

# **Compendium of Knowledge on HIV Infection and Nutrition-Related Issues**

*Compiled for WISHH by Cade Fields-Gardner*

## Introduction

Most recent estimates place HIV infections at about 40 million world-wide with the hardest hit areas in developing countries and Sub-Saharan Africa, the Caribbean, and India. Estimated prevalence rates vary from less than 0.1% to nearly 40% of the adult population in various countries. Countries with lower estimated prevalence rates may use prevention efforts to control the spread of HIV infection. Countries with higher prevalence rates require more intensive efforts in both prevention and treatment of HIV infection and its complications. Nutritional considerations should be included and integrated into all prevention, care, and treatment efforts as the first line of defense and as a support for other efforts.

This document was created because of the need for a central depository for current and past nutrition-related information in HIV/AIDS on which to base planning efforts and decision-making about program development. The last such comprehensive document was completed in the late 1980s and there have been many changes in the “face of HIV/AIDS” since that time, including effective treatments for control of the virus and new efforts to build prevention and treatment programs aimed at both developing and developed countries that are dependent (though not always inclusive) of food and nutrition as the most basic human need.

The goal of this project is to provide a series of documents that review and discuss the current nutrition-related knowledge and practices in HIV infection. Specific objectives for the sponsored documents are shown below:

## Objectives

1. Provide a literature review of current knowledge and practices in nutrition and HIV infection.
2. Provide six executive summaries on the topics pertinent to persons and organizations working to include nutritional considerations in their programs.
3. Develop three papers for submission to peer-reviewed journals demonstrating evidence base for nutrient needs in HIV-infected populations.
4. Develop comprehensive database of citations for use on the WISHH website.

This document can be used in several ways. It is divided into several chapters that will cover background topics on nutrition and HIV infection as well as complications of and to food and nutrition security both domestically and internationally. This document may be used to review the current literature as it stands at the date of publication and to peruse for research to support programmatic decision-making.

While there are many issues that impact on the nutrition and food issues in HIV-impacted populations, this document will confine its use to those issues that directly demonstrate an impact on nutrition and food by the disease and the impact of nutrition on the disease. In addition, a searchable database of citations reviewed will be available on the WISHH website at [www.wishh.org](http://www.wishh.org).

### Structure

Chapter 1. Interactions: Nutrition, Immunity, and HIV Infection

Chapter 2. Assessment Factors

Chapter 3. HIV Infection and Nutrient Needs

Chapter 4. Maternal-Child Nutrition in HIV Infection

Chapter 5. Lifecycle Nutrition Considerations in HIV Infection

Chapter 6. Integrating Nutrition into HIV Prevention, Care, and Treatment Efforts

### *Appendices*

Database of Relevant Citations

Summary Tables of Studies Graded for Evidence-Based Practice Questions

Glossary of Terms

## Chapter 1: Nutrition, Immunity, and HIV Infection

### **Abstract**

Both undernutrition and HIV infection cause immune dysfunction. According to the World Health Organization protein-energy malnutrition affects more than 25% of children in the world today in the form of stunting and/or underweight and may be responsible for 11 million deaths each year. HIV infection most commonly occurs in young to middle-aged adults through sexual transmission. In addition, children born to HIV-infected mothers are at risk for perinatal HIV infection. While general protein energy malnutrition is common, it is not a necessary component of the natural history of HIV disease if adequate efforts are made to prevent and maintain the body's nutrient stores and functions. Just as with any other infection or injury, alterations in the levels and functions of body nutrients should be anticipated. Resting energy expenditure and protein turnover rates are altered in HIV infection according to the severity of several factors such as viral burden, cytokine production, and symptoms or opportunistic infections. Progressive protein wasting occurs even in asymptomatic phases of HIV infection. Efforts to maintain and rehabilitate nutritional status are crucial to the survival and prevention of further immune suppression and debilitation by malnutrition.

### **Background**

The primary reason for immune suppression or dysfunction in the world today remains undernutrition. Adequate nutritional status and maintenance through food consumption is the most basic of human requirements and affects all body functions and the ability to maintain health. Immune functions that normally protect and help to restore the body in cases of infection or injury are compromised in a malnourished person. Most vulnerable are children and the elderly, whose immune functions may be immature or otherwise already compromised.

Nutritional status markers are the strongest predictors and the most reliable markers of morbidity and mortality (illness and death).<sup>1</sup> Maintenance of adequate body weight levels and adequate amounts of protein tissues (especially muscle and organ tissues) is the most important key to health and survival. Undernutrition is the most lethal form of malnutrition and efforts to roll back and eliminate this problem in the world has been seriously hampered by the HIV/AIDS pandemic in those countries that are most affected.

The human immunodeficiency virus (HIV) infects or is harbored in many cells and areas of the body, but specifically targets CD4 cells to increase and spread. As CD4 cells are used to manufacture and assemble HIV, a process that happens continuously and rapidly, they are rendered dysfunctional. When the cell is finally destroyed when HIV “buds” out from the cell to spread, CD4 cell numbers drop. CD4 cells are immune cells that coordinate the activities of part of the immune system and their infection renders them unable to complete this function, leaving the body open to infections that would not otherwise cause too much of a problem in someone

with a fully functioning immune system, called “opportunistic” infections. The level of virus found in the blood is associated with the amount of immune cell destruction and the progression of the disease.

In addition to the infection of important CD4 cells, the virus also affects many other cells. Phagocytes that engulf HIV are also rendered dysfunctional and can cause problems in important immune organ sites, such as covering surface area of the intestines causing malabsorption of nutrients and other substances that are consumed. HIV may be introduced through the gastrointestinal tract and can wreak havoc on the normal functions of this organ that is noted for very high cell turnover even without HIV.

As with any other infection or injury, HIV causes the body to break down protein stores, such as muscle tissues, to allow the formation of protective proteins that initiate immune responses. In the case of chronic HIV infection, the process of protein breakdown is continuous and challenges a person’s ability to maintain adequate levels of body protein and other nutritional stores. In addition, the protective responses alter hormonal milieu, which changes the way nutrients are absorbed, processed and assimilated, and excreted. These changes can contribute to disease progression and complications. Both situations yield constant assaults on nutritional stores and metabolism and require interventions to both assure the appropriate volume of nutrient intake and the appropriate forms and dietary patterns to enhance well-being and minimize the effects of the disease.

## Literature Review

### *Immune Suppression by Undernutrition*

Any nutrient deficiency or alteration to yield nutrients unavailable for normal body functions will lead to an increased risk for infection by impairing the protective immune response. Immune responses require adequate cell production, activation, and additional chemical mediators of immune response. Cell-mediated and non-specific immunity functions tend to be more sensitive to malnutrition than humoral immune responses. HIV infection also affects cell-mediated immunity.

In addition to cellular immune functions, malnutrition can lead to the breakdown of other barriers to infection, such as skin disorders, gastrointestinal changes, and lung barrier alterations.

### *Effect of Infection on Nutritional Status*

The effect of infection on nutritional status depends on many factors including the baseline nutritional status, the severity of the infection, and the site affected (localized or systemic). If the baseline nutritional status is borderline deficient, nutritional depletion may occur quickly. In persons with adequate nutritional status at baseline, a mild to moderate short-term infection may not deplete nutritional stores.<sup>2</sup> Chronic infections, such as chronic HIV disease, presents a challenge to the maintenance of nutrient stores.

The nutritional effects of infection should be taken into account in estimating nutrient requirements. It remains uncertain how common conditions or disease prevalence affects nutritional requirements of these subpopulations. Nevin Scrimshaw recommended that a different method of estimating requirements should be employed because of the various factors that can affect dietary needs, such as “anorexia, fever, adverse effects of treatment, impaired intestinal absorption, increased nutrient losses, and internal sequestration” among other factors.<sup>3</sup> Considerations in nutrient requirements should include

#### Mechanisms of HIV Infection

HIV infection, like other infections, induces a defensive immune response.

#### *Effect of HIV Infection on Nutritional Status*

Early on there are a number of nutritional status changes attributable to HIV infection. Very early changes in nutritional status and metabolism were seen in HIV infection. Loss of body cell mass (BCM) is especially detrimental to survival and normal body functions. In addition, loss of BCM is associated with fatigue, depression, and reduced quality of life.<sup>4</sup> Decreases in BCM and increases in extracellular fluid levels are hallmarks of infection and injury. In early HIV infection, the alterations may even out and weight levels may not change to reflect the detrimental process.<sup>5</sup>

Increases in resting energy expenditure (REE) have been documented in early HIV infection and has been associated with the level of HIV virus in the blood (viral load).<sup>6</sup> Research on this topic is equivocal and the mechanisms for alterations in REE are likely to be multifactorial and different between persons tested based on a number of risk factors, including baseline and changes in nutritional status, dietary intake, symptoms experienced, and treatment-related complications.<sup>7</sup>

Cytokine levels, mediators of immune responses, have also been implicated in elevations of REE and the loss of lean tissues regardless of treatment and even without weight losses.<sup>8</sup> High levels of cytokines in the blood that are a consequence of infection were related to wasting.<sup>9</sup> However, there appear to be differences between men and women in this finding. For instance, weight loss in women appears to favor fat loss where men tend to lose lean tissues.<sup>10 11</sup>

Additional protein intake has been recommended in many chronic infectious diseases and HIV infection is no exception. Increasing amounts of amino acids were provided to boost protein intake in patients receiving parenteral nutrition to find that an increased amount of protein can improve nitrogen balance in AIDS patients, protein turnover is highly variable and correlated with the volume of BCM as a percentage of weight, and does not follow a linear effect in altering balance through increased protein synthesis.<sup>12</sup> Another study of amino acid flux in leg tissue of HIV-infected patients compared to controls suggested that though there may be cases of adaptation through reduced protein breakdown, protein synthesis may be severely depressed allowing for a progressive wasting of protein tissues.<sup>13</sup>

### *Effects of Wasting in HIV Infection*

Nutritional status markers are independently predictive of morbidity and mortality in HIV infection. The severity of wasting can be used as a prognostic indicator in patients not taking ARVs who lose more than 20% of their weight from baseline surviving an average of 48 days compared to those losing less than 10% surviving for more than 500 days.<sup>14</sup>

Wasting processes are associated with a number of detrimental endocrine changes, such as reduced testosterone levels and elevated cortisol levels when compared to controls without wasting.<sup>15</sup> In one study, reduced testosterone levels were seen up to six months before the documentation of wasting syndrome, suggesting that a reduction in these muscle-preserving hormones may also contribute to the wasting process.<sup>16</sup> Hormone replacement therapy and hormonal modulation has been the topic of much of the research on treatment of wasting syndrome in HIV infection.

### *Effect of Co-Infection on Nutritional Status*

HIV infection with immune suppression can increase risk for co-infections leading to additional nutritional decline. Patients who have co-infection with another infection, such as tuberculosis (TB) may show a more severe pattern of malnutrition. Patients with HIV and TB co-infection appear to have an additive effect as an added inflammatory process and immune challenge. Co-infected patients showed more symptoms of oral candidiasis, diarrhea, lymphadenopathy, skin disorders and other problems compared to patients infected with TB alone.<sup>17</sup> Patients co-infected with HIV and TB were compared to patients with TB alone to find that nutritional differences were related mostly to lower CD4 cell counts (<200 cells/microL) indicative of immune suppression.<sup>18</sup> While co-infected patients showed more severe malnutrition, typically used anthropometry may underestimate the severity of malnutrition because of the expansion of extracellular fluids that adds to total weight while not contributing to the maintenance of body functions.<sup>19</sup>

In a cross-sectional study in Malawi, patients with TB or TB-HIV co-infection were compared and stratified according to viral load. Patients with low viral loads showed comparable values of micronutrients with those who were infected with TB alone, while patients with higher viral load and increasing severity of wasting showed more micronutrient alterations.<sup>20</sup>

### *Prevention of Malnutrition in Chronic HIV Infection*

A recent consensus conference of economists convened in Copenhagen identified HIV/AIDS, hunger and malnutrition, and malaria as three of the top four most important challenges facing the world today.<sup>21</sup> Investment in the prevention and treatment of these problems could yield much greater economic benefits. Not all patients with HIV infection experience wasting, though it appears to be quite common for patients to have one or more wasting episodes during the course of the disease. While chronic HIV infection, opportunistic infection, and drug-related symptoms appear to pose the greatest risk factors for weight loss and other

nutritional alterations, it is possible that containing the damage could improve survival and reduce adverse effects on morbidity and quality of life as well as improve prevention efforts.

### Evidence Based Practice Q&A

- 1-1. What consequences of HIV infection lead to malnutrition?
- 1-2. What nutrient alterations are seen in HIV infection?
- 1-3. What alterations are associated with markers of malnutrition in HIV infection?
- 1-4. How can malnutrition be prevented in HIV infection?

## Chapter 2. Nutrition Assessment Factors in HIV Infection

### **Abstract**

Nutritional status indicators are among the strongest predictors of survival in people living with HIV infection. Thus, assessment factors can be useful both as nutritional status indicators and as risk factors for disease progression. Regardless of the setting, there are hierarchies of nutritional assessment factors that can be used to determine urgent or upcoming problems that may need to be addressed in an individual or a larger target population.

### Background

Nutritional status indicators include body measures (anthropometry and others), biochemical, clinical history and status, and dietary history. Anthropometry includes various measures of body dimensions and volumes. For instance, weight and weight change are important features of health and nutritional status changes. An added measure, height, provides the ability to determine if baseline weight and changes are appropriate to maintain health or if there is additional risk for mortality through the calculated body mass index (BMI). Further measures to determine body composition, fluid shifts, and fat patterns can help to determine the reason behind and impact of disease and other factors affecting nutritional status as well as to monitor the ability of the body to appropriately respond to interventions. Body circumferences and fatfolds, bioelectrical impedance analysis (BIA), computed tomography (CT) scans, magnetic resonance imaging (MRI), dual energy Xray absorptiometry (DEXA), and other methods of body composition and patterning analysis further define problems and assist in determining appropriate interventions for both nutritional status and disease process.

Biochemical measures include disease indicators (such as viral load, CD4+ immune cell counts, c-reactive protein,) and nutritional indicators (serum albumin, prealbumin, hormone levels, and vitamin/mineral levels). Disease process has a strong impact on maintenance of nutritional health and the success of nutrition-related interventions. In addition, nutritional status has a strong impact on the effectiveness of medications and other interventions aimed at controlling the disease process.

Clinical status and history includes disease status, complicating factors (such as opportunistic infections, symptoms, and other diseases), and medication history. Opportunistic infection often initiates nutritional compromise causing symptoms that block nutrient intake (loss of appetite or pain), diminish the ability to absorb adequate nutrients (malabsorption, diarrhea), and change the way the body uses and stores nutrients (altered metabolism and hormonal changes). Both interview and laboratory findings are used to determine clinical status.

Diet history includes food and nutritional security items, food volume and quality choices, and cultural issues that affect food choices. Food and nutritional security estimations can be done at the regional, country, community, and individual

levels. For instance, regional agricultural trends, especially in developing countries, will help to determine food resources and missing pieces. Country policies on imports and exports can affect the availability of quality foods. Employment levels and the portion of the population living below poverty levels can identify at-risk populations. Estimated HIV infection prevalence and incidence can help to identify urgent needs for nutritional evaluation and interventions. Community structure can identify appropriate routes for investigation and intervention. Family composition and resources can help to determine appropriate interventions. Individual food preferences and diet recalls can determine the risk for nutritional compromise and the need for a wide range of interventions, such as education, food aid, and therapeutic feeding.

## Literature Review

### *Nutrition-Related Measures*

Typical clinical evaluation of includes various factors that contribute to the decline, maintenance, and rehabilitation of nutritional status. In addition to these items, measures of food and nutrition security, knowledge, and psychosocial and economic risk factors and indicators can assist in the development of community-based and other programs to address the nutrition-related problems associated with HIV disease.

### *Examples of Measures Related to Survival and Disease Outcomes*

Nutrition-related predictors of survival include weight loss from baseline and BMI. In HIV-infected patients weight loss of less than 5% from baseline and a body mass index of <20 were independent predictors of mortality and HIV disease progression.<sup>22 23 24 25</sup> In addition, BMI is associated with CD4 counts, making it a potentially useful surrogate marker in areas where routine laboratory measures are unlikely to occur.<sup>26 27</sup> Improvements in BMI have been related to improved survival. In one case, mild to moderate obesity was inversely related to mortality in a comparison of HIV-infected drug users and HIV-negative controls without impairing immune factors and independent of immune cell counts.<sup>28</sup> These findings that have been repeated in independent research suggest that height and weight measures and the calculation of BMI should be considered a minimum data set for all programs that provide care and treatment to HIV-infected people. In addition, BMI is related to other nutrition and disease measures that are also predictors of disease outcomes, such as anemia.<sup>29</sup>

More specific measures of lean body tissues and inflammatory processes are also independent predictors of survival. Lean body mass adjusted for height and C-reactive protein measures were more significant predictors of survival than more traditional measures of albumin, prealbumin, and weight loss in a multivariate model.<sup>30</sup> Measures of vitamin and mineral status can be difficult to interpret in the presence of chronic inflammatory infection. A diagnosis of anemia will require

differentiation between simple iron deficiency and anemia of chronic disease, both of which may be present and may require very different approaches.<sup>31 32</sup>

Serum vitamin and mineral levels can be altered by deficiency and/or altered metabolism as seen in chronic inflammatory diseases, such as HIV infection. Exploration into the specificity and sensitivity of testing is required in the context of HIV infection to determine the validity of commonly used tests for nutrient deficiencies. Such a study was conducted in 600 Kenyan women to demonstrate that serum retinol-binding protein is valid even in patients with HIV infection and an acute phase (inflammatory) response that alters nutrient metabolism.<sup>33</sup> Vitamin B12 levels may be depressed in a subgroup of patients with HIV despite adequate intake and with malabsorption problems. Interestingly, vitamin B12 and folate levels may improve after the initiation of antiretroviral therapies.<sup>34</sup> However, differentiating a real deficiency which will require supplementation from altered metabolic processes which may suggest that supplementation is contraindicated and potentially dangerous can be difficult.<sup>35</sup> Acute phase responses can lead to a low serum level of vitamin A in a comparison of women with or without HIV infection to show that low concentrations of vitamin A may reflect active infection more than a deficiency and that supplementation in those circumstances may not yield improvement.<sup>36</sup> Instead, reducing the inflammatory process by treating infection may yield better results. Such conditions should be considered in evaluating studies of nutrients that change under inflammatory conditions.

