

Micronutrient Synergy in the Control of HIV Infection and AIDS

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1. Introduction

Acquired immune deficiency syndrome (AIDS) has become a global health pandemic and the most common cause of death among young adults aged 20-24 years (Patton et al., 2009). According to the UN/AIDS Global Report published in November 2010 (UNAIDS 2010), about 1.8 million persons died from AIDS-related causes in the year 2009 alone. At the end of that year, the epidemic had left behind totally 16.6 million orphans, defined as those under 18 who had lost one or both parents to AIDS. Since the beginning of the epidemic, nearly 30 million people have died from AIDS-related causes.

At the end of 2009, an estimated 30.8 million adults and 2.8 million children were living with HIV, the human immunodeficiency virus linked to AIDS; with women accounting for just over one-half of all adults living with HIV worldwide. During the same year, about 2.6 million persons became newly infected with HIV, including 370,000 children. Of all people living with HIV, about 68% reside in Sub-Saharan Africa (UNAIDS 2010).

Despite these gruesome statistics, there is no cure in sight. Current treatment is based on the use of antiretroviral (ARV) drugs targeted against HIV at various steps in viral replication (Sleasman and Goodenow 2003). Although ARV drugs can reduce viral load in the bloodstream, they neither cure HIV infection nor restore the immune system to combat AIDS (Roederer 1998, Pakker et al., 1998). Virus is known to persist indefinitely in reservoirs of latently-infected cells and emergence of drug-resistant strains is common. Furthermore, the effectiveness of ARVs in having any clinical benefits at all depends upon a number of factors, particularly the CD4 count and the nutritional status of patients at the point at which ARV treatment is commenced (Hong et al., 2001, Paton et al., 2006). Additionally, drugs are highly toxic and are often associated with adverse side effects to various organs of the body, including the bone marrow and liver, (Fischl et al., 1987, Richman et al., 1987, Costello et al., 1988, Abrescia et al., 2008), cellular mitochondria (Carr et al., 2001), and with lipodystrophy and dyslipidemia (Carr et al., 1998).

Consequently, there is need for safe and effective, nontoxic therapy that can not only restore the immune system and keep virus multiplication/spread in check but also block AIDS progression without harming cells of the host. This review will focus on the relationship of nutrition to infection and immunity and evidence from experimental and clinical studies on the potential value of micronutrients and their combinations in controlling HIV infection and reducing symptoms associated with AIDS.

2. Nutritional deficiencies in HIV and AIDS

The relationship between nutrition, infection and immunity is well established since the early 1940's (Scrimshaw 2003, Webb and Villamor 2007). It is for instance well recognized that nutritional deficiency can lower immunity and predispose individuals to microbial infection. Conversely, nutritional supplementation can improve immune function and prevent/confer resistance to infection.

As the latent period between HIV infection and AIDS manifestation has been estimated at 8-10 years (Morgan et al 2002), nutritional cofactors, besides HIV, have been implicated in AIDS development (Beach et al., 1992, Baum et al., 1995, Jariwalla et al., 2008a, 2009). Furthermore, nutrient supplementation in asymptomatic HIV-infected individuals was shown to delay the onset of AIDS (Abrams et al., 1993, Tang et al., 1993), supporting involvement of nutritional status as a contributory factor in AIDS development.

It is universally known since the emergence of the AIDS epidemic in the early 1980's that nutritional deficiencies are prevalent in persons with HIV infection and AIDS (Gray 1984, Beach et al., 1992, Jariwalla 1995; see also Table 1). These deficits include: (i) specific micronutrient abnormalities such as reduced blood levels of the common ACE vitamins, minerals, trace elements including selenium, amino acids such as cysteine, and the tri-peptide glutathione, which displays a global systemic deficiency; (ii) macronutrient abnormalities such as protein calorie malnutrition, which has been linked to a wasting disease, characteristic of AIDS. Malnutrition has also been linked to the spread of AIDS and TB in developing countries and with reduced survival (Paton et al., 2006, Turchenko et al., 2008)

