Nutritional Support in AIDS

Module 27.1

Principles of Nutritional Therapy in HIV/AIDS

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Learning Objectives

- Become familiar with the general features and natural history of the disease;
- Understand the interactions between nutrition and clinical course in the various clinical phases of HIV infection;
- Discover the meaning of wasting syndrome and diarrhea within this context;
- Follow the nutritional impact of antiretroviral therapy (drug cocktails) as well as its side-effects;
- Gain insight into the general principles that guide nutritional assessment and prescriptions in the various HIV-infected subpopulations.

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Key Messages

- HIV infection is a major epidemic that is not under control yet, except in a few countries. It has three clinical categories;
- In group A the immune system is not compromised, and few symptoms are manifest. Category B includes patients with multiple infectious and a few non-infectious complications, consistent with immune depression, but without opportunistic infection. Category C is the most dramatic form of the disease, or AIDS proper, and presents with severe infections and AIDS-associated malignancies;
- Nutritional problems tend to follow the same pattern, being most apparent in the AIDS phase, in which true cachexia may be seen. However all HIV patients should be seen as potential nutritional risks, and deserve long-term nutritional surveillance;
• Undernutrition, with both macro and micronutrients, seems to have a deleterious impact on the clinical course, whereas optimal nutritional status and, interestingly, also obesity, tend to confer protective effects;
• The appropriate method of nutritional support depends on the clinical stage and the presence or not of diarrhea, wasting syndrome, or opportunistic infection. Appetite stimulants, anabolic agents, and oral, enteral and parenteral nutrition may each be appropriate at different stages, depending on the circumstances;
• Much attention is being given to immune stimulants including peptides, amino acids, micronutrients and antioxidants. The composition of the intestinal flora also seems to be important, and the use of fibre as well as pre and probiotics has been studied;
• Antiretroviral therapy itself triggers metabolic problems, especially the lipodystrophy syndrome, and this may require specific nutritional care.

1. What is the Current Importance of HIV Infection?

Infection by the Human Immunodeficiency Virus (HIV) is often improperly designated as AIDS (Acquired Immunodeficiency Syndrome), which corresponds to just one of its clinical phases, namely the most advanced. Caused by a slow RNA retrovirus with affinity for CD4+ lymphocytes, as well as for macrophages and a few other cells (1, 2), it is not the most tragic epidemic of the last 100 years yet. This record belongs to the Spanish flu of 1918-1919 (22 versus >30 million deaths, approximately).

Nevertheless, its economic, social and demographic consequences are so catastrophic in certain countries that the disease has been compared to the Black Plague, which decimated European cities and villages between 1347 and 1351, killing one-third of the total population.

Since the official recognition of the epidemic by the Centers for Disease Control and Prevention (CDC) in male homosexuals in the USA, in 1981 (the infection probably started in the 50's in Africa), it spread to all parts of the world, with no country spared. However, its geographical distribution is uneven with just 5% of the 40 million affected subjects being reported in affluent societies and the remainder by developing countries, of which 2/3 are in sub-saharan Africa.

Male homosexuals are still victims but are no longer the main target, which is now heterosexual men and women, along with a small proportion of children (vertical transmission) and elderly patients (1, 2).

2. How is it Classified?

According to the CDC, HIV infection becomes AIDS if the CD4+ count diminishes to <200 cells/mm³, (normal > 500/mm³), if the patient suffers from wasting syndrome, if AIDS-associated cancer is diagnosed (Kaposi’s sarcoma, Burkitt’s or immunoblastic lymphoma, primary lymphoma of the brain, or invasive cervical cancer), or if non-specific encephalopathy (AIDS dementia) or progressive multifocal leukoencephalopathy occurs (3).

