Chapter

HIV-Infected Children and Nutrition: The Friend and The Foe

Inaya Hajj Hussein, Lara Youssef, Andrea Mladenovic, Angelo Leone, Abdo Jurjus and Virginia Uhley

Abstract

The impact of nutrition on HIV-infected children has been evaluated in multiple studies. Our review of the current trends of nutrition-related studies revealed that the focus has moved from simply the disease consequences of HIV to ensuring that antiretroviral therapy-treated children are well nourished to ensure growth and development. This update aims to present the state of the art regarding nutrition of HIV-infected children and the real potential for nutrition to serve as a dynamic therapy in this group. Recent World Health Organization reports indicate that the HIV/AIDS disease is curbing in incidence worldwide despite the high 1.8 million children, less than 15 years, reported in 2017. In addition, the literature supports the complexity and bidirectional relation between nutrition and HIV. HIV infection has a substantial effect on the nutritional status, in particular, the gastrointestinal side effects, which, in turn, have a profound impact on HIV infection. Advances in the field have transformed the course of the disease into a chronic illness, where more attention was given to lifestyle and quality of life including nutrition. However, achievement of food security, nutrition accessibility, and appropriate handling of nutrition-related complications of HIV infection are remarkable challenges, particularly, in resource poor environments, where most HIV infections exist.

Keywords: HIV/AIDS, HIV-infected children, nutrition in HIV, nutrition for children, adjunct therapy for HIV

1. Introduction

Good nutrition is essential for normal growth and development of children, and it is a vital component associated with overall health. Children infected with HIV have known increased nutrient needs to maintain optimal nutrition status. In addition, the focus of nutrition interventions has moved over the past two decades, from simply supporting the patient to ensuring that the treated children are well nourished, since they have the additional nutritional demands of growth and development [1]. Related studies have also shown that nutrition is not only an adjunct therapy but potentially a primary therapy in locations with limited access to antivirals [2].

It is also well established that HIV infection has a substantial impact on nutritional status and that nutritional status has a profound effect on the course of HIV

infection [3]. The gastrointestinal side effects of HIV treatments have been well described in the literature [4].

Advances in screening and treatment modalities have decreased incidence and have transformed the course of this disease into a chronic illness [4]. In this respect, more attention has been given to the quality-of-life issues such as nutrition [3]. It is important to note that the nutrition-related complications of HIV infections, especially the achievement of food and nutrition security, are remarkable challenges, particularly, in countries of poor resources, where most HIV-infections exist. In addition, children on highly active antiretroviral therapy (HAART) require higher levels of nutritional supplementation, in particular during the initiation period of the treatment [5]. To deal with such issues, a series of guidelines have been developed by WHO and professional societies. However, the adherence to such guidelines has been reported to have encountered many obstacles in different countries.

2. Epidemiology of HIV/AIDS in children

Despite the fact that the HIV/AIDS pandemic is curbing, in 2017, there were 36.9 million people living with HIV (35.1 million adults and 1.8 million children <15 years). Only 52% of children living with HIV were receiving lifelong antiretroviral therapy (ART). In addition, 940,000 people died from AIDS-related illnesses in 2017, while AIDS-related deaths have been reduced by more than 51% since the peak in 2004 [6].

It is well established that without treatment, HIV infection causes progressive immunosuppression, due to HIV virus-mediated depletion of CD4+ lymphocytes, leaving patients at risk of developing opportunistic infections and other HIV-related disorders [7, 8]. Since the mid-1990s, the introduction of highly active antiretroviral therapy (HAART) has remarkably influenced the epidemiology of pediatric HIV type 1 infection [9]. Consequently, the prognosis of HIV-infected children has markedly improved, both in terms of mortality and morbidity [9, 10].

The mother-to-child transmission (MTCT) was basically the focus for developing new and innovative strategies to prevent vertical transmission. In the absence of preventive measures, the risk of transmission is pretty significant as it ranges between 15 and 40%. Multiple factors affect the rate of MCTC transmission; they include maternal viral load and duration of exposure. The viral transfer is also enhanced in the presence of breast lesions or vaginal delivery. In western countries (USA and Europe), the MTCT has dropped to less than 1% in the last 10 years [8]. Such a decline is basically due to the implementation of new HIV management guidelines, which include (a) antenatal testing, (b) antiviral prophylaxis early in pregnancy, (c) elective cesarean delivery before labor, and (d) avoidance of breast feeding [8, 11].

