

Siyazi Mda\*

Department of Pediatrics and Child Health, Sefako Makgatho Health Sciences University, Pretoria, South Africa

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\*Corresponding author: Siyazi Mda, Department of Paediatrics, School of Medicine, Molotlegi Street, Ga-Rankuwa, 0208, PO BOX 221, MEDUNSA, 0204, South Africa, Tel: 012 5214445; Fax: 012 521 3627; E-mail: siyazi.mda@gmail.com

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## Review Article

# Nutritional Supplementation in HIV-Infected Children: A Review

### Abstract

The nutritional status of HIV-infected children in terms of anthropometric indices and micronutrient concentrations is commonly compromised. Malnutrition is a risk factor for mortality at initiation of highly active antiretroviral therapy (HAART). The role of HAART is pivotal in the management of HIV-infected children. Treatment with HAART has been shown to decrease mortality and improve CD4 counts and reduce viral load. HAART has beneficial effects on the nutritional status as well. However, children who are severely malnourished have an increased risk of mortality when initiating HAART. A number of studies have thus assessed whether supplementation with macronutrients and micronutrients would improve the nutritional status and reduce morbidity and mortality in these children.

Supplementation with macronutrients seems to improve energy intake and initially improves weight gain but seems to have no effect on morbidity and mortality. Micronutrient supplementation has been shown to improve weight and reduce diarrhoeal and respiratory morbidity. Serious consideration should be given to supplementing both macronutrients and micronutrients in children initiating HAART.

## Introduction

HIV infection remains a major challenge in adults and children worldwide. It is estimated that there were approximately 3.2 million children under the age of 15 years worldwide living with HIV at the end of 2013, over 90% of these children live in sub-Saharan Africa [1]. The number of children newly infected with HIV worldwide in the same year (2013) was 240 000, and the overwhelming majority of these children are infected perinatally through mother-to-child transmission [2].

Common clinical features observed in HIV-infected children include compromised nutritional status (including moderate and severe acute malnutrition), diarrhoeal disease and respiratory tract infection [3]. Compromised nutritional status may present as moderate acute malnutrition or severe acute malnutrition. The WHO defines severe acute malnutrition (SAM) as weight-for-height Z-score < -3SD, mid-upper arm circumference (MUAC)  $\leq$  11.5 cm in children aged 6 months to 5 years, visible wasting and nutritional oedema [4]. On the hand, moderate acute malnutrition is defined as weight-for-height between -2 and -3 SD or MUAC < 12.5 cm but  $\geq$  11.5 cm, without nutritional oedema in both instances [5]. Guidelines for the management of SAM have been developed and refined by the WHO and are designed to reduce mortality in these children [6]. The management of HIV-infected children with SAM, which includes the WHO 10 steps to management of SAM, is similar to that of children with SAM who are not HIV-infected [6].

Children with compromised nutritional status are more prone to acquiring diarrhoeal disease and respiratory tract infections (including pneumonia and tuberculosis) [7,8]. Repeated episodes of diarrhoeal disease and respiratory tract infections in turn worsen the nutritional status, thus creating a vicious cycle [7].

In the absence of treatment, HIV infection in children progresses

rapidly when compared with adults. Without treatment more than 50% of children perinatally infected with HIV die within the first two years of life [9]. Antiretroviral drugs are the mainstay of treatment in HIV-infected persons. The development of highly active antiretroviral therapy (HAART) is considered as one of the important successes of modern medicine; HAART has changed HIV from a virtually universally fatal illness to a chronic illness [10]. Indeed early diagnosis of HIV and initiation of HAART has been noted to reduce mortality [11]. The provision of antiretroviral therapy for the prevention of mother-to-child transmission of HIV has had markedly reduced the incidence of HIV globally [1]. Since 2009, a 43% decline in new HIV infections among children from countries that had the highest number of pregnant women living with HIV, has been observed [1]. However, while there has been a major improvement in access to HAART, only 23% of the estimated 3.2 million children living with HIV were receiving HAART by December 2013 [2].

## Risk factors for mortality in children initiating HAART

The introduction of HAART has markedly reduced the mortality of HIV-infected children. However, there are number of factors associated with early mortality in children initiating HAART. These include low CD4 counts, advanced HIV clinical stage, stunting, underweight, anemia and co-infection with tuberculosis (TB) [12,8]. Co-infection with TB has been noted to be common in HIV-infected children [8]. Compromised nutrition is also common seen in children infected with TB [8]. Nutritional supplementation may thus be important for HIV-infected children who are co-infected with TB.

