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The importance of nutritional care in HIV-infected children in resource-limited settings

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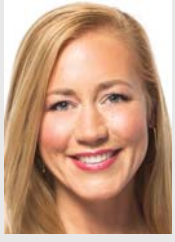

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Renewed efforts to provide proper nutritional care are essential for appropriate pediatric HIV management. Current studies support the use of vitamin A and macronutrients that increase caloric and protein intake. With additional research on key issues such as the needed composition and timing for nutritional supplementation, we can determine the best strategies to support the growth and development of HIV-infected children in resource-limited settings. Malnutrition among children is common in the resource-limited settings where HIV infection is most prevalent. While malnutrition is associated with higher morbidity and mortality for HIV-infected children, there is only limited evidence to guide the use of nutritional support for HIV-infected children. The best studied is vitamin A, which is associated with improved mortality and clinical outcomes. Zinc and multivitamin supplementation have not consistently been associated with clinical benefits. Limited research suggests macronutrient supplementation, which typically uses enriched formulas or foods, improves key anthropometrics for HIV-infected children, but the optimal composition of nutrients for supplementation has not been determined. More research is needed to understand the most efficient and sustainable ways to ensure adequate nutrition in this vulnerable population.

Among the many challenges faced by people living with HIV, malnutrition has been a relentless struggle. Malnutrition and nutrition-related issues remain a common cause of death for children around the world, in particular for those who are HIV-infected. Recent reports have indicated that malnutrition contributes to the death of approximately 3.1 million children annually or 45% of child deaths in 2011 [1]. In the resource-limited settings where the vast majority of the world's children live, poverty, malnutrition and disease create vulnerability on top of vulnerability. Approximately 20–30% of severely malnourished African children who are admitted for inpatient nutrition therapy are HIV-infected, and those infected children are three-times more likely to die compared to uninfected children [2,3]. Multiple studies have found that weight loss and wasting are independent contributing factors to poor clinical outcomes and mortality in HIV-infected patients. Healthcare providers, care systems and investigators need information about the continued importance of appropriate nutritional care for HIV-infected children. To do this, we will discuss the current literature regarding nutritional care in this population, challenges related to nutritional care and next steps for improving the comprehensive care we provide to HIV-infected children.

Malnutrition is typically measured by the WHO standards that employ global reference standards to compare anthropometric measures of weight-for-age, height-for-age and weight-for-height with z-scores, as well as mid-upper arm circumference. Weight-for-age z-scores of -1 to -2 represent mild malnutrition, z-scores of -2 to -3 represent moderate malnutrition and z-scores ≤ -3 represent severe malnutrition. As noted by Myatt's

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2006 review of methods detecting malnourished children, mid-upper arm circumference, in addition to other clinical indicators, can be a useful screening tool for malnutrition in the community [4]. Mid-upper arm circumference is increasingly being used to help predict mortality in severely malnourished children [5].

Malnutrition is common among HIV-infected children. In Kenya, in a study of 3255 HIV-infected children enrolled in an outpatient HIV program, the median weight-for-age z-score was -1.9 (-2.7 to -1) [6]. Even with effective antiretroviral therapy, severely affected children may still develop marasmus or kwashiorkor, which significantly increases the risk of poor clinical outcomes. In a study in Uganda and Zimbabwe, HIV-infected children hospitalized with marasmus or kwashiorkor had 24-week mortality rates of 32 and 20% (respectively) after starting antiretroviral therapy, whereas only 1.7% of children not hospitalized for these conditions had died at 24 weeks ($p < 0.001$) [7].

Addressing the major problem of malnutrition requires understanding the nutritional deficits in children with HIV, which encompass both macronutrients and micronutrients. Macronutrients include carbohydrates, proteins and fats, typically in the form of food items or formula. Micronutrients are vitamins and trace minerals, which we typically give in medicinal form. Vitamin A, vitamin E, vitamin B6 and B-12, folate, zinc, iron, copper and glutathione are the micronutrients most commonly found to be low in HIV-infected children [8–11]. Most studies of micronutrient status only measure these serum levels; fewer studies exist that look at the clinical outcomes associated with supplementation with these micronutrients. We will focus our discussion on these clinical outcomes from nutritional supplementation used in resource-limited settings.

