REVIEW

Nutrition in HIV-Infected Infants and Children: Current Knowledge, Existing Challenges, and New Dietary Management Opportunities

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ABSTRACT

HIV infection and undernutrition remain significant public health concerns for infants and children. In infants and children under these conditions, undernutrition is one of the leading causes of death. Proper management of nutrition and related nutrition complications in these groups with increased nutrition needs are prominent challenges, particularly in HIV-prevalent poor-resource environments. Several studies support the complexity of the relation between HIV infection, nutrition, and the immune system. These elements interact and create a vicious circle of poor health outcomes. Recent studies on the use of probiotics as a novel approach to manage microbiome imbalance and gut-mucosal impairment in HIV infection are gaining attention. This new strategy could help to manage dysbiosis and gut-mucosal impairment by reducing immune activation, thereby potentially forestalling unwanted health outcomes in children with HIV. However, existing trials on HIV-infected children are still insufficient. There are also conflicting reports on the dosage and effectiveness of single or multiple micronutrient supplementation in the survival of HIV-infected children with severe acute malnutrition. The WHO has published guidelines that include time of initiation of antiretroviral therapy for HIV-pregnant mothers and their HIV-exposed or HIV-infected children, micronutrient supplementation, dietary formulations, prevention, and management of HIV therapy. However, such guidelines need to be reviewed owing to recent advances in the field of nutrition. There is a need for new intervention studies, practical strategies, and evidence-based guidelines to reduce the disease burden, improve adherence to treatment regimen, and enhance the nutrition, health, and well-being of HIV-infected infants and children. This review provides up-to-date scientific information on current knowledge and existing challenges for nutrition therapy in HIV-infected infants and children. Moreover, it presents new research findings that could be incorporated into current guidelines. *Adv Nutr* 2021;12:1424–1437.

Keywords: HIV, nutrition, HIV-infected infants and children, current HIV-knowledge in infants, nutritional management of HIV infected children, WHO HIV management guidelines

Introduction

Since the earliest confirmation of first known cases of infection with HIV in 1959, the prevalence of children infected with HIV has grown dramatically due to an increase in the number of HIV-infected women of childbearing age (1).

Globally, as at 2019, there were about 38 million people living with HIV, of which aproximatelly 1.8 million were children aged <14 y (2). During the same period, the number of new infections across all ages was around 1.7 million people, including about 150,000 children aged <14 y (2). As at the end of june 2020, an estimated 26 million people had access to antiretroviral therapy (ART), but available data showed that only 54% of children aged <15 y were receiving lifelong ART in 2019 (2).

The transmission of HIV from an HIV-positive mother to her child during pregnancy, labor, delivery, or breastfeeding is called mother-to-child transmission (MTCT) (3). MTCT is a significant contributor to the HIV pandemic, accounting for 9% of new infections globally (4). In the absence of any intervention, the transmission rate ranges from 15% to 45% (3).

Early testing and treatment are crucial to reduce HIV-related mortality and morbidity among infants. In their absence, 50% of children with HIV will die by the age of 2 y, and 80% will not live to their 5th birthday (5).

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Abbreviations used: ART, antiretroviral therapy; ARV, antiretroviral; BMD, bone mineral density; HAART, highly active antiretroviral therapy; HCMV, human cytomegalovirus; MTCT, mother-to-child transmission; PD, persistent diarrhea; RCT, randomized control trial; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; sTfR, soluble transferrin receptor; VDD, vitamin D deficiency; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

Failure to suppress HIV remains a serious problem among children, aggravated by a lack of child-friendly formulations of the newest and most effective antiretroviral (ARV) drugs originally designed for adults (6).

Adequate child nutrition is best achieved through the consumption of a balanced healthy diet. It is essential for normal growth and development and vital for health and survival for all individuals regardless of HIV status (7). Infants deserve unique attention because of increased nutrient needs. Thus, adequate nutrition of HIV-infected infants becomes critically important to prevent undernutrition, particularly because of their nutritional needs and dependency on adults for their care (8). This has been illustrated by studies that have shown a high prevalence of undernutrition among HIV-infected children (9–12).

According to the WHO, dietary interventions for HIV-infected children should focus on issues of food security, particularly in terms of quantity and quality of the diet (8). However, attainment of food security, nutrition accessibility, and appropriate handling of nutrition-related complications of HIV infection are remarkably challenging, especially in poor environments with limited resources where most HIV infections exist (13). Undernutrition, as presented here, is a form of malnutrition, which refers to both undernutrition caused by deficiencies of energy and/or micronutrients and overnutrition due to excessive energy intake that leads to overweight and obesity. Undernutrition can be manifested according to its intensity in stunting, underweight, and wasting, commonly accompanied by micronutrient deficiencies (13). Severe acute malnutrition (SAM), is the most extreme and visible form of undernutrition characterized, in children aged <60 mo, by extreme wasting and weight-for-height *z*-score (WHZ) below −3 SDs of the median WHO growth standards (14). SAM is common in HIV-infected children (15–17). Given the additional challenges facing HIV-infected infants and older children, such as opportunistic infections, growth faltering, and nutritional deficiencies, it is essential to review new information on the optimal feeding regimens for HIV-infected children with SAM. Furthermore, it is also essential to elucidate the most effective strategies for treating HIV-infected children accompanied by acute or persistent diarrhea. To address these issues, a series of guidelines have been developed by the WHO (8) and professional bodies (18, 19). However, different countries have reported challenges in adhering to such guidelines. The objective of this narrative review is to provide up-to-date scientific information on current knowledge of nutrition in HIV-infected infants and children and explore new scientific evidence that could be incorporated into current nutrition management guidelines.

