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A.S.P.E.N. Clinical Guidelines: Nutrition Support of Children With Human Immunodeficiency Virus Infection

Nasim Sabery, MD, MPH[1]; Christopher Duggan, MD, MPH[2]; and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors

The clinical characteristics of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) in children differ substantially from those in adults, and these differences are important to consider in providing both medical and nutrition care. Growth failure, wasting, and loss of active lean tissue are all associated with increased mortality and accelerated disease progression. The use of highly active antiretroviral therapy (HAART) has improved the prognosis and life span of children infected with HIV (HIV+) and has reduced rates of wasting. However, the emergenceof HIV-associated lipodystrophy (HIVLD) has emphasized the extensive nutrition and metabolic manifestations of HIV infection. Maintaining the nutrition status of the HIV+ child is therefore crucial for optimal health outcomes.

Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization comprised of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of nutrition support therapy. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. These clinical guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing clinical guidelines since 1986.[1-3] Starting in 2007, A.S.P.E.N. has revised these clinical guidelines on an ongoing basis, reviewing about 20% of the chapters each year in order to keep them as current as possible.

These A.S.P.E.N. Clinical Guidelines are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, practitioners must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement but not replace professional training and judgment.

These clinical guidelines were created in accordance with Institute of Medicine recommendations as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances."[4] These clinical guidelines are for use by healthcare professionals who provide nutrition support services and offer clinical advice for managing adult and pediatric (including adolescent) patients in inpatient and outpatient (ambulatory, home, and specialized

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Table 1. Grading of Guidelines and Levels of Evidence

Grading of Guidelines	
A	Supported by at least two level I investigations
B	Supported by one level I investigation
C	Supported by at least one level II investigation
D	Supported by at least one level III investigation
E	Supported by level IV or V evidence
Levels of Evidence	
I	Large randomized trials with clear-cut results; low risk of false-positive (alpha) and/or false-negative (beta) error
II	Small, randomized trials with uncertain results; moderate to high risk of false-positive (alpha) and/or false-negative (beta) error
III	Nonrandomized cohort with contemporaneous controls
IV	Nonrandomized cohort with historical controls
V	Case series, uncontrolled studies, and expert opinion

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care) settings. The utility of the clinical guidelines is attested to by the frequent citation of these documents in peer-reviewed publications and their frequent use by A.S.P.E.N. members and other healthcare professionals in clinical practice, academia, research, and industry. They guide professional clinical activities, they are helpful as educational tools, and they influence institutional practices and resource allocation.[5]

These clinical guidelines are formatted to promote the ability of the end user of the document to understand the strength of the literature used to grade each recommendation. Each guideline recommendation is presented as a clinically applicable statement of care and should help the reader make the best patient-care decision. The best available literature was obtained and carefully reviewed. Chapter author(s) completed a thorough literature review using MEDLINE®, the Cochrane Central Registry of Controlled Trials, the Cochrane Database of Systematic Reviews, and other appropriate reference sources. These results of the literature search and review formed the basis of an evidence-based approach to the clinical guidelines. Chapter editors work with authors to ensure compliance with the author's directives regarding content and format. Then the initial draft is reviewed internally to ensure consistency with the other A.S.P.E.N. Guidelines and Standards and reviewed externally (either by experts in the field within our organization and/or outside of our organization) for appropriateness of content. The final draft is then reviewed and approved by the A.S.P.E.N. Board of Directors.

The system used to categorize the level of evidence for each study or article used in the rationale of the guideline statement and to grade the guideline recommendation is outlined in Table 1.[6]

The grade of a guideline is based on the levels of evidence of the studies used to support the guideline. A randomized controlled trial (RCT), especially one that is double-blind in design, is considered to be the strongest level of evidence to support decisions regarding a therapeutic intervention in clinical medicine.[7] A systematic review (SR) is a specialized type of literature review that analyzes the results of several RCTs. A high-quality SR usually begins with a clinical question and a protocol that addresses the methodology to answer this question. These methods usually state how the literature is identified and assessed for quality, what data are extracted, how they are analyzed, and whether there were any deviations from the protocol during the course of the study. In most instances, meta-analysis (MA), a mathematical tool to combine data from several sources, is used to analyze the data. However, not all SRs use MA.

A level of I, the highest level, will be given to large RCTs where results are clear and the risk of alpha and beta error is low (well-powered). A level of II will be given to RCTs that include a relatively low number of patients or are at moderate to high risk for alpha and beta error (underpowered). A level of III is given to cohort studies with contemporaneous controls or validation studies, while cohort studies with historic controls will receive a level of IV. Case series, uncontrolled studies, and articles based on expert opinion alone will receive a level of V.

Practice Guidelines and Rationales

Table 2 provides the entire set of guideline recommendations for nutrition support in children infected with HIV.

1. Nutrition assessment of children who are HIV+ should be performed at baseline and serially. (Grade: D)

Rationale: Growth failure is common in children who are HIV+ and is associated with greater mortality risk. While birth weights and gestational ages are not different among children who are HIV+ and uninfected (HIV–), by age 3 months[8,9] and up to 5 years,[10] children who are HIV+ have lower weight and height. In fact, wasting syndrome is among the Centers for Disease Control and Prevention (CDC) criteria used to categorize children in clinical category C (severely symptomatic)[11] (Table 3). Clinical and laboratory factors associated with this malnutrition include history of pneumonia, maternal illicit drug use during pregnancy,

Table 2. Nutrition Support Guideline Recommendations in Children with Human Immunodeficiency Virus (HIV) Infection

Guideline Recommendations	Grade
1. Nutrition assessment of children who are HIV+ should be performed at baseline and then serially.	D
2. Anthropometry and body composition studies should be performed.	E
3. Oral nutritional supplements or enteral tube feedings may improve weight and growth in children who are HIV+ with growth failure.	C
4. Antiretroviral therapy improves growth in children who are HIV+.	E
5. Children with HIV lipodystrophy should have laboratory evaluation and clinical management of hypertriglyceridemia and hypercholesterolemia.	D
6. Supplementation with multivitamins should be provided to pregnant and lactating women who are HIV+.	B
7. Micronutrient supplementation should be considered in children who are HIV+.	C
8. Women who are HIV+ in resource-rich settings are advised to formula feed exclusively, while in resource-poor settings, exclusive breastfeeding is recommended.	B

lower infant CD4 count, and increased HIV-1 RNA viral load.[10] Decreased nutrient intake, increased energy requirement, malabsorption, and psychosocial issues may all contribute to undernutrition in the pediatric HIV population. Growth failure is a prognostic indicator of mortality in pediatric HIV infection.[12-14]

See Tables 3 and 4.

