



Introduction to Nutritional Approaches to HIV/AIDS

LEANNA J. STANDISH

Nutrition is the most extensively researched of all the diverse areas of complementary and alternative medicine (CAM) in the treatment of HIV/AIDS. This extensive research uses not only in vitro methods but also observational and clinical studies in HIV-infected humans. Numerous papers have been published studying the in vitro immunological and virological effects of single nutrients. Most of the human studies focus on measuring serum and cellular levels of nutrients, such as minerals, vitamins, and antioxidants, thought to be pertinent to HIV disease progress. Many studies suggest that the levels of important nutrients are lower in people infected with HIV and that these levels correlate with disease progression.¹⁻³

Results from several epidemiological studies suggest that deficiencies of certain nutrients, such as vitamin A, may be associated with a poor immune status and that higher intakes of micronutrients at baseline were associated with higher CD4⁺ T-cell counts. Longitudinal observational studies of HIV-positive cohorts suggest that slowed disease progression is associated with an increased intake level of certain nutrients. Tang et al⁴ conducted an epidemiological study of 281 HIV-positive men, which provided evidence that certain dose ranges of dietary micronutrient intake of vitamins B₁, B₂, B₆, C, and niacin were associated with slowed disease progression, whereas high doses of zinc and vitamin A were associated with faster progression to AIDS. In another epidemiological study, Abrams



4

Nutritional Deficiencies in AIDS Patients

A Treatment Opportunity

JEONGMIN LEE
KOZO YOSHIKAWA
RONALD ROSS WATSON

ABSTRACT

Immune dysfunction resulting from infection with the human immunodeficiency virus (HIV) is a major health threat to populations in North America and throughout the world. Since HIV-infected persons in industrialized nations can survive a previously life-threatening infection through the use of effective medical therapies, malnutrition and wasting are becoming central issues in the health care plans of long-term survivors. Nutrition is a fundamental intervention in both the early and the ongoing treatment of HIV disease. Nutrition therapy, in coordination with other medical interventions, can extend and improve the quality and quantity of life in individuals infected with HIV and those living with acquired immune deficiency syndrome (AIDS).

Medical nutrition therapy involves an assessment of nutritional status and treatment. Research on the relationship between nutrition and HIV infection is essential for understanding the mechanisms of wasting and for determining the effectiveness of medical nutrition therapy. This chapter uses currently published research papers to review the mechanisms and consequences of malnutrition in HIV/AIDS patients.

INTRODUCTION

An individual's nutritional status influences morbidity and mortality (M&M) in many diseases, regardless of the disease process. Nutrition should be central in the

treatment of HIV infection because of the chronic nature of HIV and the numerous related opportunistic infections (OIs) that affect the digestive tract. Because undernutrition adversely affects immune defenses in people who do not have HIV, nutritional deficiencies in HIV-infected people accelerate the development of severe immunodeficiency. Although it has been poorly studied, nutritional supplementation may therefore overcome nutritional deficiency and immunosuppression in AIDS. Recently vitamin E deficiency was identified in HIV-infected people.¹ Another study showed that vitamin E replacement slowed the development of immune deficiency.^{2,3} An associated editorial concluded that more research is needed on the benefits of vitamin supplementation to slow the loss of immune defenses and promote well-being in HIV-infected persons and that supplementation should start now while research is underway.⁴ Therefore we reviewed vitamin and mineral deficiencies in AIDS patients and concluded that they are prevalent and should be treated, since they accentuate immune damage.

A macronutrient deficiency such as wasting, a common occurrence in HIV disease, is a protein-calorie malnutrition and is caused by inadequate calorie and protein intake, absorption, or use. The resulting loss of weight and muscle mass is directly associated with a deterioration in health and increased mortality. The loss of lean body mass (LBM) is associated with a greater incidence of OIs, further deterioration in immune function, and poorer nutritional status.⁵ Because malnutrition has a direct impact on immune function, maintaining the nutritional status of the HIV-infected patient is a central concern.

