Complex interactions between malnutrition, infection and immunity: relevance to HIV/AIDS infection

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SUMMARY
Various grades of protein-energy malnutrition, usually complicated by concurrent micronutrient deficiencies, occur extensively in Nigerian populations who are consequently, immunologically compromised. The affected individuals present with marked tissue depletion of the antioxidant nutrients, including glutathione (γ-glutamyl-cysteinyl-glycine) and its enzymes. HIV infection in deprived subjects intensifies the nutritional deficits and further enhances cellular oxidative stress. The latter, by modifying the functions of such transcription factors as NF-κB, contributes to HIV replication and acceleration of disease progression. In the HIV-infected individual who is usually anorexic, the marshalling of nutrient resources from endogenous sources to promote optimal immune function is of high importance, but this is compromised in the malnourished. The importance of good nutrition in HIV management in Nigeria is not diminished by the advent of antiretroviral drugs, whose metabolic effects on underprivileged, malnourished subjects are yet to be carefully characterized.

INTRODUCTION
The Federal Republic of Nigeria, like many other countries in sub-Saharan Africa, is a country of bewildering contradictions where the majority residing in the rural areas and in the poor, overcrowded urban slums lack the basic essentials of life, while the relatively few, affluent, educated class engage in gluttonous lifestyles. It is estimated that 24 per cent of sub-Saharan Africans live on less than US $1.00 daily.1 For Nigeria, 70 per cent of the population is estimated to be living on or below the poverty line, a marked negative change from the 15 per cent rate 45 years ago. This translates to about 85-89 million Nigerians living below the international poverty benchmark which is defined in economic terms, and thus ignores other important confounding components such as access to adequate food, safe water, and health services, as well as the capacity to improve their condition.2 There is a two-way link between poverty and illness in that the former promotes hunger and exposure to environmental risks (eg poor sanitation, inadequate and unhealthy foods, etc), while the latter diminishes productivity and drains the limited family resources.

For maintenance of optimal health, humans require a well-balanced diet consisting of a complex mixture of good quality macronutrients (carbohydrates, lipids and proteins) and micronutrients (vitamins and minerals), plus water and several useful but non-nutrient components of foods (eg organic phytochemicals). The dietary habits/practices of sub-Saharan Africans including Nigerians have been examined in several reports.3,4 Foods consumed by Nigerians, particularly the underprivileged majority, are monotonous, and the daily intakes do not provide the recommended dietary
allowance (RDA) for energy and the essential nutrients. Thus, malnutrition has for decades remained an unsolved endemic health problem in the country. In the technically developing world including Nigeria, malnutrition is an important underlying cause of childhood deaths associated with infectious diseases (eg diarrhea, malaria, measles, acute respiratory illnesses) even though it is rarely mentioned due to the conventional way that cause of death data is reported and analyzed. Malnutrition is also prevalent in adult Nigerians, particularly in women of child-bearing age and in pregnant women, with more than 50 per cent of the latter anaemic. The anaemia could be due to cellular deficiencies of several micronutrients (eg iron, folate, retinol, cobalamin) and presence of parasitic infestations, particularly malaria. The premise of this report is that pre-existing malnutrition, especially in the face of a heavy burden of co-infection by endemic diseases, is an important factor predicting the clinical history of HIV infection in Nigerian children and adults. The report also examines very briefly, some of the nutritional obstacles militating against adequate management of the disease in impoverished Nigerian communities.

MALNUTRITION IN PRE-NATAL LIFE AND INFANCY

The prevalence of low birth-weight in underprivileged Nigerian communities, particularly in the northeastern and northwestern states is as high as 20 per cent, and this is attributable mainly to intra-uterine growth retardation (IUGR) rather than to prematurity. This observation is suggestive of a high prevalence of maternal malnutrition and infections during pregnancy. Thus, malnutrition in many impoverished Nigerians may commence in pre-natal life. The adverse consequences of IUGR may affect the prenatal phase of the development of lymphoid tissues, resulting in impairment of immune function, particularly cell-mediated immunity (CMI). The effects become apparent early in post-natal life, with the consequences continuing into adulthood in terms of increased vulnerability to disease. Additionally, ‘programming’ of the endocrine axes which occurs during critical phases of foetal development, may be compromised by IUGR.