2. Anthropometry and body composition studies should be performed. (Grade: E)

Rationale: Children with HIV infection can have a significant loss of lean body mass, even in the absence of weight loss.[18] Weight in children who are HIV+ can be misleading, since fluid shifts caused by vomiting, diarrhea, and altered fluid status can transiently alter the measured weight. Additionally, body mass changes associated with HIV wasting such as preferential loss of fat, loss of lean body mass, and changes in body composition due to HIVLD may not be adequately assessed without body composition evaluation. Anthropometric measures, including mid–arm muscle area, subscapular skinfold, and triceps skinfold, can better reflect fat and lean body mass compared with weight and height measurements alone. Quantification of lean and fat mass is of special importance in these patients due to the increasing incidence of lipodystrophy.

See Table 5.

3. Oral nutritional supplements or enteral tube feedings may improve weight and growth in children who are HIV+ with growth failure. (Grade: C)

Rationale: When the nutrition assessment indicates that a child fails to meet growth standards, nutritional supplements have restored weight and growth in some children.[22] If oral interventions fail, enteral tube feeding improves weight gain in children with growth failure.[23,24] In the circumstance of severe malnutrition, nutrition therapy with an elemental diet may be more effective than higher caloric intake of a standard formula for weight gain.[25] Accurate energy and protein requirements for children who are HIV+ have not yet been established.

See Table 6.

4. Antiretroviral therapy improves growth in children who are HIV+. (Grade: E)

Rationale: Children born to mothers who are HIV+ in both developing and developed countries have lower weight and height *z* scores from birth to at least 5 years of age.[15,21] Growth failure is a prognostic indicator of mortality in pediatric HIV infection.[12-14] The incidence of wasting has fallen since the implementation of HAART; however, multiple factors continue to contribute to growth failure. Children with a virologic response (those who reach HIV viral load <400 or 500 copies/mL) or have significant reduction (>1.5 log) in viral load to therapy tend to have a greater increase in weight and height compared with virologic nonresponders.[16,26] HAART therapy has been shown to increase weight- and height-for-age, while body mass index (BMI) remains unchanged.[16,26]

See Table 7.

5. Children with HIV lipodystrophy should have laboratory evaluation and clinical management of hypertriglyceridemia and hypercholesterolemia. (Grade: D)

Rationale: While initiation of HAART includes many benefits, it has transformed HIV into a chronic disease with the increased risk of metabolic complications. HIVLD has 3 main components: abnormal blood lipid profiles (hypertriglyceridemia and hypercholesterolemia), insulin resistance, and body fat redistribution.[30] Children and adolescents who are HIV+ may exhibit features of lipohypertrophy, lipoatrophy, or a combination of the 2. Lack of consensus of the definition of HIVLD has made its characterization difficult.

Table 3. Human Immunodeficiency Virus (HIV) Clinical Categories

N: No signs or symptoms	A: Mild Signs and Symptoms (2 or more of the following criteria, but not in B or C)	B: Moderate Signs and Symptoms	C: Severe Signs and Symptoms
	Lymphadenopathy	Anemia, neutropenia, or thrombocytopenia	Bacterial infections of the following types, >2 in 1 y: septicemia, pneumonia, meningitis, bone or joint infection, abscess
	Hepatomegaly	Bacterial infection (1)	Candidiasis
	Splenomegaly	Oral candidiasis (>2 mo duration)	Cryptococcus
	Dermatitis	Cardiomyopathy	Cryptosporidium
	Parotitis	Cytomegalovirus (onset less than age 1 mo)	Cytomegalovirus
	Recurrent or persistent respiratory tract infections, sinusitis, or otitis media	Diarrhea, recurrent	Encephalopathy
		Hepatitis	Herpes simplex ulcer >1 mo
		Herpes stomatitis, recurrent (>2 episodes within 1 y)	Histoplasmosis
		Herpes bronchitis, pneumonitis, or esophagitis (onset less than age 1 mo)	Kaposi's sarcoma
		Herpes zoster, >2 episodes	Mycobacterium tuberculosis, disseminated
		Leiomyosarcoma	Mycobacterium avium intracellulare
		Lymphocytic interstitial pneumonitis	*Pneumocystis carinii* pneumonia
		Nephropathy	Progressive multifocal leukoencephalopathy
		Nocardiosis	Toxoplasmosis
		Persistent fever	Wasting syndrome (failure to thrive)
		Varicella, disseminated	

Adapted from U.S. Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency infection in children less than 13 years of age. In: MMWR, ed. *Vol 43: Center for Disease Control Surveillance Summary*; 1994:1-9.

Moreover, signs of HIVLD are more difficult to identify in children and adolescents than in adults because of subtle fat redistribution and physical changes during puberty. Estimates of the prevalence of HIVLD in children and adolescents range from 13% to 67%.[19,27,30-34] The development of symptoms has been linked to protease inhibitor (PI) therapy,[33-35] duration of HAART therapy,[30,33] nucleoside analog–containing regimens, and increasing doses of medications.[36] There is increased association of HIVLD with puberty[33,37] and female gender.[30] Management of lipodystrophy complications in children who are HIV+ has not been well studied.

See Table 8.