MICRONUTRIENT ABNORMALITIES	
Vitamins	Trace Elements
Vitamin A	Selenium
Vitamin B12	Zinc
Vitamin B6	
Vitamin C	Amino Acids
Vitamin E	Cysteine
	Peptides
	Glutathione
MACRONUTRIENT DEFECITS	
Protein Calorie Malnutrition	
Abnormal Lipids (Dyslipidemia)	

Table 1. Commonly occurring nutritional deficiencies in HIV infection and AIDS

3. Impact of nutritional deficiencies

Micronutrient deficiencies in particular vitamin and mineral deficiencies can promote and strengthen microbial growth by weakening the immune system of the host, making it prone to acquiring new infections (Scrimshaw 2003, Webb and Villamor 2007; see Fig 1).

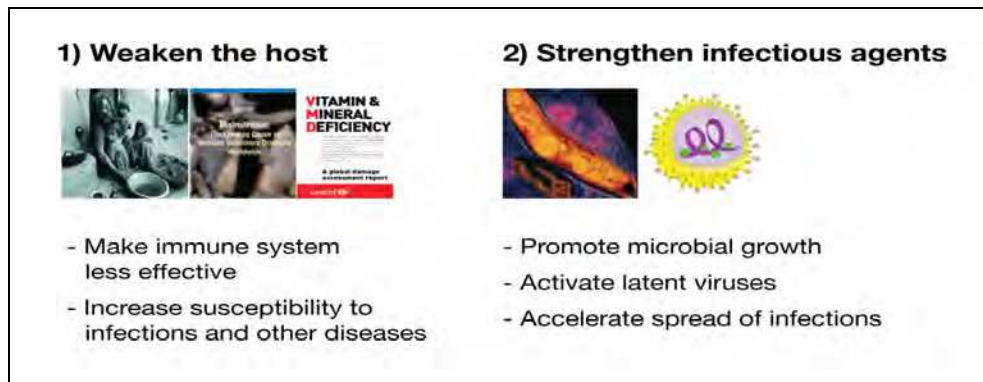


Fig. 1. Impact of micronutrient deficiencies on infectious diseases

4. Essential role of micronutrients in cell physiology and immunity

Micronutrients are essential for sustaining all cellular functions including metabolic reactions in the cytosol and biochemical functions within cellular organelles (Fig 2). Vitamins and minerals are needed in smaller amounts than proteins, fats and sugars but without them, cells cannot convert food into biological energy and build different body structures.

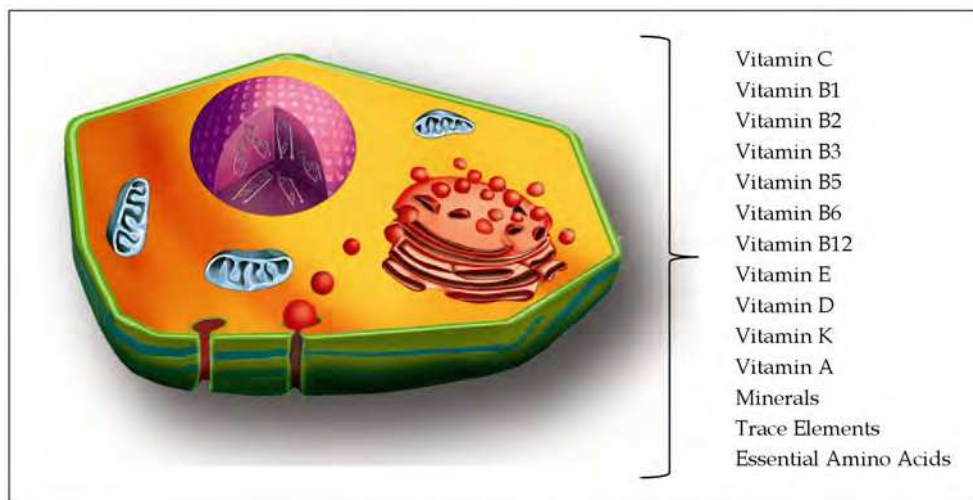


Fig. 2. Micronutrients are essential for sustaining all cellular functions

Micronutrients are also critical for optimum functioning of the immune system including cell-mediated immunity, antibody production (humoral immunity) and optimum thymus function (Fig. 3).

