatment at their respected time at 215 sites in 35 counties. They had two CD4 counts of 500 cells per cubic millimeter at least two weeks apart within 60 days before the start of the study. Pregnant and breastfeeding women were among the exclusion criteria. Women that became pregnant during the study remained in the study group. Patients with CD4 counts of more than 500 were randomly assigned to start ART or wait until CD4 counts decreased to 350 cells per cubic millimeter. Then patients waited until the development of AIDS or any condition that dictated the use of ART (Lundgren et al., 2015). The median CD4 count was 651 cells per cubic millimeter, and HIV RNA viral load was 12,759 copies per milliliter. The median age was 36, and 27% of all patients were women. The primary endpoint was any AIDS-related event, that includes death form AIDS or any AIDS defining event. This occurred in

42 patients. The secondary endpoint included severe AIDS-related events, serious non-AIDS related events, death from any cause, grade four events (potentially life-threatening events not resulting from AIDS that require medical intervention), and unscheduled hospitalizations for reasons other than AIDS. In 2015 toward the end of the study, 98% of the immediate initiation group and 48% of the deferred initiation group used ART. The median CD4 count for the deferred initiation group was 408 cells per cubic millimeter, and the median time until initiation was three years. At the start of ART, the median HIV RNA levels were 13,462 for immediate initiation and 41,525 for deferred initiation (Lundgren et al., 2015). There was 98% full viral suppression for immediate initiation and 97% for deferred initiation at 12 months (Lundgren et al., 2015). The drugs that were primarily used for initial treatment in both groups were tenofovir (89% in both groups), emtricitabine (89% immediate and 88% deferred), and efavirenz (73% immediate and 51% deferred) (Lundgren et al., 2015).

The results for the study were as follows: The primary endpoint occurred in 42 patients in the immediate initiation group while 96 patients in the deferred initiation group. The hazard ratio is 0.43, 95% confidence interval CI, $P<0.001$. Hazard ratios for serious AIDS-related and serious non–AIDS-related events were 0.28, 95% CI, $P<0.001$ for the immediate initiation and 0.61, 95% CI, $P=0.04$ for the deferred initiation (Lundgren et al., 2015).

The authors of the study declared no affiliations and nonbiased. The study was conducted over 35 sites in different counties, and the patients were randomly chosen. The study group was small and was conducted over five years. The data was broken down into subgroups of age, sex, race, geographic region, smoker, Framingham risk, viral load, and CD4 count. The data was also broken down into primary and secondary endpoint illnesses. This data broke it

down into more sections than needed. It shows how ART is the standard treatment for HIV (Lundgren et al., 2015).

SMART Study

The progression of treatment in HIV with antiretroviral therapy has decreased morbidity and mortality. However, the problems with adherence, resistance, and adverse events have created barriers to treatment. The SMART study is a randomized trial researching the treatment of viral suppression versus episodic antiretroviral therapy use. Five thousand four hundred seventy-two participants were randomly assigned to groups of drug conservation (2720 patients) and viral suppression (2752 patients) (Lundgren et al., 2009). The viral suppression group was the control group and used the current guidelines for antiretroviral therapy. The drug conservation strategy group was based on CD4 thresholds. The antiretroviral therapy was deferred until CD4 counts were less than 250 cells per cubic millimeter and then would be initiated or reinitiated until the CD4 counts were greater than 350 cells per cubic millimeter. It also allowed the initiation of treatment if the participants developed symptomatic responses to HIV. The participants were older than 13 years of age and were not pregnant or breastfeeding, along with a CD4 count exceeding 350 cells per cubic millimeter. The primary endpoint was new or recurrent opportunistic disease or death. The CDC defines qualifying events as AIDS. Secondary endpoints included the death of any cause, serious opportunistic disease, significant cardiovascular, renal, or hepatic disease, and any grade 4 adverse events.

Before randomization, the patient's CD4 count, highest recorded plasma HIV RNA level, CD4 percentages, and HIV RNA baseline was obtained. Follow-up visits were scheduled at one and two months, every two months for the first year, and every four months in the second and subsequent years. At each visit, markers were obtained that consisted of CD4 count and HIV

RNA level. In addition, at each annual visit, a 12-lead EKG was completed (Lundgren et al., 2009).

January 10th, 2006, the board of the SMART study recommends stopping the enrollment of the SMART trial due to safety risks in the drug conservation group. It appeared to be very unlikely that the superiority of the drug conservation treatment would be shown. At this time, all participants were advised to restart antiretroviral therapy.

The diagnostic data was collected at the termination of the trial. The baseline median of CD4 counts was 597 per cubic millimeter for the viral suppression group and 250 per cubic millimeter for the drug conservation group. 71.7% of participants had plasma HIV RNA levels of 400 copies or less per milliliter (Lundgren et al., 2009). One hundred twenty participants in the drug conservation group and 47 participants in the viral suppression group suffered events from opportunistic diseases or death of any cause. The hazard ratio for the drug conservation group versus the viral suppression group had a 95% confidence interval, $P < 0.001$ (Lundgren et al., 2009). Hazard ratios for death from any cause were 95% confidence interval, $P = 0.007$ (Lundgren et al., 2009). Major cardiovascular, renal, and hepatic diseases were 95% confidence level, $P = 0.009$ (Lundgren et al., 2009).