6. Supplementation with multivitamins should be provided to pregnant and lactating women who are HIV+. (Grade: B)

Rationale: Supplementation with standard pregnancy multivitamins in pregnant and lactating women in the developing world has been associated with improved fetal and childhood outcomes in 1 large randomized control trial.[39-42] In this trial, multivitamin supplementation was shown to improve infant outcomes (eg, decrease prematurity, increase birth weight, decrease the incidence of small gestational age infants) and to improve childhood outcomes (higher CD4 counts, decreased diarrhea, and improved development).[39-42] Another trial investigated the effects of zinc supplementation vs placebo on pregnant women and found no adverse effects on woman or infants compared with pregnant mothers who received placebo.[43]

Because of its recognized modulation of the immune system, supplemental vitamin A was investigated in pregnant women who are HIV+. While some trials found improved infant outcomes (Table 9), 2 large trials suggested an increased rate of mother-to-child HIV transmission in a subset of the population with high-dose supplemental vitamin A,[44,45] while other smaller trials found no effect.[46,47] High-dose vitamin A supplementation in HIV+ mothers is not currently recommended, since it does not reduce[47-49] and may increase mother-to-child HIV transmission.[44]

See Table 9.

7. Micronutrient supplementation should be considered in children who are HIV+. (Grade: C)

Rationale: The micronutrient status of children who are HIV+ continues to be an area of intense research. Supplementation of multivitamins and micronutrients, at the required dietary allowance dosage, may be indicated in children who are HIV+. In the United States, children who are HIV+ may have reduced dietary intake of vitamin E,[51] calcium, and vitamin D.[52] Consumption of a multivitamin is associated with better bone mineral density in children who are HIV+.[52] Selenium deficiency has been linked with increased mortality risk in children who are HIV+.[53] The majority of research to date has been conducted in developing countries where micronutrient deficiencies are common regardless of HIV status, making it difficult to differentiate the etiology of nutrient deficiencies secondary to HIV/AIDS or background rates of micronutrient malnutrition. In 1 study, vitamin A supplementation in children who are HIV+ was shown to decrease diarrhea, upper respiratory tract infections, and mortality.[54,55] In another study, zinc supplementation was associated with no change in respiratory tract infection, CD4 counts, or HIV viral load, but it decreased diarrhea illness in children who are HIV+.[56]

See Table 10.

8. Women who are HIV+ in resource-rich settings are advised to formula feed exclusively, while in resource-poor settings, exclusive breastfeeding is recommended. (Grade: B)

Rationale: HIV transmission through breastfeeding may account for as much as 12%–16% of postnatal transmission.[59-61] In developed countries, it is recommended that mothers who are HIV+ exclusively formula feed to avoid the risk of HIV transmission.[62] In resource-poor settings, the practical aspects of implementation of formula feeding may be difficult due to unsafe water, lack of availability of milk substitutes, varying cultural norms, and risk of maternal stigmatization.[62] Maternal characteristics that place infants at increased risk for HIV transmission include higher plasma and milk HIV viral load, mastitis, and decreased maternal CD4 count.[62] Furthermore, the protective factors of breastfeeding in these environments may include decreased diarrheal illness and decreased mortality. The World Health Organization recommends that when replacement feeding is feasible, acceptable, affordable, sustainable, and safe, then avoidance of breastfeeding by women who are HIV+ is recommended.[63] Otherwise, in the developing world, the morbidity and mortality of infants born to mothers who are HIV+, whether exclusively fed breast milk or formula, may be equivocal.[64,65,66] Should breastfeeding be selected, exclusive breastfeeding is advised, as it is associated with decreased vertical transmission and infant mortality compared with mixed feeding regimens.[60,67] Furthermore, a 6-month period of exclusive breastfeeding may be recommended, as the risk of transmission significantly increases with time.[67] Peripartum maternal and infant antiretroviral prophylaxis during breastfeeding may also decrease the risk of HIV transmission to the infant postnatally.

See Table 11.

Acknowledgment

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A.S.P.E.N. Board of Directors Providing Final Approval

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Table 4. Nutrition Assessment in Children With HIV Infection

Study	Population	Study Groups	Results	Comments
Villamor et al[14] 2005 III	687 children admitted to hospital in Tanzania with pneumonia, 1993–1997	HIV– (n = 590), HIV+ (n = 58); mean age at enrollment18 mo	Risk factors for mortality: HIV+ (RR 3.92, 95% CI 2.34–6.55, $P < .0001$); age <24 mo, low MAC, anemia; stunting and wasting independently predict mortality; HIV+ stronger predictor in children with wasting (RR 5.16, 95% CI 2.52–10.6) than those without wasting (RR 1.56, 95% CI 0.53–4.57, *PInt* = .05)	HIV+ and undernutrition strong predictors of mortality
Newell et al[15] 2003 III	Children born to HIV+ mothers followed at 11 centers in 8 European countries	HIV – (n = 1403), HIV+ (n = 184); followed from age 0–10 y	Birth, no difference ht or wt; age 6–12 mo, HIV– 1.6% taller, 6.2% heavier than HIV+; age 8–10 y, HIV– 10% taller, 44% heavier than HIV+; age 10 y, HIV– 7 kg heavier, 7.5 cm taller than HIV+	HIV+ children with poor growth relative to HIV– children
Verweel et al[16] 2002 III	HIV+ children on HAART therapy	HIV+ (n = 24); age 0.4–16.3 y at baseline	48 wk before HAART median HAZ decreased from –0.088 to –1.22 at baseline; baseline to 96 wk after HAART, median HAZ increased from 0.20 to 0.95 ($P = .052$); 48 wk before HAART median WAZ decreased from 0.041 to –0.74 at baseline; baseline to 96 wk after HAART, median WAZ increased from 0.34 to 0.60 ($P = .056$); No significant change in BMI-Z after 96 wk HAART	HAZ & WAZ but not BMI improved with HAART therapy in HIV+
Miller et al[17] 2001 III	Children of pregnant, HIV+ mothers in 4 cities in the United States	HIV+ (n = 92), HIV– (n = 439); age 0–5 y	Age 6 mo, HIV+ lower wt ($P = .01$), ht ($P < .001$), WHZ ($P = .03$), remained low until age 5 y	Malnutrition at age 6 mo significant through age 5 y
Bailey et al[8] 1999 III	Children (HIV– and HIV+) born to HIV+ mothers vs healthy controls	HIV+ (n = 68) from HIV+ mothers, HIV– (n = 190) from HIV+ mothers, indeterminate HIV status (n = 63), HIV– (n = 256) from HIV– mothers	Age 3 mo, HIV+ significantly lower ht; low WAZ in HIV+ vs HIV– (RR 2.54, 95% CI 1.66–3.89, $P < .0001$); controlled for mother's ht, RR of stunting in HIV+ vs HIV– (RR 2.10, 95% CI 1.30–3.39, $P = .003$); RR of underweight in HIV+ vs HIV– (RR 2.56, 95% CI 1.63–4.03, $P = .001$)	Stunting and wasting significant in untreated HIV+ children by age 3 mo
Berhane et al[12] 1997 III	Children born to HIV+ Ugandan women 1990–1992, and controls from HIV– mothers	HIV– (n = 251) from HIV+ mothers, HIV+ (n = 84) from HIV+ mothers, HIV– (n = 124) controls; followed at ages 0 and 6 wk, and 6, 12, and >15 mo	At birth, HIV– from HIV+ mother with lower birth wt, length than from HIV– mother; at age 1 y, mortality increased with low WAZ; WAZ <+0.75 vs >+0.75 (OR 2.74, 95% CI 1.12–6.67, $P = .03$); WAZ <+1.0 vs >+1.0 (OR 3.39, 95% CI 1.28–8.97, $P = .021$); WAZ <–1.5 vs >–1.5 (OR 4.87, 95% CI 1.27–18.67, $P = .024$)	In HIV+, low WAZ predicts mortality