Current Status of Knowledge

Malnutrition and the immune system in HIV-infected infants

In low- and middle-income countries, about half of all deaths in children aged under 5 y are linked to undernutrition (20). Undernutrition puts children at a higher risk of dying from common infections. It increases the frequency and severity of infections such as tuberculosis, oral and esophageal candidiasis, pneumonia, skin infections, and persistent diarrhea (PD), resulting in delayed HIV recovery (20–22). Several studies have shown a high prevalence of undernutrition in HIV-infected children, especially in sub-Saharan Africa (23–27). The co-occurrence of the 2 conditions is interlaced in a vicious cycle of worsening illness and deteriorating nutritional status (20).

Immunological variations such as systemic inflammation, increased proinflammatory mediator concentrations, and impaired cellular immune responses are attributed to malnutrition (28). This leads to increased susceptibility to infections, especially when worsened by HIV. HIV gradually weakens a patient's immune system by attacking CD4 T-cells, resulting in the development of opportunistic infections (29). Undernutrition is also characterized by functional and structural alterations in the intestinal mucosa, which is associated with chronic intestinal inflammation (22). The impact of undernutrition (30, 31) and dysbiosis in the gut microbiome (32) has been hypothesized as a primary cause for persistent intestinal inflammation and epithelial damage.

In HIV infection, the breakdown of the intestinal barrier, depletion of gut-resident $CD4^+$ T-cell populations, and mucosal immune dysregulation result in microbial translocation that drives systemic immune activation (33). In a study by Muenchhoff et al. (17), malnutrition, age, microbial translocation, monocyte, and CD8 T-cell activation were independently associated with decreased rates of $CD4^+$ immune recovery after 48 wk of ART. SAM has been associated with increased microbial translocation, immune activation, and immune exhaustion in HIV-uninfected children, but with worse prognosis and impaired immune recovery in HIV-infected children on ART.

Anemia, a likely consequence of micronutrient deficiencies, like iron, folate, and vitamin B-12, is also a common hematological complication of undernutrition and HIV infection (34–36). This condition may result in growth impairment of children (37). Furthermore, coexistence commonly occurs between iron deficiency and HIV infection (38). In HIV infection, ferritin, a marker of iron deficiency, may be altered by inflammation (39, 40). This has been confirmed by the study of Frosch et al. (39), who found elevated levels of ferritin in HIV-infected individuals without correlation with iron deficiency anemia. In this latter investigation, the iron biomarker soluble transferrin receptor (sTfR) was the best predictor of anemia in the HIV-infected participants, and (sTfR) was also associated with a 6-fold increase in the odds of anemia. Hassan et al. (41) concluded that humoral, nonspecific immunity (phagocytic activity and oxidative burst), and IL-6 are influenced in patients with iron deficiency anemia. Other evidence also suggests that anemia is associated with an increased risk of all-cause mortality and tuberculosis among HIV-infected individuals, regardless of anemia type, and the magnitude of the risk is higher with more severe anemia (38).

PD and dehydration are also associated with undernutrition and a weakened immune system, including that caused by HIV infection in children (42, 43). There is low certainty on the use of antibiotic therapy (e.g. nitazoxanide) in children with PD (44, 45). Adequately powered trials are needed to assess the effect of micronutrients and nitazoxanide, as well as other interventions, for the treatment of diarrhea in HIV-infected and -exposed children. Currently, there is emerging interest in nutrient-based interventions, including the use of pre- and probiotics, as a novel strategy to manage gut microbiome imbalance and gut-mucosal impairment and to reduce immune activation, thereby potentially forestalling the outcome of PD in children (44, 45). Probiotics may also improve the resident gut microbiome in adults with HIV (46). Even though the beneficial effects of probiotics are quite promising, their effectiveness in the intestinal mucosa are strain dependent, and not all interventions are equally effective (45, 47). Prebiotics are also used to modulate resident gut homeostasis and selectively promote the growth of beneficial bacterial species (48). Studies showing the effects of pre- and probiotics on gut microbiota, inflammation, and other health conditions in HIV-infected individuals are presented in **Table 1**.