The author group did receive consulting, advising, and lecture fees/grants from many drug companies, hospitals, and committee resources. Delineations of possible conflict of interests can be strained due to the study results and the fact that the study was abruptly terminated, that the conflicts of interest were minimal. There were compelling clinically significant results that the episodic antiretroviral strategy provided an excess risk for opportunistic disease or death of any cause. This study provided excellent information, and it had a broad age group and used many biometric markers. The downside to this article is that it

does not subdivide the patient population into ethnicities or geographic areas. However, these attributes are not needed for this article. Expanding on the external validity would lead to more data collection to see possible trends. This also proves that antiretroviral therapy is an excellent standard treatment, but compliance is needed to decrease risk (Lundgren et al., 2009).

Theme 2: HIV and Zinc

Zinc has a vital role in our cell's immunity. It helps decrease the production of oxidative stress byproducts malondialdehyde, 4-hydroxyalkenals, and 8-hydroxydeoxyguanine, as well as tumor necrosis factor (TNF) alpha and IL-1β (Shah et al., 2019). Zinc deficiency can be caused by multiple factors: chronic illness, malabsorption, depressed immunity, diarrhea, impaired host defense, and insufficient dietary intake. It is known that nutritional deficiencies adversely affect a patient's health outcome.

> A recent study conducted by Martinez [39] examined the effects of low serum zinc on HIV-infected patients afflicted with comorbid liver disease. Nearly 25% of HIV patients are co-infected with hepatitis C, which results in an accelerated progression to liver cirrhosis and hepatocellular carcinoma. In this study, 487 HIV-mono-infected and HIV-HCV co-infected individuals had blood draws periodically to measure plasma zinc and mitochondrial DNA 8-hydroxyguanosine levels to determine their relationship to oxidative damage and to calculate fibrosis-4 (FIB-4) scores to determine progression of liver disease. The authors concluded that lower plasma zinc levels were associated with increased mitochondrial oxidative stress and accelerated progression of liver fibrosis. (Shah K et al, 2019)

Zinc serum levels and C-reactive protein (CRP) levels to assess the role of zinc in inflammation of HIV patients. It was found that higher concentrations of zinc serum levels were associated

with lower levels of inflammation and lower levels of CRP, though the results were not statistically significant (Shah et al., 2019).

The authors are all geographically located on the east coast of the United States of America. The article had extensive general information about the role of zinc in the body inflammation process and the reactive oxygen species. This review was used to update the review that was published in Nutrition Research in 2007. It concluded that further studies needed to be done for a definitive result.

Zinc Supplementation and Inflammation in Treated HIV

The study is a randomized double-arm study; the participants were enrolled at University Hospitals Case Medical Center in Cleveland, OH, which was conducted to assess the effects of zinc supplementations on inflammatory markers in monocyte activation in HIV patients on ART. The 52 participants were 18 years or older, living with HIV in the United States (U.S.), with a zinc level lower than 75 ug/dL in the last 60 days. All participants had an HIV infection and were on ART for at least three months. Inclusion criteria of HIV RNA <400 copies/mL within the last four months prior to the study. Patients were excluded if they were pregnant, lactating, or had an infectious or inflammatory pathology. Other eliminating factors included uncontrolled diabetes and known cardiovascular disease. The Recommended Daily Allowance (RDA) for zinc intake is 11 milligrams (mg) for men and eight mg for women. Normal zinc serum levels range between 75-150 ug/dL. Zinc dosing, either 45 mg or 90 mg, was chosen due to its safe use in non-HIV studies for one year in duration. Zinc gluconate was used due to it being the most prescribed zinc supplement and the available safety data. Fasting blood draws were obtained and measured upon entry. At 16 weeks for monocyte activation soluble CD14, C-reactive protein, tumor necrosis alpha receptor I and II, lipopolysaccharide-binding protein, a marker of microbial

translocation, and a marker of gut integrity, intestinal fat acid-binding protein were measured by Enzyme-linked Immunosorbent Assay (ELASA). Zinc adherence and adverse events were assessed upon entry and weeks four, ten, and sixteen. The research was divided into groups, twenty-five participants were given zinc gluconate capsules at 45 mg (low dose) and 27 participants were given 90 mg (high dose) for 16 weeks. (Dirajlal-Fargo et al., 2019). After 16 weeks, biomarkers were reexamined. Patients were randomly assigned using statistical analysis system (SAS) software, 77% were male, and 73% were African American (Dirajlal-Fargo et al., 2019). The low dose arm participants were significantly older and had a longer duration of ART. All laboratory personnel were blinded to treatment assignments. After 16 weeks, there was a 94% retention rate, with one participant lost in the low dose arm and three participants lost in the high dose arm (Dirajlal-Fargo et al., 2019). 88% of the participants in the low dose arm and 96% of participants in the high dose arm reached zinc levels > 75 ug/dL (Dirajlal-Fargo et al., 2019). 48-60% of participants had a reduction in biomarkers. The circulating zinc levels increased from a median of 74 to 91 ug/dL in the low-dose arm and from 73-100 ug/dL in the high-dose arm (Dirajlal-Fargo et al., 2019). The margin of change overall for all markers ranged from 8-21% (Dirajlal-Fargo et al., 2019).

The authors are all physicians from the Cleveland and Columbus, Ohio area. There were no signs of conflict of interest or bias reported from the staff and personnel conducting the study. Strong external validity was assessed in this study due to an increased number of biometric markers, though there are no long-term data on the progression of disease processes. The study is a pilot study to look at the need for further investigation. The sample size was small, and the duration was short. The study also had primarily male and African American participants instead of a diverse group for the study. There were P values for the outcomes; thus, statically can be

proven. Novel data suggested a positive change in biometric markers, and biomarkers associated with other comorbidities.