Two developments have had the greatest impact on the outcome of pediatric HIV infection:

- The availability and use of highly effective, combination antiretroviral therapy (ART) and

- The early initiation of ART in HIV-infected infants [11]. Although the mortality rate in HIV-infected children is still considerably higher than the pediatric general population, it has decreased to 0.5–0.9 per 100 children per year in recent years [9].

Mortality rates in resource-limited environments were 4.5, 6.9, and 7.7% at 1, 2, and 3 years, respectively. These rates are similar to those observed among children in developed settings [12]. Despite these encouraging results and increasing access to

ART, mortality remains high for HIV-infected children in low- and middle-income countries. Risk factors for mortality in the first year of ART treatment include young age, low CD4 percent, advanced clinical disease, anemia, and low weight for age [13, 14]. In resource-limited countries, HIV can infect the most productive family members, especially parents, reducing agricultural production and the economic capacity of the household, causing insecure provision of food for children [2].

3. HIV infection and malnutrition in children

The cooccurrence of HIV and malnutrition together increases comorbidities and mortality in affected individuals [15]. Severe acute malnutrition (SAM) is of particular concern in children with HIV [1]. SAM is defined by the World Health Organization (WHO) as a weight-for-height z-score of less than −3, or a mid-upper arm circumference (MUAC) of less than 11.5 cm in children aged 6 months to 5 years. It can present as either marasmus (protein energy malnutrition nonedematous), kwashiorkor (edematous disease), or as marasmic-kwashiorkor. However, marasmus is seen more commonly in HIV-positive children. Although the prevalence of children with HIV and severe acute malnutrition (SAM) is variable, mortality from SAM is more than three times higher in HIV-positive children than HIV-negative children. In addition, they have a higher risk of infectious comorbidities and complications [15–17]. Nine out of 10 studies on HIV-infected children, conducted in countries with limited food resources, described low height for age, and all 10 studies reported poor weight gain. Such malnutrition was described under several forms:

- Chronic malnutrition: In this category, there is small height for age caused by several in utero infections. Such infections, which can also occur in early childhood, could be coupled with other deficiencies. Such malnutrition has a significant impact on the normal development of 39% or 56 million children less than 5 years [18].

- Acute malnutrition: In this form, there is low weight for height resulting from a recent infection or a deficiency, whereby vital functions are impaired, leading to more mortality. However, the situation could be reversed with the appropriate nutritional support. It affects 9% or 13 million children less than 5 years in sub-Saharan Africa [18].

- Underweight: In this group, there is also low weight for age. The child is thin, and it is hard to differentiate it from the two other groups. However, it could be considered as an indicator to follow up on the nutritional status of a child. It has been reported to impact 21% of children below 5 years of age in sub-Saharan Africa (30 million children). In brief, wide regional disparities have been reported in the prevalence of malnutrition in individuals infected with HIV. West and Central Africa are among the most impacted by underweight and acute malnutrition (22 and 11%, respectively), while the highest chronic malnutrition rates are found in East Africa 42% [18].

4. Malnutrition and the immune system

The relationship between malnutrition and HIV in children is complex. These two conditions interact and can create a vicious circle of poor health outcomes. Moreover, multiple studies have documented the positive effect of appropriate

	HIV-infected (n = 16)	HIV-negative (n = 46)	p-Value
		Mean ± SEM	
Fatty acid metabolites			
• NEFA (mmol/L)	0.65 ± 0.10	0.54 ± 0.06	0.285
• Total ketones (μmol/L)	826 ± 259	424 ± 95	**0.0387**
Acylcarnitines			
• C2 (μmol/L)	22.3 ± 3.5	14.4 ± 2.4	0.0103
• Even-chain acylcarnitine molar sum (μmol/L)	24.0 ± 3.7	16.0 ± 2.6	**0.0108**
Hormones			
• Insulin (μIU/ml)	1.81 ± 0.48	2.45 ± 0.45	0.321
• Growth hormone (ng/ml)	12.4 ± 2.7	11.0 ± 1.3	0.380
Adipocytokines*	**n = 13**	**n = 46**	
• Leptin (pg/ml)	69.8 ± 26.6	292 ± 52	**0.0163**
• Total adiponectin (ng/ml)	8049 ± 1081	15,268 ± 1133	**0.0017**
• HMW adiponectin (ng/ml)	4409 ± 757	9356 ± 761	**0.0014**
Amino acids			
• Alanine	153 ± 27.4	217 ± 16.2	**0.0330**
• Valine	100 ± 10.7	75.6 ± 6.3	**0.0248**
• Phenylalanine	79.6 ± 7.7	43.0 ± 4.5	**0.0067**
• Amino acid molar sum (μmol/L)	1230 ± 62	1190 ± 51	0.417
Inflammatory cytokines			
• IL-2 (pg/ml)	7.7 ± 2.7	3.6 ± 1.2	**0.0158**
• TNF-α (pg/ml)	43.0 ± 5.5	37.4 ± 9.5	**0.0248**
Other			
• Glucose (mg/dl)	77.1 ± 7.9	85.9 ± 3.9	0.474
• Creatinine (mg/dl)	0.30 ± 0.04	0.27 ± 0.03	0.296
• Triglycerides (mg/dl)	177.6 ± 14.0	122.9 ± 12.2	**0.0008**