The pathological basis of AIDS is a dysfunctional immune system clinically indicated by abnormally low levels of white blood cells. Micronutrients are essential for blood formation,

including white blood cells. Of particular importance are: vitamin B-3, vitamin B-5, vitamin B-6, vitamin B-12, vitamin C, folic acid and iron. Any textbook of biology or biochemistry documents these scientific facts. Moreover, no less than nine Nobel Prizes in Medicine have been awarded to date on the discovery of the health benefits of vitamins, relevant to their role in cellular physiology and impact on the immune system (Nobel Prize Committee website, Nobelprize.org).

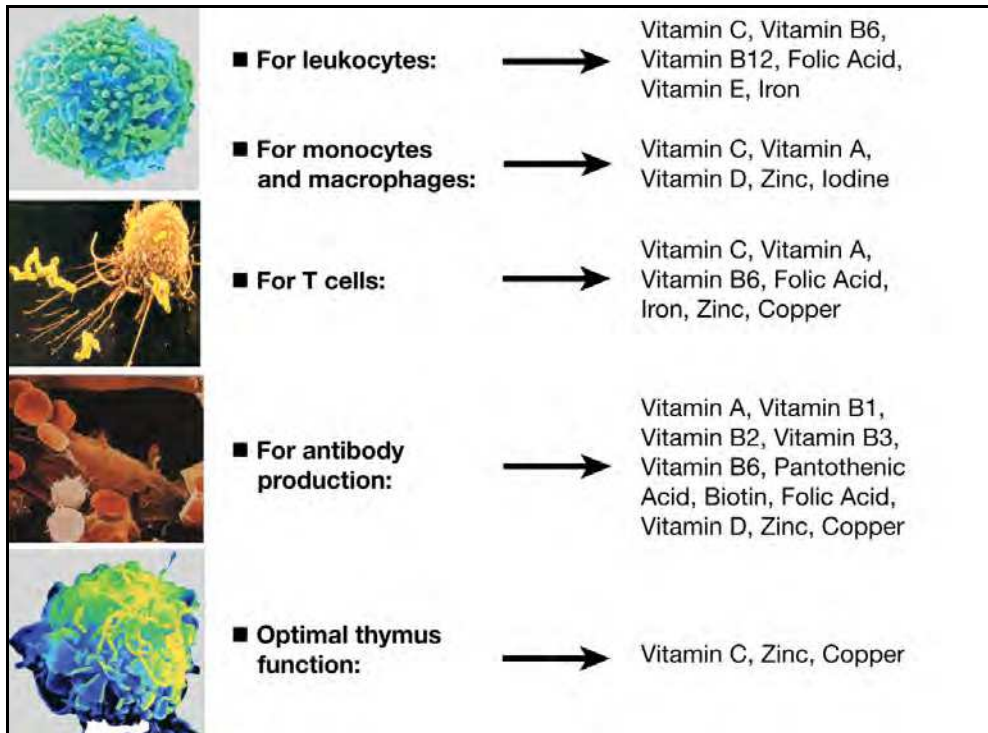


Fig. 3. Nutrients are critical for optimum immune defense of a host

5. Role of micronutrients in suppression of virus infection

Additionally, experimental studies have shown that specific micronutrients can suppress virus infection at various steps in the viral life cycle that include blocking (a) virus entry, (b) virus multiplication, (c) virus activation in latently infected cells and (d) virus spread (Fig 4).