(continued)

Table 4 (continued)

Study	Population	Study Groups	Results	Comments
Lepage et al[13] 1996 III	Children born to HIV+ mothers or those born to HIV− mothers in Rwanda, enrollment of mothers 1988–1989	HIV+ (n = 46) from HIV+ mothers, HIV− (n = 140) from HIV+ mothers, HIV− (n = 218) from HIV− mothers; followed at age 0 and every 3 mo until age 4 y	Until age 30 mo, WAZ and HAZ in HIV+ < HIV− (P < .017); Between 12–36 mo, WAZ score lowest; After age 9 mo HAZ score <2 SD in HIV+ children; only at ages 3, 6, 24, and 36 mo is WHZ low in HIV− (P < .017); WAZ and HAZ in HIV− not different from controls	HIV+ more likely stunted than HIV−
Miller et al[18] 1993 III	Children born to HIV+ mothers and referred to HIV clinic in Massachusetts, 1986–1991	HIV− (n = 37), HIV+ (n = 52); followed from age 0–21 mo	Age 21 mo, HIV− vs HIV+ WAZ [SE]: 0.12 [0.18] vs −0.68 [0.16], P = .002; WHZ [SE]: +0.55 [0.16] vs +0.11 [0.26], P = .03; MAC: 64% [5.32] vs 43% [6.54], P = .01	Birth wt not different, by age 21 mo HIV+ more malnourished

BMI-Z, body mass index z score; CI, confidence interval; HAART, highly active antiretroviral therapy; HAZ, height-for-age z score; ht, height; MAC, mid–upper arm circumference; OR, odds ratio; *Plnt*, *P* Interaction term; RR, relative risk; SD, standard deviation; SE, standard error; WAZ, weight-for-age z score; WHZ, weight-for-height z score; wt, weight.

Table 5. Anthropometry in Children With Human Immunodeficiency Virus (HIV) Infection

Study	Population	Study Groups	Results	Comments
Taylor et al[19] 2004 V	Children enrolled in phase I/II HIV treatment protocols, 1999–2001	HIV+ (n = 98); HAART (n = 59), protease inhibitor (n = 39)	During puberty, 10% with lipodystrophy and dyslipidemia, 52% no lipodystrophy but dyslipidemia, 38% neither	Unidentified physiological changes with puberty may predispose patients treated with protease inhibitors to lipodystrophy and dyslipidemia
Jaquet et al[20] 2000 V	HIV+ French children	HIV+ (n = 39), varied antiretroviral therapy; age 9.1 ± 4 y	Lipodystrophy in 33%, with higher fasting insulin levels; dyslipidemia in 23% with no lipodystrophy	
Arpadi et al[21] 1998 IV	HIV clinic in New York	HIV+ (n = 34) age 4–11 y; growth failure (n = 18), no growth failure (n = 16), healthy controls (n = 52); FM, FFM by DXA	In HIV+ boys with growth failure, lower FFM, HAZ, WAZ than healthy boys; In HIV+ girls with growth failure, lower FFM, ht, BCM/ht, HAZ, WAZ than HIV– girls without growth failure and healthy girls; FM not different from healthy controls	FFM, BCM depleted in HIV+ and/or growth failure, but FM maintained

BCM, body cell mass; DXA, dual energy x-ray absorptiometry; FFM, fat-free mass; FM, fat mass; HAART, highly active antiretroviral therapy; HAZ, height-for-age *z* score; ht, height; WAZ, weight-for-age *z* score.