TABLE 1 Effect of prebiotics and probiotics on HIV infection

Study/country/duration	Objective	Study design	Sample characteristics / size	Summary of findings
d'Ettorre, et al. (49) Italy48 weeks	Investigate the potential benefits of 48 wk of probiotics supplementation on immune function and on immune activation status	Longitudinal trial	HIV positive (18–80 y) with persistent undetectable concentrations of HIV-RNA *N* = 20	Probiotic supplementation significantly reduced the levels of immune activation on CD4 T-lymphocytes. Supplementing cART with probiotics may improve GI tract immunity and thereby mitigate inflammatory sequelae, ultimately improving prognosis
Yang et al. (50) USA 90 d	Study the safety and immune effects of oral probiotic *Bacillus coagulans* (GBI-30, 6086) with potential immunomodulatory effects	RCT	Adults with chronic HIV-1 infection with suppressed viremia *N* = 24	*Bacillus coagulans* probiotic preparation was safe and well tolerated in persons with chronic HIV-1 infection on suppressive cART and increased the percentage of CD4+ T compared to control. There was also a possible benefit of this probiotic for residual inflammation
Klatt et al. (46) USA 5 mo of intervention	Benefits of probiotic/prebiotic supplementation of antiretrovirals SIV-infected Asian macaques	RCT	Pig-tailed macaque (*Macaca nemestrina*) infected with 3000 TCID50 of SIVmac239 i.v. *N* = 11	The symbiotic, prebiotic, and probiotic supplementation of ARV treatment enhanced GI immune function (thereby mitigating inflammatory sequelae), increased reconstitution of colonic CD4+ T-cells, and reduced fibrosis of lymphoid follicles in the colon
Serrano-Villar et al. (51) Spain 6 wk	Assess the interactions among immunomodulatory derivatives, the microbiota, and immunological markers of disease progression after dietary supplementation with prebiotics	RCT	Viremic untreated (VU) HIV+ subjects, ART virally suppressed patients and control (HIV–) *N* = 44	Significant declines in indirect markers of bacterial translocation and T-cell activation. Increases in the abundance of *Faecalibacterium* and *Lachnospira* strongly correlated with moderate but significant increases of butyrate production and amelioration of the inflammatory biomarkers soluble CD14 and high-sensitivity C-reactive protein, especially among VU
Gori et al. (48) Italy 16 wk	Investigate the possible microbial- and immune-modulating effects of dietary supplementation with prebiotic oligosaccharides in (HAART)-naive HIV-1-infected adults	RCT	HAART-naive HIV-1-positive adults and controls *N* = 57	Dietary supplementation with a prebiotic oligosaccharide mixture significantly results in improvement of the gut microbiota composition, reduction of sCD14, CD4+ T-cell activation (CD25), and improved NK cell activity in HAART-naive HIV-infected individuals
D'Angelo et al. (47)	Use of probiotics to prevent and attenuate several gastrointestinal manifestations and to improve gut-associated lymphoid tissue (GALT) immunity in HIV infection	Review	HIV-infected patients *N* = 24	There was no indication that critically ill and high-risk participants taking probiotics were more likely to experience adverse events than control participants with the same health status

ARV, antiretroviral therapy; CD25, IL-2 receptor α chain; cART, combination antiretroviral therapy; CD4+, cluster of differentiation 4+; GI, gastro-intestinal; HAART, highly active antiretroviral therapy; NK, natural killer; RCT, randomized control trial; sCD14, soluble cluster of differentiation 14; SIV, Simian immunodeficiency virus; TCID, tissue culture infective dose.

In a multicountry analysis of the impact of diarrhea among several cohorts of HIV-infected children followed from birth until the age of 24 mo, Checkley et al. (52) found that the adjusted odds of stunting increased by 1.13 for every 5 episodes of diarrhea (95% CI: 1.07–1.19) and by 1.16 for every 5% unit increase in longitudinal growth (95% CI: 1.07–1.25). This confirmed an earlier study by Richard et al. (53), in which diarrhea was associated with a small but measurable decrease in linear growth over the long term.

The relation between HIV infection, nutrition, and the immune system in infants and children is complex. These conditions interact and can create a vicious circle leading to poor health outcomes.

Nutritional status of HIV-infected infants and children

Abnormalities in weight and height are adverse nutritional outcomes in children living with HIV (11, 54) and can be considered markers of disease progression and significant contributors to morbidity and mortality (54). Poor nutritional status of HIV-infected children, including those who have already started ART, is closely associated with increased risk of premature death. HIV-infected children who are significantly underweight are much more likely to die than HIV-infected children who are not malnourished (55). Similar findings have been described in adults living with HIV, including adults receiving ART (56).

Causes of growth impairment in HIV-infected children may include reduced food intake and opportunistic infections that affect food consumption, nutrient absorption, and metabolism leading to weight loss (8). HIV-infected children remain at high risk of wasting and stunting within the first 5 y of follow-up treatment (11). ART has been shown to have a positive effect on weight and, to a lesser extent, on growth (57). However, Sofeu et al. (11) concluded that a mother or child's HIV infection status affects the child's growth during the first years of life, regardless of the availability of ART. In a study by Feucht et al. (58), weight improved in the first 12 mo, and height improved more slowly over the entire 5-y follow-up period in HIV-infected children initiated on ART before the age of 5 y. The overall prevalence of undernutrition among HIV-infected children in a hospital in Cameroon was 68.7%. In this study, 63.6% were stunted [height-for-age *z*-score (HAZ) < -2], 37.8% were underweight [weight-for-age z-score (WAZ) < -2], and 18.4% exhibited wasting WHZ < -2 (23). In another investigation by Poda et al. (24), the prevalence of underweight, stunting, and wasting in HIV-infected children aged <5 y was 77%, 65%, and 63%, respectively. Akintan et al. (59) concluded that HIV-infected children are 3 times more wasted, stunted, and underweight than HIV-uninfected children.

