Nutritional Care of the Child with Human Immunodeficiency Virus Infection in the United States: A Historical and Contemporary Perspective

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9.1 INTRODUCTION AND EPIDEMIOLOGY

The global pandemic of human immunodeficiency virus (HIV) infection has had grave consequences in the lives of affected infants, children, and adolescents, with more than 33% of infant and child mortality attributed to HIV infection in endemic locations [1]. In settings where voluntary and public resources are insufficient to provide long-term care, millions of children initially cared for by relatives have now been orphaned. However, many guardians themselves get sick or become overwhelmed by the number of dependents for whom they have to provide care. The growing number of street children and child-headed households are often the outcomes of a chain of events that begin with the HIV infection of a mother, her partner, or both.

In the United States, perinatal transmission has decreased to such a significant extent that current estimates indicate less than 200 infants born with HIV annually [2,3]. With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral (ARV) prophylaxis, scheduled cesarean section delivery, and avoidance of breastfeeding, the rate of transmission events has decreased to less than 1% in the United States and Europe [4–8]. However, there remains an unacceptable annual rate of newly diagnosed HIV-1 infections among infants in the United States, with the persistence of marked racial and economic disparities [9].

Most pediatric HIV infections (>90%) are caused by vertical transmission, with events more common to areas where antenatal HIV seroprevalence is high [10]; 21 countries in sub-Saharan Africa and in South, East, and Southeast Asia account for more than 90% of the pregnant women needing ARVs to prevent vertical transmission. However, global rates of new HIV infections and prevalence among young people have fallen in many countries, likely due to reductions in vertical transmission rates and improvement in access to effective cART, which has decreased secondary transmission events.

9.2 PEDIATRIC HIV-1 INFECTION: A CLINICAL OVERVIEW

9.2.1 The Pathophysiology of Pediatric Compared with Adult HIV Infection

Perinatal infection occurs at a time of relative immunologic immaturity. The inability to control viremia exposes the thymus and other lymphoid tissue to HIV-1–mediated destruction at a time of active thymopoiesis and lymphopoiesis [11]. Given that the virus is transmitted from the mother and that the degree of human leukocyte antigen class I sharing between mother and infant is high, the virus could evade the protective immune response of the newborn, which results in accelerated disease progression [12].

In contrast to adults, HIV-1-related symptoms, CD4+ T cell depletion, or both develop in most untreated vertically infected children within the first few years of life [13]. In addition, plasma HIV-1 ribonucleic acid (RNA) levels remained elevated over the first 2 years among infants [14] and do not decrease to less than 10^5 copies/mL through at least the third year of life [15]. The prolonged elevation of plasma HIV-1 RNA levels may be related to the kinetics of viral replication, the size of the pool of host cells that are permissive to viral replication, and immature virus-specific immune responses.

9.2.2 The Bimodal Distribution of Pediatric HIV-1 Infection

The infection in perinatally infected infants and children progresses more rapidly than in adults. Although 4% of the world's population with HIV-1 infection comprises children, 20% of all AIDS deaths were previously in this group. Early studies before the era of cART indicated that a subset of children (~25%) progressed very rapidly to AIDS within 1 year. The median time to AIDS for the remaining 75% was 7 years [13].

In adults, opportunistic infections (OIs) are often secondary to the reactivation of pathogens acquired before HIV infection. In contrast, in infants and children with vertical infection, OIs often reflect primary acquisition of host pathogens during ongoing HIV replication and advancing immunosuppression. For example, young children with active tuberculosis more often present with miliary disease.