MACRONUTRIENT DEFICIENCY AND PROGRESSION TO AIDS

Energy Expenditure

Resting energy expenditure (REE) correlated positively with the presence of HIV infection. REE was 10% higher in stable HIV-positive subjects and AIDS patients than in healthy controls.^{6,7} Grunfeld found that REE was higher in HIV-positive patients, AIDS-related complex (ARC) patients, and AIDS patients who did not have concomitant OIs than it was in healthy controls, as long as the patient's oral intake was sufficient to maintain body weight (BW).⁸ This finding contrasts

with AIDS patients who had concomitant infections, which resulted in increased REE, decreased oral intake, and weight loss. There was no compensatory decrease in REE, as might be expected with decreased oral intake. Failure to regulate REE as an adaptation to anorexia or malabsorption is often stated as the major cause of weight loss in individuals with AIDS. However, total energy expenditure (TEE) in HIV-infected patients was not significantly different from that in healthy controls but was decreased slightly in weight-stable AIDS patients.⁶ With a spectrum of REE for hospitalized ARC and AIDS patients without malabsorption or uncontrolled infection,⁹ 6% were hypometabolic, 26% were normal-metabolic, and 68% were hypermetabolic. Hypermetabolism is characteristic of cachexia (i.e., muscle wasting, inefficient use of energy, and loss of LBM), as seen in cancer and other chronic disease states, whereas hypometabolism is an appropriate compensatory response to starvation and protein-energy malnutrition.

It is unclear if weight loss correlates with the metabolic rate, since some studies show a decrease in energy expenditure during periods of weight loss.^{8,10} Although REE increased in HIV-positive and AIDS patients, changes in weight correlated not with REE but with caloric intake.⁸ The most common physiological causes of hypermetabolism, such as pregnancy, adolescence, and exercise, do not usually lead to wasting, perhaps because of higher caloric intake and metabolic adaptation.¹¹ The etiology of possible hypermetabolism remains unclear, since increased hormones or tumor necrosis factor (TNF) were not found in patients with high REE.^{12,13} Whether or not chronic hypermetabolism occurs, frequent fevers associated with secondary infections in HIV-infected patients may result in short-term increased REE.⁵ Malignancy may also raise REE.¹⁴ It is, however, unclear if hypermetabolism is sufficient to cause wasting in the absence of other processes, although hypermetabolism may occur in some HIV-infected patients.¹¹

Body Weight and Composition

Body wasting, particularly loss of body cell mass (BCM), is an increasingly prevalent AIDS-defining condition and is an independent risk factor for death in HIV-infected patients. Although they had the same BW as the controls, HIV-positive male patients had less BCM, greater potassium depletion,

less intracellular water, more extracellular water, decreased serum proteins (e.g., albumin, retinol-binding protein [RBP]), and decreased total iron binding capacity (TIBC). This depletion occurred to a greater extent in the patients with diarrhea. Compared with normal values, body fat was also depleted but was similar to that of a control group of healthy homosexual males. Loss of body fat was found even in the earlier stages of HIV infection and was more severe than loss of BCM. Female patients had a larger decrease in body fat than male patients, whereas males showed a greater relative depletion of BCM than body fat. In more stable ambulatory patients with AIDS, however, weight loss was not associated with reductions in LBM, body fat, or total water, and the explanation for weight loss was unclear.¹⁵

In a follow-up retrospective study of wasted AIDS patients during the 100 days before death, BCM (decreased 50%) was reduced out of proportion to weight loss (decreased 33%).¹⁶ In patients who died within 100 days of a body composition measurement, those with the lower BCM died sooner. Specifically, a loss of 37% of BW was associated with death. This study revealed that the progression of wasting was independent of body fat changes but was associated with loss of BCM. Thus a patient could have a normal BW yet a low BCM and still be at risk for death due to malnutrition.

Pathophysiology of Malnutrition in HIV Disease

A number of possible etiologies of weight loss in HIV infection exist. HIV wasting syndrome also may be multifactorial in etiology.¹⁷ Multiple etiologies may be present in a single patient. The most likely etiologies can be divided into the broad categories of (1) decreased food intake, (2) malabsorption, (3) alterations in metabolism, (4) cytokine effects, (5) endocrine dysfunction, (6) steroids and growth hormones, (7) primary muscle disease, and (8) alcohol abuse.