Table 6. Oral Nutritional Supplements or Enteral Tube Feedings in Children With Human Immunodeficiency Virus (HIV) and Growth Failure

Study	Population	Study Groups	Results	Comments
Rollins et al[22] 2007 II	HIV+ South African children with prolonged diarrhea	HIV+ with standard support (n = 83) milk + porridge (100–110 kcal/kg/d, protein 2.2 g/kg/d) vs HIV+ protein-supplemented milk formula (n = 86) (150 kcal/kg/d, protein 4–5.5 g/kg/d) for 8 wk; age 6–36 mo	At 26 wk, improved WAZ (–2.63 vs –1.32; $P < .05$) and HAZ (–3.14 vs –2.82; no P value provided) in supplemented vs standard support	Weight gain better with protein-supplemented formula; mortality high in both groups (22%, 29%)
Amadi et al[25] 2005 I	HIV+ children with malnutrition in Zambia	Elemental diet (EN n = 100) 70 kcal/mL vs 100 oral liquid formula diet soy + skim milk 100 kcal/mL (control n = 100) for 4 wk	Weight gain improved in EN vs control (z score increase +1.23 IQR (0.89–1.57) > control +0.87 IQR (0.47, –1.25; $P = .002$)	In severely malnourished population, improved wt gain in EN vs soy + skim milk in spite of widespread intestinal infection
Miller et al[23] 1995 V	HIV+ children in Massachusetts with growth failure	6 mo gastric EN with 110 kcal/kg/d (n = 27); age 0–6 y	Weight gain with improved energy intake ($r = 0.65$, $P = .002$); WAZ increased –2.1 SE [0.14] to –1.6 SE [0.14], WHZ –0.98 SE [0.16] to –0.15 SE [0.17]; for every unit change in WAZ, 2.8-fold reduced risk of death	Follow-up limited to 6 mo
Henderson et al[24] 1994 V	HIV+ children with growth failure in United States	8.5 mo polymeric formula (n = 18); age 3–159 mo	WAZ (SD) improved from baseline z –2.1 ± 1.0 to –1.5 ± 1.4, $P = .04$; WHZ (SD) from –1.1 ± 1 to +0.13 ± 1.0, $P = .01$; and arm fat area z (SD) from –1.8 ± 1.3 to –0.62 ± 1.2, $P = .0004$ increased with EN; HAZ (SD) not improved, z –1.9 ± 0.8 to –1.7 ± 1.6	Energy intake not reported

EN, enteral nutrition; HAZ, height-for-age z score; IQR, interquartile range; r, correlation coefficient; SD, standard deviation; SE, standard error; WAZ, weight-for-age z score; WHZ, weight-for-height z score.

Table 7. Growth in Children With Human Immunodeficiency Virus (HIV) and Treated With Antiretroviral Therapy

Study	Population	Study Groups	Results	Comments
Guillen et al[26] 2007 IV	HIV+ Spanish children, 97% perinatal infection	HIV+ (n = 212); changes from baseline wt, ht, BMI at 12, 24, 36, 48, and 60 mo after HAART	39% with lipodystrophy; HAART significantly increased WAZ and HAZ but not BMI-Z at each time point	HIV+ children with catch-up growth after HAART, with better response in those with <500 HIV copies/mL
Scherpbier et al[27] 2006 III	HIV+ PI naive children treated with nelfinavir and 2 nucleoside reverse transcriptase inhibitors in the Netherlands	HIV+ (n = 39) followed median 227 wk; median age 4.7 y	In first year after HAART, increased WHZ –0.3 to 0.5 (no *P* value or interquartile range available) but not HAZ or WHZ over 240 wk in virologic responders (*P* = .50 and .57, respectively)	In the first year of HAART therapy, WHZ but not WAZ or HAZ increased
Nachman et al[28] 2005 IV	HIV+ children in U.S. AIDS Clinical Trials studies	HIV+ (n = 192); age 4 mo to 17 y; growth 16 wk after HAART	At baseline, HIV+ shorter than HIV– with HAZ –0.57 (95% CI –0.73 to –0.41, *P* < .001); HAART increased WAZ to normal by wk 48, HAZ toward normal by wk 96; younger children gained ht more rapidly (*P* < .001); children with greater baseline viral loads gained wt more rapidly (*P* < .001)	HAART improves average wt gain of HIV+ children by 1 y treatment, and ht to nearly normal after 2 y
Miller et al[17] 2001 IV	HIV+ children in New York, New Jersey, and Massachusetts, 1996–1999	HIV+ with PI therapy (n = 67), followed 2.4 y	Drug therapy improves WAZ 0.46 ± 0.11, (*P* < .001), WHZ 0.49 ± 0.20 (*P* < .016), AMC 11.5 ± 3.8 cm (*P* < .003); no change in HAZ 0.17 ± 0.10 (*P* = .1)	In addition to reducing viral load, PI therapy in children improves growth
Arpadi[29] 2000 III	U.S. children recruited from outpatient clinics, 1996–1997	HIV+/GF+ (n = 16) vs HIV+/GF– (n = 26)	In HIV+/GF+ mean viral load 1.5 log units > HIV+/GF–, 4.89 ± 1.08 vs 3.43 ± 1.63 × 102 copies/mL (*P* = .0009); energy intake lower 5640 ± 653 vs 8305 ± 490 kJ/d (*P* = .003); energy balance (based on REE and TEE) lower in HIV+/GF+ 674 ± 732 vs 1448 ± 515 (*P* = .030)	In HIV+/GF+ children, poor energy intake and growth associated with increased HIV replication

AIDS, acquired immune deficiency syndrome; AMC, arm muscle circumference; BMI-Z, body mass index *z* score; CI, confidence interval; HAART, highly active antiretroviral therapy; HAZ, height-for-age *z* score; HIV+/GF+, HIV positive with growth failure; HIV+/GF–, HIV positive without growth failure; ht, height; PI, protease inhibitor; REE, resting energy expenditure; TEE, total energy expenditure; WAZ, weight-for-age *z* score; WHZ, weight-for-height *z* score; wt, weight.