9.2.3 The Clinical Course of HIV-1 Infection in Children

Without effective cART, the most common OIs in children include serious bacterial infections such as pneumonia and bacteremia. Common co-pathogens and OIs that are difficult to eradicate without successful immune reconstitution include chronic mucosal or disseminated infections with herpesviruses, namely, cytomegalovirus (CMV), herpes simplex virus (HSV), human herpes virus 8 (HHV8) and varicella zoster virus (VZV). Primary disseminated and reactivated tuberculosis is a major cause of morbidity and mortality among children with HIV in communities where infection with the pathogen is endemic. Disseminated disease with *Mycobacterium avium* complex may occur in children with HIV and advanced immunologic deterioration. *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP) is a common and serious OI associated with a high mortality rate. Pneumonia most often manifests between 3 and 6 months of age in infants with vertically acquired HIV infection. Candidiasis (topical, oral, esophageal, and tracheobronchial) is the most common fungal infection in these children.

Causes of acute and chronic central nervous system (CNS) infections include those caused by *Cryptococcus neoformans*, and *Toxoplasma gondii.* Less commonly observed OIs include cryptosporidiosis and systemic fungal infections. Clinical presentations include hepatosplenomegaly, failure to thrive, oral candidiasis, recurrent diarrhea, parotitis, cardiomyopathy, hepatitis, nephropathy, developmental delay, encephalopathy, lymphoid interstitial pneumonitis, recurrent bacterial infections, and specific malignancies. Malignancies include non-Hodgkin B-cell Burkitt-type lymphomas, leiomyosarcomas, and Kaposi sarcoma, which are commonly described in children with HIV who are of sub-Saharan African ethnicity.

In the United States, in clinical practice, the number of OIs seen in children with HIV has decreased, reflecting the widespread use and

administration of effective cART regimens. However, OIs continue to be the presenting symptom of HIV infection in infants due to lack of antenatal testing in mothers or in adolescents and young adults who are increasingly infected through horizontal transmission.

9.2.4 Intestinal Dysfunction Associated with Pediatric HIV Infection

The intestine is a primary target organ for HIV. HIV infection causes a depletion of CD4+ T lymphocytes in gut-associated lymphoid tissue, including selective loss of a subset of T helper cells called *Th17 lymphocytes*, which are important in gut mucosal containment of extracellular pathogens such as *Salmonella typhimurium.* Th17 cells are lost early in retroviral infection and are not replenished over time. This depletion impairs long-term gastrointestinal (GI) mucosal integrity and permeability, causing increased bacterial translocation and immune activation. The intestinal mucosa is also the main reservoir of HIV in the body despite effective virologic suppression with cART. Among untreated children with HIV, as many as 80% will have one or more intestinal disorders at a given time, with iron malabsorption present nearly 50% of the time [16].

9.2.4.1 HIV Enteropathy

HIV enteropathy is secondary to direct HIV-mediated injury and indirect immune-mediated injury to the GI tract mucosa in the absence of specific opportunistic enteropathogens, perhaps reflecting selective loss of Th17 lymphocytes. HIV enteropathy can occur in children and adolescents at all stages of HIV infection. Clinical manifestations include chronic diarrhea, increased intestinal permeability, malabsorption, and malnutrition. Histologic changes include lymphocytic infiltration of the GI tract mucosa, villous atrophy and blunting, and crypt hyperplasia [17,18]. A direct cytopathic effect of HIV on the intestinal mucosa is supported by the observation that clinical signs and symptoms improve after initiation of effective cART in association with virologic suppression and immune reconstitution of CD4+ T cells [19].

9.2.5 Enteropathogens and Diarrhea in Pediatric HIV Infections

Acute, recurrent, and chronic diarrhea associated with malabsorption and growth impairment frequently occur in children with untreated HIV infection and advancing immunosuppression. Commonly identified infective enteropathogens include bacteria (*Salmonella*, *Shigella* sp.), viruses (including rotavirus, adenovirus, CMV), parasites (*Entamoeba*, *Giardia*, *Cryptosporidia*, *Microsporidia*, *Isospora*), and opportunistic fungi [20]. In children with HIV, frequent and persistent watery diarrhea is the most

common presentation of cryptosporidial, microsporidial, and isosporidial infections, associated with abdominal cramps, fever, vomiting, anorexia, weight loss, and poor weight gain [7].