Prevent viral entry into cells (Vitamin C, EGCG)

Stop viral multiplication (Vitamin C, N-Acetylcysteine)

Prevent activation of "silent" viruses (Vitamin C)

Limit spread of infections (Lysine, Vitamin C)

In the case of HIV, micronutrients have been shown to block virus expression at all stages of virus-host interactions, which include acute infection, chronic expression and activation from latently infected cells (Fig 5). The specific micronutrients demonstrated to affect different phases of virus infection are listed in Table 2. Most of them are reducing agents

with antioxidant properties. They include: vitamins C and E, amino acid thiols such as cysteine or its derivative N-acetyl cysteine (NAC), disulfides such as alpha-lipoic acid, tripeptides such as glutathione and its derivative glutathione monoester, polyphenols such as epigallo-catecheine gallate (EGCG from green tea) and the trace element selenium. Among them, ascorbic acid (vitamin C or ascorbate) is the most versatile, capable of blocking HIV replication in all phases of HIV infection namely, acute, chronic and latent infection (Harakeh et al., 1990; Harakeh and Jariwalla, 1991, 1995). Cysteine and glutathione monoester inhibit chronic HIV expression (Mihm et al., 1991; Kalebic et al., 1991) whereas NAC and selenium are effective in inhibiting HIV activation in latently-infected cells (Roederer et al., 1990, Harakeh and Jariwalla 1991; Sappey et al., 1994). It has been reported that alpha-lipoic acid can block acute infection (Bauer et al., 1991) and flavonoids including the polyphenol EGCG inhibit HIV at an early stage, blocking interaction of the virus with

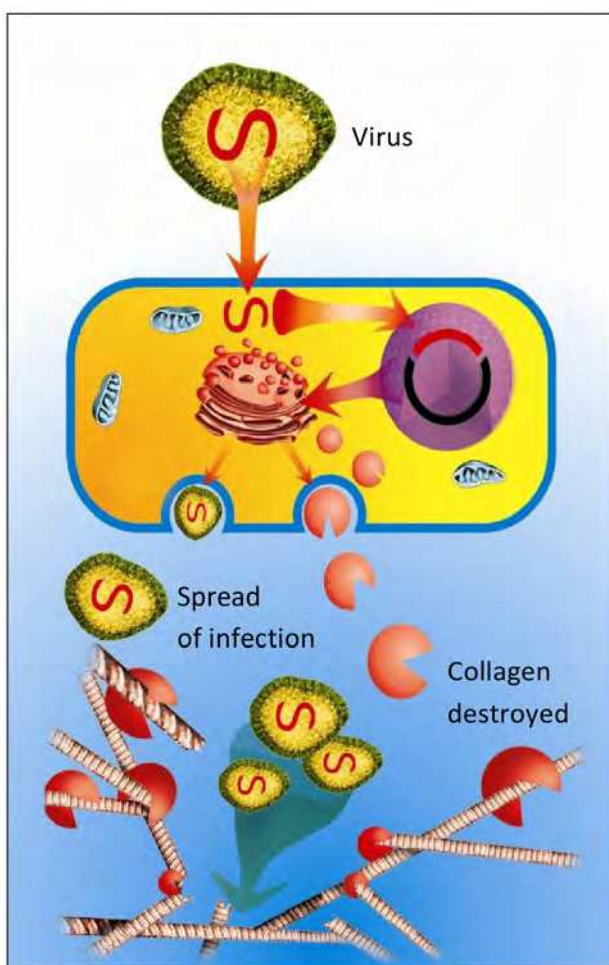


Fig. 4. Nutrients can directly suppress viral infections

host-cells receptor (Mahmood et al., 1993, Fassina et al., 2002). More recently, green tea extract enriched in such polyphenols (80% by weight) was shown to suppress HIV production in chronically and latently infected cells (Jariwalla et al., 2010).