Associations between abnormal body fat distribution and pediatric HIV disease have been established in various studies (60–62). HIV infection itself is a factor that causes lipodystrophy syndrome in children who are being treated with antiretroviral medications (63) and could refer to abnormal fat accumulation (lipohypertrophy) or localized loss of fatty tissue (lipoatrophy) (64).

Micronutrient deficiencies are also widely prevalent in HIV-infected children receiving highly active ART (HAART), irrespective of social class (65). In a study of HIV-infected children by Anyabolu et al. (65), the prevalence of zinc, selenium, and vitamin C deficiency were 77.1%, 71.4%, and 70.0%, respectively, compared with 44.3%, 18.6%, and 15.7% in HIV-negative controls.

Given the relation between HIV, nutrition, growth faltering, and survival of children living with HIV, it becomes crucial that nutritional assessment and support should be an integral part of the care plan of HIV-infected children. Proper dietary support to meet nutritional needs and ART initiation are essential before irreversible stunting occurs. New intervention studies aimed to optimize the required nutritional support to attain growth normalization are needed.

Problems affecting feeding practices among HIV-infected infants and children

In poor settings with limited resources, knowledge, perceptions, and practices of HIV-positive mothers concerning the feeding of their infants are inadequate (66, 67). This implies that a sizeable percentage of infants are at increased risk of acquiring HIV through inappropriate feeding. However, Mnyani et al. (68) reported higher knowledge scores regarding infant feeding practices during HIV infection among women with HIV than women without HIV. In HIV infection, cultural factors and functional social support are important influences on safe infant feeding choices (68, 69). Fear of the mother of HIV transmission to the child has been reported by Remmert et al. (70) as a common reason for not breastfeeding their exposed-uninfected infants. This could be the result of misleading information about the safety of breastfeeding and the risks associated with formula feeding. In a large survey involving mothers and their infants in 99 primary health care (PHC) clinics in South Africa, about a quarter of them did not receive breastfeeding advice at the clinic (71). In a meta-analysis of 18 studies in Ethiopia, the national pooled prevalence of exclusive breastfeeding and mixed feeding practices among HIV-positive mothers was 63.43% and 23.11%, respectively (72). High rates of formula feeding were also reported among women with HIV (73).

According to the WHO guidelines (74), it is recommended (with substantial evidence) that mothers living with HIV and fully supported for ART, should exclusively breastfeed their infants for the first 6 mo. Furthermore, breastfeeding with complementary feeding may continue $\leq$2 y or beyond. Exclusive breastfeeding of HIV-exposed infants in the first 6 mo of life has been reported to be associated with reduced mortality over the first year of life compared with mixed feeding and replacement feeding (74).

Oral diseases are also common problems in HIV-positive children (75). Oral candidiasis is the most frequently found HIV-related oral manifestation which can affect infants' feeding practices (67, 68). Dental diseases also affect HIV-infected children. The quality of life and daily activities of HIV-infected children affected by oral and dental diseases result in eating difficulties and other functional limitations

(76). A recent study in HIV-infected patients has also found that oral candidiasis might be a useful marker for the evaluation of immune status in patients with HIV/AIDS (77).

An association between CD4+ count and the presence of oral lesions has been demonstrated in the literature (78, 79). However, Yengopal et al. (80) found no substantial evidence of a significant association between the presence of dental caries among HIV-positive children and CD4 counts and viral load, meaning that a more robust trial to gain new scientific evidence is needed to ascertain the linkage between oral diseases and CD4+ count in HIV-infected children.

All this information indicates that infants and children remain at risk of HIV complications from inappropriate feeding practices. Within this context, breastfeeding, particularly exclusive breastfeeding during the first 6 mo of life, plays an important nutritional role in the management of HIV-infected infants and children.

ART and nutrition

ART treatment has significantly improved life expectancy, health care, and survival for people living with HIV in the past 2 decades (81). It has also substantially decreased mortality and morbidity of the pediatric HIV-infected population (82). However, despite evidence of the potential benefit of ART use in HIV-related survival, severe wasting (WHZ < -3) appears to be a strong independent predictor of survival in HIV-infected children receiving ART (83). In a study on the impact of HAART on the nutritional status of HIV-infected children, moderate and severe underweight were both independent predictors of a positive shift in nutritional status (WAZ and WHZ) after 24 mo of follow-up (84). Older studies have demonstrated severe wasting to be associated with death in children after ART initiation (55, 85, 86). New studies have shown increased risk of mortality in HIV-infected children who are underweight at the initiation of ART (87, 88). In a previous study, ART initiation resulted in improved weight and height gains among severely malnourished children (82). Still, the observed increases were not enough to reach optimal growth when compared with nonmalnourished children. ART initiation and nutritional supplementation at an early age have been found to be a significant factor for improvement in growth outcomes and better nutritional status in the long term (89). This observation has been confirmed by a number of studies in children indicating that the earlier the treatment, the better the nutritional response in weight and height (37, 90). Additional randomized control trials (RCTs) are needed to assist in determining the optimal timing of ART and nutritional intervention in HIV-infected malnourished infants and children.