True deficiencies can be seen in cases of reduced nutrient intake and malabsorption, both common issues in people living with HIV infection. Starting at birth, the gastrointestinal tract requires exposure to both nutrients and antigenic microbes to develop immune cell function and cytokine responses. Nutrient deficiencies can result from imbalances of nutrients and gut flora as well as an impairment of immune response in the gut.<sup>37</sup>

#### *Examples of Measures Associated with Disease and Treatment-Related Alterations*

Nutritional indices may differ due to confounding conditions and co-infection. In a small study comparing men with asymptomatic HIV infection to those with symptoms, BMI and lean tissues were similar despite the findings of increased REE and protein breakdown.<sup>38</sup> The compensation appeared to be an increase in energy intake and protein synthesis. Lower protein catabolism and synthesis are signs of starvation processes, which has been documented in chronic HIV infection.<sup>39</sup> A low-grade impairment in protein synthesis even in apparently asymptomatic HIV infection that can lead to progressive wasting has also been documented. This loss of lean tissues appears to continue to be common regardless of the use of ARVs and may be related more to cytokine production than dietary intake. Weight losses may be contained by increased energy intake to compensate for elevated REE, but the protein stores may require additional intervention.

A recent history of AIDS-defining diagnoses can predict wasting processes. Opportunistic infection has been associated with the initiation of an acute wasting process whereas gastrointestinal involvement is associated with chronic wasting.

Both have been tied to both decreased nutrient intake and increased metabolism.<sup>40 41</sup> Altered metabolism, especially of protein and fat, may impair efforts to rehabilitate nutritional status with nutrient-based therapies and should be considered in assessment and intervention strategies.

In HIV-infected intravenous drug users, lower BMI and alterations in vitamin and mineral levels, such as vitamins B6 and B12 and minerals selenium and zinc despite similar energy intake levels when compared to HIV-infected non-drug users.<sup>42</sup>

### *Measures to Monitor Interventions*

Whether the goal is to improve food and nutrition security of a population or body mass index of an individual, nutrition-related interventions should be monitored for desired and potentially adverse effects. Measures should be sensitive and specific as well as purposeful to direct patient care. Minimum data sets of measures can be instituted for general health impact evaluation, such as BMI. In addition, measures to determine improvements in levels of body stores that impact the ability to adequately process medication therapies may include estimations of body cell mass. For instance, if a goal is to improve protein status of the body, a measure of nitrogen balance may require an understanding of dose-related responses and the additional nitrogen required for deposition as well as achieving an “in/out” balance. Close monitoring of potentially problematic interventions, such as those aimed at reversing an apparent iron deficiency anemia, may include routine evaluation for potential toxicity in iron stores and further differentiation of anemia types. Additionally, indirect effects of nutrient-related interventions should be considered, such as social and economic markers.

### Evidence-Based Practice Q&A

- 2-1. What measures should be a part of a minimum data set?
- 2-2. What measures can be used to determine appropriate interventions?
- 2-3. What measures are necessary to determine the effectiveness of interventions?

## Chapter 3. Nutrient Needs in Chronic HIV Infection

### **Abstract**

The World Health Organization released a technical advisement report to review current research supporting nutrient recommendations in persons with HIV infection. This report noted a general increase in calorie needs with inadequate data to support alterations in protein, fat, and many micronutrient requirements. While nutrient needs are individually determined, an understanding of nutrient needs based on commonly presenting co-morbidities may help to more specifically define the changes in nutrient requirements that may occur differing presentations may more realistically address the needs of populations in highly affected regions of the world.

### Background

The World Health Organization released a report on “Nutrient requirements for people living with HIV/AIDS” based on a technical consultation in Geneva, Switzerland in May 2003.<sup>43</sup> In this paper, it was concluded that energy requirements may increase as necessary to maintain weight and physical activity by about 10%, symptomatic HIV infection presents greater challenges and potential increases in energy needs of 20-30% to support adult weight maintenance, and that HIV-infected children may require 50-100% additional energy to restore lost weight. Reversal of stunting requires adequate and sustained access to food.

This report also concluded that protein studies in HIV were insufficient to make a recommendation beyond the requirement of 12-15% of total energy intake. There was insufficient research to support changes in fat calorie requirements. And while there is some evidence that interventions with micronutrients may be beneficial in nutritionally challenged populations with HIV infections, recommendations were held to ensure RDA levels of nutrient intake. In addition, the report suggested that rehabilitation from micronutrient deficiency may require greater levels of intake and that high levels of problematic micronutrients (vitamin A, zinc, and iron) have the potential to produce adverse outcomes. Evidence for changes in standard recommendations based on non-HIV infected populations for iron-folate and vitamin A supplementation was considered lacking and no modifications were recommended. The report considered caveats specific to HIV infection for fat and micronutrients but did not mention the potential for alterations in protein absorption and metabolism. For instance, the report mentioned that altered fat intake may be required in cases of persistent diarrhea to reduce the common problem of fat malabsorption-induced diarrhea. However, the presence of fever and diarrhea, both common consequences of HIV infection, medication interactions, and opportunistic infections will typically increase protein requirements and were not considered in this report.

The knowledge gaps mentioned in this report included the effect of HIV infection on nutrient requirements throughout the lifecycle, what are optimal intakes

of nutrients in the presence of metabolic stress including gastrointestinal infection or other co-infection, what are the safe upper limits for nutrients in the context of HIV infection, what effect nutritional status and interventions have on HIV disease and related complications, and what is the interaction between nutrition and antiretroviral therapies.

For operational research, the report suggested evaluating the response to food and nutritional recovery and determining a need for policy change specific to interventions targeted to HIV-infected populations.

In addition, the WHO issued a set of guidelines to determine HIV infection and disease progression in resource limited settings where confirming laboratory values may be more difficult to obtain. The clinical case definition for pediatric HIV infection may not be sensitive enough to adequately discriminate between HIV-infected and non-infected children.<sup>44</sup>

## Literature Review

### *Nutrition Issues in HIV-Infected Children*

Regardless of the classification of death for children worldwide (70% are attributed to diarrheal illness, respiratory infection, and immunizable diseases), malnutrition may have the strongest impact on mortality.<sup>45</sup> Growth indicators are often compromised in pediatric HIV infection. While energy expenditure may be similar between HIV-infected children with normal growth compared to those with growth deficits, energy intake appears to be significantly lower in growth impaired children. In addition, more severe HIV disease stage, increased inflammatory markers (cytokines), and decreased levels of insulin-like growth factor (IGF-1) and serum proteins are associated with growth impairment in children with HIV infection.<sup>46</sup>

There may be difference in the type of malnutrition experienced by children who are HIV-infected compared to those who are not. In Zimbabwe a cross-sectional look at children admitted to the hospital (68 HIV-infected and 72 non-infected) suggested that marasmus and marasmic kwashiorkor were the predominant forms of malnutrition in infected children while kwashiorkor was more common in non-infected children ( $p < 0.001$ ). During their admission, 32 (22.8) children died. Their mortality was closely associated with less than 60% of their expected weight while it was not associated specifically with HIV infection.<sup>47</sup>

In Malawi 250 severely malnourished children older than 1 year of age were evaluated to find that more than a third were HIV-infected and the mortality rate of the whole group was 28%. This study supported the notion that marasmus is the predominant form of malnutrition ( $p < 0.0001$ ). Breastfed infants with malnutrition were more likely to be HIV infected than infants who were not breastfed.<sup>48</sup> In South Africa a group of 181 children ranging from 3 months to 4 years of age were evaluated for causes and consequences of diarrhea. Thirty-one children were HIV-positive and were more likely to be malnourished ( $p < 0.001$ ) and there was a trend toward more common chronic diarrhea ( $p = 0.07$ ) though there was no significant

difference in the types of pathogens seen in the stool.<sup>49</sup> This study suggested that the defining difference in HIV-infected versus non-infected children was the prevalence of malnutrition. Diarrheal disease was also explored in 200 Zambian children, 108 of whom were HIV infected. While the pathogens were not significantly different, marasmas was more common in HIV infection and kwashiorkor was more common in uninfected children. Lower Z scores were seen for weight for age ( $p < 0.0001$ ) and similar differences were seen for weight for height, height for age, and midarm circumference measures. Mortality in 39 (20%) of the children was most related to marasmus and cryptosporidiosis.<sup>50</sup>

1854 children under five years of age in Dar es Salaam, Tanzania were evaluated for nutritional status and HIV infection. Stunting was seen in 32%, underweight in 15%, and wasting in 3%. HIV infection and low birthweight were associated with stunting and wasting.<sup>51</sup>

Failure to thrive, or chronically impaired growth and malnutrition, is common in HIV infected infants. Both maternal and child risk factors are associated with failure to thrive defined as age and sex-adjusted weight score of  $\leq -2.0$ .<sup>52</sup> Growth impairment was associated with smoking and the use of illicit drugs in pregnancy. Risk factors of children include pneumonia, low CD4 cell counts, exposure to ARVs (non-PI) within three months of birth, and viral load.

Many children have existing malnutrition at baseline and may require more energy and protein to achieve growth, especially after bouts of diarrhea. Increased protein levels can improve catch-up growth rates to restore nutritional status in malnourished children.<sup>53</sup>

In Zimbabwe, the relationship between HIV infection, bacteremia, and nutritional status was explored in 212 children between 0 and 5 years of age who died at home and were brought to the hospital within 3 hours of death. 122 of these children were HIV infected and 110 were malnourished. There was a strong association between malnutrition and bacteremia ( $p < 0.001$ ) and the authors suggested that there was additional association with HIV infection that malnutrition could not explain.<sup>54</sup>

Several co-factors contribute to health decline and malnutrition in chronic HIV infection, including infections and symptoms of diarrhea, nausea, and appetite losses. In Zambia, of 1266 children enrolled in the study, a high prevalence of HIV infection was associated with tuberculosis, malnutrition, pneumonia, and diarrhea with a significantly higher mortality rate among HIV-infected children (19%) compared to uninfected children (9%) ( $p < 0.0001$ ).<sup>55</sup> In India, children presented with a number of infections, mostly oral candidiasis and pulmonary tuberculosis. In this study there were 7% who presented with diarrhea.<sup>56</sup>

HIV-positive children ( $n=6$ ) compared to controls ( $n=4$ ) in addition to a perpetual protein catabolism due to the inability to downregulate this process. This process can lead to growth failure and potential for secondary infections.<sup>57</sup>

A study of whole body protein turnover was conducted in 26 children, including 10 HIV-infected and growth retarded children, 12 HIV-infected children without growth retardation, and 4 controls. Whole body protein turnover was 42%

greater in the HIV+ growth retarded children and 24% greater in non-growth retarded HIV-infected children compared to controls. Significant relationships were found between the whole body protein turnover rate and variables of Z scores for height ( $p=0.05$ ), weight for age ( $p=0.01$ ), and protein intake ( $p=0.02$ ) while there was no relationship between turnover and resting energy expenditure and CD4 cell count. The authors suggested that it may be possible to achieve protein balance if there is an adequate intake of calories and protein.<sup>58</sup>

In children the protein response to HIV infection includes an increase in acute phase protein synthesis (APPs) and a negative protein balance. Protein intake may be lower in HIV-positive children ( $n=6$ ) compared to controls ( $n=4$ ) in addition to a perpetual protein catabolism due to the inability to down regulate this process. This process can lead to growth failure and potential for secondary infections.<sup>59</sup> HIV infection drives the increase of whole body protein turnover as a normal response to infection to allow the body an opportunity to defend itself. It appears that children with marasmus and acute infection experience higher turnover rates with net conservation of these amino acids to produce protective proteins than children with kwashiorkor and acute infection, who typically have a higher mortality rate.<sup>60</sup> This finding could have important implications on assessment and treatment of children with HIV and co-infections.

#### *Nutrition Issues in HIV-Infected Adults*

Maternal health affects pregnancy outcomes. HIV infection in pregnant women has yielded negative pregnancy outcomes, such as low weight gain during pregnancy and low birth weight of the child.

Several reviews have been written to describe the causes, consequences and treatment strategies for weight loss and wasting. The best predictors for survival with HIV infection are nutritional markers of weight, body mass index (BMI), and body cell mass. In a study of predictors of survival it was noted that contributors to malnutrition may include a reduced nutrient intake, increased resting energy expenditure, chronic diarrhea, and opportunistic infections. Strongest predictors of survival included CD4 cell counts, lean body mass adjusted for height, and the inflammatory marker of C-reactive protein. Patient age, stage of disease, use of antiretroviral therapies, and previous opportunistic infections were not associated with survival.<sup>61</sup>

Weight losses of any type are risk factors for mortality in HIV-infected populations. Weight loss can occur in fat-free mass, body cell mass, and fat. Weight loss episodes may be documented as weight lost from baseline (premorbid) weight or as any weight loss from other previously documented weights. Interestingly, there appears to be a higher prevalence of wasting (35% higher in one cohort) more recently than in the first two years after the introduction of HAART combinations, though improvements were seen in those receiving nutrition intervention.<sup>62</sup> Weight loss is multifactorial and may represent a variety of different types of weight and differing consequences. Acute infections can lead to preferential loss of lean tissues. Once lean tissues, particularly body cell mass, are depleted through both acute

infection challenges, reduced nutrient intake, and malabsorption the person with HIV infection is likely to show a normal response of hypometabolism. In patients with malabsorption there may not be an adequate additional intake of energy to balance and maintain weight. Even so, clinically stable patients may be able to maintain adequate energy balance for periods of time, which suggests that the wasting process may be intermittent rather than a linear decline.<sup>63</sup>

Higher levels of resting energy expenditure have been documented in HIV infection. While the level of energy expenditure is related to the level of calorie burning lean tissues, the level remains higher per kilogram of fat-free mass in HIV infected women compared to controls.<sup>64</sup> In a comparison of 22 HIV-infected patients with 8 controls, protein turnover rate was significantly increased in the symptomatic AIDS patients (n=14). Fat oxidation was greater in HIV infection than in controls. The authors suggested that though protein turnover may be increased, there was no significant impairment in anabolic response to nutrition support.<sup>65</sup>

A potential contributor to muscle wasting may include altered muscle protein metabolism in HIV infection. Nine HIV-infected men with documented wasting, 14 HIV-infected men without wasting, and six controls were evaluated for muscle metabolism. The results suggested that AIDS wasting was a result of preferential loss of muscle protein and the inability to sustain an increased protein synthesis.<sup>66</sup>

Protein metabolism was explored by comparing 9 asymptomatic AIDS patients with 13 controls. This study suggested that there is both a lower protein catabolism and synthesis rate suggesting a starvation-type response. The authors of this study suggested that this process could contribute to the risk for opportunistic infection.<sup>67</sup>

Co-infection presents additional challenges to the maintenance of nutritional status and overall health. Tuberculosis infects an estimated 1.86 billion individuals or nearly a third of the world's population.<sup>68</sup> Tuberculosis (TB) is the most common co-infection with HIV in developing countries and both are known as wasting diseases.<sup>69</sup> While both alone are wasting diseases, even lower body weight, body mass index, and fat-free mass has been documented in people with HIV-TB coinfection.<sup>70 71</sup> In men and women with pulmonary tuberculosis with or without HIV infection (n=261 and 278 respectively) in Uganda, there were no significant differences seen in BMI or the number of patients below a BMI of 19 in each group. However, mean BMI was approximately 18 in men and approximately 19.5 in women, both below the level of 20 that is associated with increased risk of mortality.<sup>72</sup> Authors speculated that poor nutritional status may be a greater risk factor for TB coinfection than HIV infection alone. In another study, normal BMI and even obesity seemed protective against TB infection in HIV-negative men.<sup>73</sup> In this study, lower BMI, body cell mass (BCM), and fat mass were associated with more advanced HIV infection as indicated by a CD4 cell count of less than 200.

