these questions and others will emerge through further analyses of the data from the HPTN 052 study and subsequent trials.

Drugs to prevent HIV-1 transmission are being investigated in both infected and uninfected persons. In HIV-1–negative persons, drugs can be used before or after high-risk exposure (or both). The use of 1% tenofovir topical gel as a microbicide in women[7] and of oral combination therapy with tenofovir and emtricitabine in men who have sex with men[8] has reduced rates of HIV-1 acquisition by 39% and 44%, respectively, findings that have provided strong encouragement for these approaches.

In HIV-1–positive persons, the use of antiretroviral agents to prevent secondary transmission has led to a variety of proposed test-and-treat strategies.[1,9] The dovetailing of individual and public health benefits that are suggested by the findings of the HPTN 052 study provides a major impetus for these initiatives to move forward.

Antiretroviral therapy is by no means perfect and is not the ultimate answer to controlling and ending the HIV epidemic. Adverse events, emergence of drug-resistant viral strains, maintenance of adherence, sustainability, and cost are just some of the concerns. However, this is precisely the wrong time to limit access to antiretroviral therapy in resource-limited settings, since we have the tools in hand to maintain or restore health in infected persons and reduce transmission to their sexual partners.

Aggressive programs to diagnose and treat HIV infection as part of a comprehensive care package and multiple approaches to the prevention of transmission that have been tested in well-designed clinical trials have the potential to preserve health and control the epidemic until a safe and effective HIV vaccine is a reality.

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1. Dieffenbach CW, Fauci AS. Thirty years of HIV and AIDS: future challenges and opportunities. Ann Intern Med 2011;154:766-71.
2. Gilks CF, Crowley S, Ekpini R, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet 2006;368:505-10.
3. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010. (http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.)
4. World Health Organization. PMTCT strategic vision 2010-2015: preventing mother-to-child transmission of HIV to reach the UNGASS and Millennium Development Goals. (http://www.who.int/hiv/pub/mtct/strategic_vision.pdf.)
5. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493-505.
6. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet 2010;375:2092-8.
7. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010;329:1168-74.
8. Grant RM, Lama JR, Anderson PL, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587-99.
9. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet 2009;373:48-57.

Nutrition Support in Critical Illness — Bridging the Evidence Gap

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The modern field of specialized nutrition support began with seminal studies showing that parenteral nutrition could stimulate growth and development in infants, as well as wound healing and convalescence in adults with the severe short bowel syndrome, who until that time had been unable to survive with enteral nutrition alone.[1,2] Later, technical developments and recognition that malnutrition among hospitalized patients was common[3] led to growth in nutrition support services. By the 1980s, the use of specialized regimens of enteral and parenteral nutrition were routine in intensive care units (ICUs) worldwide, despite little evidence from rigorous, controlled clinical trials supporting the efficacy of these interventions.[4,5]

With time, there has been improved awareness about complications related to the use of

enteral and parenteral nutrition, along with improved control of blood glucose levels and delivery of reduced caloric loads.[4-8] The use of parenteral nutrition in ICUs has diminished markedly, given evidence that enteral nutrition may be generally superior for clinical outcomes.[6-8] However, substantial areas of uncertainty remain (Table 1). Guidance has been based largely on expert opinion and on data from observational and small clinical trials, rather than on rigorous comparative effectiveness research.[6,7,9,10] The 2009 European and American–Canadian clinical practice guidelines for ICU nutrition support differ in their recommendations for the initiation of parenteral nutrition in patients who are not expected to achieve adequate nutrient intake with enteral nutrition (oral diet or tube feedings).[9,10] European guidelines suggest that parenteral nutrition be initiated within the first few days after ICU admission,[9] whereas American–Canadian guidelines suggest withholding parenteral nutrition for 7 days in patients without preexisting malnutrition.[10]

Table 1. Major Areas of Uncertainty in the Nutritional Support of Patients in the Intensive Care Unit (ICU).*

Clinical effect of various durations of minimal or no feeding
Optimal timing for the initiation and duration of therapy with enteral nutrition, parenteral nutrition alone or in combination with enteral nutrition, and micronutrients (known essential vitamins, trace elements, and minerals) in enteral and parenteral nutrition
Efficacy of various doses of energy, fat, and protein in enteral and parenteral nutrition
Effect of altered essential and nonessential amino acids (including glutamine) in parenteral nutrition
Efficacy of various doses and formulations of micronutrients in enteral and parenteral nutrition
Efficacy of alternative lipids (e.g., fish oil, olive oil, structured lipids, medium-chain triglycerides, and others, alone and in combination) in enteral and parenteral nutrition
Clinical efficacy of commercially available tube feedings containing combinations of antioxidants, antiinflammatory lipids, arginine, glutamine, and nucleotides in subgroups of patients
Efficacy of longer-term enteral or parenteral nutrition (or both) as needed in the post-ICU hospital and home setting
Effect of approaches for enteral and parenteral nutrition support in specific diagnostic subgroups of patients

* Enteral nutrition includes oral complete supplements; specific oral protein, calorie, or micronutrient supplements; and complete tube feeding formulations, and parenteral nutrition refers to complete intravenous formulations.