The two periods of highest vulnerability to growth failure in the human are during intrauterine development, and the transition from exclusive reliance on breast milk to weaning diets. Exclusive breastfeeding in the first three months of life is very rare in Nigerian communities. The reported prevalence varies from less than 2 per cent to about 12 per cent. Supplementary weaning foods used include glucose water, unpasteurized cow’s milk, herbal tea, and various indigenous cereal-based diets usually prepared under less than hygienic conditions. Immunization coverage against common childhood diseases, eg measles, is extremely low in such communities. Thus, in deprived Nigerian children, growth faltering, including linear growth retardation (LGR) or stunting, becomes easily noticeable with the discontinuation of exclusive breastfeeding at about 3-4 months, and continues until about 36-48 months of age, an observation extensively reported in other developing countries. Malnutrition and a continuous burden of immunostimulation by environmental antigens account for the occurrence of LGR in infants and children. The importance of exclusive breastfeeding in the first few months of life in protecting against otitis media, urinary tract infections, and other infections attacking the host via mucosal membranes, is well-documented, and may be relevant to HIV infection. The infancy-childhood-puberty (ICP) model divides human growth into three, additive, partly super-imposed phases, with the infancy phase extending from mid-gestation to about 3-4 years of life. Since stunting in children is a cumulative process, it is conceivable that the severe growth failure observed in the impoverished Nigerian communities commences prenatally.

MALNUTRITION, INFECTION, AND IMMUNITY: A BRIEF REVIEW

There is a complex three-way relationship between malnutrition, the immune system and infection, with malnutrition eliciting immune system dysfunctions which in turn promote increased vulnerability of the host to infection, and the latter intensifying the severity of malnutrition (fig. 1). The immune dysfunctions associated with malnutrition are referred to as Nutritional-Acquired Immune Deficiency Syndrome (NAIDS). Malnutrition alters all defence mechanisms including anatomic barriers, cell-mediated immune (CMI) responses, phagocytic cell/microbicidal functions, and humoral (antibody and complement responses) among many others. Some of the immunological changes observed in malnourished individuals are summarized in table 1 and they bear a striking resemblance to those encountered in HIV infection. The malnourished African is often characterized by functional complement deficit, diminished opsonic
capacity of serum, diminished avidity of antibody response, inhibition of neutrophil and macrophage migration, reduced intracellular killing capacity of phagocytic cells, decreased secretory IgA (sIgA) production, and endocrine function adaptations such as diminished synthesis of insulin and increased circulating levels of growth hormone and the glucocorticoids. The normal circulating cortisol rhythm may also be abolished.

Table 1. Some immunological changes in malnutrition*

<table>
<thead>
<tr>
<th>Immunological parameters</th>
<th>Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular immunity</strong></td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>decreased (++)</td>
</tr>
<tr>
<td>Helper T cells</td>
<td>decreased (++)</td>
</tr>
<tr>
<td>Helper: suppressor T-cell ratio</td>
<td>inverted</td>
</tr>
<tr>
<td>Immature T cells</td>
<td>increased (++)</td>
</tr>
<tr>
<td>Cytotoxic T cells</td>
<td>decreased (++)</td>
</tr>
<tr>
<td>Helper T-cell activity</td>
<td>decreased (++)</td>
</tr>
<tr>
<td><strong>Humoral immunity</strong></td>
<td></td>
</tr>
<tr>
<td>Serum immunoglobulins</td>
<td>increased (++)</td>
</tr>
<tr>
<td>Immune complexes in serum</td>
<td>present (+)</td>
</tr>
<tr>
<td>Primary antibody responses</td>
<td>diminished (+)</td>
</tr>
<tr>
<td>Circulating immunoglobulin secreting B cells</td>
<td>increased (++)</td>
</tr>
<tr>
<td>Antibody affinity</td>
<td>decreased (++)</td>
</tr>
<tr>
<td>Secretory IgA</td>
<td>decreased (++)</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Thymic hormones</td>
<td>variable</td>
</tr>
<tr>
<td>Serum complement</td>
<td>decreased (++)</td>
</tr>
<tr>
<td>Inhibitory factors in serum</td>
<td>present (+)</td>
</tr>
<tr>
<td>Anatomic barriers</td>
<td>impaired</td>
</tr>
<tr>
<td>Mucosal immunity</td>
<td>impaired</td>
</tr>
<tr>
<td>Gastrointestinal function</td>
<td>increased (+)</td>
</tr>
<tr>
<td>Circulating free cortisol level</td>
<td>increased (+)</td>
</tr>
<tr>
<td>Plasma levels of inflammatory mediators</td>
<td>increased (+)</td>
</tr>
<tr>
<td>Salivary gland function</td>
<td>impaired</td>
</tr>
</tbody>
</table>

* Data refers to PEM and is adapted from references 27-29; Note: (mild : +), (moderate: ++).