Various opportunistic infections are also AIDS-defining conditions (Table 1).
### Table 1 AIDS-defining conditions

- Candidiasis of the esophagus, trachea, bronchi or lungs
- Disseminated or extrapulmonary coccidioidomycosis, histoplasmosis, or infection by *Mycobacterium avium* complex, *M. kansasii*, or other non-tuberculosis *Mycobacteria*
- Extrapulmonary cryptococcosis
- Chronic intestinal cryptosporidiosis or isosporiasis
- Cytomegalovirus retinitis with loss of vision, or any location outside liver, spleen and lymph nodes
- Chronic Herpes simplex ulcer, esophagitis, bronchitis or pneumonitis
- Pneumocystis carinii pneumonia
- Recurrent non-specific pneumonia
- Brain toxoplasmosis, *Salmonella* septicemia

### 3. What are the Nutritional Repercussions?

From its first description the consumptive features of HIV disease was apparent. Indeed, in many parts of Africa it is known as “slim disease”, and wasting syndrome is a common AIDS defining characteristic. It corresponds to weight loss of >10%, plus either chronic diarrhea (at least two loose stools per day for >=30 days) or chronic weakness and documented fever (for >=30 days, intermittent or constant), in the absence of a concurrent illness or condition other than HIV infection that could explain the findings (e.g., cancer, tuberculosis, cryptosporidiosis, or other specific enteritis) (3, 4, 5).

Of course, if not correctly addressed, wasting will not stop at 10% weight loss, and will proceed to fully fledged cachexia and death, as seen in the western world in the early 80’s, and in many poor countries today.

Even before the onset of wasting syndrome and other severe complications, in Category B patients (Table 2), significant malnutrition may already be detected.

### Table 2 CDC Categories of HIV infection

- **Category A**
  - Asymptomatic situations or others free from systemic immune compromise
  - Asymptomatic HIV infection, Persistent generalized lymphadenopathy, Acute (primary)
  - HIV infection with accompanying illness, or History of acute HIV infection

- **Category B**
  - Co-infections and other troubles, but less severe than those in the AIDS-list
    - Fever > 38.5°C or diarrhea > one month
    - Orofaringeal or persistent vulvovaginal candididasis
    - Herpes zoster (2+ episodes or > one dermatome)
    - Listeriosis, bacillary angiomatosis
    - Advanced cervical dysplasia ou cervical carcinoma in situ
    - Pelvic inflammatory disease, tubo-ovarian abscess
    - Oral inflammatory disease, tubo-ovarian abscess
    - Oral hairy leukoplakia, Peripheral neuropathy
    - Idiopathic thrombocytopenic purpura

- **Category C**
  - All alternatives mentioned in Table 1 and preceding text

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4. What is the Pathophysiology of Nutritional and Metabolic Derangements?
HIV infection may cause fever, malaise, loss of appetite, lymphadenopathy and other systemic effects resulting in negative energy balance and weight loss, even before CD4+ lymphocyte counts become critically depressed and widespread immune deficiency appears. Opportunistic infections in the mouth, throat or gastrointestinal tract, including parasitic infestations, along with respiratory problems such as pneumonia, bronchitis and sinusitis may be warning signs of immune dysregulation, and potentially interfere with general well-being and nutritional status. Tuberculosis is a common and severe co-infection, and indeed the AIDS epidemic is fueling a worldwide resurgence of this almost forgotten curse.

Hypermetabolism, hormonal imbalance and high levels of cytokines, particularly of TNF-alpha, are documented in advanced stages but are often part of the early changes as well (6, 7, 8). The negative contribution of psychological factors cannot be underestimated, including social stigmatization and exclusion, anxiety and depression. This may be especially true with prostitutes and other sex workers, alcohol or drug addicts, children and elderly patients (9, 10).

5. Are there Interactions between Malnutrition and Retroviral Disease?
HIV infection can lead to nutritional depletion through decreased food intake, malabsorption, increased utilization or excretion of nutrients, metabolic alterations, and excessive cytokine production among other causes (Table 3). Certain causes of malnutrition are particularly prominent in children, including, steatorrhea, increased intestinal permeability and intestinal iron malabsorption (8, 10).