Prevention of MTCT of HIV

MTCT of HIV occurs when HIV is transmitted from an HIV-infected mother to her infant during pregnancy, labor, delivery, or through breastfeeding (91). An HIV-infected pregnant woman has a 15–45% likelihood of transmitting the virus to her child in the absence of ART intervention; however, with ART, the risk can be reduced to $<5\%$ (92). Placental macrophages, also known as Hofbauer cells, found within the chorionic villi of the human placenta, are vital mediators that prevent in utero transmission of HIV-1 (93). These cells have been shown to have a phenotype associated with regulatory and anti-inflammatory functions (94). They possess intrinsic adaptations that expedite the isolation of HIV-1 in intracellular compartments allowing access of HIV-1-specific antibodies and antiretroviral drug entry in utero, thereby offsetting MTCT (93).

Several studies have reported strong associations of some pathogens such as human cytomegalovirus (HCMV), viremia (95), malaria (96), and tuberculosis (97) with the in utero transmission of HIV-1, thereby contributing to the high incidence of MTCT. Maternal placenta HCMV infection facilitates inflammation, chronic villitis, and trophoblast damage, providing potential HIV-1 access into the primary receptor (CD4) and coreceptor (CCR5) target cells (95).

Choices on whether or not HIV-infected mothers ought to breastfeed their babies are based on comparing the potential risks of infants acquiring HIV through breastfeeding with the elevated threat of loss of life from malnutrition, diarrhea, and pneumonia if the infants are not exclusively breastfed. Accumulating evidence has shown that giving antiretroviral medicines to the mother or the infant significantly reduces the risk of HIV transmission through breastfeeding (98). A study by Chan et al. (99) on HIV detection among 42 breastfeeding Kenyan women showed that at 6–14 wk postpartum, 21.4% had HIV RNA detected in plasma and 14.3% in breast milk. However, when adjusting the time of beginning ART, earlier ART initiation in pregnancy was significantly associated with plasma suppression of the virus.

The WHO therefore recommends that mothers living with HIV should breastfeed for $\geq$12 mo and may continue breastfeeding for $\leq$24 mo or longer (similar to the general population) while being fully supported for ART adherence (91). Mothers known to be HIV infected should be provided with lifelong ART or antiretroviral prophylaxis to reduce HIV transmission through breastfeeding. The risk of MTCT of HIV can be significantly reduced through the provision of maternal ART as early as possible during pregnancy or preconception (91).

In summary, the available information indicates that the best prevention strategy and management of HIV-infected mothers to lower the risk of HIV transmission from mother to child include the early use of antiretroviral agents and optimum nutritional support for pregnant and lactating women as well as their children. Other management strategies include rapid HIV testing, monitoring, and support for antiretroviral adherence as well as counseling on infant feeding.

Nutrition as an Adjunct Therapy

Dietary formulations for feeding severely malnourished infants

The management of SAM in children can be divided into 2 phases: stabilization and rehabilitation (100). In the

stabilization phase, F-75, a starter, low protein (0.9 g per 100 mL) milk-based therapeutic diet with relatively low energy [75 kcal (314 kJ) (101)] is administered for a period of 2 to 7 d. Once the child is stabilized, ready-to-use therapeutic foods (RUTFs) can then be administered during the rehabilitation phase (75, 78). RUTFs are semisolid products (which include milk powder, sugar, peanut butter, vegetable oil, vitamins, and minerals) developed initially as a home-based follow-up treatment, usually made according to a standard, energy-rich formula defined by the WHO (102). Treatment of SAM in infants for 6 mo to 1 y in clinics has not been beneficial, especially in rural areas; hence the use of home-based therapies has been found to be better (103). Home-based treatment can be either food prepared by a caregiver (such as flour porridge or energy- and nutrient-dense locally available foods), or RUTF provided by a clinic (103). The WHO recommends the same therapeutic feeding approaches in HIV-infected children aged under 5 y with SAM versus HIV-uninfected under-5 children with SAM (104). However, the metabolic and nutrient needs of HIV-infected children, in whom persistent anorexia is frequent, should be better defined.

RUTF has transformed the treatment of SAM, providing foods that are safe to use at home and ensure rapid weight gain (105). Low acceptability has been found to occur for standard RUTF products (106), most likely because of the high milk content of the standard RUTF formulation that makes it expensive for sustainable use in resource-poor settings (107). However, progress has been made in terms of increasing acceptability of RUTF by using locally grown ingredients (108). Irena et al. (109) reported that the removal of milk powder and the inclusion of locally available grains and pulses could reduce the cost of ingredients by about a third. Innovative RUTF formulations with reduced milk protein or no milk protein have been evaluated in different study settings (107, 109–111). Results indicate that alternative RUTFs can be effective in managing SAM in children. However, there is no consistency regarding the reported superiority when using different new formulations as compared to the standard RUTF. For example, the WHO is currently reviewing the efficacy and safety of new RUTF formulations (containing alternative sources of nondairy protein or <50% of proteins coming from milk) for treating infants and children aged 6 mo or older with uncomplicated SAM and appetite (112). The primary reason is to reduce the production cost of these formulations and increase coverage by replacing milk (the most expensive ingredient) with other sources of protein.