Most research on micronutrient supplementation in HIV-infected children in resource-limited settings focuses on vitamin A, which is generally found to be associated with reduced morbidity and mortality. Vitamin A has been associated with a reduction in child mortality rates in multiple studies [12,13]. One study found vitamin A to reduce all-cause mortality in HIV infected children by up to 63% [12]. Vitamin A has also been associated with increased CD4 counts and decreased HIV-associated morbidity, such as cough and diarrhea [14]. Within one cohort, vitamin A supplementation was also associated with a significant increase in the height of HIV-infected children between 6 and 18 months of age [15]. There is heterogeneous evidence regarding the outcomes of vitamin A in the perinatal period, in part because of Fawzi's 2002 study on vitamin supplementation which showed vitamin A may increase HIV-1 transmission during breast feeding [16]. However, improved outcomes are consistently reported for both HIV infected and uninfected children between the ages of 6 and 59 months [17,18].

Zinc and multiple micronutrient supplements have also been studied in HIV-infected children in resource-limited settings. Less evidence supports the use of zinc or multiple micronutrient supplements. In contrast to studies of HIV-uninfected children in similar settings, zinc has not been consistently associated with reductions in diarrhea for HIV-infected children [19,20]. Only one study found a significant decrease in mortality rates with zinc supplementation [21]. Studies of multiple micronutrient supplementations do not suggest decreases in the rates of diarrhea or pneumonia [20,22,23]. Moreover, multiple micronutrient supplementation has not been found to significantly change mortality, growth or CD4 counts [23].

Macronutrient supplementation holds much more promise for improving clinical outcomes in HIV-infected children. Ready-to-use therapeutic foods and enhanced formulas are forms of macronutrient supplementation that are frequently utilized in children with severe malnutrition. HIV-infected children consistently gain weight with both types of interventions [24–28]. In some studies, co-morbid conditions, such as diarrhea, have also decreased with these forms of macronutrient supplementation [24,25]. No significant improvements in CD4 counts have been shown consistently. Whey protein is another macronutrient that has been studied in HIV-infected children. Whey supplementation did not significantly improve hemoglobin levels or leukocyte counts; however, the intervention group had fewer associated co-infections [29].

Another option for macronutrient supplementation is spirulina. When given with traditional meals of millet, fruits and vegetables, spirulina is associated with increased weight gain in HIV-infected patients when compared to those given traditional meals alone (15 g/day vs 10 g/day), along with a suggestion of improvement in anemia [30]. Although it should be noted that both the intervention and control groups received traditional meals, and both groups were found to have a significant increase in weight-for-height and weight-for-age z scores [30].

Food itself has been found to be a powerful agent to improve malnutrition and improve clinical outcomes for children with HIV. In Kundu's 2012 study, food rations were given at clinic appointments to see if it improved HIV clinic adherence. Not only did this intervention achieve its primary goal but also it was associated with improved CD4 counts, weight gain and reduced AIDS-defining illnesses and hospitalizations [31]. The results of this study are particularly interesting for health care providers working in food insecure areas where HIV-related stigma is prevalent. This stigma may discourage individuals from going to clinic and receiving appropriate care. If a food incentive motivates individuals to come to clinic, to receive life-saving medications and results in improved clinical outcomes, then healthcare systems need to consider the long-term implications of offering food rations to HIV-infected patients in resource-limited settings.

Despite understanding that malnutrition is a critical aspect of comprehensive pediatric HIV care, we still have large gaps in our understanding of how nutritional supplementation can be implemented most effectively. Interest in optimizing nutritional health in HIV-infected children is evident in the medical community, with multiple systematic reviews and an updated Cochrane Review being published within recent years [32–34].

However, the existing literature on how nutritional supplementation impacts clinical outcomes is surprisingly limited, particularly for macronutrient and food supplementation. Little is known about what specific composition of macronutrients would have maximal benefits in this population or at what ages it might be most critical to offer supplementation. Most of the interventions examined are ones that have been used in severe malnutrition in populations that are not HIV-infected. Because HIV-infected patients have higher mortality rates when severely malnourished compared to those who are not infected, there may be important differences in pathophysiology that requires adjustment of macronutrient interventions.

Children are a vulnerable population worldwide; HIV-infected children face additional burdens from malnutrition, poverty and disease. Effective, sustainable macronutrient supplementation might be critical to their potential to develop into healthy, productive adults. In contrast, international funding for food programs is rapidly shrinking. Targeted research to identify food and macronutrient supplementation with the greatest benefits specifically for HIV-infected children would guide advocacy and policy decisions around pediatric care, as well as the delivery of aid and the clinical management of these children. Investments in proven strategies such as vitamin A supplementation and macronutrient supplementation may allow us to preserve children's unique capacity for growth and development. In addition, we need to re-focus efforts on other interventions to prevent and treat diarrhea and other infectious diseases among children with malnutrition. These co-morbid conditions only worsen the prognosis of a malnourished HIV-infected child, increasing the already grim mortality rates.

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