**Excludes patients on ARVs.*
Adapted from [22].

Table 1.
Relevant baseline metabolic profile of HIV-infected and HIV-negative patients. Bold values denote statistical significance at the p<0.05 level.

nutrition of vitamins and antioxidants, cofactors of metabolic pathways, in enhancing and potentiating the immune system. On the other hand, malnutrition has also been implicated in impairing immunity, which could even lead to an immunodeficiency status with degraded lymphoid tissue containing lower concentrations of CD4 cells, target of HIV [5, 15]. In such a weak or deficient immune system, the ability to combat infections is reduced. Consequently, malnutrition can speed up the progression of the HIV/AIDS disease by creating a favorable environment, which contributes to the oxidative stress, which accelerates the death of the immune cells and increase viral replication. Stressing the necessity of vitamin A and iron, some authors associated their deficiencies with higher mortality risk among HIV/AIDS

patients [19]. In fact, HIV-infected patients have, in general, an enhanced activity of proinflammatory cytokines (TNF-α, IL-1, IL-6, and others), which can cause in children among other side effects retarded growth and a loss in body weight. At the same time, such immune-compromised children will acquire opportunistic infections, which will decrease by themselves the intake of food, thus leading to the aggravation of the immunodeficiency state and the higher incidence of several overlapping infections, such as tuberculosis, oral and esophageal candidiasis, pneumonia, skin infections, and persistent diarrhea. All these complications will negatively affect the nutritional status. In addition, anemia, which is a possible consequence of malnutrition, is also a complication of HIV infection that can cause growth retardation in children [2, 15, 20]. These children often require highly aggressive management protocols including intensive antimicrobial administrations and the provision of a well-balanced nutritional, higher caloric diet [20, 21]. The cooccurrence of tuberculosis adds another complication related to the decrease in the sensitivity of tuberculin skin test (TST), which is used as an indicator for management. This issue is aggravated further in immune-compromised children from HIV and severe malnutrition; there is a block of the immune reaction, type IV hypersensitivity, needed for a reactive TST, consequently affecting the appropriate management protocol [20, 21].

In addition, it was documented that the energy needs increase in HIV-infected children compared to normal children by almost 10% in the early stage of the disease. However, such an increased demand will go up to 20–30% in symptomatic HIV with opportunistic infections and to 50–100% in case of severe malnutrition. These data are based on studies in HIV-infected adults or in non-HIV-infected children and, therefore, have a low level of evidence [2]. A major finding of these studies is that HIV-infected children with SAM present with significant reductions in the adipocytokines, leptin, and adiponectin that are associated with mortality during inpatient hospitalization. In addition, HIV-infected and HIV-negative patients presented with similar degrees of wasting and edema, who achieved similar rates of growth and recovery [22]. Accordingly, as evidenced in **Table 1**, a baseline metabolic profile including amino acid levels was suggested for HIV-infected and HIV-negative patients [22].

5. Nutrition as an adjunct therapy

The introduction of therapeutic nutrition support and appropriate fluid rehydration has improved the rehabilitation process, shortened hospital stays of HIV-uninfected severely malnourished children, and addressed micronutrient and macronutrient deficiencies [19]. In the stabilization phase, F-75 is given as a therapeutic food. It is a low-protein milk-based formula diet. It is followed gradually by F-100 over a couple of days. The transitional phase until rehabilitation phase is reached. F-100 is a milk formula with higher protein and energy content than F75. However, the ready-to-use therapeutic food (RUTF) has replaced the F-100, especially in cases of severe acute malnutrition. In general, RUTF are pastes, no liquids, containing a combination of milk powder, electrolytes, and micronutrients. They provide the child with the same nutrients as F-100 plus iron [3, 4, 7]. As for rehydration, ReSoMal is commonly used. It contains approximately 45 mmol Na, 40 mmol K, and 3 mmol Mg per liter [19]. However, the metabolic and nutrient needs of HIV-infected children, in whom persistent anorexia is frequent, should be more clearly defined. In case of severe diarrhea often associated with high mortality rates, the provision of suitable feeding protocols is highly recommended. In brief, protocols for appropriate nutrition support therapy for severely malnourished infants below age 6 months are needed [23].