Untreated chronic severe diarrhea may cause malnutrition, failure to thrive, severe dehydration, or a combination of all these problems. GI tract disease caused by CMV may include esophagitis, gastritis, pyloric obstruction, hepatitis, pancreatitis, colitis, ascending cholangitis and cholecystitis. Signs and symptoms may include nausea, vomiting, dysphagia, epigastric pain, icterus, and watery diarrhea. Stools may be bloody. Sigmoidoscopy in CMV colitis provides nonspecific results, showing diffuse erythema, submucosal hemorrhage, and diffuse mucosal ulcerations. Specific causes of diarrhea in representative adult subjects with AIDS are presented in Table 9.1 [21]. Data reflect prospective follow-up of 1,933

TABLE 9.1   Infectious gastrointestinal manifestations of HIV/AIDS

Site	Manifestation or infecting organisms
Oral	Candidiasis
	Herpes simplex virus
	Human papillomavirus
	Oral hairy leukoplakia
	Kaposi sarcoma
	Lymphoma
Esophagus	Candidiasis
	Cytomegalovirus
	Herpes simplex virus
	Cryptosporidiosis
	Kaposi sarcoma
	Lymphoma
Stomach	Cytomegalovirus
	Cryptosporidiosis
	Kaposi sarcoma
	Helicobacter pylori
Small intestine	Giardiasis
	Cryptosporidiosis
	Cytomegalovirus

(Continued)

TABLE 9.1 (Continued)

Site	Manifestation or infecting organisms
Colon	*Salmonella* sp.
	Enteroaggregative *Escherichia coli*
	Blastocystis hominis
	Isospora belli
	Rotavirus, calcivirus, astrovirus, coronavirus, picobirnavirus
	Adenovirus
	Shigella sp.
	Mycobacterium sp.
	Lymphoma
	Cytomegalovirus
	Salmonella sp.
	Shigella sp.
	Campylobacter sp.
	Entamoeba sp.
	Lymphoma
	Clostridium difficile
	Adenovirus
Anus/rectum	Kaposi sarcoma
	Lymphoma
	Squamous cell carcinoma
	Papovavirus
Hepatobiliary	*Mycobacterium* sp.
	Cytomegalovirus
	Cryptococcus, histoplasmosis
	Hepatitis B, hepatitis C, or hepatitis D
	Cryptosporidiosis
	Kaposi sarcoma
	Microsporida
Pancreas	Cytomegalovirus
	Mycobacterium sp.
	Cryptosporidiosis

participants in the Swiss HIV Cohort Study; 560 diarrheal episodes were evaluated by standardized stool examination, with intestinal infections diagnosed in less than 50% of chronic diarrheal episodes [22].

The site and severity of infection vary according to the infecting organism. Oral mucosal ulcerations secondary to infectious agents such as *Candida albicans*, CMV, or HSV cause inflammation and pain during swallowing or after eating, which may lead to reduced oral intake. Opportunistic enteropathogens such as *Cryptosporidium*, CMV, and microsporidia [23] may affect the hepatobiliary system and pancreas in addition to the GI tract, resulting in vomiting, abdominal pain, and malabsorption.

9.2.6 HIV and Tuberculosis Co-Infection

In resource-limited settings, disease with *Mycobacterium tuberculosis* is the most common cause of death in subjects with HIV. HIV and tuberculosis (TB) accelerate disease progression and mortality and are associated with marked clinical wasting; the extent of wasting is related to the severity of TB [24]. The largest proportion of newly diagnosed children with HIV in many US centers are foreign born and at higher risk of prior and potentially ongoing exposure to TB. TB is almost always transmitted to children by an adult, most commonly a household contact, and the infection in children is primary infection rather than reactivated disease as in adults. There should be an increased index of suspicion of TB infection and disease in children with HIV, particularly in the context of clinical wasting and a low threshold for empiric antituberculosis therapy, even when diagnostic investigations fail to identify a TB-causing organism.