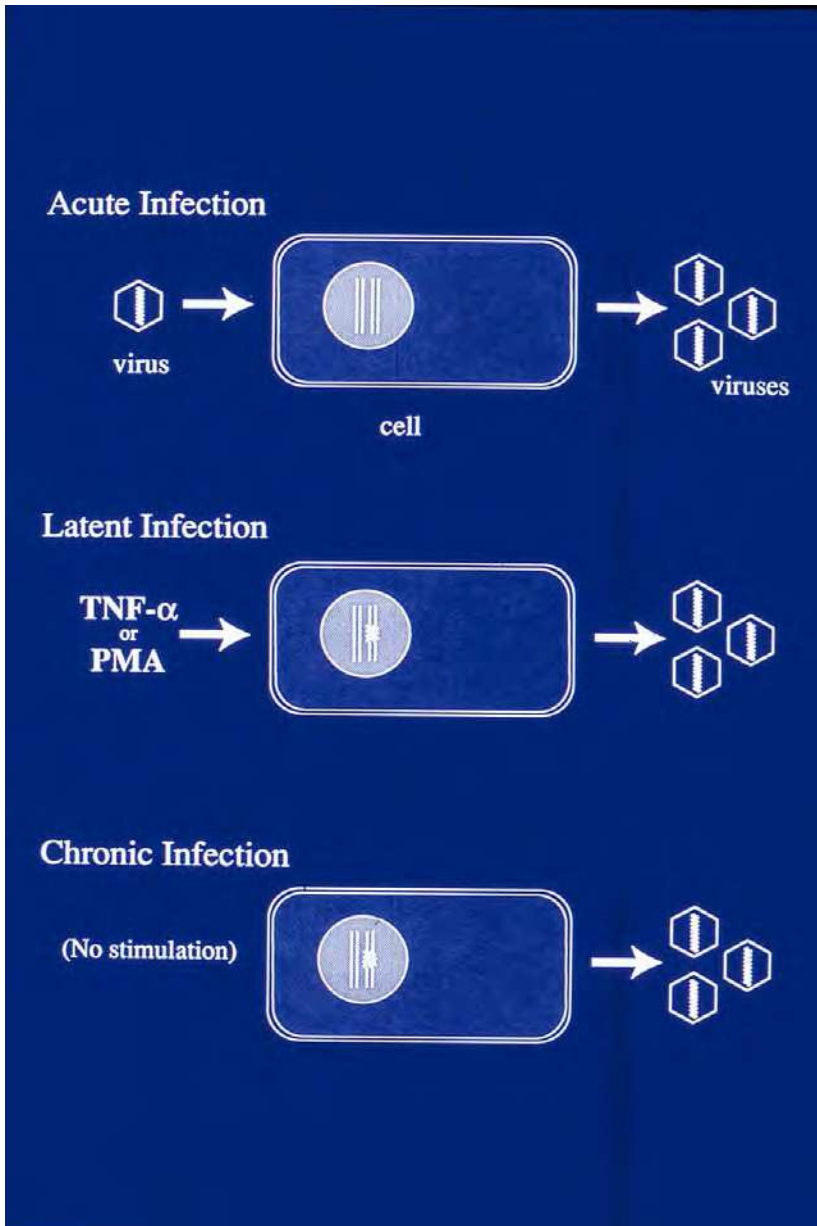


Fig. 5. Micronutrients can target different stages in HIV-host cell interaction

Nutrient	Inhibitory Effect Targeted at	Reference
Vitamin E	Latent infection	Suzuki <i>et al</i> 1993
Vitamin C	Acute, chronic and latent infection	Harakeh and Jariwalla (1991, 1995)
Cysteine, alpha-lipoic acid	Chronic and acute infection	Mihm <i>et al</i> 1991, Baur <i>et al</i> 1991
NAC, Selenium	Chronic and latent infection	Roederer <i>et al</i> 1990, Harakeh & Jariwalla 1991, Sappey <i>et al</i> 1994.
Glutathione monoester	Chronic infection	Kalebic <i>et al</i> 1991
Flavonoids, EGCG, green tea extract	Acute infection	Mahmood <i>et al</i> 1993, Fassina <i>et al</i> 2002, Jariwalla <i>et al</i> 2010
Nutrient mixture (NM)*	Synergistic HIV suppression in chronic and latent infection	Jariwalla <i>et al</i> 2010