Decreased Food Intake

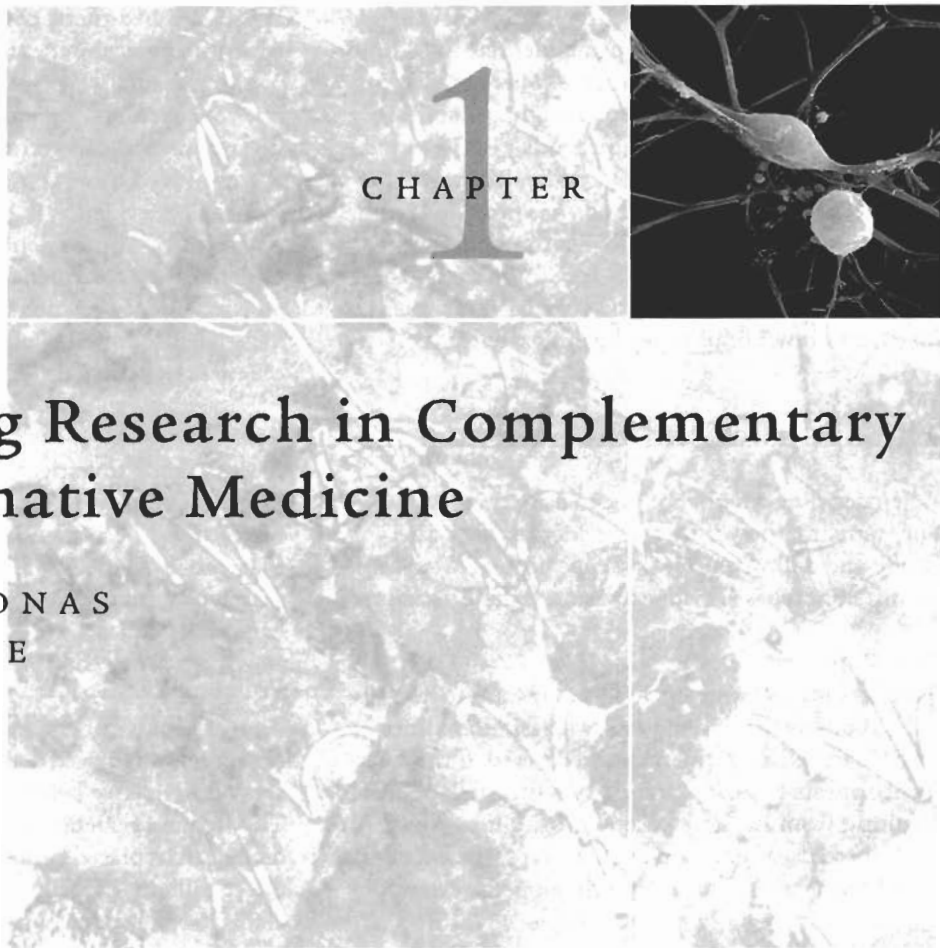
Decreased food intake may result from anorexia or nausea secondary to medications, systemic illness (mediated by cytokines), neurological disease, or oral or esophageal pathology (e.g., dry mouth, odynophagia, ulcers, or malignancy).¹⁸ Taste and smell loss due to medications, oral pathology such as candidiasis, and peripheral or

central nervous system (CNS) disease are well documented in HIV-infected patients. These chemosensory abnormalities can impair food intake and contribute to wasting. Additionally, fatigue, dementia, and peripheral myoneuropathies influence a patient's ability to obtain food. Monetary considerations also play a role. Dependence on other people to prepare or purchase food may also limit a debilitated patient's intake.

Malabsorption

Oral, esophageal, stomach, pancreatic, biliary, hepatic, and small and large intestine pathology can influence the absorption of nutrients. Malabsorption, chronic diarrhea, or both may be secondary to infections, malnutrition, medications, enzyme deficiencies, malignancies, and HIV enteropathy.¹⁹ Diarrhea is found in over 50% of AIDS patients with pathogens, including *Cytomegalovirus*, herpes simplex virus, adenovirus, *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, *Mycobacterium avium-intracellulare*, *Giardia*, *Entamoeba*, *Cryptosporidium*, *Microsporidium*, and *Isospora*.¹⁹ Gastrointestinal dysfunction, especially malabsorption, is prevalent in advanced HIV infection, with or without identifiable pathogens. Villous abnormalities are frequent in these HIV-infected individuals, and small intestinal dysfunction has been demonstrated by abnormal D-xylose absorption tests, Schilling tests, C-14 glycocholate absorption, and the presence of steatorrhea.^{13,20} Small intestinal pathology or pancreatic insufficiency may lead to fat malabsorption, weight loss, and depletion of fat-soluble vitamins in HIV-infected persons. Fat malabsorption occurred in 48% of a range of HIV-infected patients using a C-14 triolein breath test.²¹