Table 8. Lipodystrophy in Children With Human Immunodeficiency Virus (HIV)

Study	Population	Study Groups	Results	Comments
Ene et al[30] 2007 III	All HIV+ children in Brussels clinic except those with severe illness, steroids, or immunomodulators, 2002	HIV+ (n = 88), 84% on ART, 89% African; age 11.1 (range 3–19) y; A = children with fat redistribution, B = children with metabolic abnormalities only, C = children with no fat redistribution or metabolic abnormalities	A vs B vs C mean (SD) BMI: 19.5 ± 3.1 vs 18.4 ± 3.1 vs 18.4 ± 2.4; WAZ: –0.04 ± 1.35 vs +0.42 ± 1.91 vs +0.02 ± 1.40; HAZ: –0.89 ± 1.42 vs –0.11 ± 0.99 vs –0.40 ± 1.37; no statistically significant differences among 3 groups	No difference in BMI-Z, WAZ, or HAZ relative to fat redistribution or metabolic abnormalities
Carter et al[32] 2006 III	Population from Perinatal Collaborative Transmission Study (United States)	HIV+ (n = 178); followed age 9–15 y	47% with hypercholesterolemia (>200 mg/dL on any measure), 67% with hypertriglyceridemia (>150 mg/dL on any measure)	
Beregszaszi et al[33] 2005 III	Population from 3 pediatric clinics	HIV+ (n = 130); mean age 10 y (2–18 y)	24.6% with lipodystrophy; 19% with HDL <1 mm/L; 22% with cholesterol or triglycerides >2 SD above the mean; 13.2% with insulin resistance	
Farley et al[34] 2005 III	Children of HIV+ women in United States and Puerto Rico	HIV+ (n = 1812), HIV– (n = 187); age 4–19 y	Hypercholesterolemia prevalence 13% (95% CI 11.1–14.3) in HIV+ vs 4.8% (95% CI 2.2–8.8) in HIV–; adjusted for confounders, risk factors include PI use (OR 5.3, 95% CI 3.1–9.2), age 4–6 y (OR 2.9, 95% CI 1.7–4.9), age 6–12 y (OR 1.9, 95% CI 1.3–2.9), Hispanic (OR 1.8, 95% CI 1.2–2.5), White (OR 2.2, 95% CI 1.4–3.3), and HIV RNA <400 copies/mL (OR 2.3, 95% CI 1.7–3.2)	
European Lipodystrophy Group[38] 2004 V	HIV+ children in Europe from 30 clinics	HIV+ (n = 477); median age 9.7 y (3–18 y)	Fat distribution = 26% (22.1–30.2), central lipohypertrophy = 8% (5.4–10.3), peripheral lipohypertrophy = 7.55% (7.15–12.7), hypercholesterolemia (>200 mg/dL) = 27% (21.6%–32.7%), hypertriglyceridemia (>150 mg/dL) = 21% (16.4–26.4); risk factors female gender, increased age, symptomatic HIV, length of time on ART	
Sanchez Torres et al[31] 2005 V	HIV+ children in Spain	HIV+ (n = 56); mean age 9.5 y (21 mo to 18 y)	Hypercholesterolemia (>180 mg/dL) = 57%, hypertryglyceridemia (>130) = 71%, lipodystrophy = 25%, lipohypertrophy = 12.5%; fat redistribution more common in children age >11 y; 87% on ART, 77% on HAART	

ART, antiretroviral therapy; BMI, body mass index; BMI-Z, body mass index *z* score; CI, confidence interval; HAART, highly active antiretroviral therapy; HAZ, height-for-age *z* score; HDL, high-density lipoprotein; OR, odds ratio; PI, protease inhibitor; RNA, ribonucleic acid; SD, standard deviation; WAZ, weight-for-age *z* score.

Table 9. Multivitamin (MV) Supplementation in Mothers With Human Immunodeficiency Virus (HIV) Infection

Study	Population	Study Groups	Results	Comments
Humphrey et al[44] 2006 I	Infants of HIV+ women in Zimbabwe	Infants randomly assigned within 96 h of delivery to 1 of 4 treatment groups: mothers and infants received vitamin A (n = 1103), mothers received vitamin A and infants received placebo (n = 1126), mothers received placebo and infants received vitamin A (n = 1144), and mothers and infants received placebo (n = 1122); vitamin A doses: 400,000 units in mothers and 50,000 in the mothers and infants; all infants BF	Vitamin A supplementation did not impact mother-to-child HIV transmission or mortality to age 2 y; in infants HIV– at birth but HIV+ at age 6 wk, neonatal vitamin A reduced mortality 28% ($P = .01$) but maternal supplementation had no effect; in infants HIV– at 6 wk, all vitamin A regimens associated with ~2-fold higher mortality ($P < .05$)	While vitamin A supplementation to HIV+ neonates improves survival, supplementation may increase risk of death in breast-fed HIV– children
Fawzi et al[50] 2003 I	HIV+ pregnant women in Tanzania and their children	Pregnancy and lactational maternal vitamin A supplement as 30 mg β-carotene + 5000 IU vitamin A (n = 397), pregnancy MV with no vitamin A (n = 388), pregnancy MV with vitamin A (n = 400), placebo (n = 391); HIV+ children (n = 108), HIV– children (n = 556) at age 1.5–24 mo	Children with MV less diarrhea than those with no MV (RR 0.83, 95% CI 0.71–0.98, $P = .03$); no difference in diarrhea with vitamin A; HIV+ children's mean CD4 count higher in MV vs no MV group ($P = .0006$)	
Kumwenda et al[46] 2002 I	HIV+ pregnant women in Malawi	Iron and folate (n = 357), 10,000 units vitamin A (n = 357)	Vitamin A with no effect on mother-to-child HIV transmission; vitamin A with less risk of low birth wt (14% vs 21%, $P = .03$), anemia at age 6 wk (23.4% vs 40.6%, $P < .001$)	
Coutsoudis et al[47] 1999 I	HIV+ pregnant women in South Africa	Maternal vitamin A as 5000 units retinyl palmitate and 30 mg β-carotene 3rd trimester and 200,000 units retinyl palmitate at delivery (n = 368); placebo (n = 360)	No difference in HIV+ in children at age 3 mo; women with vitamin A had less risk of preterm delivery (11.4% vs 17.4%, $P = .03$)	Vitamin A supplementation protects against preterm delivery

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Table 9 (continued)