Depletion of muscle mass/body cell mass in adults may occur relatively early in the course of the disease (12), suggesting that its cause may be related to underlying HIV infection, rather than to an accompanying opportunistic infection. However, accompanying factors like drug or alcohol abuse or the presence of intestinal parasites may also influence nutritional status in HIV-infected people. Several groups have shown that clinical stability is associated with nutritional stability (13). In this sense, weight loss may be episodic and related to an acute disease complication. In contrast to men, HIV-infected women tend to exhibit larger decreases in body fat relative to lean body mass, although after the advent of AIDS they also lose lean body and muscle mass substantially (14) (Table 4).

Table 3 Physiological derangements and nutritional homeostasis

| · Fever, hypermetabolism |
| · Fatigue, malaise |
| · Psycho-social troubles |
| · Diarrhea and malabsorption |
| · Candida esophagitis |
| · Reduced gastric acid secretion, intestinal bacterial overgrowth |
| · Other gastrointestinal derangements |
| · Increased glucocorticoids, hormonal imbalance, cytokine dysregulation |
Table 4 Protein and calorie deficit

- Poor appetite
- Compensatory hyperphagia
- Weight loss, muscle loss
- Hypoalbuminemia, anemia
- Reduced triglyceride and cholesterol fractions
- Changes in body composition
- Low functional status, failure to thrive
- Bone changes
- Derangements of fatty acid metabolism
- Wasting and cachexia

5.1 Synergy between Malnutrition and AIDS
In some series malnourished subjects pay an exorbitant price in the form of complications. Loss of as little as 5% body weight may be associated with a 2.5 fold increased risk of death. Opportunistic infections may also occur in 61% to 176% more commonly in weight losing patients (7). In AIDS patient’s appetite and albumin levels have been shown to correlate with survival and the same applies to weight loss in pre-AIDS HIV infection (24, 25).

The expression NAIDS (Nutritional AIDS), although seldom used nowadays, was not introduced into the literature for trivial reasons (26). Protein-calorie malnutrition, with or without micronutrient deficiency, may trigger atrophy of lymphoid tissue, decreased T-helper/suppressor ratio, diminished absolute CD4 count, impaired delayed hypersensitivity, poor response to vaccination, and increased serum immunoglobulin concentrations.

Malnutrition in HIV infection is associated with a rapid decrease in CD4 cell numbers and an increased rate of opportunistic infections (1, 2, 3, 4). Such features are well known in the HIV population but when resulting from nutrient deficit instead of viral damage, they are potentially reversible by nutritional repletion. In HIV and AIDS patients, maintenance of weight and good nutritional status delays progression of the disease and improves survival (25, 26, 27).

5.2 The Problem of Diarrhea
Diarrhea is considered the greatest cause of morbidity and mortality among HIV+ patients in the world (16). In developing countries, chronic diarrhea is directly associated with more rapid disease progression and death (28).

Some of its causes are factors that help to establish the diagnosis AIDS, but virtually any bacterial, viral or parasitic infection may be responsible. Malabsorption may be another component of intestinal dysfunction during HIV disease (16, 17). Although the pathophysiology has not been conclusively elucidated, bacterial overgrowth has been incriminated by some. Others emphasize the role of immune suppression rather than jejunal morphologic change, suggesting that a close interaction exists between intestinal absorption, nutritional condition, and immune derangement (29).

6. Are Micronutrients Relevant in this Context?
Vitamin and trace-metal depletion in HIV patients has been convincingly demonstrated in various settings, and not only in poor countries. Evidence is particularly strong for deficiencies of antioxidant elements such as selenium, vitamin A, E, C and carotenoids (23, 30).
Subnormal thiamin levels are a problem, not only in advanced HIV disease, but also in asymptomatic individuals. Magnesium and other B vitamins may also be lacking. Multivitamin replenishment has been the subject of very promising trials (31).

In pre-AIDS children Periquet et al confirmed deficiencies of lycopene (carotenoids), retinol and tocopherol accompanied by low transthyretin and serum albumin levels, although only after the development of full blown AIDS did changes become severe (32).