Further studies need to be conducted. However, the values have shown that it can treat zinc deficiency while fighting inflammation, with increased gut epithelial barrier dysfunction. Thus, zinc supplementation would never be discouraged from the results of this data (Dirajlal-Fargo et al., 2019).

Theme 3: HIV and Vitamin A

An observational study suggests that micronutrient status is a factor in the advancement of HIV. The study enrolled 1,078 pregnant women infected with HIV in a double-blind placebo-controlled trial. The goal is to explore the outcomes of daily intake of vitamin A, beta carotene, B, C, and E supplementation. The study took place in Dar es Salaam, Tanzania, and enrollment was over two years. The median follow-up time was 71 months. All participants were randomly assigned to treatment. 271 to receive multivitamins B (20 mg B1, 20 mg B2, 25 mg B6, 100 mg niacin, 50 ug B12), C (500 mg), E (30 mg), and folic acid (0.8 mg) (Fawzi et al, 2004). 268 to receive multivitamins and vitamin A in the exact dosages as above. 272 to receive vitamin A (30 mg of beta carotene plus 5000 IU of vitamin A) alone. 267 to receive a placebo treatment. All treatments were oral dosing. Timing of treatment and other medications were not reported. All women received standard antenatal folic acid and iron. Upon delivery, the women in the two groups that received vitamin A were given an additional dose of vitamin A at 200,000 IU. In comparison, the women in the other two groups were given a placebo. All children received a dose of vitamin A every six months, according to the standard care of Tanzania. Overall compliance was measured by the number of tablets absent at the monthly visits. It was also documented that no participants were currently on ART. Monthly visits where data was collected

were conducted at a study clinic where a history and physical exam were performed to assess for signs of HIV-related complications. HIV was determined by stage per the-World Health Organization (WHO) criteria based on the history and physical exam. For women who were was unable to attend the clinic, home visits were conducted. Neighbors and relatives were asked about the vital status. No data or complications were collected at these visits. Verbal-autopsy techniques were used to approximate any cause of death. Any cause of death that could not be explained was considered unrelated to AIDS. Three hundred forty-three women died during follow-up, while 243 were related to AIDS, 82 were due to AIDS, 61 to pulmonary tuberculosis, three to extrapulmonary tuberculosis, 10 to anemia, 14 to meningitis, five to stroke, 23 to pneumonia, 21 to diarrhea, and 24 to fever (Fawzi et al., 2004). Blood samples were assessed at baseline and every six months, focusing on T-cells subgroups (CD4, CD 8, and CD3). A random sample of 300 women were selected to examine the effects of supplements on viral load. Blood samples were taken at baseline, time of selection, and midpoint between the two for these women. The viral load was quantified using Roche Amplicor 1.5 assay, with a mean of 2.8+/-1.5.

The results showed that multivitamin supplements delayed the progression of HIV and provided an effective, low-cost means of delaying initial ART in HIV-infected women (Fawzi et al., 2004). A total of 299 women progressed to stage 4 in compliance with WHO standards: of which 67 of the women received multivitamins, 70 women received multivitamins plus vitamin A, and 79 women received vitamin A alone, and 83 women received the placebo (Fawzi et al., 2004). The group that received multivitamins were less likely to progress to stage 4 than the placebo group (relative risk 0.71; 95% CI, P=0.04) (Fawzi et al., 2004). The multivitamin group also had beneficial effects on outcomes of advanced disease, including progression to stage 4

(relative risk 0.50; 95% CI; P=0.02) or progression to stage 3 or higher (relative risk 0.72; 95% CI; P=0.003) (Fawzi et al., 2004). The multivitamins had more of a productive effect in the first two years, although effects were also seen at four years. Vitamin A did not have any significant benefits on reducing oral ingestion gastrointestinal manifestations of HIV or fatigue, rash, and acute upper respiratory tract infections. The CD4 counts were higher by 48 cells per cubic millimeter among the group that took multivitamins than the placebo group (95% CI, P=0.01) (Fawzi et al., 2004). The viral load was lower in the group who received multivitamins (95% CI, P=0.02), though the addition of vitamin A with the multivitamin reduced the benefits (95%CI, P=0.40) (Fawzi et al., 2004). In a secondary analysis, vitamin A is compared with the absence of vitamin A on the likelihood to progress to stage 4 with no significant effect (95%, P=0.16), stage 3 (95% CI, p=0.05), and stage 2 (95% CI, p=0.01) (Fawzi et al., 2004). Women who receive multivitamins had higher CD4 counts (95% CI, P=0.01) and lower viral loads (95% CI, P=0.02) compared to vitamin A CD4 (95% CI, P=0.30) and viral load (95% CI, P=0.68) (Fawzi et al., 2004).

The multivitamins that contain vitamin B complex, vitamin C, vitamin D, and vitamin E delayed the progression of HIV in affected women. Vitamin A alone had weaker effects, and results were not significantly different and those of the placebo. The use of multivitamins also reduced the incidents of oral ulcers, oral thrush, difficulty swallowing, vomiting, nausea, and diarrhea. In addition, lower viral loads in higher CD 4, CD 8, and CD3 cell counts were observed using multivitamins than in the placebo (Fawzi et al., 2004).