HIV infection is associated with a reduced whole body protein flux whereas TB is not associated with abnormal protein metabolism. While protein anabolism is possible in healthy controls (n=11) and even in the tuberculosis alone (n=10) and HIV infection alone (n=10) groups, the HIV with TB coinfection (n=8) group was associated with impaired anabolism response to feeding.<sup>74</sup>

Chronic diarrhea and wasting have historically been features of HIV infection in both developed and developing nations. In Zambia, 262 HIV-infected adults and children were evaluated for weight loss and chronic diarrhea. Weight loss was closely related to the presence of chronic diarrhea. Children presented with diarrhea in about half of the cases regardless of HIV status, however weight loss, and specifically marasmus diagnosed as <60% of expected weight without edema, and tuberculosis was significantly more common in children with HIV infection. More than a third of the HIV-infected children presented with marasmus, more than half with chronic diarrhea, and nearly two-thirds with weight loss. In adults, both chronic diarrhea and wasting was more common in HIV infected patients than in uninfected adults. Mortality was most common in adult patients with chronic diarrhea ( $p<0.01$ ) and lymphadenopathy ( $p<0.04$ ) when adjusted for other risk factors. The authors conclude that the prevention and nutritional rehabilitation in cases of chronic diarrhea may be especially important to prevent weight loss, wasting, and death.<sup>75</sup> Diarrhea can affect up to 90% of patients with HIV infection, especially those with significant immune suppression. Diarrhea is associated with increased morbidity and mortality in HIV infection and is especially problematic in developing countries. Multiple causes may include unsanitary conditions, medication or herbal interactions, malnutrition, and infections. Treatment includes prevention and treatment of causes as well as restoration of fluids and electrolytes to prevent further dehydration.<sup>76</sup>

#### *Metabolic Disorders in HIV Infection*

Metabolic alterations are a common finding in any inflammatory condition, but especially problematic in chronic, life-long inflammatory diseases, such as HIV infection. Many of the metabolic alterations are related to or affect nutrient status in the body and therapies can range from nutrient-based strategies to adjunctive therapies aimed at balancing hormonal milieu. While not common, lactic acidosis can be a mild to severe and even life-threatening condition related to oxidative stress and medication interactions, particularly on nucleoside ARV therapies. A cross-sectional study of 350 HIV infected patients suggested that hypothyroidism prevalence was approximately 16% ranging from subclinical to overt hypothyroidism which correlated with the use of stavudine and low CD4 cell counts. The authors suggested screening for patients with low CD4 counts and receiving stavudine.<sup>77</sup>

Equivocal results have been seen for changes to androgenic hormones in women. Compared to controls ( $n=16$ ) and HIV-infected women without physical evidence of lipodystrophy ( $n=14$ ), women with lipodystrophy ( $n=9$ ) showed a syndrome of hyperandrogenemia characterized by increased levels of total testosterone, free testosterone, and luteinizing hormone. While lipodystrophy appears to be correlated with hyperandrogenemia in women the relationship between this finding, lipodystrophy, and insulin resistance requires additional exploration.<sup>78</sup> Another study suggested that women with wasting may experience androgen deficits that lead to the additional consequences of osteopenia and osteoporosis, while the preservation of muscle mass appeared to have a preservation effect on bone density.<sup>79</sup>

However, in another study in HIV-infected women who had a low body mass index or weight loss (n=69), nearly half had lower than expected levels of testosterone compared to 8% of the control population. A weight loss of 10% from maximum weight levels was correlated with depressed levels of testosterone. The use of antiretrovirals did not appear to be related to androgen levels.<sup>80</sup>

Diagnosis of androgen deficiency includes free testosterone levels and treatment includes intramuscular testosterone injections or transdermal patches or gel to normalize testosterone levels in both men and women may help to improve weight, lean body mass, energy, and quality of life.<sup>81</sup>

### Nutrition Interventions

Treatment for HIV infection is essential to the maintenance of nutritional status. Prior to treatment, interventions should be aimed at preserving nutritional reserves. The ability of antiretroviral therapies to reverse nutrition problems related to HIV infection is incomplete. With the use of highly active antiretroviral therapy regimens HIV-infected persons may gain weight primarily as fat without simultaneous restoration of important lean tissues. In such cases, additional efforts that may include nutrient modulation, exercise, and hormonal treatments may be required.<sup>82</sup>

Interventions range from basic education and nutrient support to the correction of metabolic abnormalities and other disease management strategies.<sup>83</sup> In both TB and HIV programs, nutrition-related interventions have been important features of successful treatment programs. Food or supplements for adults and children have been used as incentives to attend and adhere to treatment programs for tuberculosis.<sup>84</sup>

#### *Counseling and Calorie-Containing Supplements Intervention*

The nutrient intake of HIV-infected populations may vary according to many factors, including stage of illness. In general, HIV-infected persons may increase calorie intake in an effort to balance against the catabolic process, and still have less than optimal body mass indexes.<sup>85</sup> The ability to respond to enhancements in calories and protein may depend on the appropriate anabolic response of the body. In some cases, HIV-infected patients may develop an “anabolic block” preventing the calories from being effectively integrated and normalizing body tissues, particularly body cell mass.<sup>86</sup>

The use of calorie containing supplements with counseling was compared to nutritional counseling alone in 50 patients showed that patients were able to increase calorie intake by about 600 calories per day. Both groups gained weight and body cell mass, with fairly significant increases in fat-free mass from baseline by week 8 (p<0.05). The authors suggested that though supplements can displace some caloric intake through foods, they may improve adherence to a weight gain program.<sup>87</sup>

Increased nutrient intake was achieved by tube feeding for 18 children (15 under the age of two years) which resulted mostly in improved weight with less improvement seen for height.<sup>88</sup>

A study of 35 malnourished children between 24 and 59 months of age who showed signs of chronic and acute malnutrition showed a higher than standard protein intake resulted in significant improvement in weight and fat-free mass within 21 days. Thus the researchers suggested that a protein intake level of up to 200% normal recommendations can accelerate the catch-up growth process and should be considered.<sup>89</sup> In malnourished elderly patients without disease, an increase from recommended levels of protein intake of up to 15% of calories was increased to 19.4% of calories and yielded a significant difference in weight gain and fat-free mass gain through the stimulation of nitrogen kinetics and improved protein deposition into muscle tissues. The authors of this study suggested that improving the ratio of protein to calories in malnourished patients may significantly improve the desired outcome of improving weight and specifically the volume of lean tissues, muscle strength, and functional status.<sup>90</sup>

High protein diets may be required to reverse catabolism. A study that combined high-protein oral supplements with medroxyprogesterone acetate (an appetite stimulant and antineoplastic agent) or placebo showing that protein (specifically amino acid) utilization may be more efficient in the presence of the hormone.<sup>91</sup>

How much protein is required to achieve a positive protein balance in HIV is quite variable. In one small six-patient study, protein balance was achieved by one patient at as little as 0.6 g/kg of amino acid infusion, while another patient required 1.8 g/kg amino acid infusion to achieve the same result.<sup>92</sup>

Food interventions were compared to oral nutrient supplementation in 46 patients in two 45 day periods with a cross-over design. Nitrogen balance improved in the oral supplementation group and weight gain achieved was sustained over the 90 day follow-up period.<sup>93</sup> Protein balance may not be enough when the goal is to rehabilitate lost protein stores and a positive nitrogen balance should be maintained until rehabilitation has occurred.

While nutrient interventions are essential, a randomized, controlled trial comparing an immune-enhancing calorie-containing formula to a standard formula showed no significant differences in nutrition or immune cell outcomes.<sup>94</sup> A peptide-based formula with n-3 fatty acids was compared to a standard calorie-containing formula. Results showed an improved weight and fat mass in both groups with a significant improvement in CD4 cell counts in the peptide/n-3 fatty acid-containing formula.<sup>95</sup>

Lipodystrophy is associated with cardiovascular risk and the inability to appropriately store fat. A very low fat diet has been recommended in cases of lipodystrophy to reduce the LDL cholesterol and the availability of free fatty acids for depositing as fat. In addition, the authors recommended further actions to improve insulin resistance and lipid metabolism, such as aerobic exercise.<sup>96</sup>

Food records were reviewed to compare differences in diet between men who had developed altered fat patterns (n=47) and men without fat changes (n=47). Men

without altered fat consumed more calories, protein, and fiber as well as included resistance exercise and did not smoke.<sup>97</sup> In a review of dietary intake and metabolic alterations in 85 patients, fiber, alcohol, and the consumption of polyunsaturated fatty acids were related to insulin resistance and hyperlipidemia. The authors suggested that dietary modification of these nutrients may assist to normalize insulin and lipid levels.<sup>98</sup>

### *Micronutrients*

Intervention with micronutrient supplementation has been most concentrated in the area of mother to child transmission (MTCT). While much more research is warranted, several studies have concentrated on the impact of single and multivitamins on disease progression and survival.

The effect of vitamin supplementation on weight gain during pregnancy was tested in 1075 pregnant and HIV infected women in Tanzania in four groups: placebo (n=234), vitamin A alone (n=239), multivitamins without vitamin A (n=237), and multivitamins with vitamin A (n=247). The group taking multivitamins containing vitamin A showed the best results with a significant weight gain (p=0.04) and a 29% reduced risk for low weight gain that women who received multivitamins alone without vitamin A. There was no effect seen in the placebo and vitamin A alone groups. Women in earlier stages of HIV infection fared better than those in stage II and higher.<sup>99</sup>

A case study suggested that intravenous thiamine added to total parenteral nutrition was able to reverse an episode of ARV-induced (nucleoside) lactic acidosis. In addition to thiamine and riboflavin, an overall high-dose regimen of intravenous B vitamins was suggested for nucleoside-induced lactic acidosis.<sup>100</sup>

Vitamin E was explored for its ability to enhance CD4 cell counts and to determine the mechanism of this enhancement. The researchers conducted a cell culture study with and without vitamin E to find differences. The cell cultures with vitamin E showed the ability to prevent cell destruction, thus increasing total numbers, while the cell cultures without vitamin E showed the expected CD4 cell destruction reducing total cell counts.<sup>101</sup> The authors suggest further research on both vitamin E and retinoic acid to reduce CD4 cell death in HIV infection. Vitamin C exposure in cell cultures suggested that high doses may be toxic to infected T-cells thus reducing viral production.<sup>102</sup> The role of antioxidants at the cellular level appears to be complex and varies according to antioxidant, cell line, and mechanism for reducing the destructive effects of HIV infection.

Oral supplements of vitamins C (1 g/d) and E (0.6 g/d) were tested against controls (n=7) for effects on AZT-induced oxidative damage to show that the oxidative damage is reduced significantly in patients taking the antioxidant supplements (n=5) for a period of one month.<sup>103</sup>

## Recommendations Based on Current Evidence

In answer to the question about how much of each nutrient a person with HIV infection and co-morbidity needs, there is evidence to support three primary recommendations and suggestions to consider others.

### *Calories*

Resting energy expenditure appears to be increased in most studies, however total energy expenditure may not be increased. This suggests an inability to downregulate catabolic activity in the face of a starvation response that would normally be induced, such as that seen in tuberculosis patients without HIV co-infection. In cases of severe marasmus, patients may be able to downregulate the catabolic process reflected in resting energy expenditure because of a significant loss in the calorie-using body cell mass stores. While evidence is equivocal in some cases, it generally supports an increase in energy requirements, particularly in cases of opportunistic infections. Intensive nutrition intervention may be required to achieve a balance of energy intake and weight stabilization in HIV infection. In a group of 54 patients not treated for HIV infection, progressive weight loss was reversed in 18 patients, halted in 31 patients, and continued in 5 patients.<sup>104</sup> This study suggested that intensive nutrition counseling followed by efforts to adequately feed patients at rehabilitation levels can stop and reverse detrimental weight losses.

### *Protein*

Not nearly as much investigation has been focused on protein needs. Several studies have established that the protein turnover rate is high and remains high in the face of starvation in people with HIV infection. This dysregulation appears to be efficient in maintaining the production of both positive and negative acute phase proteins. Studies of high protein oral supplements suggest the ability to achieve weight gain, anabolism, and weight stability. One small study quantified the amount of infused amino acids needed to maintain a zero or even positive nitrogen balance, which demonstrated that nitrogen balance can be accomplished in chronic HIV infection at a range from minimum needs in a healthy person of 0.6 g/kg/day up to 1.8 g/kg/day. While the small study probably cannot represent a complete range of changed protein needs, this indicated that there is a potential for maintenance or restoration of nitrogen balance at from between the approximate DRI to 2.25 times the DRI or from the minimum protein maintenance level for health persons to 3.0 times that level.

Interestingly, while calorie levels vary between individuals, the WHO general recommendations for an increase of between 10%-30% for calories and the maintenance of protein intake at up to 15% yields between 1.5 to 2.0 or more times the protein Daily Recommended Intake (DRI) for adults.<sup>105</sup> In addition, we know from metabolic studies in other disease states that the level of negative nitrogen balance is related to the level of weight loss and to fever. However, even when fever subsides, negative nitrogen balance may continue for several days to weeks,

continuing to deplete the body's important protein stores.<sup>106</sup> The provision of additional protein sources beyond that expected for healthy individuals can blunt the loss of body proteins during this phase of infection.<sup>107</sup>

While achieving nitrogen balance is desirable in cases where the body's protein stores are within a normal and functional range, a higher level of protein intake may be necessary to achieving a positive nitrogen balance to support deposition and rehabilitation of protein stores, particularly in the muscle and organ tissue compartments.

### *Fat and Carbohydrates*

Beyond energy needs, fat and carbohydrate requirements have not been well explored. Dietary manipulations are more likely to be based on co-morbidities such as hyperlipidemia and diabetes. Such dietary manipulations have not been well explored in the context of HIV infection, but are standard clinical practice.

### *Fiber*

Fiber-rich diets have been recommended in HIV disease based on the presence of co-morbidities that may be controlled using fiber as a part of a multifactoral regimen that included additional dietary modulation, exercise, and (in some cases) medications.

### *Micronutrients*

Recommendations for micronutrient intake in HIV infection remain at approximately the DRI levels. However, just as for other nutrients, co-morbidities should be considered. For instance, the presence of diarrhea may require replacement of several lost micronutrients including zinc and electrolytes. General recommendations suggest obtaining micronutrients from food as the most efficient source. However, in resource-limited settings where micronutrient-rich foods may be seasonal, the addition of a well-rounded micronutrient supplement that contains vitamin A is advised and may slow disease progression.

### Summary

Much more investigation is required to contribute to the body of literature that will be used to make recommendations regarding the nutritional management of people living with HIV infection and AIDS. Specific questions that remain unanswered include: What are the range of features that may affect nutritional status maintenance and rehabilitation that characterize HIV-infected populations? Should guidelines and policies be based on meeting the needs of the extremes of the range or on the most common features? If guidelines are based on the least common denominator of the asymptomatic and generally healthy person with a very low viral load, high CD4 cell counts, and with no risk for co-morbidities, what percentage of the population will be undertreated or ineligible for appropriate nutrition

interventions and the least of all possible requirements, what will the impact on the efficacy of feeding or other nutrition-related programming be?

### Evidence-Based Practice Q&A

3-1. What nutrition-related issues have been documented in children and adults with HIV infection?

3-2. What metabolic disorders that affect nutritional status maintenance have been documented in HIV infection?

3-3. What nutrition-related interventions have been explored and what is the potential for successful treatment of nutrition-related disorders in HIV infection?

3-4. What nutrient-based recommendations have been made and what documentation supports recommendations?

3-5. What are reasonable nutrient-based prevention and treatment strategies in resource limited settings?  
resource-limited settings?

## Chapter 4: Maternal-Child Nutrition in HIV Infection

### **Abstract**

HIV infection can initiate or exacerbate under-nutrition and can significantly impact pregnancy and maternal/child health outcomes. Maternal nutrition status affects fetal and child growth, the ability to breastfeed, and maternal and child survival. Both macronutrition and micronutrition are important features of evaluation and treatment in nutritional programs. Protein energy malnutrition can suppress immune function and protection, which feeds the downward spiral of disease progression, health decline, and mortality. Micronutrient malnutrition can limit the ability of the body to utilize energy and protein sources. Of particular interest in women and children are the problems with anemias, including iron or folate deficiency, anemia of chronic disease, and the initiation of anemias through bouts of infection with parasites and malaria. Both prevention and treatment strategies for resolving macronutrient and micronutrient under-nutrition should be included as primary interventions in maternal and child care and especially in persons exposed to HIV infection.

### Background

The interactions between HIV infection, nutrition, and maternal and child health are complex and ultimately cause declines in health and survival. Nutrient deficits of virtually any kind, including macronutrients and micronutrients, can result in immune deficits and result in infection and a higher risk of mortality.

Nutritional status of women can have a strong impact on pregnancy outcomes and the subsequent health and survival of children, even before pregnancy begins.<sup>108</sup> Malnutrition and infection during pregnancy can result in a low birth weight, which can lead to a number of health problems in infants and children.<sup>109</sup> Chronic malnutrition can alter both prenatal and postnatal development of the immune system and may cause long-term and difficult to reverse effects on immune response to infection and other challenges.<sup>110</sup>

Challenges in resource-limited settings and environmental issues require tailored solutions within each community, family, and individual to improve the benefit and reduce the risk or detriment to each intervention considered.

