Role of micronutrients in the control of HIV and AIDS

AIDS has become a global health crisis and a leading cause of death in the developing world. Since 1981, more than 25 million people worldwide have died from this immunodeficiency syndrome and 12 million AIDS orphans have been left behind in Africa alone. According to the UNAIDS/World Health Organization (WHO) 2006 AIDS epidemic update, the number of people living with HIV (human immunodeficiency virus), the virus linked to AIDS, has grown from 8 million in 1990 to nearly 40 million at the end of 2006. Despite improvements in access to antiretroviral (ARV) drugs, the death toll from AIDS in 2006 was close to 3 million, indicating the need for alternative/complementary therapeutic modalities.

Characteristics and Causality of AIDS

AIDS is characterised by progressive depletion of a specific group of immune cells called (CD4+) helper T lymphocytes whose loss leads to opportunistic infections and cancer. Since 1983, AIDS has been linked to infection by HIV, which primarily infects CD4+ T cells. Several mechanisms have been proposed for the depletion of CD4+ cells that include: direct cytolysis by HIV, defective T cell regeneration, immune unresponsiveness and T cell death by apoptosis [Vassena et al. (2007), Proc Natl Acd Sci USA 104: 2355-2360]. Although HIV has been correlated with AIDS, the virus infects only a small proportion of CD4 cells and T cell apoptosis occurs primarily in uninfected bystander cells, suggesting the involvement of other factors.

Very early in the AIDS epidemic, it was recognised that protein calorie malnutrition and specific micro-nutrient deficiencies were common in HIV and AIDS patients [Baum et al. (1995), AIDS 9: 1051-1056]. Since micronutrients are essential for immune function (see below), nutritional abnormalities can impair immune-cell production and play an important role in AIDS development.

Current antiretroviral treatment and its limitations

Conventional treatment is based on the use of ARV drugs directed against HIV. Although ARVs can lower HIV level in the blood, they can neither restore the immune system nor cure AIDS. Effectiveness of ARVs also wears out with time and the drugs are expensive and not readily accessible in developing countries. Most importantly, ARV drugs are highly toxic to the bone marrow as well as other organs including heart, muscle, liver and nerves [Lewis and Dalakas (1995) Nature Medicine 5: 417-22]. Consequently, ARVs can further weaken the immune system and pose a potential risk for AIDS development.

Two uncontrolled surveys of the effects of anti-HIV drugs on asymptomatic HIV-positive patients, one conducted in the USA and another in Canada, reported mortality rates from AIDS of 8.8% and 6.7% respectively [Palella et al. (1998) New England Journal of Medicine 338: 853-60; Hogg et al. (2001) J American Medical Association 286: 2568-77]. These surveys did not determine AIDS mortality in drug-free controls. However, the global AIDS development rate for all HIV-positive persons in the world (only a minority of whom took ARV drugs) was estimated by the WHO to be 1.4% for the year 2000, which fell between that of the above two surveys [WHO (2001), Part I Weekly Epidemiological Records 76 (49), 381-384]. Assuming that everyone who developed AIDS in 2000 died in the same year, the global AIDS mortality rate would still be 1.4%, which is 4- to 6-fold lower than the 6.7-8.8 per cent rate reported in the Canadian and US surveys for HIV-positive people on ARV drugs. Hence, ARV drugs could pose a potential risk for AIDS development in HIV-positive people. A more recent study of HIV patients in Singapore reported that malnutrition at the time of starting ARV treatment was significantly associated with reduced survival, [Paton et al. (2006) HIV Medicine 7: 323-30] indicating the need for nutritional therapy to effectively combat AIDS.

Essentiality of micronutrients for cellular functions

Vitamins and minerals are essential for sustaining life. Their role in building cellular structures, generating biological energy and acting as biocatalysts of multiple enzymatic processes in the body are well documented in the textbooks of biochemistry and cell biology.

Although vitamins, minerals and trace elements are required in much smaller quantities than proteins, fats or sugars, without them none of the food component can be utilised in cellular metabolism. Suboptimal micronutrient intake is not easy to detect because our body has not developed clear warning signals for their deficiencies such as the ones alerting us about shortages in oxygen (suffocation), water (thirst) and food (hunger). Research has shown that individual requirements for particular vitamins or minerals vary, depending on many factors such as one's genetics, age, health status, environment and other factors. In some cases micronutrient intakes well above the average levels

recommended for the general public (RDA) can alleviate various pathological conditions [Ames et al, Am J Clin Nutr, (2002) 75: 616-658].

Relationship of micronutrients to infection and immunity

Close interrelationship between nutrition and resistance to infections has been recognised since the early 20th century. Analysis of trends in mortality during the last 150 years has shown that decline in death caused by infectious diseases, commonly attributed to development of antibiotics and modern medical technology, was actually occurring long prior to emergence of these technologies and was related to improved nutrition, better food supply and sanitation [McKeown T, The Role of Medicine: Dream, Mirage or Nemesis? Princeton University Press, Princeton, 1976].