The authors did not report any conflict of interest or acceptance of funding from any hospital, drug company, or foundation. The authors had a diverse educational background consisting of Ph.D.'s, M.D.'s, Doctor of Science, and master’s in biology. The group worked in

many different departments such as nutritional Epidemiology, Biostatistics, Immunology, Harvard School of Public Health, Community Health, Microbiology, Internal Medicine, and Muhimbili University College of Health Sciences, Dar es Salaam, Tanzania. The study was unbiased, and the data was gathered in a standardized manner. The clinical significance was evident. However, the scientific data resulted opposite of what was hypothesized, and much information was gained from the study.

Mixed Carotenoids and Micronutrients

This study evaluated the supplementation of mixed carotenoids and the effects on the health and survival of AIDS patients. This is a prospective, placebo-controlled, double-blind, randomized, multicenter trial. The trial contained 331 adults with all participants being at least 18 years old, HIV seropositive, and at risk for progression of HIV. Disease progression was measured by CD4 T-lymphocyte counts and plasma HIV-1 viremia levels. Patients were excluded if CD4 T-lymphocyte counts showed improvement with protease inhibitor anti-HIV therapy, had missed two earlier clinic appointments, had acute opportunistic infection, or had severe pre-existing hepatic dysfunction. They were randomly chosen using a computer program to be placed into two groups (Austin et al., 2006).

Both groups received daily oral formulated multivitamins including vitamin A, trace elements, and a prior treatment plan. Group One being 166 participants that received daily oral multivitamins including vitamin A and trace elements and served as the control group. Group 2 being 165 participants that received daily oral naturally mixed carotenoids equivalent to 120,000 International Unit (I.U.), beta carotene daily (Austin et al., 2006). Augmentation was acquired in two forms, carotenoids and multivitamins or Co formulated into one tablet. Both groups' tablets looked identical and were taken twice a day or four tablets a day. In the beginning, the daily

dose of medication was measured by assays to be 88% of the formulated dose and had reduced to 13% of beta carotene during the study. This is still several times larger than the recommended estimated daily intake. A complete medical history, previous diagnosed medical conditions, medications taken, and opportunistic infections were assessed at the baseline visit. In addition, a physical exam, CD4, CD8, plasma HIV-1 viral load, and carotene levels were obtained. As mentioned previously, participants were examined quarterly, and laboratory tests were retained and were valid within 30 days of the quarterly appointment. The medications were dispensed quarterly, and self-adherence was reported.

278 (84%) participants were tested at the end of the study due to many reasons (Austin et al., 2006). Thirty-six deaths occurred, 13 from the carotenoid treatment group and 23 from the control group (Austin et al., 2006). Twenty-five in the carotenoid group and 36 in the control group had a new or recurrent age-defining event or death. In both groups, there was no significant difference in the number of participants hospitalized for reasons not related to AIDS-defining illness (95% CI, P=0.99) or experiencing new or recurrent episodes of AIDS-defining illness (95% CI, P=0.56) (Austin et al., 2006). Serum carotene concentration showed a statistically significant increase from baseline with carotenoids treatment at three months ($P<0.0001$), six months ($P<0.0001$), nine months ($P<0.0001$), 12 months ($P<0.0007$), and 18 months ($P<0.001$) (Austin, J. et al., 2006). CD4 T-lymphocyte count showed a statistically significant increase from baseline with carotenoids treatment at 12 months (P=0.04), 15 months (P=0.007), and 18 months (P=0.008) (Austin, J. et al., 2006). Plasma viral load showed no change with carotenoids treatment. The control group showed a risk of increased death than the carotenoids treatment group (95% CI, P=0.03) (Austin et al., 2006). The participants with higher serum carotene had a statistically significant reduction of risk of death (95% CI, P=0.04) (Austin

et al., 2006). There is also a reduced risk of death with higher baseline CD4 counts (95% CI, P=0.005, per 25 cells increase) (Austin et al., 2006). Effects of other predictors, death, or new or recurrent age-defining event or baseline ART were insignificant.

The authors were all physicians from different sites. No bias or conflict of interest was discovered during this study. The study provided useable knowledge; it showed baseline carotene concentrations were low. The flaws with the study came from the lack of dosing consistency throughout and the abrupt termination of the trial. Even with the premature termination of the trial, data were collected for carotene levels up to 18 months. It showed the importance of carotene in the diet with the increased carotene, CD4 levels, and risk reduction of AIDS-related illness or death (Austin et al., 2006). This study demonstrated through statically significant data greater importance for augmentation with carotene over vitamin A supplementation. In correlation with previous studies, this research study will assist providers with a better understanding of the importance of nutritional supplementation management in HIV patients.

Theme 4: HIV and Vitamin E

This is a cross-sectional study conducted with 182 participants that are HIV positive men and women from ages 20 to 59 years old, with a CD4 count > 200 cells per cubic milliliter and has received ART for at least six months (Kaio et al., 2014). The study took place in Brazil at the AIDS treatment referral center. Participants were excluded due to pregnancy, cancer, acute infections, use of minerals in vitamins, recent surgery, unavailable lab data, motor deficits impairing physical examinations, and mental conditions that could interfere with the ability to be interviewed. Participants had to complete a socioeconomic, lifestyle, biochemical, immunological, clinical, and ART data questionnaire. Labs could be used up to six months