Although wasting can be treated in HIV-uninfected children with nutritional therapy alone, effective regimens for HIV-infected children need to be developed.

The use of high-energy therapeutic nutrition support (e.g., F100 or RUTF) is part of standard care that can start the soonest regardless of the ART starting date. However, high mortality (38%), within 4–6 weeks, remains an issue. Many children will gain weight with nutrition support alone. Sometimes, CD4 cell count could be used to monitor the nutritional needs and to identify those needing treatment [15]. However, other reports pointed out that CD4 cell counts do not seem to improve after the provision of nutritional therapy. In brief, community therapeutic care methods, strengthened by local production of ready-to-use therapeutic foods, require fewer staff to run programs and ensure compliance. It is also worth noting that the HIV epidemic has generated a new group of children requiring nutrition rehabilitation unit-based care [20].

The situation becomes more complicated when opportunistic infections enter the picture, necessitating the use of anti-infective medications in malnourished children. Such drugs have a wide range of toxicity, which worsen the nutritional status of the children [18, 21]. Such children require urgent stabilization of multiple physiological parameters including hypoglycemia, dehydration, and electrolyte imbalance. Nutritional support is generally tailored to each case with consideration given to the rate of weight gain [10, 21].

Although interventions with multiple nutritional regimens increase energy and protein intake, in such situations, they led to no improvement in the morbidity and mortality rates compared to placebo. Observational studies have reported that the recovery from acute malnutrition and underweight using ready-to-use therapeutic food (RUTF) in populations of malnourished children, including some infected with HIV, was often complete with these products [2, 17, 19]. It was also noted that severe wasting makes the clinical assessment of dehydration difficult, so the presence of metabolic acidosis and lethargy are often the clinical indications available to prompt rehydration and nutritional interventions. Unfortunately, there are also currently inadequate data on the optimum regimen of supportive care (e.g., for shock) in the malnourished child who has adapted to a reduced body mass and organ system function. Appropriate dietary therapies are needed for this increasing population, as the standard F-75 and F-100 formulas are likely unsuitable [3, 21]; they might lead to the refeeding syndrome. Refeeding syndrome can be defined as the potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving artificial refeeding whether enterally or parenterally [19].

Besides, in Jesson and Leroy review, vitamin A was used as a primary therapy; it decreased pediatric mortality by 50% whatever the cause and improved short-term growth, in untreated HIV-infected children in Tanzania [2].

6. Antiretroviral therapy (ART) and nutrition

It is well documented that the availability of highly active antiviral therapy (HAART) for the past two decades or so has decreased remarkably the mortality and morbidity of the disease in both adults and children, thus transforming it into a chronic infections disease [9]. The prognosis of HIV-infected children has markedly improved in the HAART era, both in terms of morbidity and mortality as mentioned earlier, despite the fact the mortality rate in HIV-infected children is still considerably higher than the pediatric general population [9, 23].

In Tanzania, when ART became available, the recovery was improved, especially when ART was initiated in children at the same time as nutritional support than when it was initiated later [2].

In the literature, there seems to be conflicting recommendations about when and how to begin nutrition support with ART. Some studies have reported that if ART

is started when children have severe wasting due to malnutrition, they have higher rates of mortality compared to those with less clinical markers of malnutrition. However, studies were not conclusive about the time to start nutritional support [5, 15]. A recent retrospective study finding suggests that starting ART early in malnourished children results in higher rates of nutritional recovery and weight gain than if ART is delayed. In a study performed on a cohort of children in Africa, 59% of Zambian children were initially underweight and almost three quarters (72%) had slowed down or stopped growth when ART was administered. In these children, prominent improvements in both weight and height were recorded when nutritional support started in the initial stage after diagnosis at the same time as ART. In fact, the best increase was observed among children who were most underweight. Therefore, these lifesaving medications should not be delayed, and child health systems should embrace this approach in a programmatic manner [5, 21].