Prevention of maternal to child transmission (MTCT) plays a large role in the development of guidelines and programs to address nutritional adequacy during pregnancy, lactation, and infant/child feeding. Several guidelines address special feeding issues for HIV-infected women and their children.<sup>111 112 113</sup> In general populations, breastfeeding is considered a

benefit in several ways, including the reduction of mortality rates of infants. Avoidance of breastfeeding by HIV-infected mothers significantly reduces the risk for transmission of HIV infection to their child.<sup>114</sup> Limitations to the ability to feed infants with breast milk substitutes include accessibility, affordability, stigma, and the potential for higher risk mixed feeding. Guidelines for women in resource-limited settings who may experience these problems generally suggest exclusive breastfeeding with early cessation with a quick transfer to formula or other feeding. The rationale is that though breastfeeding can expose the child of a mother who is HIV-infected, most infants will not seroconvert to HIV-positive and may be safer and confer more protection to the child's health than the use of mixed feeding or breast milk substitutes that may not be as safely prepared.<sup>115</sup> In addition, antiretroviral (ARV) medications may be provided during breastfeeding to lower viral load in breast milk and provide short-term sustained protection to the child against seroconversion.

There may be considerable confusion by health care professionals, counselors, and women who must make choices about recommendations for pregnancy, lactation, and child feeding that may differ from non-infected persons. Tailored recommendations have been suggested for population subsets according to current practices and guidelines that may vary. However, this process to consider and tailor guidelines, educate those who impact choices, and put appropriate materials into practice may take sizeable effort. Outcomes of such efforts should be documented and shared with other programs seeking to benefit women and children with HIV infection.

## Literature Review

### *Pregnancy*

Pregnancy requires additional nutrients in order to support maternal health and fetal growth. Additional calories, protein, and several micronutrients are needed. Each stage of pregnancy is crucial to both ongoing and future physical and mental development in children. General recommendations to maintain nutritional stores, overcome deficiency, and promote appropriate growth and development for the fetus and child have been used for pregnant and lactating women that are living with HIV infection.

Nutritional status before, during, and after pregnancy has a significant impact on the health of both mother and child. The impact of macronutrient and micronutrient adequacy on pregnancy outcomes is fairly well understood.<sup>116</sup> In a study of 467 HIV-infected women and their children, body mass index and vitamin A status of the mother were associated with low birth weight and a shorter length at birth and subsequent growth failure.<sup>117</sup> Anemias associated with deficiency and chronic disease are challenging for evaluation and intervention during pregnancy. Iron and folate-rich foods are

important in the prevention and treatment of this serious threat that may be responsible for up to 20% of maternal deaths in Western Africa.<sup>118</sup>

There is ongoing debate about the value of micronutrient supplementation in resource-limited settings for pregnancy outcomes and disease progression in children and pregnant mothers.<sup>119</sup> Clear evidence-based recommendations for nutrient supplementation may not be available at this time.<sup>120</sup> There are a number of investigations that have been suggestive of a role for micronutrients in achieving optimal outcomes and guidelines generally suggest nutrient adequacy as a goal.

Nutrient toxicity and additional nutrient deficiency are possibilities when single nutrients are supplemented.

Some investigation has suggested supplementation of micronutrients to improve child survival in cases of HIV-infection, immune impairment, and nutritional compromise in pregnant and lactating women.<sup>121</sup> A clinical trial designed to demonstrate the potential effect of multi-micronutrient supplementation beyond the usual iron and folate provision on child length and birth weight suggested that micronutrients may not significantly affect outcomes.<sup>122</sup> This may require additional scrutiny because of the potential effect of maternal nutrition on childhood health. Though vitamin A supplementation does not appear to significantly affect MTCT, it is apparent that there is potential for general pregnancy outcomes improvement.<sup>123</sup> Zinc is important to immune function and can easily be depleted by chronic diarrhea. In such cases or other cases of deficiency, efforts with special attention to assuring the rehabilitation of zinc status may result in reduction in risk for infectious disease and mortality.<sup>124</sup>

### *Breastfeeding/Weaning*

It is estimated that without antiretroviral medication treatment approximately 30% of children may become perinatally infected with 5% occurring during pregnancy, 15% during birth, and 10% during breastfeeding periods. On the African continent, rates of transmission were estimated at 25-45%.<sup>125</sup> Weight loss during pregnancy can increase the transmission rates.<sup>126</sup> Putting current knowledge about prevention and treatment into practice could prevent MTCT more than 95% of the time.<sup>127</sup> Yet, in 2002 there were 800,000 new infant HIV infections, 90% of which occurred in sub-Saharan Africa. It is estimated that more than 10 million deaths have occurred in children under the age of five years. While alternatives to breastfeeding, such as infant formulas, are generally recommended for infant feeding by HIV-infected mothers, it is difficult to accomplish in resource-limited settings for many reasons.

WHO guidelines suggest that exclusive breastfeeding may be an appropriate choice for mothers when the alternatives are not affordable, feasible, accessible, sustainable, and safe (referred to as AFASS).<sup>128</sup> While this guideline has been used to determine the appropriateness of the

introduction of breastmilk substitutes, the problems faced by mothers in choosing to abruptly wean their children remains a challenge beyond the recommended exclusive breastfeeding period. Approximately 1.5 million of HIV-related deaths in children under five years old may be associated with inappropriate breastfeeding practices. The choices are complicated by economic, social, and other medical factors, such as maternal health.<sup>129 130</sup>

In a retrospective review of data from multicenter studies on 9424 infants and mothers, both exclusive and partial breastfeeding practices appeared to confer protections.<sup>131</sup> In this cohort study, diarrheal illness and lower respiratory infections were predictive of death and hospital admission. The authors recommended keeping predominant breastfeeding as an option rather than shifting to exclusive breastfeeding because both methods appeared to confer similar benefits. However, this recommendation does not take into consideration the potential effect of maternal HIV infection.

Prevention of MTCT (pMTCT) programs have sought solutions to making sure that appropriate and informed decisions are made by the mother about infant feeding options. Choices to breastfeed or use replacement feeding for newborns of mothers with HIV infection are guided by many factors, including cultural traditions, health or other beliefs, social stigma, resources, and maternal or family preferences. Because stigma and the potential for repercussions surrounding HIV disclosure, it was thought that couples counseling could reduce the risk for adverse social events. However, a study of the effectiveness of such an approach suggested that disclosure remains an important and stigmatized issue. In this study even though women were more likely to accept HIV testing when they were involved in couples counseling, their use of prophylactic medications to prevent transmission to their child and adverse social events were the same as women who were individually counseled in the antenatal setting.<sup>132</sup>

Treatment for maternal HIV infection to reduce viral load and improve CD4 immune cell counts can reduce the risk for MTCT significantly. Because viral load immediately after infection tends to be its highest, it is also the point of highest risk for MTCT. This means that HIV-negative mothers should be counseled on prevention for HIV infection during the perinatal period.

The general guidelines for informed choices on infant feeding have been evaluated in various settings. In India feeding practices were documented and found that there are a complex set of issues that face women who need to make such informed decisions. Site-specific information and evidence was recommended to tailor the guidelines to better meet the needs of local populations while reducing mortality risk for infants.<sup>133</sup> Exclusive breastfeeding, mixed feeding, and formula feeding were compared in 306 infants in Uganda and found a significantly higher risk of transmission for breast and mixed feeding. In this study, the first few weeks of life were a pivotal period for the transmission of HIV to infants via breastmilk.<sup>134</sup> Mixed

and exclusive breastfeeding appeared to have similar transmission rates. In South Africa, fewer pathologic events occurred when women appropriately breastfed their children for six months.<sup>135</sup>

Risk for transferring HIV infection increases for several reasons, including longer duration of breastfeeding, mixed feeding, maternal mastitis, cracked and bleeding nipples, abscesses and other causes of breast inflammation, oral lesions in the infant, gut permeability and inflammation in the infant, or new maternal HIV infection during breastfeeding stages.<sup>136</sup> Mastitis can remain subclinical and not readily detected in women who breastfeed. In Malawi, 250 women showed that over a period of 12 months postpartum more than 27% had at least one episode of subclinical infectious or non-infectious mastitis.<sup>137</sup>

Considering the high risk for death with malnutrition and respiratory infections related to malnutrition and HIV infection, infants who are provided with prophylaxis for such complications may benefit from medications that can prevent infectious complications.<sup>138</sup> However, a risk vs. benefit evaluation of such interventions should be undertaken because they may also be associated with an increase in the incidence of diarrhea, another contributor to malnutrition and mortality.

Maternal health issues may be lost in the context of breastfeeding, where the welfare of the child is a primary consideration. However, maternal health and perceptions of health can influence these practices. In Malawi a small group of women were asked about their perceptions of health and body shape. In this group of 22 HIV-infected women a larger body shape and fatness was perceived as a sign of health where a smaller body shape was perceived as a sign of disease.<sup>139</sup> In exploring two different scenarios where an HIV-infected woman may breastfeed, it was their perception that breastfeeding promotes the progression of disease in the mother.

Current recommendations that can be tailored to meet the needs and preferences of the mother and child include the following key strategies:

- Exclusive breastfeeding
- Optimal techniques to avoid cracked nipples, milk stasis, and mastitis
- Prompt treatment of breast problems
- Safe sex practices during breastfeeding period
- Nutrition support for the breastfeeding mother
- ARV access for women who require it

Special care should be taken to consider the link between maternal and child health in designing programs and providing care to HIV-infected women of child-bearing age. Adequate preparation and support is important to allow women to breastfeed according to their informed choice.

### *Child Nutrition*

HIV infection is a strong risk factor and predictor of survival in children. The challenge of child nutrition is adequacy for growth and development. Children who are HIV-infected are at a higher risk for malnutrition and associated infections. There are three basic types of malnutrition, including weight for age, height for age, and weight for height, which are indicators for under-nutrition, stunting, and wasting. Early in childhood all of these categories of nutritional status require adequate calories, and height additionally requires adequate protein. By the age of 24 months, height growth deficits should be addressed and corrected. After that age, height deficits are likely to be irreversible.

In Tanzania a study of 687 children with 90 deaths suggested that the preventable problems of stunting, low mid-upper arm circumference, anemia, and lack of household access to an adequate water supply were related to mortality. In this prospective cohort HIV infection was a stronger predictor of death when wasting was present in children.<sup>140</sup>

An important feature of nutritional management in HIV infection or perinatal exposure to HIV is the close attention to gastrointestinal disorders that can quickly deplete body stores in children.<sup>141</sup> The gastrointestinal tract is one of the targets of HIV infection by causing immune suppression -- leaving the gut open to infection and by altering absorptive capacity of the gut and supporting liver and pancreas functions. Simultaneous treatment for HIV, gastrointestinal infections, and nutritional rehabilitation are required.<sup>142</sup>

Respiratory illness and diarrhea are common features of HIV infection during childhood. A strong predictor for these problems is the level of protein-energy malnutrition. While prophylaxis for respiratory illness is important for children at risk due to a depleted immune system, nutritional improvement is an essential feature of successful prevention and treatment.<sup>143</sup>

Anemia of chronic disease is a prominent feature of chronic HIV infection and is associated with disease status.<sup>144</sup> This may be exacerbated by the existence of iron-deficiency anemia that is common in both developing and developed countries in children and pregnant/lactating women. A well-rounded diet is required for adequate iron absorption and utilization. A controlled trial of 697 pregnant women with HIV infection suggested that the addition of vitamin A supplements to iron and folate supplementation could improve pregnancy outcomes and reduce infant anemia.<sup>145</sup>

Nutrient intervention with iron supplementation requires special caution<sup>146 147</sup> and may be most safely accomplished by emphasizing adequate and bioavailable iron sources in the diet. However, risk vs. benefit analyses must be considered in tailoring an appropriate response in a given population or person.<sup>148</sup>

Several studies of nutrient interventions were undertaken. In one study that emphasized macronutrient supplementation and weight gain in HIV-infected children who were malnourished at baseline.<sup>149</sup> This study suggested that weight gain to an appropriate weight for height was possible through supplementation of macronutrients as a part of home-based intervention after discharge from the hospital. Another study on nutrition support with elemental diet based on amino acids was compared to an intact protein-based diet in rehabilitating nutritional status and health in 106 HIV-infected children and 90 HIV-negative children to find that the elemental diet resulted in an improvement in diarrhea and is the likely reason for subsequent improvement in recovery, including improved hemoglobin levels and weight gain.<sup>150</sup> In addition, micronutrient studies suggest a benefit for reversing nutrient deficits early in HIV infection and as a low cost adjunctive therapy to support other management strategies.<sup>151 152 153</sup>

Both macronutrients and micronutrients should be provided, consumed, and absorbed adequately to work well. Prevention of nutritional compromise is an important strategy for child nutrition because of the difficulty in reversing the signs of chronic malnutrition that commonly occur in children exposed to HIV infection. Symptom management, prevention and timely treatment for opportunistic and other infections, and adequate treatment when it is appropriate for HIV infection will be essential features to maintain adequate nutritional status, including growth and development, in children who are exposed to HIV infection.

### *Integrating Interventions*

Nutritional status defines the ability of the body to maintain normal function and composition. Under-nutrition, including protein-energy malnutrition and micronutrient deficiencies, can increase risk for infection and other detrimental events, such as diarrhea and wasting.<sup>154</sup> Because this relationship is well documented, it is important to integrate nutritional rehabilitation and maintenance efforts to support medical, social, and economic programs that seek to address such diseases as chronic HIV infection.

Malnutrition and its risks to survival and illness can be diminished with appropriate intervention in HIV infection for both mothers and children. There is a gap between developed and developing countries in the implementation of programs to improve child health that has long been recognized.<sup>155</sup> HIV care requires multifaceted interventions that integrate nutritional strategies to support health, improve survival, and diminish the effects of disease, including the potential for MTCT.

Tailoring assessment and intervention strategies to community response to HIV/AIDS can support local efforts. With a growing orphaned population in Malawi, several categories of responses were determined with a preference for community-based care that allows orphans to maintain a

family and tribal connection that would not be available in institutional models.<sup>156</sup> Such integrated care is likely to take into considerations the social, economic, and medical aspects of the disease as well as nutrition.<sup>157</sup>

Infection, including HIV infection, can cause a loss of appetite and changes in food tolerances. Although inadequate macronutrient and micronutrient intake are often features before clinical malnutrition is apparent, such early deficiencies can compromise immune function development in children and set up a vicious cycle of decline that is difficult to break. General health programs aimed at pregnant or lactating women and their children should take into account nutritional stability. Additional special care is required to tailor interventions to the food-related needs of growing children to slow disease progression, delay antiretroviral therapies, and increase survival with and without anti-HIV treatment.<sup>158</sup>

Long-term survival with chronic HIV infection, particularly with the use of ARVs, is not trouble-free. There is some evidence that with depleted immune systems immune restoration is incomplete, which continues to manifest in events related to impaired immune function.<sup>159</sup>

Some trials have demonstrated a restorative effect of macronutrients and micronutrients to overall body functions. It has been suggested that prevention efforts and nutritional status rehabilitation and maintenance will be important features of a carefully implemented program to manage chronic HIV infection.<sup>160</sup>

## Summary

General advice for maintaining nutritional status and health of women and children exposed to HIV infection are similar to other guidelines, with the exception of tailored responses that are required to meet the needs of intermittent and chronic illnesses.

Pregnant women need additional support to assure that they are adequately treated for HIV, opportunistic or other infections, and nutrition-related problems to assure that their newborn is as healthy as possible. Breastfeeding choices are complicated and confusing to many women who are asked to carefully weigh the issues in order to choose the best and most workable method for their child and self. Additional evidence is also required to further define risks and benefits or various breastfeeding options.

Nutrition for children who are HIV-infected or perinatally exposed to HIV infection is a primary therapy for health maintenance and recovery from adverse medical events. Antiretroviral therapy adds another area of concern onto the already complicated picture for mothers, infants, and children. Careful tailoring of guidelines and other recommendations according to individual needs is most likely to yield successful interventions.

## Evidence-Based Practice Q&A

- 4-1. What preventable and nutrition-related risk factors have been documented in maternal health and HIV infection?
- 4-2. What consequences to child health may be addressed through which interventions to improve maternal nutrition?
- 4-3. What is the impact of breastfeeding modalities on the transmission of HIV infection?
- 4-4. What interventions have been documented in the prevention and restoration of nutrition-related problems in children with perinatal HIV infection or born of HIV-infected mothers?
- 4-5. What challenges to the implementation of interventions have been documented?

## Chapter 5: Lifecycle Nutrition Considerations in HIV Infection

### **Abstract**

HIV infection is an important public health, development, economic, and political issue around the world affecting people of all age groups. Variations in nutritional challenges and needs throughout the lifecycle can be intensified by the presence of chronic HIV infection or even the exposure to HIV in children of HIV-infected mothers. The complex array of body balances are altered by HIV infection and can lead to such problems as failure to thrive, delayed puberty, and episodes of malnutrition. In addition, long-term survival and treatment of HIV infection is related to a number of additional diseases that are commonly associated with aging and obesity. Lifecycle stage should be considered in the development of guidelines and programs that address HIV disease management and nutrition.

### Background

New HIV infections estimated in 2001 included approximately 16% under the age of 15, 42% in the 15-24 year old age group, and 42% in 25-49 year olds.

Each phase of the lifecycle presents challenges to nutritional status. Growth and development during infancy through early adulthood requires additional calories, protein, and selected micronutrients to accomplish in the face of chronic HIV infection. Maintenance of body tissues and function during adulthood may require careful disease management, including symptom management, assurance of food access, and close monitoring for nutrition-related complications. Prevention and treatment of co-existing conditions and additional chronic disease is especially important in HIV-infected persons. Chronic inflammatory response, as seen in HIV infection, can accelerate or exacerbate conditions often associated with aging, such as cardiovascular diseases, insulin resistance and diabetes, and osteopenia/osteoporosis. Ongoing medical care access will be important to improve health outcomes at all lifecycle stages with HIV infection.