Table 2. Action of micronutrients on phases of HIV infection

* containing (vitamin C, green tea extract, lysine, proline, arginine, NAC, selenium)

6. Our approach to controlling virus infection with nutrient synergy

Although specific, single nutrients have been shown to suppress HIV in previous studies, little attention has been directed at blocking virus expression with nutrient combinations. To investigate this, we have utilized the principle of nutrient synergy i.e. use of nutrients in combination at low to moderate (physiological) levels for prevention and control of disease (Rath and Niedzwiecki 1996, Rath *et al.*, 2005, Jariwalla *et al.*, 2008a, 2009). The principle underlying nutrient synergy is that nutrients work in the body in harmonious synergy, not isolation, and they allow for maximal benefits when used in combination at physiological doses. In nutrient synergy 1 + 1 is more than 2 (Fig 6). We have applied this principle to both experimental studies of HIV infection as well as the in vivo evaluation of a defined multi-micronutrient supplement in AIDS patients in a community wide setting.

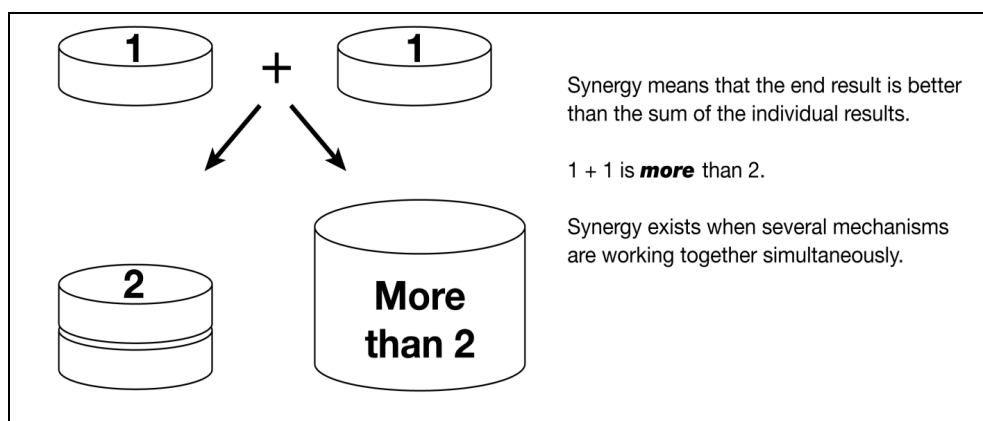


Fig. 6. The benefits of nutrient synergy

All nutrients work in our bodies in harmonious synergy, not in isolation.

Nutrient Synergy allows for achieving maximum health benefits and keeping cellular processes in balance using smaller quantities of nutrients. Use of single vitamins in very high-doses or a randomly selected nutrient combination is not recommended as an optimal approach to health.

7. Experimental studies in HIV infection

Studies conducted by us of micronutrient combinations in laboratory cultures of HIV infected cells have provided further support for nutritional efficacy in viral immunodeficiency disease (Jariwalla et al., 2010). In these studies, we compared the ability of micronutrient combinations to single nutrients in the suppression of HIV replication in both chronically and latently infected cells. H9-HTLV IIIB is a model, chronically-infected T lymphocytic cell line that constitutively produces HIV cytopathic virus in the cell culture supernatant (Popovic et al., 1984, Gallo et al., 1984, Harakeh et al., 1990, Harakeh and Jariwalla 1991). Exposure of these cells to low/moderate concentrations of single micronutrients such as ascorbic acid, green tea extract and the amino acids such lysine produced only small inhibitory effects on virus production. In contrast, exposure of cells to combinations of micronutrients conferred significantly greater HIV suppression compared to single nutrients, indicating a synergistic effect. A nutritional mixture (NM), consisting of vitamin C, green tea extract, amino acids (lysine, proline, arginine), NAC and selenium also gave enhanced suppression of HIV production in this cell line compared to single nutrients (Jariwalla et al., 2010; see also Table 2). A similar inhibitory effect on cytokine-stimulated virus expression was obtained in latently infected T cells, indicating that micronutrients cooperate to suppress virus expression in both chronically and latently-stimulated cells (Jariwalla et al., 2010; Table 2).