Although severe malabsorption is limited to patients who have advanced HIV disease with CD4⁺ T-cell counts <100 and usually <50 cells/ml, overt malabsorption has not been described in early HIV infection. However, studies indicate that subclinical malabsorption may play a role in early HIV disease without evidence of diarrhea. The D-xylose test was abnormal in 25% of patients with early HIV disease,²² and the lactulose mannitol permeability test was abnormal in 16%.²³ In addition, the hypometabolic status and reduced glucose cycling in clinically stable AIDS patients could be explained by subclinical malabsorption.^{15,24} Hypochlorhydria has been found in 74% of AIDS patients²⁵ and is a permissive factor for enteric infections and bacterial overgrowth of the small intestine.²⁶ Furthermore, hypochlorhydria de-



CHAPTER 1

Evaluating Research in Complementary and Alternative Medicine

WAYNE B. JONAS
KLAUS LINDE

Complementary and alternative medicine (CAM) is that subset of practices that is not an integral part of conventional health care but is still used by patients for the treatment and prevention of illness. Surveys done in 1990 and 1997 show an increase in CAM use of almost 45% in the United States during that time. Visits to CAM practitioners increased from 400 million per year to more than 600 million per year—surpassing the number of visits to primary care physicians. Out-of-pocket expenses for these practices rose from \$14 billion to \$27 billion in the last 7 years.¹ CAM is an important part of the public's health care. As its use rises, obtaining reliable information about the

safety, effectiveness, and mechanism of these practices requires quality clinical investigation. This chapter addresses issues to be considered when conducting and evaluating research on these practices.

RESEARCH EVALUATION PRINCIPLES IN MEDICINE

Scientific Methods

Scientific methods have only recently been applied to medicine. Technologies for examining cellular functioning, the genetic regulation of life, and the mechanisms of infectious disease have been applied only in the last 100 years. The randomized controlled clinical trial (RCT) is just 50 years old and has

The views, opinions, and assertions expressed in this chapter are those of the authors and do not reflect official policy of the Department of the Army, Department of Defense, or the U.S. Government.

been an established standard for testing new drugs for only 25 years. Statistical principles have also only recently been applied to medicine. There are various types of research methods, including laboratory techniques, observational methods, RCTs, meta-analysis, qualitative research, and health services research. The use of these methods has provided better precision and more control over the body and the public's health than ever before. Which of these methods are essential for the clinical researcher to know, and how should they be integrated?

The Audience and the Evidence

When deciding whether or not to use a therapy, everyone wants to know if there is evidence that a therapy is safe and will work. Yet different groups often look for different types of evidence to make these decisions.

Patients

Patients or their family members may want to hear details about other individuals with similar illnesses who have used a treatment and recovered. If the treatment appears to be safe and there is little risk of harm resulting from it, these success stories may convince patients to use the treatment. This type of evidence is called *anecdotal* or, if more fully developed, a *case report*.

Practitioners

Physicians, who see many patients a day, often want a different type of evidence. They realize that what works in one case may not work in another, so they need more than a few patient recovery stories before they can recommend a therapy. They often want to know what the likelihood or probability is that a patient will recover or have an adverse effect based on a series of similar patients who have received the treatment. For example, out of 100 patients who received a specific treatment for a condition did 20% or 80% improve, and how many had side effects? They also want to know about the complexity of using the therapy, including its cost and inconvenience. This type of evidence comes from observational or clinical outcomes data.