### Literature Review

#### *Infancy and Childhood*

Feeding options vary according to resources available to mothers or other caregivers faced with the decisions. Recommendations in developed countries state that women who are HIV-infected should not breastfeed their offspring.<sup>161</sup> The World Health Organization presents recommendations for developing countries where the use of infant formulas may not be feasible.<sup>162</sup> The South African guidelines for breastfeeding by HIV-infected mothers suggests that formula feeding requires that adequate formula (about 20 kg)

should be continuously available and accessible by the parent or care giver during the first six months, sanitation capability and a clean water supply should be present, knowledge and skills for preparation and feeding of formula is assured, and health services and monitoring for the child is accessed.<sup>163</sup> Education and informed choices are key features in the successful implementation of guidelines. The Centers for Disease Control and Prevention (CDC) offers a training module that allows for varying guidelines to be inserted.<sup>164</sup>

While there is little data on the impact of micronutrients in children who are HIV infected, vitamin A supplementation was recommended to reduce morbidity and mortality with or without HIV infection.<sup>165</sup>

Manifestations of HIV infection in children include oral thrush (candidiasis), tuberculosis, recurrent respiratory infections, bacterial skin infections and dermatitis, and chronic diarrhea.<sup>166</sup> Each of these conditions increases risk for malnutrition. In South Africa the WHO clinical case definition was tested in pediatric patients to discriminate between HIV infection and HIV-negative children. Manifestations more commonly seen in children with HIV infection included marasmus, hepatosplenomegaly, oral thrush, and generalized lymphadenopathy.<sup>167</sup>

In developing countries where tuberculosis is a significant threat, children born to HIV-infected mothers are more often exposed to tuberculosis. Children with HIV infection and tuberculosis were younger, more underweight, and were six times more likely to die than their HIV-negative counterparts in a study of children in Ethiopia.<sup>168</sup> The strongest predictor of outcome in this group was weight for age.

### *Adolescence*

Both childhood and adolescent periods are particularly vulnerable to HIV infection due to social and economic vulnerability and dependency. Information targeting young people has addressed issues in developed and developing countries.<sup>169 170</sup>

During adolescence sexual development is an important part of general growth. Hormonal alterations that support this development can be altered by both malnutrition and by chronic HIV infection and its associated treatments. Immunosuppression has been related to a delay in sexual development for perinatally infected children.<sup>171</sup> Disclosure of HIV status to the adolescent is an important step in supporting self care.

Dietary intake is particularly important to maintain an appropriate body weight and composition. Poor diet choices and intake can lead to both under-nutrition and over-nutrition. In the United States, HIV-infected adolescents and young adults were surveyed for their eating habits and measured for body mass index.<sup>172</sup> Results suggested that obesity was common with a prevalence of nearly 52%. Factors associated with overweight or obesity included being a woman, the number of hours of television watched

(marker of sedentary habits), and previous dieting. Poor diet habits were associated with television watching. These results are similar for non-infected youth and suggest that education and other forms of improving diet and activity will be important to health in adolescents who are HIV-infected. This same group of researchers found that dietary choices were poor in this group for micronutrients that are associated with immune function, suggesting the need for diet education and intervention to improve the quality of food intake.<sup>173</sup>

Complications of chronic disease and treatments are apparent in children and adolescents. A review of data on 1812 children between the ages of 4 and 19 years old with HIV infection showed a 13% prevalence of hypercholesterolemia compared with less than 5% prevalence in uninfected children. The strongest predictor of this cardiovascular disease risk was the use of protease inhibitor antiretroviral medications.<sup>174</sup>

### *Adulthood*

Most of the exploration of altered metabolic processes has been done in adults. Dietary interventions have been investigated for their effect on complications of disease and treatment.

A small study of asymptomatic HIV-infected men compared to controls showed that while body mass index was not different between the two groups, HIV-infected men at more, had higher protein breakdown and synthesis, and a higher resting energy expenditure (which was related to protein breakdown). The effect of eating more during asymptomatic phases of HIV infection where protein breakdown and synthesis rates are higher appears to assist in maintenance of body weight and body composition.<sup>175</sup> This finding makes a case for prevention of detrimental alterations to nutrition and health status by ensuring adequate food intake even during infections when cytokine levels can lead to a loss of appetite.

AIDS-defining illnesses increase the risk for nutritional compromise in the form of wasting. Episodes of wasting and recovery of body weight closely follow opportunistic infection events.<sup>176</sup> Prevention of opportunistic diseases then becomes an important prevention and therapeutic option to maintain and improve nutritional status.

Changes in the body's response to calories and specific nutrients may change body functions and other aspects of health. In a study of 25 HIV-infected patients, a calorie load yielded higher insulin and triglyceride levels.<sup>177</sup> Elevated insulin levels can lead to altered fat deposits in patients with treated and even those who were untreated chronic HIV infection. High-fiber diets appear to be protective against this effect.<sup>178</sup>

Chronic inflammatory disease can lead to oxidative stress and cell damage that is associated with wasting and changes in body defense mechanisms. In one study to determine the impact of dietary counseling, recommendations were made to 40 patients to improve food sources of

micronutrients. Improved antioxidant status and micronutrient intake was seen in this group.<sup>179</sup>

Micronutrient status and the ability to recover and maintain status can be altered by treatments for HIV infection. For instance, in untreated HIV infection, small increases in serum B12 could be realized with additional dietary intake. However, with the addition of protease inhibitor drugs, it appears that the improvement is blunted with improved intake of vitamin B12.<sup>180</sup>

### *Older Age*

The population of HIV-infected adults is aging.<sup>181</sup> It appears that a number of the complications of chronic HIV infection have much in common with aging and can accelerate or otherwise exacerbate this process.<sup>182</sup> Changes that are related to both aging and chronic HIV infection and its treatments include elevated risk for cardiovascular and related diseases, diabetes and insulin resistance, and bone mineral losses. In addition, aging men and women experience changes in sex hormone levels and production that drive additional health risk markers and body composition changes, such as the loss of muscle tissues and strength. Treatment for any of the complications commonly seen in aging should take into consideration HIV status and potential interactions with disease and its associated treatments.

Immunodeficiency in the elderly is commonly caused by malnutrition. The overlay of HIV infection complicates this picture and may make treatment difficult in this population, particularly in developing countries.<sup>183</sup>

### Summary

HIV infection and its related treatments present a challenge to the maintenance and restoration of sound nutritional status. Lifecycle changes present an additional subset of challenges including growth and development in infants and children, maintenance in adults as well as the elderly. Evaluation and recommendations are included in the guidelines that have been developed for the management of HIV disease in many countries around the world.

## Chapter 6: Integrating Nutrition into HIV Prevention, Care, and Treatment Efforts

### **Abstract**

Concern and knowledge about the interactions between nutrition and disease must be applied to programs addressing HIV disease management. Various forms of programs, pilot projects, and other intervention strategies have been implemented and tested. Assessment that may include an inventory of existing resources, environmental issues, food security, medical conditions, and other issues is the foundation for building a tailored and structured plan of intervention. Success stories should move beyond case studies and provide an evaluation of data to support the case that nutritional interventions have an important impact on health and survival outcomes in people living with HIV/AIDS.

### Background

The link between nutrition and disease, nutrition, and overall health maintenance has been intently explored for more than 65 years. The impact of nutritional status maintenance and nutrient therapy has been documented widely since the early 1960s.<sup>184 185 186 187 188 189 190</sup> Yet, in the case of HIV infection, it was necessary to restate and re-explore the features of nutrition and its impact on this disease in particular to establish a clear need to develop strategies for intervention.<sup>191 192 193</sup> For instance, it is well-known that the severity of infection will yield a negative protein balance.<sup>194</sup> Yet, little research to determine the impact of nutrient intervention to shore up the balance of protein has been completed aside from a contribution to weight gains.

After becoming well-accepted in clinical settings where HIV-related specialties have been developed by health care professionals, the role of nutrition and the value of nutrition-related intervention have been explored in the international and public health arenas. The development of programs with a medical focus within a setting that traditionally addressed food security without a medical focus has been challenging.<sup>195 196</sup>

There are still many social issues surrounding HIV infection that contribute to under-nutrition and mortality, such as orphaned children. In 2001 there were an estimated 14 million children who were orphaned (when mother or both parents died) by HIV-related complications and death. Local, regional, and international responses must include strategies to integrate medical nutrition therapy and general food security into their programs in order to improve coping mechanisms.<sup>197</sup>

Programs seek to positively impact social and health outcomes through addressing factors that impact these issues. To accomplish this, assessment of needs and assets are required. This assessment will assist in tailoring

general guidelines for integration into social, developmental, and medical programs. General needs assessment and other ways to assess specific nutrition issues may include surveys and measures to not only determine problem areas, but also to determine the reasons behind expected and unexpected successes in coping with adverse conditions and disease.<sup>198</sup> Because HIV disease adversely affects nutritional status in complex ways, care to integrate nutritional management into overall health care plans and goals by qualified and trained personnel is an essential feature to better assure positive outcomes in integrated programs.<sup>199</sup> New ways of thinking are slowly integrating clinical care with humanitarian and development programs with hopes of better addressing the global HIV pandemic.

In addition, with the advent of highly active antiretroviral therapies, long-term survivors have experienced an acceleration of diseases commonly associated with aging and lifestyle choices, such as smoking, drinking, and diet. Interventions for these complications require special attention to other aspects of disease management to safely and appropriately integrate counseling and other intervention measures. Interventions to support nutritional status maintenance may include dietary modulations and other forms of medical nutrition therapy as well as adjunctive therapies such as exercise, smoking cessation, anabolic medications, and medications or other strategies to reduce the risk for cardiovascular diseases, bone mineral losses, and insulin resistance.

## Literature Review

### *Education Interventions*

Education on how to make appropriate infant feeding choices is an important feature of prevention of maternal-to-child transmission (pMTCT) programs. Women who do not know their HIV status may not be able to make the appropriate and informed decisions necessary for feeding their infant, which may result in increased child mortality. In a study of feeding practices in 116 Zimbabwean women, HIV-infected women who did not know their HIV status made inappropriate feeding decisions, such as introducing complementary foods and weaning their babies earlier, resulting in underfeeding.<sup>200</sup> The women who were HIV-infected in this study reported more previous child deaths than mothers who were HIV-negative.

Because breastfeeding is probably the most viable option for infant feeding by HIV-infected mothers in resource-limited settings, a Safer Breastfeeding Programme was introduced in KwaZulu-Natal in South Africa where risk factors were individually determined and addressed with counseling.<sup>201</sup> Mothers in this program were taught how to heat treat expressed breastmilk in order to reduce vertical transmission risk. However, the heat-treatment option was met with limited success during the first six-month period. Authors of this report suggested that heat treatment may be a

better option after the first six months of exclusive breastfeeding and that better promotion is needed to make this safer feeding option viable for many women.

The ZVITAMBO Project in Harare, Zimbabwe works to support pMTCT activities in rural mission hospitals through HIV counseling and testing, antenatal and infant feeding education, prophylactic use of medication to prevent HIV transmission and other infections, and micronutrient supplementation. In this project, education and counseling were provided on prevention of breast-feeding-related MTCT. Compared to mothers who were not enrolled in the new program, these mothers were more than eight times more likely to exclusively breast feed and overall knowledge improved with expanding exposure to the program.<sup>202</sup> Because of the complexity of pMTCT and infant feeding choices, it has been recommended that appropriately trained personnel should deliver the education and counseling services that support informed choice and tailored recommendations.<sup>203</sup>

The HIV PRO-SELF Program has been used to improve patient education and self-care behaviors. Behavioral intervention to delay recurrences of candidiasis through the improvement of oral hygiene behaviors suggested that regular instruction on self-care behaviors may be able to affect medical events.<sup>204</sup> This type of program has also been put into place for other aspects of HIV-related care, such as pain, and has the potential to improve health outcomes and reduce health care costs. The Positive Self-Management Program in San Diego uses a weekly meeting format for seven sessions to learn self-management of many aspects of health and HIV care, including nutrition. The program was seen to be acceptable and useful as a technique to improve health care outcomes, such as the severity of symptoms and health-related behaviors.<sup>205 206</sup>

#### *Feeding Interventions: General*

Direct feeding programs and medical nutrition therapeutic products have been used to improve nutritional and general health in populations impacted by HIV/AIDS. Evaluations of populations that demonstrate inadequate nutrient intake or other nutrition-related problems within any setting may benefit from the addition of nutrition-related services and products.<sup>207 208</sup> Counseling has been combined with nutrient-based interventions, suggesting that for weight gain goals, a combination of approaches may be most appropriate. In Spain, dietary counseling was pitted against counseling and nutritional supplementation with a standard polymeric formula to find that formula use was more associated with weight gain than counseling.<sup>209</sup> In Germany, oral supplements and counseling yielded positive results. The authors in this study suggested that oral formulas may partially replace food intake, but that the ability to adhere to a weight gain regimen may be improved with supplementation.<sup>210</sup> Another

study compared nutrition counseling alone with nutrition counseling plus supplementation with a medical nutritional supplement to find that both groups were able to achieve an increased nutrient intake in about half of the participants.<sup>211</sup>

Nutrition education and intervention programs were integrated into community programs by dietitians in New York where food consumption and medical nutrition supplemental products were introduced. This program suggested that participants could achieve the nutritional goal of improving nutrient intake and recovering weight in the face of increased nutritional needs.<sup>212</sup>

Various types of medical nutrition products may be employed depending upon the needs and resources available. In a multicenter trial, standard polymeric formulas were compared with an immune-enhancing formula and a control group receiving no supplemental nutrients. In this study, participants were able to achieve similar improvements in weight, body composition, nutrient intake, and laboratory values regardless of the type or addition of nutrient formulas to nutrition counseling.<sup>213</sup>

Further specialized formulas were investigated in a trial of an omega-3 fatty acid and peptide-containing supplement versus a standard polymeric formula. Both groups were able to improve their weight and the special formulation appeared to improve CD4 count after three months of intervention.<sup>214</sup>

Long-term survivors may experience altered metabolic responses that increase risk for insulin resistance and diabetes, cardiovascular diseases and hypertension, and other co-existing disease. Dietary modulations may include efforts to control blood glucose, insulin response, blood lipids, and inflammatory processes.<sup>215 216</sup> In addition, physical changes that may result from insulin resistance and other metabolic changes may benefit from dietary intervention.<sup>217</sup> Obesity, specifically central obesity, is becoming a significant health problem for people with long-term treated HIV infection. Dietary interventions have been recommended to prevent and treat obesity and related health problems.<sup>218</sup>

### *Feeding Interventions: Nutrient-Specific*

Several nutrient alterations have been seen in HIV infection, as with other infectious diseases. Alterations in macronutrient and micronutrient intake, absorption, utilization, and excretion are seen in chronic HIV infection. Efforts to more specifically address the alterations have included the pharmacologic use of nutrients as therapeutic agents beyond the restoration of adequate intake.

Food-related intake was explored to find that diets high in protein-rich animal foods appeared to blunt the decline in body proteins as compared to a carbohydrate-rich diet of mostly staple foods, such as maize.<sup>219</sup> Research on vitamins and minerals for levels in the body, adequacy in the diet, and the

potential benefit for supplementation has been conflicting and even confusing.<sup>220 221</sup>

Vitamin A has received attention for its role in maternal and child health maintenance. Based on trials of vitamin A supplementation yielding a decrease in mortality and morbidity, recommendations have been made to integrate vitamin A into clinical care programs for children.<sup>222</sup> Vitamin A research, in particular, was highly conflicting. A recent study implicated vitamin A in potentially increasing risk of MTCT when compared with a multivitamin/mineral supplement. Previous research suggested the need for vitamin A supplementation to prevent transmission.<sup>223 224</sup>

Metabolic derangements seen in long-term survivors with chronic HIV infection may require additional attention to nutrition-related care. Oxidative stress, which is the depletion of antioxidants by the body's overproduction of pro-oxidants, has been associated with the wasting process. Wasting of both weight and body cell mass (muscles and organ tissues) are of primary concern because of the association of this type of tissue with survival.

Pharmaceutical interventions to improve weight and body cell mass have included general calories, protein, amino acids, vitamins, minerals, and other substances have been investigated. Because of the adverse effect of chronic infection on antioxidant status and wasting, glutamine and antioxidant therapy was tested to determine if weight and body cell mass may benefit from such supplementation.<sup>225</sup> Markers of oxidative stress may be reduced with supplementation of antioxidant nutrients.<sup>226</sup> It was suggested that supplemental nutrients may be especially important to explore in populations where ARVs are unaffordable.

Bone mineral density declines have been seen in chronic HIV infection along with lower serum levels of vitamin D. Some clinicians have suggested that vitamin D and calcium supplementation as well as other therapies may be helpful to maintain bone mineral density.<sup>227 228</sup>

Special care should be taken to integrate nutrient-based interventions carefully. Food, nutrients, and other aspects of care can interact and may, in fact, compete. For instance, high doses of vitamin C may reduce the levels of the protease inhibitor (ARV) indinavir.<sup>229</sup> Unfortunately, many of the interactions between nutrients and medications or other treatment strategies remain unknown.