before the entry of the study. In addition, height and weight were measured, and nutritional status was assessed as Body Mass Index (BMI). ART regiments were divided into three groups: two nucleoside analog reverse-transcriptase inhibitors (NRTIs) and one non-nucleoside analog reverse-transcriptase inhibitor (NNRTI); 2 NRTIs and one protease inhibitor (P.I.) plus ritonavir; two NRTIs and other classes including fusion inhibitors, integrase inhibitors, entry inhibitors, and P.I.'s plus fusion inhibitors, integrase inhibitors, entry inhibitors. With the NRTIs plus NNRTIs being the reference group. Compliance is considered 95% of medication taken during the last three days before application to study (Kaio et al., 2014). Blood samples were taken after a 12 hour fast in a dim-lit room to prevent degradation of vitamin E. Samples were then centrifuged at 3000 Revolution Per Minute (RPMs) for 15 minutes then stored at 80 degrees Celsius until analysis. Alpha-tocopherol levels were measured because it is the most active form of vitamin E. Total cholesterol and triglycerides were measured by cholesterol oxidase-phenol ampyrone and glycerol phosphate oxidase-phenol ampyrone colorimetric enzymatic methods. CD4 in viral loads was also monitored. Baseline cholesterol, triglycerides, CD4 levels, BMI, and clinical comorbidities were used as control variables.

The results showed a significate decrease of a 4.12 omul/L decrease in mean alpha-tocopherol concentrations (P.0.037) (Kaio et al., 2014). Significant differences were observed between alpha-tocopherol concentrations in cholesterol ($P<0.001$) (Kaio et al., 2014). The average increase of 0.082 umol/L per 1 mg/dL increase in cholesterol. The ART regimen, duration, and compliance were responsible for 19% of the variations in alpha-tocopherol. This is solid evidence that ART will cause a decline in alpha-tocopherol levels. It is possible that HIV patients will benefit from vitamin E supplementation while on ART, especially on NRTI, with

other classes. More studies are needed to investigate further the association between ART, infection, and vitamin depletion.

The authors consisted of physicians and nutritionists, which were all located in Brazil. After the completion of reviewing this study, there was no bias or conflict of interest. The study was funded through the Department of Nutrition and the Department of Medicine at Federal university. Although the study was completed well, it offered other biomarkers that have not been used before. The cholesterol values added new information to the absorption and use of vitamin E as alpha-tocopherol. Some of the participants were older, which vitamin E values were different. This allowed the results of CD4 counts not to be used. Another group divided by age may have solved this problem (Kaio et al., 2014).

Vitamin A and E

This non-concurrent prospective study looked at any associations between vitamin A and E serum levels and the risk of HIV infection, first AIDS diagnosis, CD4 cell decline < 200 cells per cubic milliliter, immortality (Tang et al., 1997). Three hundred twelve study participants were HIV-1 infected homo-/bisexual men in the Baltimore/Washington, DC site of the Multicenter AIDS Cohort Study. C-reactive protein and serum albumin levels were collected in 308 of the participants. The serum albumin was calculated using a colorimetric assay, with ranges of 35-50 g/l. C-reactive protein (CRP) levels were calculated using enzyme-linked immunosorbent assay, and levels below 8.0 mg/l were considered normal, and above 8.0 mg/l were considered elevated. The variables were based on data collection at each clinic visit. Dietary intake was assessed by self-administered food frequency questionnaires, which consisted of frequency of consumption and portion size in the last 12 months. Brand name of foods, amount of vitamin supplements taken, unlisted foods, types of fat used for cooking and baking

were also documented. A nutrient analysis program developed for this questionnaire determined food and supplements combined with vitamin A and E. HIV-1 serostatus was determined by enzyme immunoassay and a western blot test. Subjects were then divided into three categories based on CD4 levels at the time of entry: <500, 500-750, and >750 sales per cubic milliliter (Tang, A. et al., 1997). Body mass index was calculated. HIV-related symptoms were defined as one or more of the following lasting two or more weeks: persistent/recurring fever > 37.8°C, oral thrush, persistent diarrhea, persistent fatigue, and unintentional weight loss of 4.5 kg. Alcohol consumption was divided into two categories: less than or equal to two times per week and more than twice per week. Participants were placed into two categories based on their smoking status: smoking/non-smoking. Data was also collected on the use of antiretroviral drugs and pneumocystis carinii new pneumonia prophylaxis before the onset of AIDS. Three outcomes were examined, including time from baseline to first CD4 cell count < 200 sales per cubic milliliter, time from baseline to death, and time from baseline to first AIDS diagnosis.

Out of the 312 men in this study, the mean age was 34 years old, while the range was 30-65. The mean CD4 count was 643 +/- 314 cells per cubic milliliter (Tang et al., 1997). 81% of the participants were asymptomatic with their current infection, 55% had elevated CRP levels, and 23% had low albumin levels. Over the nine-year study, 163 (51%) men progressed to AIDS, 162 (52%) died, and 180 (58%) reached CD4 cell count lower than 200 cells per cubic milliliter (Tang et al., 1997). Only 271 participants returned the food frequency questionnaire. Vitamin A serum levels were not dependent on vitamin A intake from food (P=0.72) or food and supplements together (P=0.74) (Tang, A. et al., 1997). The correlation of serum vitamin E in vitamin E intake from food was not significant (P=0.29) and in serum vitamin E and intake from food and supplement vitamin E (P=0.0001) (Tang, A. et al., 1997). In the highest quartile,

vitamin E (>23.5 umol/l) shows a 34% decrease in risk of progression to AIDS compared to those in the lowest quartile (95% CI, P = 0.41-1.06) (Tang, A. et al., 1997). This was significant when comparing the highest quartile vitamin E to the remainder of the cohort (95% CI, 0.45-0.98) (Tang et al., 1997). The risk of progression to AIDS with vitamin A is unclear during this study. Vitamin A levels were uniformly in normal high ranges. Neither vitamin had any association with CD4 cell decline to < 200 sales per cubic milliliter. The study showed that high serum levels of vitamin E could be associated with slower HIV-1 progression. There was no relationship between vitamin A and disease progression (Tang et al., 1997).