A study by Sunguya et al. (113), among HIV-positive children in a clinical setting in Dar Es Salaam, Tanzania, showed that provision of a RUTF formula, made of plumpy'nut, for ≥4 mo did not increase the average weight gain in HIV-infected children, especially when given ART. Moreover, an RCT of children with SAM, aged 6–59 mo, revealed that the standard RUTF was not superior to locally produced fish-based RUTF on its effect on weight gain (106). One trial reported a weight gain of 3.45 g/kg/d in a group of children receiving indigenously prepared RUTF over 8 wk compared with 2.38 g/kg/d in the group receiving standard nutrition therapy during the same period (111). When comparing recovery in children aged <5 y, based on weight gain of ≥15% (109, 114), or midupper arm circumference (MUAC) of >12.4 cm without edema (115), there was no significant difference between standard RUTF versus RUTF using alternative formulations. In other studies, there was no significant difference between standard RUTF and alternative diets when measuring improvement after 16 wk (116) or 6 mo of interventions (111). In a meta-analysis by Schoonees et al. (103), comparing standard RUTFs with different formulations for children aged 6 mo to 5 y, the evidence did not favor a particular formulation, except for relapse, which is reduced with standard RUTF. The comparison between standard RUTFs and other experimental formulas are depicted in **Table 2**. It can be observed that experimentally modified food formulations equally improve survival and nutritional status of children with SAM when compared to standard RUTFs, and in some cases, the new experimental diets were superior to the standard.

There is a dearth of information on the effect of standard RUTF on mortality, especially in the context of HIV-infected infants (97). It is, therefore, important to assess the effectiveness and cost analysis of formulations of ready-to-use foods for the nutritional management of SAM in HIV-infected infants and children using properly designed RCTs with standardized outcome measures that include diarrhea and other complications. It is strongly recommended to provide appropriate feeding protocols and nutrition support for severely malnourished HIV-infected infants, especially in the case of severe diarrhea, which is often associated with high mortality (90).

Micronutrient supplementation

Micronutrient deficiencies are common among patients with HIV (117). Trials testing the effectiveness and safety of vitamin A in HIV-positive children in Africa found a beneficial effect on mortality and growth (118–120). In a meta-analysis by Irlam et al. (121), the overall mortality rate of 267 HIV-infected children receiving vitamin A supplementation was approximately halved. The WHO recommends high doses of vitamin A supplementation for HIV-infected infants and children aged 6–59 mo, in resource-poor settings where the prevalence of vitamin A deficiency (serum retinol 0.70 μmol/L or lower) is 20% or higher (122).

In a cross-sectional study involving children with perinatally acquired HIV on stable ART for ≥6 mo, higher plasma selenium concentrations were associated with lower systemic inflammation and more elevated gut integrity markers (123). The plasma selenium concentration was associated with a higher proportion of T-cell activation (124) whereas zinc supplementation, in a pilot study, increased circulating zinc concentrations and modulated biomarkers associated with clinical comorbidities in HIV-positive adults (125). In a randomized, double-blind, placebo-controlled trial in infants (aged 6 wk, baseline) born to HIV-positive mothers in Tanzania, Liu et al. (126) found that daily

TABLE 2 Comparison of standard ready-to-use therapeutic foods formulations compared with experimental modified formulas/dietary approaches