## Summary

While the link between nutrition and disease is well known, there is much about the potential for nutrition intervention in HIV infection that is less well understood. HIV-infection, related complications, and treatments can lead to significant nutritional alterations. These alterations can contribute to morbidity and mortality. General diet intervention and specific nutrient intervention for both asymptomatic and symptomatic HIV infected

populations has demonstrated benefit. In addition, single nutrient interventions have demonstrated some potential for adverse effects and poor outcomes.

Guidelines for nutrition in HIV should address the need to integrate care in a tailored fashion to best address the needs of populations and individuals while protecting against potential adverse effects. Conflicting and confusing evidence has complicated this process. Additional research is required to support nutritional guidelines to address the needs and issues faced by populations impacted by HIV infection.

### Evidence-Based Practice Q&A

- 6-1. What interactions between HIV infection, disease complications, and nutritional status have been documented?
- 6-2. What foods or nutrients hold promise in delaying disease progression and health decline?
- 6-3. What feeding recommendations can be made with research evidence positive to support health outcomes?
- 6-4. What pharmaceutical uses of nutrients, including vitamin and mineral supplementation, hold promise for positive health outcomes?
- 6-5. What potential toxicities or other problems may be seen with nutrient-based therapies in chronic HIV infection?

## References

---

- <sup>1</sup> Tang AM et al. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2002;31(2):230-236.
- <sup>2</sup> Scrimshaw NS, Suskind RM. Interactions of nutrition and infection. *Dent Clin North Am.* 1976;20(3):461-472.
- <sup>3</sup> Scrimshaw NS. Effect of infection on nutrient requirements. *Am J Clin Nutr.* 1977;30:1536-1544.
- <sup>4</sup> Wagner GJ et al. *J Psychosom Res.* 2000;49(1):55-57.
- <sup>5</sup> Ott M et al. *Am J Clin Nutr.* 1993;57(1):15-19.
- <sup>6</sup> Shevitz AH et al. *AIDS.* 1999;13(11):1351-1357.
- <sup>7</sup> Garcia Luna PP et al. *Am J Clin Nutr.* 1999;70(2):299-300.
- <sup>8</sup> Roubenoff R et al. *Am J Physiol Endocrinol Metab.* 2002;283(1):E138-E145.
- <sup>9</sup> Kelly P et al. *QJM.* 1996;89(11):831-837.
- <sup>10</sup> Swanson B et al. *Nutrition.* 2000;16:11-12.
- <sup>11</sup> Forrester JE et al. *Am J Clin Nutr.* 2002;76(6):1428-1434.
- <sup>12</sup> Selberg O et al. *Metabolism.* 1995;44(9):1159-1165.
- <sup>13</sup> Breitkreutz R et al. *J Mol Med.* 2001;79(11):671-678.
- <sup>14</sup> Cheblowski RT et al. *Am J Gastroenterol.* 1989;84(10):1288-1293.
- <sup>15</sup> Coodley GO et al. *JAIDS.* 1994;7:46-51.
- <sup>16</sup> Dobs AA et al. *J Clin Endocrinol Metab.* 1996;81(11):4108-4112.
- <sup>17</sup> Madebo T et al. *Scand J Infect Dis.* 1997.
- <sup>18</sup> Shah S et al. *J Nutr.* 2001;131(11):2843-2847
- <sup>19</sup> Niyongoabo T et al. *Nutrition.* 1999;15(4):289-293.
- <sup>20</sup> Van Lettow M et al. *BMC Infect Dis.* 2004;4(1):61.
- <sup>21</sup> Mandelbaum-Schmid J. *Bull WHO.* 2004;82(7):554-555.
- <sup>22</sup> Wheeler et al. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;18(1):80-85.
- <sup>23</sup> Tang AM et al. *J Acquir Immune Defic Syndr.* 2002;31(2):230-236.
- <sup>24</sup> Jones CY et al. *Clin Infect Dis.* 2003;37(Suppl 2):S69-S80.
- <sup>25</sup> Castebon K et al. *Am J Epidemiol.* 2001;154(1):75-84.
- <sup>26</sup> Van Der Sande MA et al. *J Acquir Immune Defic Syndr.* 2004;37(2):1288-1294.
- <sup>27</sup> Mekonnen Y et al. *Ethiop Med J.* 2003;41(Suppl 1):61-65.
- <sup>28</sup> Shor-Posner G et al. *J Acquir Immune Defic Syndr.* 2000;23(1):81-88.
- <sup>29</sup> Semba RD et al. *Clin Infect Dis.* 2002;34(2):260-266.
- <sup>30</sup> Melchior JC et al. *Nutrition* 1999;15(11-12):865-869.
- <sup>31</sup> Butensky E et al. *J Assoc Nurses AIDS Care.* 2004;15(6):31-45.
- <sup>32</sup> Phillips KD, Groer M. *J Assoc Nurses AIDS Care.* 2002;13(3):47-68.
- <sup>33</sup> Baeten JM et al. *Am J Clin Nutr.* 2004;79(2):218-225.
- <sup>34</sup> Hepburn MJ et al. *Int J STD AIDS.* 2004;15(2):127-133.
- <sup>35</sup> Remacha AF et al. 2003;77(2):420-424.
- <sup>36</sup> Baeten JM et al. *J Acquir Immune Defic Syndr.* 2002;31(2):243-249.
- <sup>37</sup> Cunningham-Rundles S et al. *Nutr Rev.* 2002;60(5 pt 2):S68-S72.
- <sup>38</sup> Crenn P et al. *J Nutr.* 2004;134(9):2301-2306.
- <sup>39</sup> Breitkreutz R et al. *J Mol Med.* 2001;79(11):671-678.
- <sup>40</sup> Macallan DC. *J Nutr.* 1999;129(1S Suppl):238S-242S.
- <sup>41</sup> Macallan DC et al. *N Engl J Med.* 1995;333(2):83-88.
- <sup>42</sup> Forrester JE et al. *Public Health Nutr.* 2004;7(7):863-870.
- <sup>43</sup> Nutrient requirements for people living with HIV/AIDS: a report of technical consultation. World Health Organization, Geneva, 13-15 May 2003.
- <sup>44</sup> Van Gend CL, ML, Sauer PJ, Schoeman CJ. Evaluation of the WHO clinical case definition for pediatric HIV infection in Bloemfontein, South Africa. *J Trop Pediatr.* 2003;49(3):143-147.
- <sup>45</sup> Pelletier DL, Frongillo EA, Schroeder DG, Habicht JP. The effects of malnutrition on child mortality in developing countries. *Bulletin of the World Health Organization,* 1995;73(4):443-448.

- <sup>46</sup>Johann-Liang R, O'Neill L, Cervia J, Haller I, Giunta Y, Licholai T, Noel GJ. Energy balance, viral burden, insulin-like growth factor-1, interleukin-6 and growth impairment in children infected with human immunodeficiency virus. *AIDS* 2000;14(6):683-690.
- <sup>47</sup>Ikeogu MO, Wolf B, Mathe S. Pulmonary manifestations in HIV seropositivity and malnutrition in Zimbabwe. *Arch Dis Child* 1997;76(2):124-128.
- <sup>48</sup>Kessler L, Daley H, Malenga G, Graham S. The impact of the human immunodeficiency virus type 1 on the management of severe malnutrition in Malawi. *Ann Trop Paediatr*. 2000;20(1):50-56.
- <sup>49</sup>Johnson S, Henderson W, Crewe-Brown H, Dini L, Frean J, Perovic O, Vardas E. Effect of human immunodeficiency virus infection on episodes of diarrhea among children in South Africa. *Pediatr Infect Dis J* 2000;19(10):972-979.
- <sup>50</sup>Amadi B, Kelly P, Mwiya M, Mulwazi E, Sianongo S, Changwe F, Thomson M, Hachungula J, Watuka A, Walker-Smith J, Chintu C. Intestinal and systemic infection, HIV, and mortality in Zambian children with persistent diarrhea and malnutrition. *J Pediatr Gastroenterol Nutr*. 2001;32(5):550-554.
- <sup>51</sup>Matee MI, Msengi AE, Simon E, Lyamuya EF, Mwinula JH, Mbena EC, Mbena EC. Nutritional status of under fives attending maternal and child health clinics in Dar es Salaam, Tanzania. *East Afr Med J* 1997;74(6):368-371.
- <sup>52</sup>Miller TL, Easley KA, Zhang W, Orav EJ, Bier DM, Luder E, Ting A, Shearer WT, Vargas JH, Lipshultz SE; Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group; National Heart, Lung, and Blood Institute, Bethesda, MD. Maternal and infant factors associated with failure to thrive in children with vertically transmitted human immunodeficiency virus-1 infection: the prospective, P2C2 human immunodeficiency virus multicenter study. *Pediatrics*. 2001;108(6):1287-1296.
- <sup>53</sup>Kabir I, Malek MA, Mahalanabis D, Rahman MM, Khatun M, Wahed MA, Majid N. Absorption of macronutrients from a high-protein diet in children during convalescence from shigellosis. *J Pediatr Gastroenterol Nutr*. 1994;18(1):63-67.
- <sup>54</sup>Wolf BH, Ikeogu MO, Vos ET. Effect of nutritional and HIV status on bacteraemia in Zimbabwean children who died at home. *Eur J Pediatr*. 1995;154(4):299-303.
- <sup>55</sup>Chintu C, Luo C, Bhat G, DuPont HL, Mwansa-Salamu P, Kabika M, Zumla A. Impact of the human immunodeficiency virus type-1 on common pediatric illnesses. *J Trop Pediatr* 1995;41(6):348-353.
- <sup>56</sup>Madhivanan P, Mothi SN, Kumarasamy N, Yephthomi T, Venkatesan C, Lambert JS, Solomon S. Clinical manifestations of HIV infected children. *Indian J Pediatr*. 2003;70(8):615-620.
- <sup>57</sup>Jahoor F, Abramson S, Heird WC. The protein metabolic response to HIV infection in young children. *Am J Clin Nutr*. 2003;78(1):182-189.
- <sup>58</sup>Henderson RA, Talusan K, Hutton N, Yolken RH, Caballero B. Whole body protein turnover in children with human immunodeficiency virus (HIV) infection. *Nutrition* 1999;15(3):189-194.
- <sup>59</sup>Jahoor F, Abramson S, Heird WC. The protein metabolic response to HIV infection in young children. *Am J Clin Nutr*. 2003;78(1):182-189.
- <sup>60</sup>Manary MJ, Broadhead RL, Yarasheski KE. Whole-body protein kinetics in marasmus and kwashiorkor during acute infection. *Am J Clin Nutr* 1998;67(6):1205-1209.
- <sup>61</sup>Melchior JC, Niyongabo T, Henzel D, Durack-Bown I, Henri SC, Boulier A. Malnutrition and wasting, immunodepression, and chronic inflammation as independent predictors of survival in HIV-infected patients. *Nutrition* 1999;15(11-12):865-869.
- <sup>62</sup>Tang AM. Weight loss, wasting, and survival in HIV-positive patients: current strategies. *AIDS Read*. 2003;13(12 Suppl):S23-S27.
- <sup>63</sup>Kotler DP, Tierney AR, Brenner SK, Couture S, Wang J, Pierson Jr RN. Preservation of short-term energy balance in clinically stable patients with AIDS. *Am J Clin Nutr* 1990;51:7-13.
- <sup>64</sup>Grinspoon S, Corcoran C, Miller K, Wang E, Hubbard J, Schoenfeld D, Anderson E, Basgoz N, Klibanski A. Determinants of increased energy expenditure in HIV-infected women. *Am J Clin Nutr* 1998;68(3):720-725.
- <sup>65</sup>Macallan DC, Noble C, Baldwin C, Jebb SA, Prentice AM, Coward WA, Sawyer MB, McManus TJ, Griffin GE. Energy expenditure and wasting in human immunodeficiency virus infection. *N Engl J Med* 1995;333(2):83-88.

- <sup>66</sup> Yarasheski KE, Zachwieja JJ, Gischler J, Crowley J, Horgan MM, Powderly WG. Increased plasma gln and Leu Ra and inappropriately low muscle protein synthesis rate in AIDS wasting. *Am J Physiol*. 1998;275(4 Pt 1):E577-E583.
- <sup>67</sup> Stein TP, Nutinsky C, Condoluci D, Schluter MD, Leskiw MJ. Protein and energy substrate metabolism in AIDS patients. *Metabolism*. 1990;39(8):876-881.
- <sup>68</sup> Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA*. 1999;282(7):677-686.
- <sup>69</sup> Whalen C. Punctuated HIV meds planned for TB patients. Can set-point for AIDS be kept? *AIDS Alert*. 2001. 16(7):90-91.
- <sup>70</sup> Niyongabo T, Melchior JC, Henzel D, Bouchaud O, Larouze B. Comparison of methods for assessing nutritional status in HIV infected adults. *Nutrition*. 1999;15(10):740-743.
- <sup>71</sup> Zachariah R, Spielmann MP, Harries AD, Salaniponi FM. Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death. *Trans R Soc Trop Med Hyg*. 2002;96(3):291-294.
- <sup>72</sup> Wanke CA, Silva M, Ganda A, Fauntleroy J, Spiegelman D, Knox TA, Gorbach SL. Role of acquired immune deficiency syndrome-defining conditions in human immunodeficiency virus-associated wasting. *Clin Infect Dis*. 2003;37 Suppl2:S81-S84.
- <sup>73</sup> Hemila H, Kaprio J, Pietinen P, Albanes D, Heinonen OP. Vitamin C and other compound in vitamin C rich food in relation to risk of tuberculosis in male smokers. *Am J Epidemiol*. 1999;150(6):632-641.
- <sup>74</sup> Paton NI, Ng YM, Chee CB, Persaud C, Jackson AA. Effects of tuberculosis and HIV infection on whole-body protein metabolism during feeding, measured by the [<sup>15</sup>N]glycine method. *Am J Clin Nutr*. 2003;78(2):319-325.
- <sup>75</sup> Chintu C, Dupont HL, Kaile T, Mahmoud M, Marani S, Baboo KS, Mwansa W, Sakala-Kazembe F, Sunkutu R, Zumla A. Human immunodeficiency virus-associated diarrhea and wasting in Zambia: selected risk factors and clinical associations. *Am J Trop Med Hyg*. 1998;178(6):1787-1790.
- <sup>76</sup> Katabira ET. Epidemiology and management of diarrheal disease in HIV-infected patients. *Int J Infect Dis*. 1999;3(3):164-167.
- <sup>77</sup> Beltran S, Lescure FX, Desailoud R, Douadi Y, Smail A, El Esper I, Arlot S, Schmit JL; Thyroid and VIH group. Increased prevalence of hypothyroidism among human immunodeficiency virus-infected patients: a need for screening. *Clin Infect Dis*. 2003;37(4):579-583.
- <sup>78</sup> Hadigan C, Corcoran C, Piechuch S, Rodriguez W, Grinspoon S. Hyperandrogenemia in human immunodeficiency virus-infected women with the lipodystrophy syndrome. *J Clin Endocrinol Metab*. 2000;85(10):3544-3550.
- <sup>79</sup> Huang JS, Wilkie SJ, Sullivan MP, Grinspoon S. Reduced bone density in androgen-deficient women with acquired immune deficiency syndrome wasting. *J Clin Endocrinol Metab*. 2001;86(8):3533-3539.
- <sup>80</sup> Huang JS, Wilkie SJ, Dolan S, Gallafent JH, Aliabadi N, Sullivan MP, Grinspoon S. Reduced testosterone levels in human immunodeficiency virus-infected women with weight loss and low weight. *Clin Infect Dis*. 2003;36(4):499-506.
- <sup>81</sup> Mylonakis E, Koutkia P, Grinspoon S. Diagnosis and treatment of androgen deficiency in human immunodeficiency virus-infected men and women. *Clin Infect Dis*. 2001;33(6):857-864.
- <sup>82</sup> Silva M, Skolnik PR, Gorbach SL, Spiegelman D, Wilson IB, Fernandez-DiFranco MG, Knox TA. The effect of protease inhibitors on weight and body composition in HIV-infected patients. *AIDS*. 1998;12(13):1645-1651.
- <sup>83</sup> Steinhart CR. HIV-associated wasting in the era of HAART: a practice-based approach to diagnosis and treatment. *AIDS Read*. 2001;11(11):557-560, 566-569.
- <sup>84</sup> Farmer P, Robin S, Ramilus SL, Kim JY. Tuberculosis, poverty, and compliance: lessons from rural Haiti. *Semin Respir Infect*. 1991;6(4):254-260.
- <sup>85</sup> Hogg RS, Zadra JN, Chan-Yan C, Voigt R, Craib KJ, Korosi-Ronco J, Montaner JS, Schechter MT. Analysis of nutritional intake in a cohort of homosexual men. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;9(2):162-167.
- <sup>86</sup> Hoh R, Pelfini A, Neese RA, Chan M, Cello JP, Cope FO, Abbruzese BC, Richards EW, Courtney K, Hellerstein MK. De novo lipogenesis predicts short-term body-composition response by bioelectrical impedance analysis to oral nutrition supplements in HIV-associated wasting. *Am J Clin Nutr*. 1998;68(1):154-163.