It must be emphasized that in the socio-economically deprived African, it is usually difficult to segregate changes due to malnutrition per se from those attributable to the concomitant effects of sub-clinical infections. Secretory immunoglobulin A (sIgA) is an important component of the mucosal immune system, and its reduced production in malnutrition may be relevant to increased bacterial adherence to nasopharyngeal and buccal epithelial cells, although altered expression of membrane glycoprotein receptors could play a role. Glucocorticoid excess in malnutrition contributes to the impairment of various parameters of the host’s response to infection, including inhibition of induction of the calcium-independent nitric oxide synthase (iNOS) in macrophages, neutrophils, and other cells. The potential effects of hypercortisolemia on HIV-infected individuals are the subjects of several reviews.

The cellular immune deficits observed in malnourished children include involution of the thymus with a reduction in the thymus-derived lymphocyte growth and maturation factors, arrest of lymphocyte development with reduced numbers of circulating mature CD4 helper cells, but relative preservation of CD8 suppressor cells, impairment of antibody production to T-dependent antigens, imbalance in Th1-Th2 activation depending on nature of stimuli and altered regulatory pathways, including responses mediated by the nuclear factor – κB (NF-κB), a major transcription factor involved in the development of innate and adaptive immunity.

Also reported in malnourished Africans, including Nigerian children, without overt infections are significantly increased circulating levels of inflammatory mediators [e.g., interleukin 6 (IL-6), the soluble receptors of tumor necrosis factor-α (sTNFR-p55 and sTNFR-p75), etc.] as well as C-reactive protein, compared with findings in healthy childhood control children. In both studies, the increase in plasma cytokine levels was more prominent with infections. Synthesis of cytokines is controlled by a host of extracellular factors, plasma membrane constituents, and cytosolic as well as nuclear factors. Dietary deficiency of essential fatty acids, particularly the omega 3 fatty acids, may impair endogenous production of lipoxins (trihydroxytetraene – containing eicosanoids) generated within the vascular lumen during platelet-leukocyte interactions and at the mucosal surface via leukocyte – epithelial cell interactions. Lipoxins provide counter-regulatory signals that minimize neutrophil-mediated tissue damage, and inhibit IL-1β - induced IL-6, IL-8, and matrix metalloproteinase – 3 production.

**INFLUENCE OF HIV INFECTION ON NUTRITIONAL STATUS**

As indicated in figure 1, the acute phase response (APR) is essential to the interactions between nutrition and immunity in response to infections, injury or trauma. The complex series of reactions to infection include fever, production of specific acute phase proteins, release of a broad range of inflammatory mediators (particularly the IL-1 and TNF families), anorexia,
proliferation of immune cells, activation of the pituitary-adrenal axis, endothelial cell activation, and other metabolic changes. Consequently, nutrients (e.g., iron, copper, selenium, zinc) are simultaneously compartmentalized to the tissues, lost from the body, or blocked from cellular utilization. The sequestered mineral elements are cofactors for several important antioxidant enzymes.

HIV infection induces several metabolic alterations including changes in whole-body protein turnover, increased urinary nitrogen loss, elevated hepatic protein synthesis as well as increased skeletal muscle breakdown, hypertriglyceridemia, elevated hepatic de novo fatty acid synthesis, decreased peripheral lipoprotein lipase activity, hyperglycemia, insulin resistance, and increased gluconeogenesis. In asymptomatic adults with HIV infection, loss of lean body mass is not a common finding. However, in infants and young children with HIV infection, including those without secondary/opportunistic infections, growth failure secondary to low rates of lean tissue synthesis is common along with inability to down-regulate protein catabolism. All these changes impact on the nutritional status of the victim. Figure 2 summarizes the vicious cycle involving nutritional status and the pathogenesis of human immuno-deficiency virus infection. HIV-infection affects nutritional status through reduction in food intake resulting from loss of appetite, side effects of medications, mouth ulcerations/lesions, depression, and most importantly, the prevalent severe poverty in many Nigerian communities. Other factors causing malnutrition in the HIV-infected individuals are nutrient malabsorption (e.g., malabsorption of fats and the fat-soluble vitamins, carbohydrates), and the metabolic changes which promote increased utilization of nutrients, particularly the micronutrients and antioxidants. The elevated resting energy expenditure notwithstanding, the most prominent factors promoting weight loss in HIV disease in adults are anorexia and multiple cytokine-driven metabolic disturbances, often intensified by secondary opportunistic infections. The cytokines/inflammatory