Study/objective/country /duration	Study design/ participants / sample size	Dietary formulations (RUTFs vs. control)	Recovery after intervention	Anthropometric gain (g/kg/d) during intervention	Mortality during intervention	Summary of findings
Bhandari et al. (116) compare the efficacy of RUTF-C or RUTF-L with A-HPF India 16 wk or until recovery (whichever was earlier)	RCT children 6–59 mo with SAM *N* = 906	RUTF-C (543 kcal/100 g, peanut-based with sugar, milk, vegetable oil with vitamins and mineral mixRUTF-L (528 kcal/100 g, same mix as RUTF-C) A-HPF (cereals, pulses, sugar, oil, milk, eggs)	The recovery rates with A-HPF, RUTF-C, and RUTF-L were 42.8%, 47.5% and 56.9%, respectively	The mean (SD) weight gain in the A-HPF, RUTF-C, and RUTF-L groups were 2.64 (3.47), 3.05 (3.41) and 3.52 (3.92), respectively	A-HPF = 0 RUTF-C = 2 RUTF-L = 1	Use of RUTF-L results in higher recovery rates than feeding nutrient-dense and calorie-dense home foods
Hsieh et al. (115) effect of RUTF and high oleic RUTF (HO-RUTF) on DHA and EPA status Malawi 4 wk	Randomized, blinded trial *N* = 141	Both RUTF (175 kcal/kg/d) and standard RUTF (peanuts, palm oil, soy oil, dry skimmed milk) HO-RUTF (high oleic peanut, palm oil, linseed oil, dry skimmed milk)	The recovery rate in the RUTF group was 71%, and the HO-RUTF group was 68%	Mean weight & MUAC gain in RUTF and HO-RUTF groups were (2.0 ± 2.6 g/kg/d & 0.15 ± 0.28 cm) and (2.8 ± 3.1 g/kg/d & 0.22 ± 0.31cm), respectively	RUTF group = 5 HO-RUTF group = 1	RUTF vs. HO-RUTF caused different changes in DHA (−25% vs. +4%) and EPA (−24% vs. +63%) status Anthropometric recovery was similar in both groups
Irena et al. (109) compare the effectiveness of SMS-RUTF and P-RUTF (standard RUTF) Zambia 1 wk	The nonblind, randomized trial, children aged 6–59 mo with SAM plus HIV (in some cases) SMS-RUTF group—14.2% HIV+ P-RUTF group—14.7% HIV+ *N* = 1927	SMS-RUTF (521 kcal/100 g, soybean, maize, sorghum, palm oil, sugar) P-RUTF (530 kcal/100 g, peanut paste, dried skim milk, soybean oil, sugar) The RUTFs to provide 200 kcal/kg/d	Recovery rates for SMS-RUTF and P-RUTF were 53.3% and 60.8% for the intention-to-treat (ITT) analysis	Children in the SMS-RUTF, the arm had a lower weight gain than those in P-RUTF arm ($P = 0.007$) in both edematous ($P = 0.018$) and nonedematous ($P = 0.091$) cases.	SMS-RUTF = 13.7 %P-RUTF = 12.5%	The study could not confirm their hypothesis of equivalence between SMS-RUTF and P-RUTF in nutrition management of SAM
Sigh et al. (106) to evaluate the effectiveness of BP-100™ (imported milk-based RUTF) compared to NumTrey (locally produced fish-based RUTF) Cambodia 8 wk	Single-blinded RCT children aged 6–59 mo with SAM *N* = 121	NumTrey paste (531 kcal/100 g, milk-based) BP-100™ (529 kcal/100 g, fish-based) both for 2 wk Both RUTFs to provide 200 kcal/kg/d	NA	Weight gain for BP-100™ and NumTrey was 1.06 g/kg/d and 1.08 g/kg/d, respectively	BP-100™ = 2 NumTrey = 0	The trial did not find superiority in any of the 2 products in weight gain (g/kg/d)
Jones et al. (127) develop a RUTF with elevated short-chain n–3 PUFA and measure its impact, with and without fish oil supplementation Kenya 84 d	RCT children aged 6–50 mo *N* = 61	S-RUTF standard RUTF (S-RUTF) F-RUTF [(RUTF + flaxseed oil containing elevated short-chain n–3 PUFA ALA)] FFO-RUFT [(RUTF + flaxseed oil + fish oil capsules containing long-chain n–3 PUFA EPA and DHA)]	NA	No detectable differences in MUAC, WHZ	S-RUTF = 1 F-RUTF = 3 FFO-RUTF = 2	Standard RUTF or F-RUTF (RUTF with flaxseed oil) formulations did meet the PUFA requirements of children except for FFO-RUTF

(*Continued*)

TABLE 2 (*Continued*)

Study/objective/country /duration	Study design/ participants / sample size	Dietary formulations (RUTFs vs. control)	Recovery after intervention	Anthropometric gain (g/kg/d) during intervention	Mortality during intervention	Summary of findings
Jadhav et al. (111) determine the efficacy of indigenously prepared RUTF India 8 wk	RCT children aged 6 mo–5 y with SAM *N* = 242	Indigenous RUTF (540 kcal/100 g), peanut past (25%), skimmed milk powder (24%), powdered sugar (28%), soya bean oil (21%) & micronutrients (2%). The diet provides 175 kcal/kg/d	The recovery rate in the indigenous RUTF group was 84.8% after 6 mo Standard RUTF group not reported	Rate of weight gain in indigenous RUTF = 3.45 g/kg/d. Standard RUTF = 2.38 g/kg/d	N/A	Indigenously prepared RUTF was superior in promoting rapid initial weight gain and maintaining the rate of weight gain
Thapa et al. (128) compare acceptability and efficacy of locally produced RUTF (nutreal) with defined food India 42 d	RCT children 8–45 mo with SAM	Nutreal (545 kcal/100 g, milk powder, vegetable oil, sugar, roasted peanuts, vitamins & minerals mix Defined food (precooked foods of different types containing cereals, pulses, and oil)	N/A	The rate of weight gain N/A, but the difference in the baseline and end-line weight of the nutreal group seems higher than the defined food group	N/A	Nutreal was well accepted by SAM children and showed weight gain when compared to defined food
Mallewa et al. (129) effect of RUSF on mortality Kenya, Malawi, Uganda, & Zimbabwe 12 wk	RCT HIV+ children 5–12 y & adults	Peanut-based RUSF (100 kcal/d, 92 g foil packets)	RUSF did not improve CD4 cell count recovery	Children ≥13 y in RUSF had significantly greater gains in weight, BMI, and MUAC through 48 weeks than 'no-RUSF' group	RUSF = 96 (10.9%) No-RUSF = 92 (10.3%)	RUSF only improved short-term weight gain but not mortality at ART initiation in severely immunocompromised HIV-infected individuals. Provision of lipid-based nutritional supplements to all severely immunocompromised individuals starting ART not warranted
Sunguya et al. (113) association between RUTF and malnutrition Tanzania ~4 mo	Cross-sectional HIV+ children <5 y	RUTF plumpy'nut (200 kcal/kg/d)	N/A	The percentages of underweight and wasting in RUTF group was 3.0% & 2.8% whereas non-RUTF group was 12.4% & 16.5%, respectively	N/A	The provision of RUTF for ≥4 mo was associated with low proportions of undernutrition status
Rao et al. (130) effect of nutrition supplementation in children with HIV India 1 y	Prospective observational study HIV+ children aged 1–18 y	2 scoops of protein powder and 1 serving of peanut chikki. 360 kcal	N/A	Improvement in height-for-age, weight-for-age and the *z*-scores of height-for-age, weight-for-age and BMI-for-age from baseline to 1 y after nutritional supplementation	N/A	The mean values of BMI-for-age were not statistically significant