- <sup>87</sup> Schwenk A, Steuck H, Kremer G. Oral supplementa as adjunctive treatment to nutritional counseling in malnourished HIV-infected patients: randomized controlled trial. *Clin Nutr.* 1999;18(6):371-374.
- <sup>88</sup> Henderson RA Saavedra JM, Perman JA, Hutton N, Livingston RA, Yolken RH. Effect of enteral tube feeding on growth of children with symptomatic human immunodeficiency virus infection. *J Pediatr Gastroenterol Nutr.* 1994;18(4):429-434.
- <sup>89</sup> Kabir I, Malek MA, Rahman MM, Khaled MA, Mahalanabis D. Changes in body composition of malnourished children after dietary supplementation as measured by bioelectrical impedance. *Am J Clin Nutr.* 1994;59(1):5-9.
- <sup>90</sup> Bos C, Benamouzig R, Bruhat A, Roux C, Mahe S, Valensi P, Gaudichon C, Ferriere F, Rantureau J, Tome D. Short-term protein and energy supplementation activates nitrogen kinetics and accretion in poorly nourished elderly subjects. *Am J Clin Nutr.* 2000;71(5):1129-1137.
- <sup>91</sup> Rochon C, Prod'homme M, Laurichesse H, Tauveron I, Balage M, Gourdon F, Baud O, Jacomet C, Jouveny S, Bayle G, Champredon C, Thieblot P, Beytout J, Grizard J. Effect of medroxyprogesterone acetate on the efficiency of an oral protein-rich nutritional support in HIV-infected patients. *Reprod Nutr Dev.* 2003;43(2):203-14.
- <sup>92</sup> Selberg O, Suttman U, Melzer A, Deicher H, Muller MJ, Henkel E, McMillan DC. Effect of increased protein intake and nutritional status on whole-body protein metabolism of AIDS patients with weight loss. *Metabolism.* 1995;44(9):1159-1165.
- <sup>93</sup> Charlin V, Carrasco F, Sepulveda C, Torres M, Kehr J. Nutritional supplementation according to energy and protein requirements in malnourished HIV-infected patients. *Arch Latinoam Nutr.* 2002;52(3):267-273.
- <sup>94</sup> Keithley JK, Swanson B, Zeller JM, Sha BE, Cohen M, Hershov R, Novak R. Comparison of standard and immune-enhancing oral formulas in asymptomatic HIV-infected persons: a multicenter randomised controlled clinical trial. *J Parenter Enteral Nutr.* 2002;26(1):6-14.
- <sup>95</sup> De Luis Roman DA, Bachiller P, Izaola O, Romero E, Martin J, Arranz M, Eiros Bouza JM, Alloer R. Nutritional treatment for acquired immunodeficiency virus infection using an enterotropic peptide-based formula enriched with n-3 fatty acids: a randomized prospective trial. *Eur J Clin Nutr.* 2001;55(12):1048-1052.
- <sup>96</sup> McCarty MF. Iatrogenic lipodystrophy in HIV patients – the need for very-low-fat diets. *Med Hipótesis.* 2003;61(5-6):561-566.
- <sup>97</sup> Hendricks KM, Dong KR, Tang AM, Ding B, Spiegelman D, Woods MN, Wanke CA. High-fiber diet in HIV-positive men is associated with a lower risk of developing fat deposition. *Am J Clin Nutr.* 2003;78(4):790-795.
- <sup>98</sup> Hadigan C, Jeste S, Anderson EJ, Tsay R, Cyr H, Grinspoon S. Modifiable dietary habits and their relation to metabolic abnormalities in men and women with human immunodeficiency virus infection and fat redistribution. *Clin Infect Dis.* 2001;33(5):710-717.
- <sup>99</sup> Villamor E, Msamanga G, Spiegelman D, Antelman G, Peterson KE, Hunter DJ, Fawzi WW. Effect of multivitamin and vitamin A supplements on weight gain during pregnancy among HIV-1-infected women. *Am J Clin Nutr.* 2002;76(5):1082-1090.
- <sup>100</sup> Schramm C, Wanitschke R, Galle PR. Thiamine for the treatment of nucleoside analogue-induced severe lactic acidosis. *Eur J Anaesthesiol.* 1999;16(10):733-735.
- <sup>101</sup> Li-Weber M, Weigand MA, Giaisi M, Suss D, Treiber MK, Baumann S, Ritsou E, Breikreutz R, Krammer PH. Vitamin E inhibits CD95 ligand expression and protects T cells from activation-induced cell death. *J Clin Invest.* 2002;110(5):681-690.
- <sup>102</sup> Rivas CI, Vera JC, Guaiquil VH, Veslasquez FV, Borquez-Ojeda OA, Carcomo JG, Concha II, Golde DW. Increased uptake and accumulation of vitamin C in human immunodeficiency virus 1-infected hematopoietic cell lines. *J Biol Chem.* 1997;272(9):5814-5820.
- <sup>103</sup> de la Asunción JG, del Olmo ML, Gomez-Cambronero LG, Sastre J, Pallardo FV, Vina J. AZT induces oxidative damage to cardiac mitochondria: protective effect of vitamins C and E. *Lif Sci.* 2004;76(1):47-56.
- <sup>104</sup> Burger B, Ollenschlager G, Schrappe M, Stute A, Fischer M, Wessel D, Schwenk A, Dile V. Nutrition behavior of malnourished HIV-infected patients and intensified oral nutritional intervention. *Nutrition.* 1993;9(1):43-44.
- <sup>105</sup> 2004 DRI report. 2004. Available at <http://www.iom.edu/board.asp?id=3788>.
- <sup>106</sup> Beisel WR. Effect of infection on human protein metabolism. *Fed Proc.* 1966;25(6):1682-1687.

- 
- <sup>107</sup> Powanda MC, Beisel WR. Metabolic effects of infection on protein and energy status. *J Nutr*. 2003;133(1):322S-327S.
- <sup>108</sup> Galloway R, Anderson MA. Prepregnancy nutritional status and its impact on birthweight. *SCN News*. 1994;11(6):6-10.
- <sup>109</sup> Tomkins A, Murray S, Rondo P, Filteau S. Impact of maternal infection on foetal growth and nutrition. *SCN News*. 1994;11:18-20.
- <sup>110</sup> Cunningham-Rundles S, McNeeley DF, Moon A. *J Allergy Clin Immunol*. 2005;115(6):1119-1128.
- <sup>111</sup> Smart T. Safer infant feeding. *HIV & AIDS Treatment in Practice*. 2005. Available at <http://hivinsite.ucsf.edu/InSite?page=pa-hatip-54>.
- <sup>112</sup> American International Health Alliance. Preventing mother-to-child transmission of HIV: A practical guide on feeding infants born to HIV-positive women. 2<sup>nd</sup> Edition. June 2005. Available at <http://www.eurasiahealth.org/resources/mdlDoc/1513-e.pdf>.
- <sup>113</sup> World Health Organization. Nutrition counseling, care and support for HIV-infected women: guidelines on HIV-related care, treatment and support for HIV-infected women and their children in resource-constrained settings. 2004. Available at: [http://www.who.int/hiv/pub/prev\\_care/en/nutri\\_eng.pdf](http://www.who.int/hiv/pub/prev_care/en/nutri_eng.pdf).
- <sup>114</sup> General Health Protection, Department of Health. HIV and infant feeding: guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS. September 2004. Available at: <http://bhiva.org/chiva/PDF/2004/HIVinfantSep04.pdf>.
- <sup>115</sup> Working Group on Mother-to-Child Transmission of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;8:506-510.
- <sup>116</sup> Ramachandran P. Maternal nutrition – effect on fetal growth and outcome of pregnancy. *Nutr Rev*. 2002;60(5 Pt 2):S26-S34.
- <sup>117</sup> Semba RD, Miotti P, Chiphangwi JD, Henderson R, Dallabetta G, Yang LP, Hoover D. Maternal vitamin A deficiency and infant mortality in Malawi. *J Trop Pediatr*. 1998;44(4):232-234.
- <sup>118</sup> van den Broek N. The aetiology of anaemia in pregnancy in West Africa. *Trop Doct*. 1996;26(1):5-7.
- <sup>119</sup> Fall CH, Yajnik CS, Rao S, Davies AA, Brown N, Farrant HJ. Micronutrients and fetal growth. *J Nutr*. 2003;133(5 Suppl 2):1747S-1756S.
- <sup>120</sup> Buys H, Hendricks M, Eley B, Hussey G. The role of nutrition and micronutrients in paediatric HIV infection. *SADJ*. 2002;57(11):454-456.
- <sup>121</sup> Fawzi WW, Msamanga GI, Hunter D, Renjifo B, Antelman G, Bang H, Manji K, Kapiga S, Mwakagile D, Essex M, Spiegelman D. Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS*. 2002;16(14):1935-1944.
- <sup>122</sup> Friis H, Gomo E, Nyazema N, Ndhlovu P, Krarup H, Kaestel P, Michaelsen KF. Effect of a multimicronutrient supplementation on gestational length and birth size: a randomized, placebo-controlled, double-blind effectiveness trial in Zimbabwe. *Am J Clin Nutr*. 2004;80(1):178-184.
- <sup>123</sup> Newell ML. Antenatal and perinatal strategies to prevent mother-to-child transmission of HIV infection. *Trans R Trop Med Hyg*. 2003;97(1):22-24.
- <sup>124</sup> Fischer Walker C, Black RE. Zinc and the risk for infectious disease. *Ann Rev Nutr*. 2004;24:255-275.
- <sup>125</sup> Nathoo K, Rusakaniko S, Zijenah LS, Kasule J, Mohamed K, Mashu A, Choto R, Mbizvo M. Survival pattern among infants born to human immunodeficiency virus typ-1 infected mothers and uninfected mothers in Harare, Zimbabwe. *Cent Afr J Med*. 2004;50(1-2):1-6.
- <sup>126</sup> Villamor E, Saathoff E, Msamanga G, O'Brien ME, Manji K, Fawzi WW. Wasting during pregnancy increases the risk of mother-to-child HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2005;38(5):622-626.
- <sup>127</sup> Foster C, Lyall H. Current guidelines for the management of UK infants born to HIV-1 infected mothers. *Early Hum Dev*. 2005;81(1):103-110.
- <sup>128</sup> Coutoudis A. Breastfeeding and the HIV positive mother: the debate continues. *Early Hum Dev*. 2005;81(1):87-93.
- <sup>129</sup> Coutoudis A. Breastfeeding and HIV. *Best Pract Res Clin Obstet Gynaecol*. 2005;19(2):185-196.
- <sup>130</sup> Breastfeeding and HIV International Transmission Study Group. Mortality among HIV-1-infected women according to children's feeding modality: an individual patient data meta-analysis. *J Acquir Immune Defic Syndr*. 2005;39(4):430-438.

- <sup>131</sup> Bahl R, Frost C, Kirkwood BR, Edmond K, Martinez J, Bhandari N, Arthur P. Infant feeding practices and risks of death and hospitalization in the first half of infancy: multicentre cohort study. *Bull World Health Organ.* 2005;83(6):418-426.
- <sup>132</sup> Semrau K, Kuhn L, Vwalika C, Kasonde P, Sinkala M, Kankasa C, Shutes E, Aldrovandi G, Thea DM. Women in couples antenatal HIV counseling and testing are not more likely to report adverse social events. *AIDS.* 2005;19(6):603-609.
- <sup>133</sup> Shankar AV, Sastry J, Erande A, Joshi A, Suryawanshi N, Phadke MA, Bollinger RC. *J Nutr.* 2005;135(4):960-965.
- <sup>134</sup> Magoni M, Bassani L, Okong P, Kituuka P, Germinario EP, Giuliano M, Vella S. Mode of infant feeding and HIV infection in children in a program for prevention of mother-to-child transmission in Uganda. *AIDS.* 2005;19(4):433-437.
- <sup>135</sup> Coutsooudis A. Infant feeding dilemmas created by HIV: South African experiences. *J Nutr.* 2005;135(4):956-959.
- <sup>136</sup> Embree JE, Njenga S, Datta P, Nagelkerke NJD, Ndinya-Achola JO, Mohammed Z, Ramdahin S, Bwayo JJ, Plummer FA. Risk factors for postnatal mother-child transmission of HIV-1. *AIDS.* 2000;14(16):2535-2541.
- <sup>137</sup> Nussenblatt V, Lema V, Kumwenda N, Broadhead R, Neville MC, Taha TE, Semba RD. Epidemiology and microbiology of subclinical mastitis among HIV-infected women in Malawi. *Int J STD AIDS.* 2005;16(3):227-232.
- <sup>138</sup> Coutsooudis A, Pillay K, Spooner E, Coovadia HM, Pembrey L, Newell ML. Routinely available cotrimoxazole prophylaxis and occurrence of respiratory and diarrhoeal morbidity in infants born to HIV-infected mothers in South Africa. *S Afr Med J.* 2005;95(5):339-345.
- <sup>139</sup> Bentely ME, Corneli AL, Piwoz E, Moses A, Nkhoma J, Tohill BC, Ahmed Y, Adair L, Jamieson DJ, van der Horst C. Perceptions of the role of maternal nutrition in HIV-positive breast-feeding women in Malawi. *J Nutr.* 2005;135(4):945-949.
- <sup>140</sup> Villamore E, Misegades L, Fataki MR, Mbise RL, Fawzi WW. *Int J Epidemiol.* 2005;34(1):61-68.
- <sup>141</sup> Cunningham-Rundles S, Ahrn S, Abuav-Nussbaum R, Dnistrian A. Development of immunocompetence: role of micronutrients and microorganisms. *Nutr Rev.* 2002;60(5 Pt 2):S68-S72.
- <sup>142</sup> Guarino A, Bruzzese E, De Marco G, Buccigrossi V. Management of gastrointestinal disorders in children with HIV infection. *Paediatr Drugs.* 2004;6(6):347-362.
- <sup>143</sup> Zar HJ. Prevention of HIV-associated respiratory illness in children in developing countries: potential benefits. *Int J Tuberc Lung Dis.* 2003;7(9):820-827.
- <sup>144</sup> Eley BS, Sive AA, Shuttleworth M, Hussey GD. A prospective, cross-sectional study of anaemia and peripheral iron status in antiretroviral naïve, HIV-1 infected children in Cape Town, South Africa. *BMC Infect Dis.* 2002;2(1):3-8.
- <sup>145</sup> Kumwenda N, Miotti PG, Taha TE, Broadhead R, Bigar RJ, Jackson JB, Melikian G, Semba RD. Antenatal vitamin A supplementation increases birthweight and decreases anemia among infants born to human immunodeficiency virus-infected women in Malawi. *Clin Infect Dis.* 2002;35(5):618-624.
- <sup>146</sup> Olsen A, Mwaniki D, Krarup H, Friis H. Low-dose iron supplementation does not increase HIV-1 viral load. *J Acquir Immune Defic Syndr.* 2004;36(1):637-638.
- <sup>147</sup> Semba RD. Iron-deficiency anemia and the cycle of poverty among human immunodeficiency virus-infected women in the inner city. *Clin Infect Dis.* 2003;37 Suppl 2:S105-S111.
- <sup>148</sup> Clark TD, Semba RD. Iron supplementation during human immunodeficiency virus infection: a double-edged sword? *Med Hypotheses.* 2001;57(4):476-479.
- <sup>149</sup> Ndekha MJ, Manary MJ, Ashorn P, Briend A. Home-based therapy with ready-to-use therapeutic food is of benefit to malnourished, HIV-infected Malawian children. *Acta Paediatr.* 2005;94(2):222-225.
- <sup>150</sup> Amadi B, Mwiya M, Chomba E, Thomson M, Chintu C, Kelly P, Walker-Smith J. Improved nutritional recovery on an elemental diet in Zambian children with persistent diarrhea and malnutrition. *J Trop Pediatr.* 2005;51(1):5-10.
- <sup>151</sup> Fawzi W, Msamanga G, Spiegelman D, Hunter DJ. Studies of vitamins and minerals and HIV transmission and disease progression. *J Nutr.* 135(4):938-944.
- <sup>152</sup> Singhal N, Austin J. A clinical review of micronutrients in HIV infection. *J Int Assoc Physicians AIDS Care.* 2002;1(2):63-75.
- <sup>153</sup> Fawzi W. Micronutrients and human immunodeficiency virus type 1 disease progression among adults and children. *Clin Infect Dis.* 2003;37 Suppl 2:S112-S116.