A study conducted among Ethiopian children to assess the impact of malnutrition on survival of HIV-infected children initiated on HAART revealed that independent predictors of mortality were weight-for-height Z-score below -3SD, low CD4 counts and low hemoglobin (<7.0 g/dl) [12]. In a group of South African HIV-

infected children initiating HAART, the risk factors for mortality that were observed were age younger than 3 years, severely reduced CD4 percentage (<10%), chronic diarrhoea and low weight-for-age Z-scores [13]. It was also noted that 64% of these deaths occurred within 3 months and 83% within 6 months of HAART initiation; the median follow-up period for surviving children was 22 months [13]. It is important to note that after initiation of HAART, the viral load and CD4 counts are first monitored after 6 months post initiation; therefore the vast majority of children in this study died before laboratory monitoring commenced [13]. The first 6 months post HAART initiation was also identified as the period with the highest mortality in a study conducted in a cohort of Ethiopian children receiving HAART, where 70% of deaths occurred within the first 6 months of HAART initiation [14]. The independent predictors of mortality that were noted in these Ethiopian children were low weight-for-age Z-scores, advanced clinical stage of HIV, poor HAART adherence and hemoglobin level < 7 g/dl [14]. A compromised nutritional status at initiation of HAART thus seems to be associated with increased mortality; therefore nutritional supplementation may be important for children on HAART.

### Nutritional status of HIV-infected children

The nutritional status of HIV-infected children as measured by anthropometric indices and micronutrient concentrations has been noted to be compromised. A hospital based study conducted in the Republic of South Africa revealed that the concentrations of micronutrients and weight-for-age and height-for-age Z-scores of antiretroviral therapy naïve HIV-infected children were significantly lower than those of HIV-uninfected children [15].

There are a number of reasons why HIV-infected children have a poor nutritional status. These include reduced food intake, malabsorption and diarrhoea, and impaired storage and increased utilization of nutrients [7]. The reduced food intake often affects both macronutrients and micronutrients and may occur as a result of poor appetite, difficulty and pain on swallowing, and nausea and vomiting [16]. Food insecurity due to reduced family income as a result of parental HIV-related illness also plays an important role in the reduced food intake observed in HIV-infected children [17]. Malabsorption of fats, carbohydrates and micronutrients is common with HIV infection and may be due to opportunistic infections causing diarrhoea or due to the HIV itself [7]. HIV infection has a major impact on the structure and function of the alimentary tract. The virus produces the transactivating peptide (Tat) which plays a role in the pathogenesis of diarrhoea in HIV-infected patients [18]. Tat stimulates active fluid secretion into the gut lumen and inhibits fluid absorption at the intestinal level [19,20]. The inflammation associated with the infections occurring in HIV can lead to catabolism of tissues and muscle and inefficient utilisation of nutrients. Indeed rest energy expenditure has been shown to be increased even in asymptomatic HIV-infected persons [7].

Treatment with HAART is associated with sustained improvement in growth [21]. HIV-infected children from Malawi and Uganda had significant improvements in weight-for-age and height-for-age Z-scores within one to two years of HAART initiation [22,23].

However, among the Malawian children neither the median weight-for-age Z-score nor the height-for-age Z-score reached normal values after two years on HAART among children who were underweight or stunted at initiation of HAART [22]. Likewise a study from Tanzania revealed that HIV-infected children on HAART were more likely to be underweight and/or wasted compared to HIV-uninfected children [24].

The nutritional status of HIV-infected children may affect the pharmacokinetics of antiretroviral drugs. A Ugandan study revealed that there was a difference between the pharmacokinetics of Lopinavir and Efavirenz in Ugandan children (48% of whom were malnourished) and those in children from resource-rich countries [25]. The bioavailability of lopinavir and efavirenz (but not of Nevirapine) was lower in Ugandan children [25].

### Macronutrient intervention

As previously mentioned, HIV-infected persons are at great risk of malnutrition, and this includes those who are on HAART. Nutritional interventions may thus play an important role as an adjunct to antiretroviral medicines. These nutrients may be macronutrients or micronutrients. Macronutrients may be defined as essential nutrients that are required by the body in relatively large amounts, these are carbohydrates fats and proteins [26].