Zinc is a factor in many immune responses, but there are still doubts concerning its role in HIV (26, 27). Nevertheless, a number of authors have identified reduced plasma zinc concentrations in HIV patients from different parts of the world, and specifically in CDC stage A cases (early disease) (33).

In the USA, insufficient intake of micronutrients was recently demonstrated in HIV/AIDS adolescents and young adults (34). The main deficient micronutrient in patients with acceptable CD4 cell count (>= 500) was iron, but vitamins C and E tended to be low as well. It is not known how much reduced gastric acid secretion contributes to maldigestion in general and to sideropenia in particular, but this is reported in HIV-infected persons (17).

High-risk populations such as infected drug-abusers in the USA also reportedly ingest less vitamin B6, B12, zinc and selenium than infection-free addicts (Table 3 and Table 4). There are reasons to believe that consumption of intracellular glutathione is one of the pathophysiological mechanisms involved with viral activity. Its replenishment has long being advocated, and sulfur-amino acids such as methionine, taurine, cystine and cysteine are potentially suitable precursors to achieve this. In a well-designed study, clinical supplementation of N-acetyl cysteine to HIV patients was associated with increased survival (35) (Table 5).

Table 5 Depletion of micronutrients and antioxidants

<table>
<thead>
<tr>
<th>- Vitamins</th>
<th>Vitamin A, B, C, D and E</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Minerals and trace elements</td>
<td>Calcium, Magnesium, Zinc, Selenium and Iron</td>
</tr>
<tr>
<td>- Oxidative stress</td>
<td>Reduced carotenoids, lycopene, GSH</td>
</tr>
</tbody>
</table>

7. What Effects may One Expect from Antiviral Agents?

The advent of anti-viral cocktails or HAART (highly-active anti-retroviral therapy) around 1996 was a breakthrough in the pharmacological approach to HIV infection. A virtually inexorable condition with overwhelming mortality rates started behaving like a manageable chronic disease. Typically three representatives selected from the four chemical families of anti-HIV agents (nucleoside reverse transcriptase inhibitors/NRTI, non-nucleoside reverse transcriptase inhibitors/NNRTI, protease inhibitors/PI, and more recently entry inhibitors/EI) are given in combination (36, 37).

With appropriate treatment the CD4+ lymphocyte count is restored, viral load goes down or becomes non-detectable, opportunistic infections vanish and, equally importantly, appetite is recovered and positive nitrogen balance can be achieved. In this sense, HAART is a valuable nutritional tool.

Nevertheless, treatment is not without its problems as up to 25% of subjects undergoing high-potency treatment suffer setbacks in the first year because of drug intolerance, non-compliance or microbial resistance, and additional problems can be anticipated as therapy proceeds (36, 37). Even
worse, as HAART is expensive it is believed that not more than 2.5% (1/40 million) of the world’s HIV patients are currently being treated. HAART is only indicated for part of the HIV+ population, but even in rich countries (2 million cases) not all affected people may be getting optimal therapy. From the nutritional and metabolic point of view, HAART may cause some problems of its own (Table 6).

Table 6 Side-effects of HAART protocols

<table>
<thead>
<tr>
<th>NRTI *</th>
<th>NNRTI *</th>
<th>PI *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia, nausea, vomiting</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyperlactatemia, metabolic acidosis, osteoporosis, lipoatrophy</td>
<td>Lipodystrophy (hyperlipidemia, insulin resistance, fat accumulation, atherosclerosis)</td>
</tr>
</tbody>
</table>

(*) NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors

Probably the most nutritionally and metabolically damaging drug-related syndrome due to HAART is lipodystrophy, a complex of unsightly body fat redistribution (from head, neck and limbs to thorax and abdomen) plus changes reminiscent of metabolic syndrome (36, 37) and endowed with all its undesirable long-term consequences, most notably cardiovascular complications (Table 6). Basically linked to PI use, it is a common reason for HAART protocol change, and has been the main stimulus for the development of guidelines for the prevention of cardiovascular disease in HIV+ patients (38) (Table 7).