One of the first vitamins recognised for its role in immunity was vitamin A, which was even named an 'anti-infective' vitamin [Green HN, Mellanby E, (1929) Brit Med J, 2: 691-696]. However, the discovery of sulfa antibiotics around that time led to about 50 years of neglect in clinical investigation of this and other vitamins in various aspects of infections [Beaton GH, et al (1993) ACC/SCN State-of-the Art Nutrition Policy Discussion Paper No.13, United Nations, New York].

It is well documented that clinical and sub-clinical micronutrient deficiency and infections are mutually aggravating, as infections can turn even marginal micronutrient deficiencies into severe conditions, and vice versa – namely, micronutrient deficiencies can increase susceptibility to infections. Most vitamins, such as vitamin A, vitamin C, B-group vitamins, vitamin D and E support the production of white blood cells, as well as various cytokines and cellular modulators of immunity, including antibody production. Among other important biological factors impacting immunity at cellular and organ levels are availability of minerals, such as iron, copper, magnesium, selenium and zinc.

Table 1. Micronutrients shown to suppress HIV replication at various stages of infection.

Micronutrient	Effect on HIV	Authors
Vitamin C	Suppresses virus multiplication in chronically, acutely and latently infected cells	Harakeh et al 1990, Harakeh & Jariwalla, 1995
N-acetylcysteine (NAC)	Blocks HIV expression in latently and chronically infected cells	Roederer et al 1990, Kalebic et al 1991, Harakeh & Jariwalla 1991
Alpha Lipoic Acid	Inhibits HIV reverse transcriptase activity in cell culture	Bauer et al 1991
Selenium	Lowers HIV activation after oxidative stress	Sappey et al 1994
Epigallocatechin Gallate (EGCG)	Acts as an anti-HIV agent during acute infection	Fassina et al 2002

Critical role for Micronutrients in Health has been recognized but not implemented

Today, insufficient intake of micronutrients has became a universal problem recognised by various international organisations, including the UN organisation UNICEF, which stated in a recent document that about 2 billion people worldwide suffer from vitamin and mineral deficiencies, "debilitating minds, bodies, energies and the economic prospects of nations". This problem is not limited exclusively to the developing countries. Sub-optimal intakes of micronutrients are also frequent in the industrialised world as a result of modern farming technologies, food transportation, storage and processing [Rath M, Niedzwiecki A (2005), in Malnutrition: The leading cause of immune deficiency diseases worldwide, Dr Rath Research Institute]. However, even though micronutrient deficiencies have been officially acknowledged as a worldwide problem and the solutions for that are easily available and economically viable, they are not being implemented.

Micronutrients in disease prevention and control

The last decade has expanded our understandings of the role of vitamins, minerals and other nutrients beyond supporting immune system function at the cellular level. Some micronutrients are important as direct modulators of viral and bacterial metabolism and in controlling the spread of infections in the body [Rath M, Pauling L (1992) J Orthomol Med 7: 17-23]. Among them vitamin C and the amino acids lysine and proline are critical in strengthening natural biological barriers surrounding our body cells, thereby curtailing spread of viruses and other infectious agents. Vitamin C, N-acetylcysteine (NAC) and green tea polyphenols can also suppress the multiplication of viruses directly (Table 1) or decrease their infectivity. This new cellular medicine approach is based on micronutrient synergy rather than individual components and their random combinations. Clinical applications of specifically selected micronutrient combinations acting in biological synergy have been proven effective in various pathological conditions (www.drrathresearch.org).

Natural control of aids with micronutrient supplementation

AIDS is the major health problem linked to malnutrition and micronutrient deficiency. Research in cellular medicine has revealed that micronutrients can modify the course of viral infection and restore the functionality of the immune system in a nontoxic fashion. Studies conducted with both single and multiple nutritional supplements have shown that micronutrients act to control HIV infection and AIDS in three specific ways, which include: (i) suppression of virus multiplication and spread; (ii) restoration of cell-mediated immune responses and (iii) slowing the rate of AIDS progression and reducing the severity of AIDS-defining and disease-related symptoms.

Table 2. Beneficial effects of micronutrients and their combination in clinical studies of HIV-infected patients.

Micronutrient(s)	Clinical Improvement Seen	Authors
Vitamins C (1000 mg daily) and E (800 IU daily)	Lowered oxidative stress and viral load	Allard et al 1998
Vitamins C and E	Prevented damage to muscle cell mitochondria induced by AZT	de la Asuncion et al 1998
N-acetylcysteine (NAC)	Conferred statistically significant survival advantage over placebo	Herzenberg et al 1997
High-dose NAC and Vitamin C	Improved immune responses and lowered viral load in patients with advanced AIDS	Muller et al 2000
Multivitamin (B-complex, C and E) supplements	Significantly reduced risks of adverse pregnancy outcomes including fetal death among HIV-infected women in Tanzania	Fawzi et al 1998, 2004
Multivitamin supplements	Improved mortality among HIV-infected individuals living in Bangkok	Jiamton et al 2003
Broad-spectrum micronutrient supplement	Improved CD4 count in HIV-infected persons on ARV therapy	Kaiser et al 2006

Table 3. Changes in severity of AIDS defining symptoms in persons with AIDS before (0 weeks), after second visit (5 weeks) and third visit (12 weeks) of micronutrient supplementation.