8. Clinical nutrition studies in AIDS patients

Based on the above scientific evidence of micronutrient effectiveness in laboratory cultures of virally-infected cells, we have incorporated the use of micronutrients in natural control of HIV infection. Our studies conducted in persons with AIDS symptoms have provided further support for micronutrient efficacy in viral immunodeficiency disease (Jariwalla et al., 2008a, 2009). This *in vivo* confirmation of micronutrient efficacy was demonstrated in AIDS patients in a community wide program conducted in South Africa between 2005 and 2008. In this community program, the Dr. Rath Foundation donated a micronutrient supplement to the South African National Civic Organization (SANCO) who distributed it among people affected by AIDS in various townships in South Africa.

The micronutrient supplement contained vitamins and trace elements (except iron) that are known to modulate the immune system (listed in Fig. 3) plus selenium, essential minerals and other important nutrients such as amino acids, green tea extract, bioflavonoids, N-acetyl cysteine, inositol and coenzyme Q10. This supplement was given to subjects to be taken 3 times a day with meals. The characteristics of participants, patient selection, informed consent, administration of questionnaire grading AIDS-defining symptoms and the evaluation methodology were reported previously (Jariwalla et al., 2008a, 2009).

The first township where a pilot nutritional program was evaluated was Khayelitsha, a township near Cape Town (Jariwalla et al., 2008a). In this pilot protocol, 56 AIDS patients completed all 3 examinations and their completed questionnaires were evaluated for

changes in severity of symptoms seen after the first 3 visits (8-12) weeks from the beginning of micronutrient supplementation. Table 3 lists the AIDS-defining symptoms for Africa, other physical symptoms, pain symptoms and symptoms of well-being. Tables 4-6 show a summary of the impact on these symptoms from micronutrient supplementation. The results showed that within 10-12 weeks, the micronutrient supplement statistically significantly suppressed all AIDS-defining symptoms compared to baseline. The supplement also significantly suppressed other physical symptoms frequently seen in AIDS patients including state of well-being (Jariwalla et al., 2008a).

AIDS-Defining Symptoms	Symptoms of Well Being
Fever	Appetite
Diarrhoea	Energy
Cough	Enjoyment of life
Weight loss	Fear of future
TB	Concentration
Oppurtunistic infections	Anxiety
	Depression
Other Physical Symptoms	Insomnia
Swollen glands	Fatigue
Colds, flu	
Rashes	
Wounds, sores, ulcers	
Headache	
Bloating, gas	
Other physical symptoms	

Table 3. AIDS-Related Symptoms, Conditions and Diseases Monitored in Community Wide Micronutrient Program

The micronutrient supplement evaluated in Khayelitsha was also rolled out in KwaZulu Natal district (near Durban) where a very large group (522 patients) completed all 3 exams and questionnaires. Similar to Khayelitsha, the same trend in reduction of AIDS-defining symptoms, other physical AIDS-associated symptoms and pain symptoms was seen (Tables 4-6). The results were also confirmed in two other townships (Western Cape and Free State), for a total of 813 participants from all 4 townships (Tables 4-6).