Table 7 Practical approach to lipodystrophy, metabolic syndrome and atherosclerosis (38)

<table>
<thead>
<tr>
<th>Clinical and biochemical work-up:</th>
<th>Body mass index, cigarette addiction, arterial blood pressure, blood glucose, lipid profile, HIV medication, cardiovascular symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis and treatment:</td>
<td>Change in HAART regimen, diet, exercise, smoking cessation, lipid lowering drugs, other medications for heart or blood pressure</td>
</tr>
<tr>
<td>Selected patients:</td>
<td>Echocardiogram, stress testing, heart catheterization</td>
</tr>
</tbody>
</table>

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8. Is Obesity a Risk Factor in HIV Infection?

Obese adolescents and adults with HIV infection have been recognized in increasing numbers in countries with a high prevalence of obesity such as the USA. Optimal nutritional guidance for such population is still unknown and has been debated recently (39).

Obese and non-obese young people apparently acquire HIV infection at similar rates. In the USA, among women with CD4 + T cells \( \geq 500 \text{ cells/microL} \), one in four was overweight and one in five was obese. Surprisingly, even when CD4 + T cells diminished to \( <200 \text{ cells/microL} \) excessive body weight was still a problem.

The primary underlying causes for abnormal adiposity were evidently unbalanced diet and lifestyle, however, HIV patients are no different from those in the rest of the population. In keeping with the observation of accelerated disease progression in wasting and cachexia, both men and women with excessive body weight display a more favorable course of the disease, with by lower rate of occurrence of the first CD4 cell count \( <200 \text{ cells/mm}^3 \). It is now recognized that both higher initial BMI and subsequent increases in BMI are associated with less risk of HIV progression (40).

Weight loss is, therefore, not advised for HIV infected patients. Each case should be managed appropriately, should metabolic syndrome, HAART-induced lypodystrophy or other metabolic and cardiovascular complications occur.

9. What is the Current Approach to Nutritional Replenishment?

HIV/AIDS-precipitated malnutrition and cachexia are serious life-threatening conditions, for which nearly all possible resources and strategies in the nutritional arsenal have been tested, from high-calorie, high-protein diets by all three routes (oral, enteral and parenteral) to all sorts of supplements (1, 2, 4, 5, 41, 44), and adjunctive medication.

Table 8 Accepted and potential options in HIV/AIDS undernutrition (1, 2, 4, 5, 41, 42, 43, 44)

<table>
<thead>
<tr>
<th>Appetite stimulants</th>
<th>Megestrol acetate</th>
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<tbody>
<tr>
<td></td>
<td>Medroxyprogesterone</td>
</tr>
<tr>
<td></td>
<td>Dronabinol</td>
</tr>
<tr>
<td>Anabolic agents</td>
<td>Growth hormone</td>
</tr>
<tr>
<td></td>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>( -3 \text{ fatty acids} )</td>
</tr>
<tr>
<td>Immune modulating nutrients</td>
<td>Arginine</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Beta-HMB (beta-hydroxy-beta-methylbutyrate)</td>
</tr>
<tr>
<td>Prebiotics and probiotics</td>
<td>Anti-cytokine drugs</td>
</tr>
<tr>
<td>Anti-proteolytic supplements</td>
<td>TNF-alpha inhibitors</td>
</tr>
<tr>
<td></td>
<td>soluble TNF-receptor</td>
</tr>
<tr>
<td></td>
<td>IFN-gamma antagonists</td>
</tr>
<tr>
<td>Virus control measures</td>
<td>Anti-HIV vaccine, HAART</td>
</tr>
</tbody>
</table>

9.1 General Principles of Nutritional Support

The most useful measures are listed in the guidelines shown in Table 9 and explained in the text below.
9.1.1 Basic Rules

- **Early nutritional assessment and lifelong follow-up** - It is common knowledge that HIV infection may be present for years with few or inconspicuous symptoms, suggesting a long period of latent virosis. In this sense, for many years it was believed that only AIDS subjects required nutritional attention;