Clinical Researchers

Scientists doing patient-oriented research may want a different type of evidence. They often want to know how much improvement occurred in a group who re-

ceived the treatment compared with another group who did not receive the treatment. For example, if 80% of the patients who received a treatment got better, but 75% of similar patients got better after only visiting a physician and getting any treatment, only 5% of the improved cases could be attributed to the treatment. This evidence is known as *comparative clinical trial evidence*. Some scientists will accept comparative evidence for a treatment only when it has come from an experiment in which blinding and randomization have been followed. This type of evidence is termed *clinical experimental* or *RCT evidence*.

Basic Scientists

Basic science investigators may want objective evidence supporting a mechanism of action. This evidence must be obtained in laboratory experiments that can explain the effects observed in clinical research or guide better clinical research. This is called *basic science evidence*.

Policymakers

Those in charge of determining public laws and health care policy often need definitive proof that a practice is safe and effective before applying it to large groups. They require evidence in which a high degree of confidence can be placed because policy errors can adversely affect millions of people and cost billions of dollars. This type of evidence comes from extensive evaluation and the synthesis of several research reports through systematic reviews, meta-analyses, and consensus evaluations performed by experts in the field.

Research Domains Relevant to Complementary and Alternative Medicine

The various types of information preferred by different audiences is obtained by different research methods. Figure 1-1 illustrates six types of research that are frequently used in the investigation of medicine and the general type of information that each of these approaches provides.

These types of research include the following:

1. **Qualitative research** includes such methods as detailed case studies and patient interviews that describe diagnostic and treatment approaches and that investigate patient preferences and relevance to those approaches. Qual-

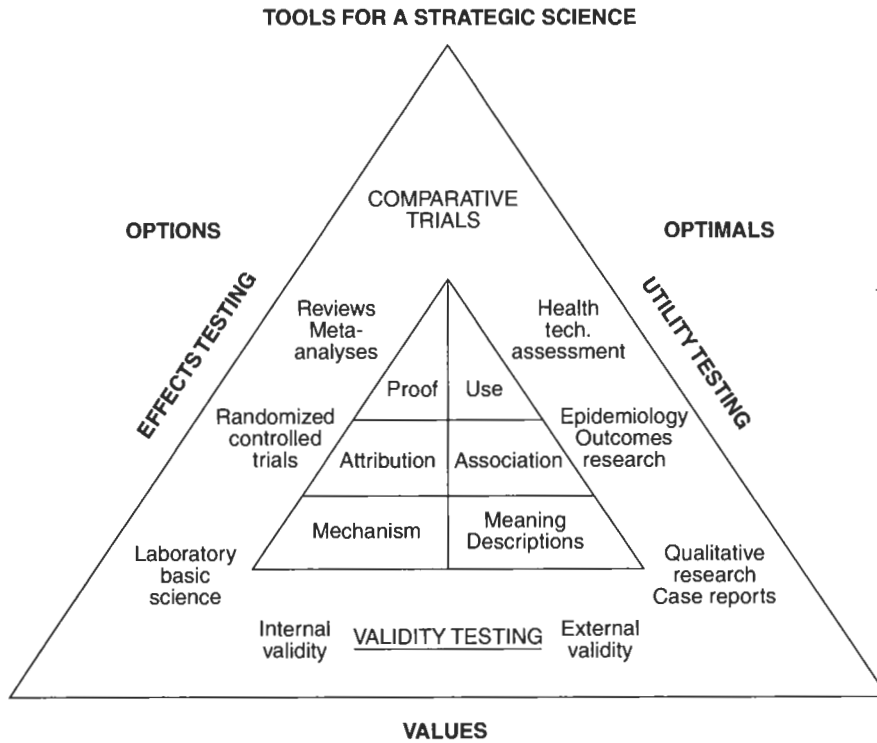


Figure 1-1 Knowledge domains.

itative approaches have been extensively developed in the nursing profession and are becoming increasingly common in primary care.

2. **Laboratory and basic science approaches** investigate the basic mechanisms and biological plausibility of practices. In vitro (cell culture and intracellular [e.g., with probe technology], in vivo (testing in normal, disease-prone, or genetically altered animals), and mixed approaches are now used extensively and are rapidly expanding into molecular realms.
3. **Observational studies**, such as practice audit and epidemiological research, outcomes research, and other types of observational research, describe associations between interventions and outcomes. Practice audits involve monitoring outcomes on all or a selected sample of patients receiving treatment. Patients are evaluated before and after an intervention to measure the effects. In these studies there may be no comparison group, or comparison groups may be developed by sampling patients

from other practices who have not been treated with the intervention or from the same practice before the intervention.