A meta-analysis of 14 trials evaluating the effectiveness of macronutrient supplements compared with no supplements in HIV-infected adults and children indicated that these supplements increased energy and protein intake [26]. While the increased energy and protein intake among those who received the supplements did increase body weight in most instances, there was no effect on CD4 cell counts and viral load [26]. These authors noted that the supplements increased weight and body mass index in the first 3 months of supplementation [26]. After this period there was no significant difference in weight and body mass index gain between those who received the macronutrient supplements and those who did not [26]. Nonetheless, it should be remembered that mortality in HIV-infected children initiating HAART seems to be highest in the first 3 to 6 months of initiation.

Macronutrient supplementation may also be of benefit in HIV-infected children who are co-infected with TB. A systematic review revealed that the provision of high-energy nutritional products seems to result in a modest increase in weight gain during treatment for active TB [27].

The WHO has developed guidelines for the nutritional care of HIV-infected children [4], and the energy requirements of these children are summarized in Table 1.

Provision of Ready to Use Therapeutic Foods (an energy-dense lipid paste made of peanut butter, milk powder, oil, sugar, minerals, vitamin, and protein mix) to HIV-infected children on HAART for at least four months, resulted in a significant improvement in weight-for-age and weight-for-height Z-scores compared with HIV-infected Tanzanian children on HAART who did not receive the foods [28].

Supplementation with macronutrients seems to improve energy

**Table 1:** Total daily calorie of HIV-infected children in kcal/kg/day.

Age	HIV-uninfected	HIV-infected (asymptomatic)	HIV-infected with complications	HIV-infected with severe complications
6 - 11 months	690	760	830	150 – 220
12 - 23 months	900	990	1080	150 – 220
2 - 5 years	1260	1390	1510	150 – 220
6 - 9 years	1650	1815	1980	75 – 100
10 - 14 years	2020	2220	2420	60 – 90

Obtained from WHO guidelines [4]

and protein intake and may also improve weight, but an effect on morbidity and mortality does not seem to have been demonstrated.

### Micronutrient Intervention

HIV infection and deficiency of micronutrients are both independently associated with immune deficiency. HIV infection often results in micronutrient deficiency partly through poor dietary intake, malabsorption of micronutrients and increased utilisation of the micronutrients. The resultant micronutrient deficiency will further suppress immunity and will cause faster progression of HIV disease. This progression will intensify susceptibility to infections (including diarrhoea) resulting in even more loss of micronutrient. This vicious cycle is well described in the review by Semba and Tang [16].

Micronutrient deficiencies have been noted to be more common in HIV-infected children compared with HIV-uninfected ones. Serum concentrations of zinc, iron and ferritin were significantly lower in HAART naïve HIV-infected South African children compared with HIV-uninfected children [15].

The provision of multiple micronutrient supplements to HAART naïve HIV-infected South African children resulted in improvement in weight-for-height Z-score and fewer episodes of respiratory symptoms compared with a placebo [29]. A review of 11 trials indicated that Vitamin A supplementation is safe and is of benefit in children with HIV infection and that zinc is safe and has the same benefits on diarrhoeal morbidity in children with HIV as in children without HIV infection [30]. The review further concluded that multiple micronutrient supplements have some clinical benefit in poorly nourished HIV-infected children [30].

### Conclusion

Undernutrition is an important risk factor for mortality in HIV-infected children who are initiating HAART. Deficiencies of macronutrients and micronutrients play a major role in the under nutrition observed in them. Children initiating HAART are at the greatest risk of mortality within the first 3 to 6 months of initiating HAART. Early diagnosis of HIV and initiation of HAART, as well as identification of malnutrition in these children is thus important. Macronutrient supplementation to HIV-infected persons initiating HAART seems to be of benefit in improving energy and protein intake and weight gain, but does not seem to have any effect on the immunological deterioration and mortality. The beneficial effects of macronutrients on weight gain in patients initiating HAART have

been noted to be mainly in the first three months. As more evidence is obtained, the role of macronutrient supplements in this population is likely to become clearer.

Micronutrient supplementation has been shown to be beneficial in improving in weight and reducing morbidity (particularly diarrhoea and respiratory symptoms) in HIV-infected children. Supplementation with both macronutrients and micronutrients in HIV-infected children initiating HAART should be implemented according to the malnutrition category, i.e. moderate or severe acute malnutrition.

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