ALA, α-linoleic acid; A-HPF, augmented energy-dense home-prepared; ART, antiretroviral therapy; MUAC, midupper arm circumference; N/A, not available; P-RUTF, peanut-based RUTF; RCT, randomized control trial; RUTF, ready-to-eat-therapeutic foods, RUTF-C, centrally produced RUTF; RUTF-L, locally prepared RUTF; SAM, severe acute malnutrition; SMS-RUTF, milk-free soy-maize-sorghum-based RUTF; RUSF, ready-to-eat supplementary foods; WHZ, weight-for-height *z*-score.

multivitamin supplementation (vitamin B complex, C and E) improved the children's hematologic status after 24 mo of intervention compared to a placebo group. However, a contrasting effect of multivitamin supplementation and zinc on iron status of infants was observed in a study by Carter et al. (131). This investigation revealed an association of multivitamins with improved iron status in infants, whereas zinc supplementation resulted in an increased risk of iron deficiency, though there was no association with increased risk of anemia in the long term.

Vitamin D deficiency (VDD) is prevalent among HIV patients (132, 133). An association between low concentrations of vitamin D and the progression of HIV disease and the immune system has been ascertained in various studies (134–136). In a retrospective cohort investigation among HIV-infected untreated adults, VDD was associated with an increased time to decline in CD4 cell count to <350 cells/μL. In a cross-sectional study by Mirza et al. (137) assessing the correlation between vitamin D status in HIV-infected children and the duration and severity of their infection, higher CD4 counts were associated with higher vitamin D concentrations. Lower bone mineral density (BMD) has been common in HIV-infected children (138); however, a high dose of vitamin D and calcium supplementation attenuate the loss of BMD (139, 140).

In general, micronutrient supplementation seems positive in infants and children with HIV. However, further RCTs are required to assess the effect of micronutrient supplements to determine the long-term impact and optimal composition and dosing of single and multiple micronutrient supplements in infants and children infected with HIV.

Conclusions

Infants and children infected with HIV deserve special attention because of increased nutrient needs for normal growth and development. The prevention of MTCT remains the best measure against HIV infection. However, despite global policies on lifelong ART amongst pregnant women to prevent or eliminate MTCT (141), adherence to maternal ART for $\geq$18 mo postpartum is low and remains a crucial challenge in resource-poor settings (142–144). The WHO guidelines on ART timing of administration for pregnant and breastfeeding HIV-positive women (145) should also include effective strategies to improve adherence to ART treatment.

There is a paucity of evidence on the effect of standard RUTF and other dietary formulations on mortality (103), especially in the context of HIV in infants. It is crucial to design more pragmatic RCTs to be able to ascertain the effectiveness of low-cost RUTFs and other formulations with standardized outcome measures such as diarrhea, anemia, and other complications of HIV in infants and children with SAM.

The initiation of ART should be immediate or within days of HIV diagnosis. Unfortunately, only 43% of all children living with HIV have access to ARV treatment (146). The WHO recommends early testing and ART initiation for HIV-infected children to reduce HIV-related mortality and morbidity (5). In addition, proper nutritional assessment, management, and support should be an integral part of the care plan to avoid irreversible consequences of undernutrition. The positive role of breastfeeding is also evident, particularly in the first 6 mo of life.

There are conflicting reports on the effectiveness of micronutrient supplementations in the survival of children living with HIV. There are no evidence-based guidelines on the types and dosage of micronutrient supplements in the context of HIV-infected children. Therefore, micronutrient supplement studies are needed to determine the appropriate dosage to build the evidence base for the management of HIV-infected children, especially when SAM is present.

The primary cause of persistent intestinal inflammation has been linked to undernutrition and dysbiosis of the gut microbiome with PD as some of the major consequences (30–32, 147). The WHO guidelines on the management of diarrhea in HIV-infected infants and children stipulates the use of vitamin A supplementation as a prevention strategy, whereas zinc supplementation, low-osmolarity oral rehydration solution (ORS), and daily micronutrients have been recommended as treatment (148). There is emerging interest in probiotic supplementation as a novel strategy to manage dysbiosis and gut-mucosal impairment to reduce immune activation, thereby potentially forestalling or enhancing the outcome of PD in children (44, 45). However, the mechanisms by which probiotics exert their effects on the gut microbiome still remain unclear, especially in HIV-infected children. There is a need for adequately powered trials to assess such effects, and this could be a novel intervention strategy in the nutritional management of PD in HIV-infected infants and children. As discussed here, the WHO and other guidelines on HIV in infants and children need to be reviewed owing to recent advances in the field of nutrition in the context of HIV.

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