In this issue of the *Journal*, Casaer et al.[11] describe a large (4640 patients), multicenter, randomized trial designed to address this area of uncertainty. Patients receiving early initiation of parenteral nutrition were given intravenous dextrose (20% solution) on ICU days 1 and 2; on day 2, enteral nutrition was begun (predominantly as tube feedings) with the addition of parenteral nutrition as needed to achieve the daily caloric intake goal (according to European guidelines). The late-initiation group began intravenous dextrose (5% solution) on day 1, enteral nutrition on day 2, and parenteral nutrition after day 7 as needed to achieve the caloric goal (American–Canadian guidelines).[6,7,10] Nutrition support after discharge from the ICU was at the discretion of the attending physicians.

The two groups were well matched at entry according to illness severity, diagnosis, demographic characteristics, and nutrition risk scores. Mortality indexes in the two groups were similar; however, the late-initiation group had a significant (6.3%) reduction in the length of stay in the ICU and slight but significant improvements in secondary outcomes (infectious complications, indexes of organ dysfunction, and length of stay in the hospital). In addition, the late initiation of parenteral nutrition was associated with a modest reduction in total hospital costs (approximately $1,600 per patient).

Casaer et al. incorporated an upper target for blood glucose of 110 mg per deciliter (6.1 mmol per liter), which was lower than the target of 140 to 180 mg per deciliter (7.8 to 10.0 mmol per liter) now used in most ICUs. Patients in the two study groups had similar levels of blood glucose, so this factor did not mediate the differential responses observed. Identical and complete intravenous preparations of vitamins and trace elements were given daily to all patients, with intravenous potassium, magnesium, and phosphorus to maintain blood levels. Thus, between-group differences are probably limited to effects of the macronutrients (calories, dextrose, amino acids, and lipid emulsion) in the parenteral nutrition. Weaknesses of the study include the necessarily unblinded design and the amino acid doses, which were lower than those recommended in current clinical practice guidelines.[9,10]

Underlying mechanisms for the outcome differences between the early-initiation group and the late-initiation group are unclear, but differ-

ences in the length of stay in the ICU and hospital may be due to the increased rates of infection and associated organ dysfunction in the early-initiation group. The authors suggest that early initiation of parenteral nutrition may be associated with the suppression of autophagy, with inadequate clearance of damaged cells and microorganisms, but other unknown factors (e.g., altered immunity and biofilm characteristics) may also be involved.

Casaer et al. clearly show that the early initiation of parenteral nutrition to achieve caloric goals of approximately 25 to 30 kcal per kilogram of body weight per day is associated with worse clinical outcomes than those in patients in whom initiation was delayed for a week. However, these data should not be overinterpreted, since between-group differences in outcome were small, rates of death in the two groups were similar, approximately 80% of the patients were not seriously malnourished at entry (nutrition risk score, ≤4), and 60% were admitted to the ICU after cardiac surgery. Also, patients who were readmitted to the ICU and those who were seriously malnourished or were receiving established enteral or parenteral nutrition at the time of ICU admission were excluded.

In addition, patients in the late-initiation group received early enteral nutrition and daily intravenous vitamins and trace elements before starting supplemental parenteral nutrition on day 8. The optimal requirements of micronutrients for patients in the ICU are unknown (Table 1).[4] Nonetheless, it may be prudent to provide complete enteral or parenteral preparations of vitamins and trace elements if parenteral nutrition is delayed in patients who cannot tolerate full enteral nutrition. Intravenous micronutrient preparations are subject to periodic market shortages; thus, consultation with health professionals and societies with experience in specialized nutrition support is important (e.g., the American Society for Parenteral and Enteral Nutrition at www.nutritioncare.org).

The findings of Casaer et al. should result in renewed attention to the nutritional needs of patients in the ICU and after their discharge from the ICU, inform the use of thoughtful nutritional care in the ICU (including the judicious use of parenteral nutrition and early use of enteral nutrition), and stimulate further study concerning the nutritional support of critically ill patients.

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1. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. JAMA 1968;203:860-4.
2. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery 1968;64:134-42.
3. Bistrian BR, Blackburn GL, Vitale J, Cochran D, Naylor J. Prevalence of malnutrition in general medical patients. JAMA 1976;235:1567-70.
4. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med 2009;361:1088-97.
5. Thibault R, Pichard C. Parenteral nutrition in critical illness: can it safely improve outcomes? Crit Care Clin 2010;26:467-80.
6. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr 2003;27:355-73.
7. Clinical Evaluation Research Unit. Critical care nutrition. Kingston, ON, Canada: Kingston General Hospital, 2009. (http://www.criticalcarenutrition.com.)
8. Heighes PT, Doig GS, Sweetman EA, Simpson F. An overview of evidence from systematic reviews evaluating early enteral nutrition in critically ill patients: more convincing evidence is needed. Anaesth Intensive Care 2010;38:167-74.
9. Singer P, Berger MM, Van den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 2009;28:387-400.
10. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2009;33:277-316.
11. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506-17.