9.3 THE IMPACT OF PEDIATRIC HIV INFECTION ON NUTRITION

9.3.1 Wasting in Pediatric HIV Infection in the Pre-cART Era in the United States

The combination of underlying HIV infection, nutritional status (particularly protein-energy malnutrition), and host immunity are inextricably interdependent. In the United States, prior to the widespread administration of effective cART, the predominant effect of advancing immunosuppression on nutritional status in children with HIV was wasting and negative energy balance, which predicted both morbidity and mortality [25].

In the pre-cART era, OIs were major precipitants of weight loss, necessitating prevention or prompt diagnosis and treatment to prevent wasting and to promote weight recovery [26]. Growth in children with HIV was

persistently below normal standards, with reduced height and weight velocities, compared with HIV-exposed but uninfected children.

In 1994, the Centers for Disease Control and Prevention (CDC) defined wasting in children younger than age 13 years as (1) persistent weight loss of more than 10% of baseline; (2) downward crossing of at least two percentile lines on the weight-for-age chart in a child aged 1 year or older; or (3) less than the 5th percentile on the weight-for-height chart on two consecutive measurements at least 30 days apart, plus chronic diarrhea or documented fever for at least 30 days, whether intermittent or constant [27].

In addition to OIs, other etiologies that contribute to abnormal growth in untreated HIV infection in children include a synergistic combination of inadequate dietary intake, GI malabsorption, increased energy utilization, and socioeconomic adversity. The prevalence of malnutrition in children with HIV varied among centers in the United States with up to 30–50% of children followed up in pediatric HIV programs having demonstrable evidence of protein-energy malnutrition, which, in turn, exacerbated the immunosuppressive effects of HIV [28]. Common patterns of wasting included an early decline in weight and height in the first 3 months of life or early linear stunting with a normal weight-to-height ratio. Progressive wasting with low weights and heights were also well recognized and more commonly associated with infectious enteropathogens. Sequential follow-up demonstrated that growth in children with untreated HIV infection remained below growth in age-matched and gender-matched uninfected controls. Malabsorption also results in macronutrient and micronutrient deficiencies.

9.3.2 Micronutrients and HIV Infection

Micronutrient deficiencies are widespread and compound the effects of HIV infection in children. Deficiency can manifest in conditions such as fatigue, reduced learning ability due to anemia (iron deficiency), and impaired immunity [29]. Such deficiencies reflect inadequate nutrient intake and the consequences of excessive losses due to OIs, diarrhea, and malabsorption, as previously described. Other micronutrients that can also be malabsorbed resulting in deficiency include vitamin B12, folic acid, thiamine, zinc, selenium, calcium, and magnesium, and fat-soluble vitamins A and D [21].

The evidence base for the specific effect of micronutrient supplementation in children with HIV is limited, but a recent Cochrane review of 11 studies with 2,412 participants made the following key recommendations for practice. Benefits of periodic vitamin A supplementation in children over 6 months of age with HIV infection in resource-limited settings were supported by data from three African trials and were consistent with evidence of benefits of supplementation in uninfected children. Zinc supplements reduced diarrheal morbidity and had no adverse effects on disease

progression in a single safety trial in South African children. Children with HIV should therefore receive zinc supplements in the management of diarrhea and severe acute malnutrition in the same way as uninfected children with the same conditions. The review emphasized that micronutrient deficiencies and immune dysfunction in children with HIV would only be restored with effective suppression of HIV replication [30].