Figure 1. Three-way interactions between infection, malnutrition and immunity
mediators involved are numerous, and the balance between the pro-inflammatory mediators (e.g. IL-1, IL-6, TNF, IL-18) which up-regulate HIV expression and the anti-inflammatory/regulatory cytokines may play an important role in the progression of the disease.49

MICRONUTRIENT DEFICIENCIES AND OXIDATIVE STRESS

A prominent feature of HIV infection/AIDS is depletion of micronutrient status,45,48 and this should be more profound in impoverished Nigerian communities with habitual low dietary intake.5,7,31 Micronutrients whose deficiencies have been extensively reported in HIV-infected individuals include selenium, zinc, magnesium, vitamin E, cyanocobalamin, retinol, vitamin C, folic acid, niacin, and 1, 25-dihydroxycholecalciferol.4,45,48 Deficiencies of these micronutrients have also been observed in malnourished Nigerian children who are serologically negative for HIV infection.5,7,31,50 Severe depletion of glutathione (γ-glutamyl-cysteinyl-glycine) also occurs in malnourished African children with and without HIV infection.5,45,50 Additional to their key roles in various immune parameters, these micronutrients are involved in the maintenance of structural and functional integrity of epithelial tissues, DNA synthesis, haemopoiesis and other physiological/metabolic functions. Many of these micronutrients function in the antioxidant defense system which is severely weakened in HIV-positive patients in the face of increased oxidative stress.48,52

About thirty-five selenoproteins have been identified and levels of the major ones in T cells are decreased in HIV infection.53,54 Selenium has important redox functions. Selenium-dependent glutathione peroxidases are involved in the reduction of damaging lipid and phospholipid hydroperoxides to harmless products.53 In vitro studies suggest that selenium blocks HIV-1 replication, and that selenium deficient HIV positive females are more likely to infect their sexual partners than those females with higher selenium status.56 It has been hypothesized that the rapid diffusion of HIV-1 in sub-Saharan Africa may be due in part to inadequate dietary intake of selenium.55 When plasma selenium and glutathione (GSH) levels are abnormal in HIV infection and plasma peroxidase activity is depleted, survival rate of the patient is significantly reduced.48,54 The depletion of systemic glutathione levels in inflammatory states, HIV-infection, and malnutrition is possibly associated with increased consumption due to oxidative stress.45,48,58 The multifaceted physiological functions of this predominant low-molecular weight thiol compound, which include antioxidant defense, regulation of immunity, and detoxification of electrophilic xenobiotics, have been reviewed in detail.58

Figure 2. Impact of malnutrition particularly antioxidant deficiency status on HIV disease process
GSH also plays an important role in blocking the ability of inflammatory mediators and other factors to promote viral replication through NF-κB activation. Cysteine supplementation in form of N-acetylcysteine, is reported to improve erythrocyte glutathione synthetic rate in severely malnourished children.

The roles of other micronutrients eg tocopherol, ascorbate, β-carotene, as free radical scavengers, are extensively covered in several publications. Very recent studies suggest that vitamin C enters the mitochondria via glucose transporter 1 (Glut 1) and protects the mitochondria from oxidative injury. The mitochondria contribute markedly to the intracellular burden of reactive oxygen species. Observational studies in several sub-Saharan African countries implicate maternal vitamin A status as playing an important role in the vertical transmission of HIV infection to infants, and there are suggestions that the risk of viral shedding of viral DNA increases considerably as serum retinol level declines below 1.4 μmol/L. What is now emerging is that mother to child transmission of the virus is best achieved through a combination of antiretroviral therapy and exclusive breastfeeding (Idigbe E, personal communication).