Study	Population	Study Groups	Results	Comments
Fawzi et al[40] 1998 I	HIV+ women 12–27 wk gestation in Tanzania	Vitamin A as 30 mg β-carotene + 5000 units vitamin A (n = 269), standard pregnancy MV and no vitamin A (n = 270), standard pregnancy MV (n = 270); placebo (n = 267); all with 200,000 units vitamin A orally at delivery	In MV vs placebo, fetal death (RR 0.61, 95% CI 0.39–0.94, *P* = .02); low birth wt (RR 0.56, 95% CI 0.38–0.82, *P* = .003); preterm birth <34 wk (RR 0.61, 95% CI 0.38–0.96, *P* = .03); SGA birth (RR 0.57, 95% CI 0.39–0.82, *P* = .002) all reduced; vitamin A supplement with no added benefit; infant wt gain over 2 y greater MV than placebo (+459 g; 95% CI 35–882, *P* = .03) but not for vitamin A groups; WAZ +0.42 (95% CI 0.07–0.68), WHZ score +0.38 (95% CI 0.07–0.68, *P* = .01) at 24 mo higher than placebo but vitamin A supplement reduced these benefits. Bailey development scores in a subset of 327 children, MV with increased psychomotor index (RR 2.6, 95% CI 0.1–5.1), less developmental delay (RR 0.4, 95% CI 0.2, 0.7) but no effect on mental development; no effect of vitamin A on development	MV, but not vitamin A, supplementation with decreased fetal death, low birth weight, prematurity; MV with no vitamin A supplementation to pregnant and lactating mothers with better nutrition outcomes in children to age 2 y; vitamin A and β-carotene reduced benefits seen with no vitamin A

BF, breast-fed; CI, confidence interval; RR, relative risk; SGA, small for gestational age; WAZ, weight-for-age *z* score; WHZ, weight-for-height *z* score.

Table 10. Micronutrient Supplementation in Children With Human Immunodeficiency Virus (HIV) Infection

Study	Population	Study Groups	Results	Comments
Tremeschin et al[57] 2007 IV	Brazilian children	HIV+ (n = 20), HIV– (n = 20) of HIV+ mothers, HIV– (n = 10) of HIV– mothers	Adequate niacin, tryptophan, zinc, pyridoxine, and energy intake by FFQ in all, adequate niacin excretion, and nitrogen status	HIV+ children with stable clinical course with no niacin deficiency
Bobat[56] 2005 I	Children with HIV infection in South Africa	HIV+ (n = 96); 10 mg zinc supplement (n = 46), placebo (n = 50); mean age 40.1 vs 36.6 mo	In zinc vs placebo, no difference in HIV–1 viral load 0.03 (95% CI 0.23–0.28) or the % CD4 T lymphocytes (difference –0.8, 95% CI 0.4–3.0). Zinc supplementation with less watery diarrhea (7.4 vs 14.5%, $P = .001$) but no difference in respiratory or ear infections ($P = .16$)	Zinc supplementation to HIV+ children does not increase viral load, may reduce diarrhea
Semba et al[58] 2005 II	HIV+ Ugandan children	Vitamin A as 60 mcg retinol every 3 mo (n = 87); 94 placebo (n = 94); from age 15–30 mo	In vitamin A vs placebo, mortality (RR 0.54, 95% CI 0.30–0.98, $P = .04$), persistent cough (RR 0.47, 95% CI 0.23–0.96, $P = .038$), diarrhea (RR 0.48, 95% CI 0.19–1.18, $P = .11$)	Vitamin A reduces mortality and infectious diarrhea in HIV+ children
Kruzich et al[51] 2004 III	U.S. youth with early HIV disease	HIV+ (n = 264), HIV– (n = 127)	By FFQ, 30% take MV, vitamin C, or iron supplements; 40% with low vitamin E intake; 18.7% inadequate vitamin A intake; 10.5% inadequate zinc intake, no difference by HIV status, HIV+ with CD4 >500 copies/mL with decreased iron intake ($P < .05$)	Cross-sectional study describes behavior, not results of intervention
Campa et al[53] 1999 V	U.S. children with perinatal HIV+ followed for 5 y	HIV+ (n = 24); from age 0–5 y	With CD4 <200 mortality (RR 7.05, 95% CI 1.87–26.5, $P = .004$); with low plasma selenium mortality (RR 5.96, 95% CI 1.32–26.81, $P = .02$); in children who died, those with low selenium levels died at younger age, suggesting more rapid disease progression	Low plasma selenium predicts mortality in HIV+ children
Fawzi et al[54] 1999 II	HIV+ Tanzanian children	HIV+ (n = 58); 200,000 units vitamin A (n = 31) at hospital admission, 4 mo, 8 mo after discharge vs placebo (n = 27)	With vitamin A, all-cause mortality (RR 0.37, 95% CI 0.14–0.95, $P = .04$); AIDS-related deaths (RR 0.32, 95% CI 0.1–0.99, $P = .05$) reduced	Clear benefit to HIV+ children of vitamin A supplements
Coutsoudis et al[55] 1995 II	South African children	HIV+ (n = 281), HIV– (n = 57), of HIV+ mothers; vitamin A as 50,000 units at 1 and 3 mo, 100,000 units at 5 mo, 200,000 units at 10 and 15 mo vs placebo (no vitamin A)	Vitamin A protective against diarrhea (OR 0.62, 95% CI 0.39–0.98) ; no difference in respiratory infections	

AIDS, acquired immune deficiency syndrome; CI, confidence interval; FFQ, Food Frequency Questionnaire; MV, multiple vitamin; OR, odds ratio; RR, relative risk.