9.4 ART IN PEDIATRIC HIV INFECTION

9.4.1 The Goals of ART During Pediatric HIV Infection

cART consists of drugs that target the life cycle of HIV at specific enzymes or receptors to inhibit replication thereby preserving or restoring immune function. Specific goals of administration of cART include maximally reduction of the plasma viral load below the limit of detection (<50 copies/mL), prevention of a selection of drug-resistant strains and maintenance of good immunologic status (repopulation with CD4 + -naïve T cells), and prevention of clinical disease progression and OIs. Clinical trials of cART in infants and children with HIV have demonstrated dramatic reductions in morbidity and mortality (>80–90%) in the United States since widespread implementation from 1996 onward, so the vast majority of infants and children with HIV-1 can now be expected to survive to adulthood [31,32].

Five classes of ARV drugs are commonly available for HIV therapy. Two classes target the enzyme reverse transcriptase—non-nucleoside reverse transcriptase inhibitors (NRTIs) and the non-NRTIs. A third class—protease inhibitors (PIs)—target viral protease, whereas integrase inhibitors target that corresponding enzyme. In addition, CCR5 inhibitors target the viral co-receptor CCR5 on permissive target cells.

9.4.2 Difficulties with Implementation of cART in HIV-Infected Children

9.4.2.1 The Emergence of Resistant Viral Variants

HIV-1 mutability is largely the result of errors introduced into the viral genome during replication. The HIV genome is approximately 10,000 nucleotides long, and each new virion has an average of one mutation. This results in a large pool of quasi-species of viral variants that are incapable of productive infection but some of which may provide an adaptive benefit, for example, the development of ART resistance, to the virion.

Drug-resistance of the virus can develop during cART administration because of poor adherence, a regimen that is not potent, or a combination

of these factors resulting in incomplete virologic suppression. In addition, primary drug resistance may occur in ARV-naive infants and children who can become infected with the resistant virus. Aggressive, multi-drug cART as early in infection as possible, with daily adherence for an indefinite period, is advocated to fully suppress viral replication and to preclude the selection or emergence of resistant viral variants. Resistance testing has enhanced the ability to choose effective initial regimens as well as second- or third-line regimens. Therapeutic strategies continue to focus on timely initiation of ARV regimens that are capable of maximally suppressing viral replication in order to prevent disease progression, preserve or restore quantitative and qualitative immunologic function, and reduce the development of drug resistance [33].

9.4.2.2 Adherence and Toxicities

Difficulties with long-term adherence to cART—particularly in infants and children because of variable drug administration, absorption, and metabolism; pretreatment with maternal cART and vertical transmission of drug-resistant virus; acceptability and palatability of medications; and refrigeration of syrup formulations in warm climates—are all well documented. Long-term follow-up of infected infants and children involves longitudinal determinations of prognostic markers, including number and percentage of CD4 T cells, and viral load [34]. Such parameters provide a useful framework for the time to initiate and change therapy but involve frequent venipuncture in minors.

Long-term toxicities include lipodystrophy syndrome [35] and lipid abnormalities, cardiomyopathy, mitochondrial toxicity and lactic acidosis, renal tubular acidosis [36], hypersensitivity reactions, and CNS toxicity. Fortunately, the availability of new drugs and drug formulations has led to the use of more potent regimens with reduced short-term toxicity, lower pill burden, and less frequent medication administration, all factors that are associated with better adherence and outcomes.

9.4.3 Nutrition and cART

Enteral [37,38] or parenteral supplementation and appetite stimulants [39] can improve the nutritional status and weight in children with untreated HIV infection but have little effect on the growth velocity of height. However, effective virologic suppression with cART was shown to improve mean weight, weight for height, and muscle mass in 67 children with HIV, in whom PI-based therapy was initiated and maintained for a median of 5 months. These effects were independent of virologic suppression and improved CD4 T-lymphocyte counts [40]. These findings were also noted in the Pediatric AIDS Clinical Trial Group 219 study, which

found that PI therapy improved both weight and height Z-score annually, after adjusting for CD4 cell count, age, gender, and race [41].