On the other hand, ART in children has been reported to result in metabolic disorders, which negatively affect the nutrition status, particularly, at the initiation and first few months of treatment. Such side effects include nausea, vomiting, dysregulated lipid metabolism [5, 11], low bond density, and increased fractures [11, 22]. Consequently, at the initiation of ART, the nutritional status must be evaluated, particularly that about half of the children taking such treatment will be underweight. Such a condition could lead to chronic malnutrition of about two-thirds of HIV-infected children in countries with limited resources with a higher two to three times risk of death.

Nutritional evaluation, monitoring, and support are strongly recommended, especially at the initiation period and the first 2 months. Such measures proved to decrease morbidity and mortality [2, 10]. Children severely immunodeficient at initiation of ART may have a better growth outcome than nonimmunodeficient children at initiation. Children treated with ART become less immunodeficient, and their nutritional status improves [2]. In general, protease inhibitors (PI)-based treatments result in decreasing viral load, less resistant mutation, and better growth compared to non-PI-based regimens. Many authors focusing on this issue have reported that the earlier the treatment was initiated in children, the better the nutritional response in weight and height was [2, 23]. Malnourished children treated with ART may develop a kwashiorkor-like syndrome of IRIS (immune reconstitution inflammatory syndrome) [21]. However, in children with severe malnutrition, there has been a concern that standard dosing of ART may be inappropriate. This concern is based on the malnourishment metabolic alterations that could lead to subtherapeutic or toxic drug levels that may contribute to viral resistance and/or safety issues [2, 5, 14].

Implementation challenges in starting and maintaining children on ART also persist and are found throughout the chain of care in sub-Saharan Africa, especially in rural areas [21].

7. Recommendations

In children, transmission of HIV through breastfeeding remains a problem. Efforts have moved in support of safer feeding by promoting exclusive breastfeeding for 6 months coupled with concomitant antiretroviral prophylaxis delivered to breastfeeding mothers or the infant [1, 18]. However, nutritional management of HIV-infected children remains a challenge in view of all the studies reviewed.

HIV-positive women living in resource-poor environments must balance opposing risks. In 2010, the WHO revised its position by recommending exclusive breastfeeding for the first 6 months of life followed by complementary foods and then accompanied by postnatal infant or maternal antiretroviral prophylaxis (WHO). In contrast,

the American Academy of Pediatrics recommends that HIV-infected mothers not to breastfeed their infants, regardless of maternal disease status, viral load, or ART and the British HIV association concurs [1, 18].

The important issue is to meet all nutrient needs and provide the required energy requirements. However, according to the WHO, some considerations are needed for safely replacing food. Such considerations are based on the fact that untreated HIV-infected patients have an increased resting energy expenditure, decreased appetite, digestion of food, and absorption of nutrients. In brief, such patients often have a range of micronutrient deficiencies. However, there are no evidence-based guidelines on the appropriate types and amounts of micronutrient supplements for HIV-infected children. The WHO has previously endorsed the use of ready-to-use therapeutic foods to reduce mortality and undernutrition [18].

8. Conclusion

In the area of nutrition and HIV, children deserve special attention because of their additional needs to ensure growth and development and their dependency on adults for adequate care. Nutritional advice and support should be a priority component of the continuum of care for HIV-infected women and children. Furthermore, case by case, the special nutritional needs of children should be determined in light of the guidelines and recommendations adopted by various professional health and medical associations. Wasting and undernutrition in HIV-infected children reflect a series of failures within the health system, the home, and the community and not just a biological process related to virus and host interactions. In brief, despite the great impact of recent pharmacologic interventions, optimal nutrition continues to be essential therapy for HIV-infected children, and it has the potential to provide adjunct immunemodulatory therapy, thus improving care and outcomes of children with HIV/AIDS.

Author details

Inaya Hajj Hussein[1*], Lara Youssef[2], Andrea Mladenovic[3], Angelo Leone[4], Abdo Jurjus[5] and Virginia Uhley[1]

1 Department of Foundational Medical Studies, Oakland University William Beaumont School of Medicine, Rochester, MI, USA

2 Faculty of Nursing and Health Sciences, Notre Dame University, Lebanon

3 School of Medicine, University of Belgrade, Belgrade, Serbia

4 Department of Experimental and Clinical Neurosciences, University of Palermo, Palermo, Italy

5 Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

*Address all correspondence to: hajjhuss@oakland.edu

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