		Severity of Symptoms		
		Before	After Taking Nutritional Supplements	
Symptom	Number of Patients	Visit 1 (0 weeks) %	Visit 2 (5 weeks) % Decrease	Visit 3 (12 weeks) % Decrease
Fever, Chills and Sweating	50	100	52	52
Diarrhea	30	100	50	51
Weight Loss	37	100	61	70
Cough	41	100	33	39
TB Symptoms	18	100	40	61
Opportunistic Infections	9	100	76	89

Symptoms were graded on a scale of 0 to 4. Data express change in severity of symptoms calculated and expressed as percent. Statistical analysis evaluated symptom improvement from beginning of programme (0 weeks) to 12 weeks of micronutrient supplementation. All changes were statistically significant with p values ranging from <0.0001 to 0.02.

Suppression of HIV multiplication and immune modulation by nutrients

Experimental studies using laboratory cultures of HIV-infected cells have demonstrated that specific micronutrients can block virus multiplication or expression at different stages of infection (Table 1). These nutrients include vitamin C, NAC, alpha-lipoic acid, selenium and Epigallocatechin gallate (EGCG), a flavanoid from green tea. Micronutrients such as NAC, lipoic acid, and vitamin C have been shown to have immune-enhancing or stabilising effects on T cells. A broad-spectrum micronutrient combination was shown recently to elevate CD4 cell count in HIV-infected subjects on ARV therapy [Kaiser et al. (2006) J AIDS 42: 523-8].

Nutrient effects on disease progression and AIDS symptoms

In addition to virus-suppressing and immune-modulating effects, micronutrient supplements have been reported to confer benefits to HIV-infected subjects in clinical studies as summarised in Table 2.

More recently, the effects of a defined micronutrient programme on the course of AIDS symptoms in HIV-positive patients was evaluated as part of a community-based nutritional health programme led by the South African National Civic Organization (SANCO) in the Khayelitsha township outside of Cape Town. Participants included 100 adult HIV positive men and non-pregnant women with advanced AIDS symptoms (CDC stage 2 or 3), without current or recent use of ARV drugs. After meeting eligibility requirements and providing informed consent, participants took a nutritional supplement (supplied in the form of tablets) consisting of a defined combination of vitamins, minerals, trace elements, amino acids, and polyphenols (from green tea) among other nutrients. Before taking the supplement (0 weeks) and after periodic visits (5 weeks and 12 weeks), a licensed physician examined the participants and assessed their health status using a questionnaire. The latter was graded on a scale of 0 to 4 to assess AIDS-defining symptoms and other physical symptoms (0 = no symptoms, 1 = mild, 2 = medium, 3 = advanced, 4 = severe).

The results for 56 participants who completed all three examinations are summarised in Table 3 and expressed as a percentage change in symptom severity. The data showed a substantial reduction after only a few weeks in severity of fever, weight loss, diarrhoea, cough and TB symptoms that constitute the five key symptoms for WHO's case definition of AIDS based on a conference in Bangui, Central Africa [WHO (1986) Weekly Epidemiological Records 7: 72-73]. In addition, the severity of fungal and opportunistic infections accompanying AIDS in nine participants were also lower after micronutrient intake. All these changes were statistically significant (p values from <0.0001 to 0.02). Significant reduction was also seen in other physical symptoms associated with AIDS such as wounds, sores, skin rashes, swollen glands, fatigue, colds, etc. Micronutrient supplements also mediated healing of skin ulcers. No adverse side effects were seen from intake of the micronutrient supplements.

Implications of micronutrients in HIV/AIDS

The results from micronutrient supplementation studies have implications for further research and adoption of nutritional therapy into public health programmes of developing countries. Specifically, micronutrient supplementation offers a safe, effective and affordable therapeutic option that may provide benefits to HIV-infected people, especially undernourished populations with a background of malnutrition. Micronutrients lowered in HIV infection have been shown to affect cell-mediated immune responses and to influence the rate of AIDS progression. Hence, nutrient supplementation may offer an opportunity for early intervention in HIV, thereby delaying the start of (toxic) ARV therapy.

Raxit J Jariwalla, Ph.D; Aleksandra Niedzwiecki, Ph.D; and Matthias Rath, MD.
Dr Rath Research Institute
1260 Memorex Drive, Santa Clara, CA 95050, USA
Tel: +1 408 588 7174
Fax: +1 408 588 7107
Email: r.jariwalla@drrath.com
Website: www.drrathresearch.org