- **Microbiologically however there is no latency at all.** From the time of primary infection virus replication advances at maximum rate, disseminating via the bloodstream to all parts of the body. In this sense, all patients except true nonprogressors (up to 10% of infected cases) harbor an infectious and inflammatory process, which should be monitored by both virological markers (CD4+ cell count, viral load) and nutritional/inflammatory observations (food questionnaire, anthropometry, body composition studies, plasma proteins, C-reactive protein, indicators of oxidative stress, measurements of specific vitamins and trace elements);

- **Fine-tuning of nutritional support** - Viral infection induces metabolic stress and activates hormones, cytokines and free radicals, all conducive to long term muscle wasting, and negative balance of nitrogen and other nutrients. However, thanks to hyperphagia and other adaptive mechanisms, patients may compensate for variable periods. Hospitalization and complete nutritional support should be reserved for severe complications. However, outpatients with apparently good health may also benefit from prophylactic oral supplements containing proteins, micronutrients, responses by antioxidants, and eventually pre/probiotics, if nutritional and virological findings indicate progressive disease;

- **As mentioned, malnutrition itself can depress CD4+ cell counts, thus compounding the negative effect of retroviral disease**;

- **Attention to diarrhea** - Diarrhea may be due to opportunistic infections, to side-effects of HAART protocols, or to HIV infection per se. In all circumstances diet prescription should be carefully addressed, including prebiotics or probiotics if changes in bacterial flora are suspected. This group of patients is subject to frequent and protracted episodes of diarrhoea, which may even become chronic. Malabsorption, both of macronutrients (fats) and certain micronutrients (iron, fat soluble vitamins etc) should always be suspected and the appropriate investigations carried out;

- **Detrimental effects of high-calorie regimens** - Patients with lipodystrophy (secondary to HAART) dyslipidemia, or other risk factors for cardiovascular disease should not receive high-calorie prescriptions, even in the AIDS phase (CDC category C). Proteins are safe and may be given in generous amounts, but carbohydrate and lipids should be tailored to individual needs and tolerance. They may be candidates for alternative energy sources such as omega-3 and omega-9 fatty acids (fish, flaxseed, canola and olive oil);

- **Early management of anemia** - Anemia is not infrequent in HIV+ populations and may be due to multiple causes, from dietetic errors to diarrhea and malabsorption, and from intestinal
parasitosis with occult bleeding to serious complications such as AIDS-associated cancer. Anemia is frequent in wasting syndrome/cachexia cases, and may require intensive and prolonged nutritional replenishment;

- **Oxidative stress and immune-enhancing agents** - This is a complex and still evolving subject, but at least there is consensus about the provision of optimal amounts of vitamins, minerals and trace elements. Recent recommendations emphasize vitamins A, B6, B12, folic acid, carotenoids, selenium and zinc;

- **Moderate exercise** - Physical activity has not been shown to be harmful in HIV/AIDS, and may stimulate appetite and protein anabolism. Even mild immunologic benefits have been occasionally observed, although these results have not been clearly confirmed (45);

- **Herbs and other alternative foodstuff** - As with most life-threatening conditions, HIV+ persons are prone to folk-medicine and other unproven dietary supplements, even when highly educated and living in industrialized countries. Indeed, internet sites are full of such suggestions although the most dangerous side-effect of these initiatives tends to be delay in seeking proper assistance; direct troubles have been reported, such as chemical hepatitis. On the other side, it is advocated than phytotherapic mixtures are rich in flavonoids coumarins, terpenoids, alkaloids, polyphenols, polysaccharides or proteins, a few of which could be beneficial. Patients should not be encouraged to pursue questionable therapies, as serious adverse reactions have been recorded, and in any case all substances used should be registered in the medical chart.

10. **Summary**

Undernutrition has been associated with HIV infection since the earliest reports of the disease, and may advance to severe wasting and cachexia. Micronutrient and antioxidant deficiencies are recognized in HIV infection. Alleviation or cure of undernutrition is feasible, and first option should be inexpensive dietary adjustments, taking in account the specific requirements of the disease.

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