Table 11. Breastfeeding (BF) in Children With Human Immunodeficiency Virus (HIV) Infection

Study	Population	Study Groups	Results	Comments
Becquet et al[68] 2008 III	BF infants of HIV+ mothers in Abidjan, Côte d'Ivoire, 2001–2003	HIV– infants at age 30 d (n = 622) ; mothers proposed 2 feeding strategies: 1) complete avoidance of BF with artificial milk provided or 2) exclusive BF with aim of complete cessation by age 3–4 mo; all mothers given replacement feedings through age 9 mo; children followed to age 2 y	BF >6 mo increased odds of postnatal HIV transmission (OR 7.5, 95% CI 2.0–28.2, P = .003); mixed feeding during first mo of life increased odds of postnatal HIV transmission (OR 6.3, 95% CI 1.1–36.4, P = .04)	Mothers received peripartum ART drug combination as in the context of a larger maternal ART drug combination trial; presented results were controlled for ART use
Rollins et al[69] 2008 III	Children born to HIV+ women in South Africa	HIV– (n = 1193); Intensive feeding support and education, supply of formula for 6 mo, frequent home visits	Overall survival by age 18 mo *not* statistically different for HIV– infants with BF ≤6 mo (RR 0.91, 95% CI 0.87–0.94, P = .03) or replacement fed (RR 0.96, 95% CI 0.90–0.98, P = .25)	
Kuhn et al[70] 2008 I	Children born to HIV+ women in Zambia	Exclusive BF to age 4 mo with abrupt weaning (n = 481); BF as long as desired with median duration 16 mo (n = 477); primary outcome HIV+ or death by 24 mo	In BF to 4 mo, 69% stopped BF in <2 d; in infants BF longer and not HIV+ at 4 mo, no difference in HIV survival at 24 mo (83.9% vs 80.7%, P = .27); in infants HIV+ by age 4 mo, higher mortality at 24 mo in the abrupt weaning group (73.6% vs 54.8%, P = .007)	Early, abrupt cessation of BF by HIV+ mothers in low-resource settings is harmful to HIV+ children
Coovadia et al[67] 2007 III	Children born to HIV+ women in South Africa	HIV– (n = 1372)	Complete feeding data in 1276 pts. In exclusively BF, by age 6 wk 14.1% HIV+ (95% CI 12.1–16.4), by age 6 mo 19.5% HIV+ (95% CI 17.0–22.4); increased risk of vertical transmission with maternal CD4 <200 copies/mL (HR 3.79, 95% CI 2.35–6.12), low birth wt (HR 1.81, 95% CI 1.07–3.06); in mixed-fed children, higher risk of HIV+ than exclusively BF (HR 10.87, 95% CI 1.51–78.0, P = .018) and than infants with mixed feeding at 3 mo (HR 1.82, 95% CI 0.98–3.36, P = .057); mortality at age 3 mo in exclusive BF 6.1% (95% CI 4.74%–7.92%) vs 15.1% (95% CI 7.63%–28.73%); death (HR 2.06, 95% CI 1.00–4.27, P = .05) in mixed feeding group	Mixed BF and BF with solids with higher risk of HIV transmission than exclusively BF

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Table 11 (continued)

Study	Population	Study Groups	Results	Comments
Palombi et al[71] 2007 IV	HIV+ women in Tanzania, Mozambique, and Malawi 2004–2006, enrolled in DREAM Program; all received HAART from 25th wk gestation	HIV+ pregnant women in 2 cohorts: strict FF guidelines from all 3 countries (n = 809), BF guideline from Mozambique only (n = 341); all materials for FF given until age 6 mo	No difference in HIV transmission at age 1 mo (1.2% in BF vs 0.8% in FF) or age 6 mo (0.8% BF, 1.8% FF, $P = .38$), no difference in mortality at age 6 mo (27/1000 y in FF vs 28.5/1000 y in FF)	Outcomes from FF may be equivalent to BF when all resources and extensive education provided
Taha et al[72] 2007 III	BF infants involved in ART prophylaxis trials in Malawi	HIV– (n = 1256) at age 6–8 wk	By end of study, 98 HIV+ and 1158 HIV– infants; cumulative risk of late transmission by 24 mo 9.65 (95% CI 7.8–11.6); weaning at age 6 mo decreases 85% of late transmission; risk factors for postnatal transmission high baseline maternal viral load (RR 3.67, 95% CI 2.55–5.27), maternal primiparity (RR 4.82, 95% CI 1.46–15.91), mastitis (RR 4.94, 95% CI 1.53–16.02)	Continuation of BF for >6 mo may increase risk of HIV infection by 7.5 times
Thior et al[73] 2006 I	Children born to 1200 HIV+ women treated peripartum with nevirapine vs placebo in Botswana	All infants with single dose nevirapine vs placebo; BF+zidovudine (n = 301), FF (n = 299)	HIV transmission higher in BF group (9.0% vs 5.6%; 95% CI for difference –6.4% to –0.4%, $P = .04$); at age 6 mo, mortality from infectious disease higher in FF than BF, 9.3% vs 4.9%, $P < .003$; by age 18 mo, mortality not different	BF with zidovudine prophylaxis not as effective as FF in preventing HIV transmission, but infant mortality higher in FF group than BF group
Iliff et al[60] 2005 III	Newborns born to HIV+ women in Zimbabwe	HIV– (n = 2060) at age 6 wk; All BF	Overall prenatal transmission 12.1%. Exclusive BF vs early mixed BF 4.03 (95% CI 0.98–16.61), 3.79 (95% CI 1.40–10.29), and 2.60 (95% CI 1.21–5.55); greater risk of transmission at ages 6, 12, and 18 mo, respectively	Part of an ancillary study to a postpartum vitamin A supplementation trial

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Table 11 (continued)

Study	Population	Study Groups	Results	Comments
Coutsoudis et al[74] 2003 III	Infants born to HIV+ women in South Africa, also participating in vitamin A intervention trial	HIV+ (n = 62), HIV− (n = 301)	HIV+ infants not BF with worse outcome than those BF (OR 4.05, 95% CI 0.91–20.1, $P = .05$)	
Nduati et al[59] 2000 I	401 infant–mother pairs in Kenya, 1992–1998	HIV−, BF (n = 212), 213 FF (n = 213), followed through age 2 y	Median duration of BF 17 mo; cumulative incidence of HIV+ in BF vs FF 36.7% (95% CI 29.4%–44.0%) vs 20.5% (95% CI 14.0%–27.0%, $P = .001$); estimated rate of transmission through BF 16.2% (95% CI 6.5%–25.9%); rate of HIV-free survival lower in BF than FF (58% vs 70%; $P = .02$)	96% compliance in BF vs 70% in FF

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; FF, formula feeding; HAART, highly active antiretroviral therapy; OR, odds ratio.

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