The authors of this study were all physicians and were funded by government grants. There were no signs of bias or conflicts of interest that could be found during this study. This study was helpful to show once again the vitamin A was not a necessary vitamin needed for decreasing the risk of progression of HIV. Vitamin E was shown again to be statistically significant with a stronger association, and with reduced progression, it would make it more beneficial to use as a dietary supplement (Tang et al., 1997). The study was conducted well, and it was the longest study (nine years) used in this scholarly project. The participants were gathered from another study group that coincided with the parameters of this study. Better data collection for diet and nutrient intake other than the diet questionnaire was needed. Less room for error if nutrient intake were taken from a controlled environment set by the study.

Theme 5: HIV and Vitamin D

Antiretroviral therapy may create risk factors for vitamin D insufficiency by changing vitamin D metabolism. This study looks at clinical parameters between vitamin D sufficient and insufficient HIV-infected patients (Coelho et al., 2015). It observes the changing parameters and insufficient patients after standardized vitamin D supplementations. Participants were enrolled

from an HIV clinic at Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation in Rio de Janeiro, Brazil. Vitamin D insufficiency was screened on patients between January 2011 and December 2013. Patients in this study were on ART as two nucleoside reverse transcriptase inhibitors (NRTI) in combination with at least one protease inhibitor (P.I.) or non-nucleoside reverse transcriptase inhibitor (NNRTI) for at least six months before entry (Coelho et al. 2015). HIV RNA level must be <50 copies/mL upon entry. Participants receiving > 400 IU vitamin D supplementation were excluded from participation. Participants had 25-hydroxyvitamins D3 (25(O.H.) D) measured by chemiluminescence assay. Vitamin D sufficiency was defined as 25(O.H.) D > 30 ng/mL and insufficiency by < 30 ng/mL (Coelho et al. 2015). Insufficient patients were given vitamin D3 (cholecalciferol) supplementations and checked every 12 weeks for 24 weeks. The group that had sufficient 25(O.H.) D were to serve as the control group and did not require additional follow-up. The insufficient group was assessed for adherence and tolerability by self-reporting and pill counts at each visit. Lumbar spine and femoral neck Z scores from DEXA scans were used to evaluate any presence of osteoporosis or osteopenia. The insufficient group was given vitamin D3 supplementation dosages of 50,000 IU orally twice weekly for five weeks and then given 8000 IU twice a week for 19 weeks (Coelho et al. 2015). Lipid profile, glycosylated hemoglobin, CD4 count, HIV RNA viral load, and fasting glucose were measured at baseline and 24 weeks. The primary endpoint was success or failure to achieve 25 (O.H.) D > 30 ng/mL after 24 weeks with vitamin D3 supplementation. The secondary endpoint was based on associations between socio-demographic and clinical features at baseline and 24-week 25(O.H.) D levels and the effects of vitamin D3 on metabolic and immunological parameters (CRP, glucose, HbA1c, triglycerides, cholesterol, BMI, and CD4).

Ninety-nine patients were enrolled, one was lost due to lack of follow-up, one withdrew consent, which left 97 participants for the net N of the study (Coelho et al. 2015). Sixty-three percent of the remaining patients had vitamin D insufficiency and started supplementation, while 34 patients were vitamin D sufficient and were considered the control group. The median age group of the participants was 45 years. The insufficient group had a mean CD4 count of 688, sufficient mean of 650, and total with a median CD4 count of 673 cells per cubic millimeter. The median time of ART was five years, and the most common agents were tenofovir (71%) and efavirenz (70%) (Coelho et al., 2015).

At 24 weeks, vitamin D3 supplementation was successful in the insufficient population to raise 25 (O.H.) D levels > 30 ng/mL in 83% of the patients (Coelho et al. 2015). Participants were classified as 24-week non-responders or repletion responders. With the median 26 ng/mL of 25 (OH)D 26 ng/mL for non-responders and 47 ng/mL 25 (OH)D for repletion responders. Responders demonstrated a 17.9 ng/mL higher 24-week serum 25 (O.H.) D with current efavirenz use (P=0.01) (Coelho et al. 2015). Protease inhibitor use showed a 16.2 ng/mL decrease in week 24 serum of 25 (O.H.) D (P=0.007) (Coelho et al. 2015). Week 24 CD4 counts were increased (median 712 cells/mm3) in both groups compared to baseline (P=0.01) (Coelho et al. 2015). With each 1.0 ng/mL increase in 25 (O.H.) D with the repletion therapy, there was a 3.3 cell/mm3 increase in CD4 count (P=0.06) (Coelho et al. 2015).

Repleting 25 (O.H.) D levels after 24 weeks was effective. Efavirenz was associated with increased post repletion 25 (O.H.) D levels. No other antiretroviral agents showed significant associations. Zidovudine was associated with lower post repletion 25 (O.H.) D levels (P=0.05) (Coelho et al. 2015). There is a link between CD4 recovery in vitamin D repletion. The correlation of CD4 counts and increased 25 (O.H.) D would suggest the benefit of vitamin D

supplementations during ART (Coelho et al. 2015). However, further data would need to be acquired for a definitive answer.