9.4.4 Body Fat Redistribution and Metabolic Changes Associated with cART

In the era of cART, following the introduction of PI-containing regimens, HIV-associated mortality decreased by greater than 80–90%, with significant declines in opportunistic and related infections [31,32]. These encouraging outcomes have been tempered by the side effects associated with ARVs. Altered body composition, lipid abnormalities, and abnormal regulation of glucose metabolism are consequences that result in an increased risk of cardiovascular disease, reflecting complications of inflammation with uncontrolled HIV infection and the specific ARV drugs as outlined.

9.4.4.1 Body Fat Redistribution

In children, adolescents, and adults, a clear syndrome of abnormal fat redistribution or lipodystrophy and metabolic changes associated with administration of cART is well described. Patterns of lipodystrophy vary from peripheral fat wasting, or lipoatrophy, in the face, extremities, and buttocks to central fat accumulation, or lipohypertrophy, in the abdomen, dorsocervical spine regions (buffalo hump), and breasts. Both conditions may occur alone or in combination [42,43] and can be difficult to assess in a growing child or adolescent, since changes in body fat occur normally during childhood and puberty [44]. Lipodystrophy in children with HIV is clinically evaluated by examination or self-report and has been documented to be as high as 32% [45].

Dual-energy X-ray absorptiometry (DEXA) quantifies total, trunk, and limb fat. Observational studies in children with lipodystrophy show decreased total and extremity fat and a greater trunk-to-extremity fat ratio in children with HIV compared with uninfected children [46,47] These changes are drug specific and associated with duration of therapy, with prolonged treatment and older age more likely to result in lipodystrophy. Treatment with NRTIs, including stavudine (d4T), zidovudine (AZT), and didanosine (ddI), is associated with a lower percentage of extremity fat and higher percentage of trunk fat and trunk-to-extremity fat ratio even after adjustment for wasting and stunting [21,43]. These changes in body fat distribution often cannot be reversed even after switching to less lipodystrophic ARV regimens.

In cohorts of children receiving a PI regimen, higher rates of dyslipidemia have been documented, with higher fasting lipids, cholesterol, and triglycerides. Lipodystrophy in patients results in much higher waist-to-hip ratios and elevated fasting insulin levels and blood pressure, which

are all significant risk factors for cardiovascular disease [21]. For children without lipodystrophy, up to one fifth show symptoms of dyslipidemia.

In summary, when selecting ARV regimens, care must be taken to consider the above life-long side effects and their consequences. At a time when newer less lipodystrophic first-line regimens, including tenofovir, abacavir, ritonavir-boosted PIs (atazanavir and darunavir), and the integrase inhibitors, most with the added advantage of once daily administration, are available in the United States, regimens that include zidovudine, didanosine, and stavudine should be prescribed less often to children with HIV to reduce these potential long-term toxicities.

9.4.4.2 Metabolic Changes

Metabolic syndrome reflects a series of clinical conditions, including elevated triglyceride, low levels of high-density lipoprotein (HDL) cholesterol, hyperglycemia and insulin resistance, increased body fat distribution around the waist, and high blood pressure, all of which collectively increase the risk of cardiovascular disease. In individuals with HIV, the prevalence of metabolic syndrome is higher than in the general population and estimated to be 7–45% [21,48]. Although uncontrolled HIV in the absence of cART can cause low HDL cholesterol and high triglycerides, as discussed previously, ARVs also induce body fat redistribution in conjunction with metabolic changes. Earlier PIs, including treatment doses of ritonavir (without boosting other PIs), nelfinavir, and ritonavir-boosted lopinavir (kaletra) were documented to increase lipid plasma concentrations, including serum triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein E and to lower HDL. Virologic control with the newer PIs, integrase inhibitors, tenofovir, and abacavir may be associated with increases in serum HDL, in the absence of these metabolic complications.