SOME NUTRITIONAL IMPLICATIONS OF ANTIRETROVIRAL THERAPY

The ‘successful therapy’ for the management of HIV infection is the combination of three antiretroviral medications, namely, nucleoside analogue reverse transcriptase inhibitors, non-nucleoside analogue reverse transcriptase inhibitors, and HIV-protease inhibitors (PIs). This therapy has revolutionized the long-term management of HIV victims in developed countries, but not without some poorly understood acute and long-term toxic effects. Among the reported effects with some nutritional implications are development of insulin resistance/diabetes, dyslipidemia, body fat redistribution (lipodystrophy), lactic acidosis, osteopenia, and osteoporosis. HIV-protease inhibitors impair vitamin D bioactivation to 1, 25-dihydroxycholeciferol (calcitriol) by suppressing the activities of hepatic 25 - and renal 1α-hydroxylases, thus contributing to bone mineral loss. Protease inhibitors, particularly ritonavir and indinavir, also inhibit cytochrome P450-3A activity. Levels and activities of the cytochrome P450 enzymes are influenced by several factors, including the diet and nutritional status of the host. Optimal drug therapy requires a good understanding of relevant pharmacokinetic principles and factors that may cause altered drug disposition, particularly severe malnutrition. The undisputed success of the antiretroviral regimens therefore needs to be strengthened by a good knowledge of the influence of chronic malnutrition on their metabolic effects.

CONCLUSION

Hunger and malnutrition remain the most devastating problems that dominate the health of underprivileged Nigerians. Nutritional status and immunological competence are among the most important determinants of morbidity and mortality. The immunological dysfunctions usually observed in malnourished Africans who are serologically negative for HIV infection show marked similarities to those seen in HIV-infected individuals.

Thus, reliance on clinical criteria alone to separate severe malnutrition from pediatric AIDS in the developing countries presents serious diagnostic problems. Schuerman and colleagues have reported that the severity of malnutrition and other clinical criteria (eg, chronic diarrhoea, failure to thrive, oropharyngeal candidiasis, generalized lymphadenopathy) are comparable between HIV-positive and -negative children studied in rural Equatorial Africa. Although a lack of consensus exists regarding the role of pre-existing malnutrition in the acquisition of HIV infection, malnutrition is, however, considered a major underlying factor in the full clinical expression of AIDS in HIV-infected individuals.

Univariate Cox proportional-hazards analysis performed to examine the effects of baseline variables on long-term survival of HIV-infected subjects, show that initial nutritional status as characterized by CD4 count, plasma albumin, prealbumin, and C-reactive protein levels, as well as degree of body weight loss, is significantly associated with survival, and that patients with low CD4 counts and/or advanced malnutrition, have markedly diminished survival rate. Similar findings have been reported by others. Semba and Tang have summarized many studies showing that increased risk of rapid progression from HIV infection to AIDS is associated with low serum levels of several antioxidant micronutrients. The same has also been reported for low levels of GSH in the CD4+ lymphocytes.

Micronutrient supplementation is known to have the
highest cost-benefit ratio among health intervention measures, and should therefore be viewed as an essential therapeutic adjunct to the antiretroviral therapies which are still limited to only a small proportion of HIV-infected individuals in resource-poor countries like Nigeria. The micronutrient supplementation protocol should take into account, the integrated nature of most of the components of the antioxidant defense network. An area that requires some study in sub-Saharan African countries is the dramatic disparity in HIV/AIDS prevalence rates reported between algal-eating populations and most of Africa. In vitro evaluation suggests that extracts of seaweeds and the alga *Spirulina* inhibit a variety of enveloped viruses including HIV-1. It may also be informative to study HIV prevalence in relation to selenium status in a country like Senegal, where calcium phosphate derived from selenium-enriched phosphorites, is used as fertilizers.

Guidelines for aggressive nutrition programmes in the management of patients with HIV infection/AIDS have been worked out in the U.S. and other resource-rich countries. Wholesale transfer of these guidelines to Nigeria is neither feasible nor recommended. Nigeria and other sub-Saharan African countries should develop their own unique national programmes. The guidelines must take into account, the dietary habits of the people, the types and extent of nutrient deficiencies, the available food resources, and the potential nutritional and health complications of endemic diseases as well as the antiretroviral therapies.

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