- <sup>154</sup> Ambrus JL Sr, Ambrus JL Jr. Nutrition and infectious diseases in developing countries and problems of acquired immunodeficiency syndrome. *Exp Biol Med*. 2004;229(6):464-472.
- <sup>155</sup> Staton DM, Harding MH. Protecting child health worldwide. Implementation is the biggest challenge slowing efforts to reduce childhood morbidity and mortality in developing countries. *Pediatr Ann*. 2004;33(10):647-655.
- <sup>156</sup> Beard BJ. Orphan care in Malawi: current practices. *J Community Health Nurse*. 2005;22(2):105-115.
- <sup>157</sup> Luo C. Achievable standard of care in low-resource settings. *Ann NY Acad Sci*. 2000;918:179-187.
- <sup>158</sup> Kruzich LA, Marquis GS, Carriquiry AL, Wilson CM, Stephensen CB. US youths in the early stages of HIV disease have low intakes of some micronutrients important for optimal immune function. *J Am Diet Assoc*. 2004;104(7):1095-1101.
- <sup>159</sup> Zhao X, Sun NC, Witt MD, Keller M, Niihara Y. Changing pattern of AIDS: a bone marrow study. *Am J Clin Pathol*. 2004;121(3):393-401.
- <sup>160</sup> Anabwani G, Navario P. Nutrition and HIV/AIDS in sub-saharan Africa: an overview. *Nutrition*. 2005;21(1):96-99.
- <sup>161</sup> Read JS: American Academy of Pediatrics, Committee on Pediatric AIDS. Human milk, breastfeeding, and transmission of human immunodeficiency virus type 1 in the United States. *Pediatrics*. 2003;112:1195-1205.
- <sup>162</sup> World Health Organization. HIV and infant feeding: guidelines for decision-makers. 2003. Available at [http://www.who.int/child-adolescent-health/New\\_Publications/NUTRITION/HIV\\_IF\\_DM.pdf](http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/HIV_IF_DM.pdf).
- <sup>163</sup> Evian C and the HIV Transmission and Breast Feeding Task Group. Policy guideline and recommendation for feeding of infants of HIV positive mothers. Available at <http://www.doh.gov.za/aids/docs/feeding.html>.
- <sup>164</sup> CDC. Infant feeding counseling. Slide show available at: [http://www.cdc.gov/nchstp/od/gap/pmtct/Presentation%20Booklet/Module\\_4.ppt](http://www.cdc.gov/nchstp/od/gap/pmtct/Presentation%20Booklet/Module_4.ppt).
- <sup>165</sup> Fawzi W. Micronutrients and human immunodeficiency virus type 1 disease progression among adults and children. *Clin Infect Dis*. 2003;37 Suppl 2:S112-S116.
- <sup>166</sup> Madhivanan P, Mothi SN, Kumarasamy N, Yephthomi T, Venkatesan C, Lambert JS, Solomon S. Clinical manifestations of HIV infected children. *Indian J Pediatr*. 2004;70(8):615-620.
- <sup>167</sup> vanGend CL, Haadsma ML, Sauer PJ, Schoeman CJ. Evaluation of the WHO clinical case definition for pediatric HIV infection in Bloemfontein, South Africa. *J Trop Pediatr*. 2003;49(3):143-147.
- <sup>168</sup> Palme IB, Gudetta B, Bruchfeld J, Huhe L, Giesecke J. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. *Pediatr Infect Dis J*. 2002;21(11):1053-1061.
- <sup>169</sup> Youth and HIV: knowledge resource on young people and HIV/AIDS. Available at [www.youthandhiv.org](http://www.youthandhiv.org).
- <sup>170</sup> Positive Life. Available at [www.positivelife.net](http://www.positivelife.net).
- <sup>171</sup> Buchacz K, Rogol AD, Lindsey JC, Wilson CM, Hughes MD, Seage GR, Oleske JM, Rogers AS; Pediatric AIDS Clinical Trials Group 219 Study Team. *J Acquir Immune Defic Syndr*. 2003;33(1):56-65.
- <sup>172</sup> Kruzich LA, Marquis GS, Wilson CM, Stephensen CB. HIV-infected US youth are at high risk of obesity and poor diet quality: a challenge for improving short- and long-term health outcomes. *J Am Diet Assoc*. 2004;104(10):1554-1560.
- <sup>173</sup> Kruzich LA, Marquis GS, Carriquiry AL, Wilson CM, Stephensen CB. US youths in the early stages of HIV disease have low intakes of some micronutrients important for optimal immune function. *J Am Diet Assoc*. 2004;104(7):1095-1101.
- <sup>174</sup> Farley J, Gona P, Crain M, Cervia J, Oleske J, Seage G, Lindsey J; Pediatric AIDS Clinical Trials Group Study 219C Team. Prevalence of elevated cholesterol and associated risk factors among perinatally HIV-infected children (4-19 years old) in Pediatric AIDS Clinical Trials Group 219C. *J Acquir Immune Defic Syndr*. 2005;38(4):480-487.
- <sup>175</sup> Crenn P, Rakotoanbinina B, Raynaud JJ, Thuillier F, Messing B, Melchior JC. Hyperphagia contributes to the normal body composition and protein-energy balance in HIV asymptomatic men. *J Nutr*. 2004;134(9):2301-2306.
- <sup>176</sup> Wanke CA, Silva M, Ganda A, Fauntleroy J, Spiegelman D, Knox TA, Gorbach SL. Role of acquired immune deficiency syndrome-defining conditions in human immunodeficiency virus-associated wasting. *Clin Infect Dis*. 2003;37 Suppl 2:S81-S84.

- <sup>177</sup> Thomas-Geevarghese A, Raghavan S, Minolfo R, Holleran S, Ramakrishnan R, Ormsby B, Karmally W, Ginsberg HN, El-Sadr WM, Albu J, Berglund L. Postprandial response to a physiologic caloric load in HIV-positive patients receiving protease inhibitor-based or nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Am J Clin Nutr.* 2005;82(1):146-154.
- <sup>178</sup> Hendricks KM, Dong KR, Tang AM, Ding B, Spiegelman D, Woods MN, Wanke CA. High-fiber diet in HIV-positive men is associated with lower risk of developing fat deposition. *Am J Clin Nutr.* 2003;78(4):790-795.
- <sup>179</sup> Gil L, Lewis L, Martinez G, Tarinas A, Gonzalez I, Alvarez A, Tapanes R, Biuliani A, Leon OS, Perez J. *Int J Vitamin Nutr Res.* 2005;75(1):19-27.
- <sup>180</sup> Woods MN, Tang AM, Forrester J, Jones C, Hendricks K, Ding B, Knox TA. Effect of dietary intake and protease inhibitors on serum vitamin B12 levels in a cohort of human immunodeficiency virus-positive patients. *Clin Infect Dis.* 2003;37 Suppl 2:S124-S131.
- <sup>181</sup> Zelenetz PD, Epstein ME. HIV in the elderly. *AIDS Patient Care STDS.* 1998;12(14):255-262.
- <sup>182</sup> Evans WJ. Protein nutrition, exercise, and aging. *J Am Coll Nutr.* 2004;23(6 Suppl):601S-609S.
- <sup>183</sup> Gavazzi G, Herrmann F, Krause KH. Aging and infectious disease in the developing world. *Clin Infect Dis.* 2004;39(1):83-91.
- <sup>184</sup> Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. *Monogr Ser World Health Organ.* 1968;57:3-329.
- <sup>185</sup> Gordon JE, Scrimshaw NS. Infectious disease in the malnourished. *Med Clin North Am.* 1970;54(6):1495-1508.
- <sup>186</sup> Bistrain BR, Blackburn GL, Scrimshaw NS, Flatt JP. Cellular immunity in semistarved states in hospitalized adults. *Am J Clin Nutr.* 1975;28(10):1148-1155.
- <sup>187</sup> Chandra RK, Scrimshaw NS. Immunocompetence in nutritional assessment. *Am J Clin Nutr.* 1980;33(12):2694-2697.
- <sup>188</sup> Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. *Am J Clin Nutr.* 1997;66(2):464S-477S.
- <sup>189</sup> Amati L, Cirimele D, Pugliese V, Covelli V, Resta F, Jirillo E. Nutrition and immunity: laboratory and clinical aspects. *Curr Pharm Des.* 2003;9(24):1924-1931.
- <sup>190</sup> Kalayanarooj S, Nimmannitya S. Is dengue severity related to nutritional status? *Southeast Asian J Trop Med Public Health.* 2005;36(2):378-384.
- <sup>191</sup> Chlebowski RT. Significance of altered nutritional status in acquired immune deficiency syndrome (AIDS). *Nutr Cancer.* 1985;7(1-2):85-91.
- <sup>192</sup> Moseson M, Zeleniuch-Jacquotte A, Belsito DV, Shore RE, Marmor M, Pasternack B. The potential role of nutritional factors in the induction of immunologic abnormalities in HIV-positive homosexual men. *J Acquir Immune Defic Syndr.* 1989;2(3):235-247.
- <sup>193</sup> Suttman U, Muller MJ, Ockenga J, Hoogstraal L, Coldewey R, Schedel I, Deicher H. Malnutrition and immune dysfunction in patients infected with human immunodeficiency virus. *Klin Wochenschr.* 1991;69(4):156-162.
- <sup>194</sup> Jahoor F, Abramson S, Heird WC. The protein metabolic response to HIV infection in young children. *Am J Clin Nutr.* 2003;78(1):182-189.
- <sup>195</sup> Wanke C. Nutrition and HIV in the international setting. *Nutr Clin Care.* 2005;8(1):44-48.
- <sup>196</sup> Anabwani G, Navario P. Nutrition and HIV/AIDS in sub-Saharan Africa: an overview. *Nutrition.* 2005;21(1):96-99.
- <sup>197</sup> Shetty AK, Powell G. Children orphaned by AIDS: a global perspective. *Semin Pediatr Infect Dis.* 2003;14(1):25-31.
- <sup>198</sup> Lapping K, Marsh DR, Rosenbaum J, Swedberg E, Sternin J, Sternin M, Schroeder DG. The positive deviance approach: challenges and opportunities for the future. *Food Nutr Bull.* 2002;23(4):130-137.
- <sup>199</sup> Fajardo-Rodriguez A, Lara del Rivero-Vera CM. Nutritional intervention in HIV/AIDS: practical guide for its implementation and follow-up. *Gac Med Mex.* 2001;137(5):489-500.
- <sup>200</sup> Gottlieb D, Shetty AK, Mapfunautsi RM, Bassett MT, Maldonado Y, Katzenstein DA. Infant feeding practices of HIV-infected and uninfected women in Zimbabwe. *AIDS Patient Care STDS.* 2004;18(1):45-53.
- <sup>201</sup> Coutsoudis A. Infant feeding dilemmas created by HIV: South African experiences. *J Nutr.* 2005;135(4):956-959.

- <sup>202</sup> Piwoz EG, Iliff PJ, Tavengwa N, Gavin L, Marinda E, Lunney K, Zunguza C, Nathoo KJ, Humphrey JH. An education and counseling program for preventing breast-feeding-associated HIV transmission in Zimbabwe: design and impact on maternal knowledge and behavior. *J Nutr.* 2005;135(4):950-955.
- <sup>203</sup> Ehrnst A, Zettersrom R. Feeding practices of HIV-1-infected mothers: the role of counselors. *Acta Paediatr.* 2005;94(3):263-265.
- <sup>204</sup> Hilton JF, MacPhail LA, Pascasio L, Sroussi HY, Cheikh B, LaBao ME, Malvin K, Greenspan D, Dodd MJ. Self-care intervention to reduce oral candidiasis recurrences in HIV-seropositive persons: a pilot study. *Community Dent Oral Epidemiol.* 2004;32(3):190-200.
- <sup>205</sup> Gifford AL, Sengupta S. Self-management health education for chronic HIV infection. *AIDS Care.* 1999;11(1):115-130.
- <sup>206</sup> Gifford AL, Laurent DD, Gonzales VM, Chesney MA, Lorig KR. Pilot randomized trial of education to improve self-management skills of men with symptomatic HIV/AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;18(2):136-144.
- <sup>207</sup> Woods MN, Spiegelman D, Knox TA, Forrester JE, Connors JL, Skinner SC, Silva M, Kim JH, Gorbach SL. Nutrient intake and body weight in a large HIV cohort that includes women and minorities. *J Am Diet Assoc.* 2002;102(2):203-211.
- <sup>208</sup> Kraak VI. Home-delivered meal programs for homebound people with HIV/AIDS. *J Am Diet Assoc.* 1995;95(4):476-481.
- <sup>209</sup> deLuis D, Aller R, Bachiller P, Gonzalez-Sagrado M, deLuis J, Iszaola O, Terroba MC, Cuellar L. Isolated dietary counseling program versus supplement and dietary counseling in patients with human immunodeficiency virus infection. *Med Clin (Barc).* 2003;120(15):565-567.
- <sup>210</sup> Schwenk A, Steuck H, Kremer G. Oral supplements as adjunctive treatment to nutritional counseling in malnourished HIV-infected patients: randomized controlled trial. *Clin Nutr.* 1999;18(6):371-374.
- <sup>211</sup> Rabeneck L, Palmer A, Knowles JB, Seidehamel RJ, Harris CL, Merkel KL, Risser JM, Akrabawi SS. A randomized controlled trial evaluating nutrition counseling with or without oral supplementation in malnourished HIV-infected patients. *J Am Diet Assoc.* 1998;98(4):434-438.
- <sup>212</sup> Topping CM, Humm DC, Fischer RB, Brayer KM. A community-based, interagency approach by dietitians to provide meals, medical nutrition therapy, and education to clients with HIV/AIDS. *J Am Diet Assoc.* 1995;95(6):683-686.
- <sup>213</sup> Keithley JK, Swanson B, Zeller JM, Sha BE, Cohen M, Hershov R, Novak R. Comparison of standard and immune-enhancing oral formulas in asymptomatic HIV-infected persons: a multicenter randomized controlled clinical trial. *J Parenter Enteral Nutr.* 2002;26(1):6-14.
- <sup>214</sup> deLuisRoman DA, Bachiller P, Izaola O, Romero E, Martin J, ARranz M, Eiros Bouza JM, Aller R. Nutritional treatment for acquired immunodeficiency virus infection using an enterotropic peptide-based formula enriched with n-3 fatty acids: a randomized prospective trial. *Eur J Clin Nutr.* 2001;55(12):1048-1052.
- <sup>215</sup> Shah M, Tierney K, Adams-Huet B, Boonyavarakul A, Jacob K, Quittner C, Dinges W, Perterson D, Garg A. The role of diet, exercise and smoking in dyslipidaemia in HIV-infected patients with lipodystrophy. *HIV Med.* 2005;6(4):291-298.
- <sup>216</sup> Hadigan C. Dietary habits and their association with metabolic abnormalities in human immunodeficiency virus-related lipodystrophy. *Clin Infect Dis.* 2003;37 Suppl 2:S101-S104.
- <sup>217</sup> Dong KR, Hendricks KM. The role of nutrition in fat deposition and fat atrophy in patients with HIV. *Nutr Clin Care.* 2005;8(1):31-36.
- <sup>218</sup> Kruzich LA, Marquis GS, Wilson CM, Stephensen CB. HIV-infected US youth are at high risk of obesity and poor diet quality: a challenge for improving short- and long-term health outcomes. *J Am Diet Assoc.* 2004;104(10):1554-1560.
- <sup>219</sup> Vorster HH, Kruger A, Margetts BM, Venter CS, Druger HS, Veldman FJ, Macintyre UE. The nutritional status of asymptomatic HIV-infected Africans: directions for dietary intervention? *Public Health Nutr.* 2004;7(8):1055-1064.
- <sup>220</sup> Mills EJ, Wu P, Seely D, Guyatt GH. Vitamin supplementation for the prevention of mother-to-child transmission of HIV and pre-term delivery: a systematic review of randomized trial including more than 2800 women. *AIDS Res Ther.* 2005;2(1):4-10
- <sup>221</sup> Lanzillotti JS, Tang AM. Micronutrients and HIV disease: a review pre- and post-HAART. *Nutr Clin Care.* 2005;8(1):16-23.

- 
- <sup>222</sup> Semba RD, Ndugwa C, Perry RT, Clark TD, Jackson JB, Melikian G, Tielsch J, Mmiro F. Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus-infected children in Uganda: a controlled clinical trial. *Nutrition*. 2005;21(1):25-51.
- <sup>223</sup> Fawzi WW, Msamanga GI, Hunter D, Renjifo B, Antelman G, Bang H, Manji K, Kapiga S, Mwakagile D, Essex M, Spiegelman D. Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS*. 2002;16(14):1935-1944.
- <sup>224</sup> Shey WI, Brocklehurst P, Sterne JA. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev*. 2002;(3):CD003648.
- <sup>225</sup> Shabert JK, Winslow C, Lacey JM, Wilmore DW. Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: a randomized, double-blind controlled trial. *Nutrition*. 1999;15(11-12):860-864.
- <sup>226</sup> Allard JP, Aghdassi E, Chau J, Tam C, Kovacs CM, Salit IE, Walmsley SL. Effects of vitamin E and C supplementation on oxidative stress and viral load in HIV-infected subjects. *AIDS*. 1998;12(13):1653-1659.
- <sup>227</sup> Garcia Aparicio AM, Munoz Fernandez S, Gonzalez J, Arrivas JR, Pena JM, Vazquez JJ, Martinez ME, Coya J, Marin Mola E. Abnormalities in the bone mineral metabolism in HIV-infected patients. *Clin Rheumatol*. 2005;Oct 6:1-3 (epub).
- <sup>228</sup> Mundy K, Powderly WG, Claxton SA, Yarasheski KH, Royal M, Stoneman JS, Hoffmann Me, Tebas P. Alendronate, vitamin D, and calcium for the treatment of osteopenia/osteoporosis associated with HIV infection. *J Acquir Immune Defic Syndr*. 2005;38(4):426-431.
- <sup>229</sup> Slain D, Amsden JR, Khakoo RA, Fisher MA, Lalka D, Hobbs GR. Effect of high-dose vitamin C on the steady state pharmacokinetics of the protease inhibitor in finavir in healthy volunteers. *Pharmacotherapy*. 2005;25(2):165-170.