9.4.5 Reduced Bone Mineral Density

When compared with population norms, children with HIV were noted to have lower-than-expected bone mineral density (BMD) for their age and gender that may have been associated with delays in growth, sexual maturity, duration of HIV infection, ethnicity, and disease severity [49]. A more recent large study of 236 American children and adolescents with HIV, aged 7–24 years, showed that males with HIV had significantly lower BMD at Tanner stage 5 compared with uninfected males [50]. Reduced BMD secondary to cART administration was first described in 2001 from DEXA scans in vertically infected children, with the severity of osteopenia directly related to lipodystrophy [51]. However, a longitudinal study from 2013 in 66 Dutch children showed an association between longer cART duration and increases in spinal BMD Z-scores [52]. Lopinavir–ritonavir

[50], full-dose ritonavir [53], and tenofovir [54] are associated with lower BMD in children. The principles of maintaining good bone health in youth with perinatal HIV infection is the same as those recommended for all youth in general. Adolescents should therefore receive at least 1,300 mg calcium per day and at least 600 IU vitamin D per day through their diet, by supplementation, or both [55].

9.4.6 Immune Reconstitution Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a disease-specific inflammatory response that can occur after treatment with ARVs is initiated, reinitiated, or changed, resulting in effective virologic suppression and immune reconstitution of naïve and memory CD4+ T cells. IRIS has been noted to occur in children who begin ART while they have severe malnutrition, are severely immunosuppressed [56], or both. Risk factors therefore include a low CD4 nadir and high viral load levels prior to the initiation of cART. These children and adolescents often have numerous documented OIs before, during, and after cART initiation [56]. Further research is needed to reduce complications and to optimize clinical management when they do occur.

9.5 NUTRITIONAL INTERVENTIONS AND ADJUNCT THERAPIES

The interaction between HIV infection and nutrition is of great importance, and these two factors are interdependent, since strategies to improve nutritional status both quantitatively and qualitatively have been demonstrated to have a beneficial effect on clinical outcome and the immunologic course of the HIV infection.

9.5.1 Clinical Outcomes Associated with and Causes of Malnutrition in Pediatric Infection with HIV

Through the course of their disease, infants and children with HIV have numerous nutritional needs, which reflects, as previously described, impaired absorption, decreased oral intake, and increased nutrient requirements. Specific adverse outcomes secondary to specific nutritional deficiencies include the inability to achieve normal weight for height; malnutrition and wasting; growth failure and stunting; and neurocognitive, neurodevelopmental, and oral motor delay often from HIV encephalopathy. Early nutrition intervention is, therefore, essential and must be addressed simultaneously with the administration of cART, antimicrobial prophylaxis, and neurodevelopmental interventions. Collectively, a

multidisciplinary approach is most effective in improving health outcomes and overall quality of life.

In the pre-cART era, the nutritional causes of malnutrition reflected (1) decreased oral intake caused by anorexia and by oral and esophageal lesions often from opportunistic pathogens, (2) gastroesophageal reflux and aspiration, (3) regression or nonattainment of key developmental milestones associated with oromotor dysfunction and impaired mastication, (4) malabsorption, (5) increased energy requirements and metabolism from OIs with associated negative energy balance, (6) vomiting and diarrhea from gastrointestinal (opportunistic) enteropathogens, and (7) indirect immune-mediated enteropathy.

9.5.2 Nutrition Interventions and Management Strategies Developed During the Pre-cART Era

At a time when effective cART was unavailable and faced with a debilitating catabolic disease and rapid disease progression in infants and children with HIV, nutritional interventions that were developed in the early 1990s by pediatric providers targeted four key areas:

1. *Prompt management of diarrhea*. In addition to isolation of opportunistic enteropathogens and prescribing appropriate antimicrobials for infectious etiologies, management of diarrhea mandates assessment of hydration status and rehydration by the oral or intravenous route.
2. *Modification of diet* in the setting of underlying food intolerance such as lactose or fat malabsorption, including pancreatic enzyme supplementation; and vitamin and mineral supplementation.
3. *Treatment of oral or esophageal lesions* with appropriate antimicrobials; other recommendations included introduction of a mechanical soft diet and nutritional supplementation.
4. *Management of nausea and vomiting.* In addition to appropriate antiemetic agents, treatment also included recommendation of small frequent meals, liquid intakes between meals, and nutritional supplementation.
5. *Management of anorexia* included small nutrient dense foods, nutritional supplementation, and appetite stimulants such as megestrol acetate.