The authors consisted of Ph.D.'s, chemists, nutritionists, and pharmaceutical professors at various universities in Brazil. No bias or conflict of interests could be determined. The study showed good evidence for the need for vitamin D supplementation in the HIV population. The study's limitations could be assessed due to the small sample size (Coelho et al., 2015). It can be difficult to link all ART agents in metabolic parameters. Dexa scans were only available to a subset of the participants; it does not represent randomization or data for the whole group (Coelho et al., 2015). Assessing adherence could not be strictly studied due to possible patient misrepresentation. The immunological, metabolic parameters evaluated were limited to those routinely done in Brazil.

A longitudinal study

This study looks at HIV patients to find any possible links between vitamin D deficiency (VDD), insufficiency (VDI), and sufficiency (VDS) (Ezeamama et al., 2016). It also assesses any CD4 cell count improvement over 18 months of highly active antiretroviral therapy (HAART). Participants were HIV-positive men and-non-pregnant women above the age of 18 that had not started Highly Active Antiretroviral Therapy (HAART) or for no longer than six months. Each participant lived within 20 Kilometers (km) of the research facility in Uganda. Participants excluded from the trial were seriously ill, pregnant women, and unable or unwilling to provide informed consent. CD4 counts were measured at baseline, three, six, 12, and 18 months as a primary indicator of urban mean recovery (Ezeamama et al., 2016). Vitamin D levels 25(O.H.) D were measured at baseline by high-performance liquid chromatography-tandem mass spectrometry. Three vitamin D levels were defined as VDD if 25(O.H.) D $\leq$ 20

ng/ml, VDI if 25(O.H.) D > 20 but < 32 ng/ml, and vitamin-D sufficient (VDS) if 25(O.H.) D ≥ 32 ng/ml with VDS (Ezeamama et al., 2016). Standardized questionnaires were used to collect socio-demographic, health, and clinical data at enrollment, three, six, 12, and 18 months. BMI, anemia, marital status, income, sex, smoking status, supplementation of vitamins B, C, and E, and placebo were all examined to the relationship of vitamin D and CD4 count status (Ezeamama et al., 2016).

The study included 398 patients. Of the patient population, 50% had not started HAART. Of the group that had started treatment, 62.8% were on nevirapine and 35.7% on efavirenz. Most of the population (73%) were female, 54% had elementary or lower education, and 77% were VDI or VDD at enrollment (Ezeamama et al., 2016). Absolute CD4 counts were persistently lower in patients that were VDD/VDI compared to HIV patients that were VDS upon entry to the study. The CD4 counts were recovered and significantly increased in the VDD/VDI group by age (P=0.009), younger than 35 (Ezeamama et al., 2016). The CD4 counts were also significant with recovered VDD/VDI with a BMI lower than 25 (P=0.044) (Ezeamama et al., 2016). The average at baseline was 150; by month 18, the average had doubled to the mean of 300 with the patients that continued their HAART. While all three groups increased CD4 levels, VDD and VDI increases were consistently lower compared to VDS.

The author group consisted of physicians, nutritionists, and statistics professors from the University of Georgia, Uganda, Harvard School of Medicine, public health, and the Department of Nutrition of Georgia. There were no signs of bias or conflicts of interest during this study. The study provided information in relationships with age and nutritional status in vitamin D deficient patients and immune recovery. Further studies need to be conducted to confirm

efficacy. Nevertheless, data collected from this study shows strong evidence that vitamin D supplementation can increase vitamin D levels and CD4 counts (Ezeamama et al., 2016).

Discussion

The current recommendations for primary treatment of HIV are one to two nucleoside reverse transcriptase inhibitors plus an integrase strand transfer inhibitor. Treatment then can be altered to set the patient's needs or to meet the resistance level. One hundred percent adherence to antiretroviral therapy is necessary for viral load suppression and CD4 elevation.
For pre-exposure prophylaxis (PrEP), two antiretroviral agents are currently FADA approved (Truvada and Descovy). Have these medications are required to be taken daily.

In the INSIGHT START trial, randomly assigned HIV patience who had a CD 4 count greater than 500 cells per cubic millimeter to start antiretroviral therapy immediately, four to defer until CD 4 counts decreased to 350 cells per cubic millimeter. The three-year study showed benefit in immediately initiating antiretroviral therapy in viral load levels, CD4 counts, time to first primary event, serious AIDS-related event, death from any cause, and grade 4 events. In addition, this study resulted in benefits from beginning antiretroviral therapy at any CD level.

The SMART trial looked at the differences between antiretroviral therapy for continuous use versus episodic use according to the CD4 levels less than 250 per cubic millimeter. The episodic therapy was continued until CD4 counts increased to more than 350 per cubic millimeter. During the 44-month study data from CD4 counts, disease or death of any cause, any significant cardiovascular, renal, or hepatic disease development, and grade 4 adverse events were collected. It was shown that episodic use of antiretroviral therapy guided by CD4 values

significantly increased the risk of opportunistic diseases and death compared to continuous therapy.

Zinc

Zinc plays a vital role in cellular immunity. It can decrease the production of oxidative stress in the body. It can occur by insufficient intake, chronic illness such as HIV, malabsorption, and depressed immunity. A study conducted by Martinez has shown low serum zinc in HIV patience with hepatic disease. This study demonstrated the HIV-infected patients that we're currently on ART with a CD4 count <200 with viral load <40 copies had a statistically significant increase in CD4 count with zincs implementation in deficient patients.