4. **RCTs** attempt to isolate or compare the specific contribution of different interventions on outcomes. In these studies researchers usually assign patients to one treatment group or another by using a method that ensures that the groups are comparable in all factors that might influence outcomes, except the treatments. Various methods, such as randomly selected numbers or computer-generated random assignment, are used. The treatment may be evaluated with or without knowledge of the assignments. The best approach is allocation concealment, where knowledge of which patients get which treatment at the time of assignment is concealed.
5. **Meta-analysis, systematic reviews, and expert review and evaluation** are methods for assessing the accuracy and precision of clinical research. Methods for expert review and summary

of research have evolved over the last several years through the use of systematic protocol-driven approaches, such as meta-analysis. These approaches are being used increasingly in place of subjective reviews to increase confidence in the idea that the effects found in clinical research are accurate and applicable across populations.

6. **Health technology assessment and health services research** examines the actual utility and impact of interventions in light of social factors, such as access, feasibility, costs, practitioner competence, patient compliance, and so forth. Often this type of research involves surveys or samplings from groups already undergoing interventions to determine the quality and costs of the treatment. Random sampling may or may not be used.

Goals of Research Types

Although certain groups may prefer one or more of these methods and the types of information they provide, information from all methods may be required for making clinical decisions. Laboratory research, RCTs, and systematic reviews or meta-analyses (left side of Figure 1-1) are usually used to determine the existence of a specific effect of an intervention or exposure or to support a theory about mechanisms. Qualitative research, observational trials, and health technology assessment (right side of Figure 1-1) are usually used to determine the probability, magnitude, and relevance of an effect in actual health care delivery. There is a tension between research performed to isolate specific effects (laboratory, RCTs, meta-analyses, etc.) and research that tries to investigate relevance and utility in the real world (qualitative, observational, health services, etc.). More than one question probably should not be investigated in a single research project, because designing research that attempts to address both specific and pragmatic questions simultaneously is difficult. To assess both specificity and utility, multiple research strategies are required. Consistent decision rules for the application of research methods are important for the development of science-based medicine.² In addition, the clinical researcher must understand what constitutes quality research within each of these evidence domains. Research quality criteria become the basis for evaluating any study or group of studies.³

Research Quality Criteria

Research quality can be assessed by using established criteria to determine the validity of information in research reports. For example, the validity of RCTs is evaluated with quality criteria that determine internal validity by assessing the likelihood that observed effects are due to bias. The general application of clinical research, including RCTs and observational trials, is evaluated with criteria that determine external validity or the likelihood that effects would occur in varied situations. There are numerous quality rating systems for evaluating clinical research. One of the best is the consort criterion, which is a widely adopted set of reporting guidelines for RCTs.^{4,5} Most criteria emphasize the importance of allocation concealment, randomization, blinding, proper statistical methods, attention to dropouts, and other factors. Other guidelines exist for reporting meta-analysis, observational trials, and diagnostic tests.^{6,7} Anyone evaluating clinical research should be familiar with those criteria.

In addition to internal and external validity, CAM research requires attention to model validity, or the likelihood that the research has addressed the unique taxonomy and context of the CAM system being investigated. Many CAM systems originate outside of Western medicine. Proper clinical research on these systems requires adequate expertise and experience in the CAM system.⁸ Often the CAM system is examined in populations for which the practice is traditional and integral to the culture. However, there can be marked variations in response to treatments in different cultures. Results produced in one culture may not translate readily to another.⁹ In addition, individual expectations and informed consent can have a significant effect on outcomes.^{10,11} The evaluation of model validity in CAM requires that these items be considered when judging the quality of clinical research. Quality criteria for internal, external, and model validity of a CAM clinical trial are listed in Table 1-1.

The likelihood of validity evaluation (LOVE) system has been applied to the evaluation of several CAM clinical research sets. When examining clinical research, the practitioner can usually focus on the types of evidence dealing with clinical trials (middle two sections of Figure 1-1). These types of evidence address the questions "Is the treatment effective?" and "What is the magnitude of the treatment's effectiveness?"