Site	Total no of patients	% decrease in AIDS-defining symptoms from baseline after 3 visits *
Khayelitsha	50	33-61%
Kwazulu-Natal (KZN)	473	37-48%
Western Cape	153	51-78%
Free State	82	23-26%

Table 4. Impact of micronutrient supplementation on AIDS defining symptom in a community wide program

*8-12 weeks except Free State (= 40 weeks)

Site	Total no of patients	% decrease in other physical symptoms from baseline after 3 visits *
Khayelitsha	45	37-60%
Kwazulu-Natal (KZN)	522	17-54%
Western Cape	153	44-83%
Free State	78	17-47%

Table 5. Impact of micronutrient supplementation on other physical symptoms in AIDS patients in community wide program

* 8-12 weeks except Free State (= 40 weeks)

Site	Total no of patients	% decrease in pain symptoms from baseline after 3 visits *
Khayelitsha	44	38-49%
Kwazulu-Natal (KZN)	511	32-50%
Western Cape	149	43-64%
Free State	79	24-35%

Table 6. Impact of micronutrient supplementation on pain symptoms in AIDS patients in community wide program

* 8-12 weeks except Free State (= 40 weeks)

9. Conclusion

The results we have seen are not in isolation. Beneficial effects of micronutrients and their combinations have been seen in clinical studies conducted by other researchers as summarized in Table 7. These studies have evaluated nutrients in combination and reported beneficial effects on various outcomes including improvement in viral and immune parameters, antioxidant protection from cellular damage, slowing of disease progression, reduction of AIDS-related symptoms and improvement of birth outcomes in pregnant women. The impact of nutritional support and vitamin and micronutrient supplementation in the treatment of HIV and AIDS is a seriously under-investigated area. Repeated calls have been made for more studies in this area by international health agencies. Although micronutrients are not a cure for AIDS, in the absence of an effective cure or vaccine and in the face of the toxicity and limited efficacy of ARVs, they are a safe, effective and affordable way to halt progression towards and even reduce the symptoms of the AIDS disease and to improve the quality of life of AIDS patients.

The implications of micronutrient supplementation results for public health and control of infectious and immunodeficiency disease are enormous. If properly evaluated, micronutrients have the potential of being incorporated into strategies for fighting viral pandemics on a global scale. Implementation of the above positive findings could save millions of lives.

Micronutrient Supplement	Clinical change	Reference
Multivitamin Supplement	Delayed onset of AIDS in HIV positive asymptomatic persons	Abrams <i>et al</i> 1993, Tang <i>et al</i> 1993
N-acetylcysteine (NAC)	Increased survival compared to placebo	Herzenberg <i>et al</i> 1997
Vitamin C plus E	1) Reduced oxidative stress, viral load 2) Prevention of AZT-induced mitochondrial damage	Allard <i>et al</i> 1998, de la Asuncion <i>et al</i> 1998
NAC plus vitamin C	Enhanced immune responses and reduced viral load in advanced AIDS	Muller <i>et al</i> 2000
Multivitamin Supplement	Reduced fetal death among HIV-infected Tanzanian women	Fawzi <i>et al</i> 1998, 2004
Multi-micronutrient Supplement	Increased survival among HIV-infected persons in Bangkok	Jiamton <i>et al</i> 2003
Micronutrient Supplement	Improved CD4 count	Kaiser <i>et al</i> 2006
Nutritional Supplements	Delayed AIDS progression in HIV-infected persons	Namulemia <i>et al</i> 2007
Alpha-lipoic acid	Enhanced blood glutathione and improved lymphocyte function	Jariwalla <i>et al</i> 2008b
Micronutrient Supplement (see text, page 8)	Reduced AIDS related and pain symptoms; improved state of well being	Jariwalla <i>et al</i> 2008a; 2009

Table 7. Clinical improvements seen upon micronutrient supplementation in HIV and AIDS patients, in peer-reviewed published studies.

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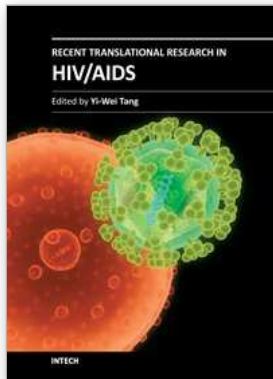
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The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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