The study done by Dirajal-Fargo and others was a pilot study conducted to show the effectiveness of zinc supplementation on circulating zinc levels. It has shown benefits in circulating zinc levels in people living with HIV. The study concluded with an increase in biomarkers associated with clinical comorbidities: C reactive protein (Inflammatory marker), tumor necrosis factor I and II, CD14, and lipopolysaccharide-binding protein (a marker of microbial translocation, marker of gut integrity, intestinal fatty acid-binding protein). All levels were decreased by 8 - 21%.

Both studies have shown benefit in zinc supplementation in people living with HIV. Circulating zinc level also increased during both studies. The increase in CD4 levels shown by Martinez and the increase in the biomarkers shown by Dirajal-Fargo can reason the start of zinc supplementation.

Vitamin A

The study that Fawzi conducted looked at the supplementation of vitamin A (Vitamin A and beta carotene), multivitamins (vitamin B, C, and E), or both on the progression of HIV. This

study looked at the risk of death related to AIDS, progression to WHO stage 4 and stage 3. The results showed that multivitamin use alone increased CD4 and CD8 counts. Vitamin A taken alone had lower benefits and was not statistically significant. Multivitamins with the help of vitamin A showed benefits in these values. The benefits of combined use were less than multivitamin use alone.

Beta carotene is an isomer and is a precursor to vitamin A. The study completed by Austin looked at the use of supplemental mixed carotenoids to improve the health and survival of AIDS patients. At the beginning of this study, serum carotene, CD4 counts, and viral load copies were evaluated. While the probability of survival was not statistically significant, mixed carotenoid treatment did show benefit over the placebo.

Vitamin A was not shown to have benefit on CD4 levels. It was shown that the multivitamin (vitamin B, C, and E) use was more beneficial than when combined with vitamin A and beta carotene. Beta carotene did show benefit alone without vitamin A, which stands to reason the use in supplementation.

Vitamin E

The goal of this study that was done by Kaio was to evaluate serum concentrations of alpha-tocopherol in patients receiving different ART regimens. The study showed a decrease of 4.12 umol/L in alpha-tocopherol levels on ART, especially with new medications. Alpha-tocopherol increased on average of 0.082 umol/L per 1 mg/dL increase in cholesterol. This could be since Vitamin E is a liposoluble compound.

A study by Tang evaluated the associations between vitamin A and E in the progression of HIV. The target values looked upon were at first AIDS diagnosis, CD4 <200 cells per cubic

milliliter, and mortality. This study showed benefits to the supplementation of vitamin E on the progression of HIV. However, no benefits were associated with vitamin A.

Evidence shows that ART will decrease alpha-tocopherol levels. Diet and supplementation can increase serum alpha-tocopherol and decrease the progression to AIDS by 34 %. The study completed by Tang also show no benefit from vitamin A, which correlates with the study completed by Austin above.

Vitamin D

HIV infection and ART can cause vitamin insufficiency and alterations of vitamin D metabolism. The study completed by Coelho looked at the repletion of vitamin D while on ART. At the beginning of the study, fasting glucose, lipid profile, 25(O.H.) D, CD4 counts, and viral load were assessed and then again at 24 weeks. Overall supplementation shows affective in repeating vitamin D levels. Though ART can play a role in the repletion. The antiretroviral medications that were used in this trial are not appropriate to the current guidelines. It showed that certain medications took longer and had a lower post-repletion level.

A study by Exeamama focused on HIV-positive patients evaluated vitamin D deficiency and insufficiency versus sufficiency and CD4 count improvements over 18 months of ART. It also showed that vitamin D deficiency in HIV patients is associated with lower CD4 counts. The results showed the benefits of vitamin D supplementations in these patients. The CD4 counts increased for all patients in this study.

The repletion of vitamin D has been shown by Coelho while on ART. It has also been shown that patients deficient, insufficient, and sufficient can benefit from Vitamin D supplementation when ART is not present. CD4 counts increased in both treatment pathways.

Conclusion

The information that has been evaluated has determined the primary course of treatment for HIV. The studies above have shown benefits with the addition of supplementation of zinc, vitamin E, A, D, along with a multivitamin (vitamin B, C, and E). It has been demonstrated that beta carotene benefits CD4 counts and viral loads over vitamin A. Some of the studies have results without ART, which is unlikely for today's standards. More importantly, there were no adverse effects of vitamin supplementation used during the studies. The increase in alpha-tocopherol with an increase in cholesterol and show importance for the need of a balanced diet for the liposoluble vitamins. More current studies are needed to show the application of supplementation with current ART protocols and medications. Long term cohort studies could show these benefits, along with case control studies to show direct results of supplementation compared to the control group. Prevention trials could be conducted as newly HIV diagnosed patients can be given supplementation prophylactically to study the affects of ART on vitamin deficiency. If carefully planned some of these trials may be done congruently.

Applicability to Clinical Practice

Providers can help counsel HIV patients to start a multivitamin supplementation for increased longevity with the information given. This can possibly increase life expectancy and prolong progression to AIDS or other comorbidities. This is an inexpensive option that can provide benefits to the patient without any adverse side effects. If the patient cannot afford the over-the-counter supplementation, then the provider has evidence to supply insurance companies or other assistance programs to help support the patient. Prenatal vitamins may be another option.

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