These early nutrition needs related to the unique physiologic demands for growth and development, so even today, interventions should be individualized according to the child's specific needs and relate to disease stage, gastrointestinal function, and growth [57]. As a corollary, the energy and protein requirements for infants and children with HIV have

not yet been established because individual needs vary, depending on age, growth, and the clinical and immunologic status that may increase energy and protein needs.

Infants and children with HIV who have slow weight gain are often prescribed high-protein, high-calorie diets. If nutritional needs are not met through a typical high-calorie, high-protein diet, then additional support may include oral nutritional supplements and overnight feeding through nasogastric or gastrostomy-tube feedings. A commercial formula with intact protein may be appropriate for children without underlying gastrointestinal pathology. Infants and children with HIV who have gastrointestinal malabsorption should receive a semi-elemental formula to maximize absorption. Elemental formulas are typically prescribed when semi-elemental formulas are not tolerated.

9.5.3 The Role of Enteral Supplementation

Infants and children with HIV who are unable to consume adequate calories orally often benefit from supplemental tube feeding. Enteral tube feeding supplementation improves weight gain in children with HIV who have growth failure [37,38]. Nasogastric tube feedings should be initially attempted and include night-time feedings, which allow the child to eat normally throughout the day. Complications relating to nasogastric tube feedings include sinusitis and the technical inability of the caregiver to place the tube or administer the feedings [21].

If delivery of feedings through a nasogastric tube improves growth, then placement of a more permanent device such as a gastrostomy tube should be considered. Enteral supplementation with gastrostomy feeding has improved nutrition in a number of chronic childhood illnesses by providing adequate energy intake to promote weight gain when oral intake is poor. Miller et al. [37] first investigated the effects of gastrostomy tube feeding on weight gain, height, body composition, immune parameters, morbidity, and mortality in 1995 on 26 children with HIV. Weight Z-scores before therapy were –1.6 and had decreased to –2.2 on initiation of nasogastric feedings. Gastrostomy tube feedings significantly improved weight Z-scores to get back to baseline approximately 5 months after initiation of feeding. Significant predictors of response to gastrostomy tube feedings included higher CD4 counts at initiation and lower weight-for-height Z-scores at baseline. These findings suggested that early intervention during acute weight loss offers the best chances of improving weight in children with HIV. Children with the greatest improvement in weight after gastrostomy tube placement spent less time in hospital and had a greater likelihood of survival compared with children who did not gain weight [37]. This small but important study demonstrated that early nutritional intervention improved quality of life and reduced morbidity in

children with HIV at a time when effective cART was unavailable. In the cART era, compliance with medical therapy is often improved with more reliable delivery of ARVs through the gastrostomy tube and is associated with improved CD4 T-lymphocyte counts, virologic suppression, and improved longitudinal growth.

Guarino et al. tested the hypothesis that nutritional support improves intestinal and immune functions in 62 Italian children with HIV; 16 received enteral nutrition through continuous feeding, and 46 received total parenteral nutrition. The authors documented a significant increase in CD4 cell count, xylose levels, and body weight in those receiving enteral nutrition, suggesting that nutritional intervention may restore intestinal absorption and increase CD4 cell numbers if initiated early in the course of pediatric HIV infection [58].

Enteral feeding is preferred over parenteral nutrition to preserve the gut structure. Parenteral nutrition should be used only in those children unable to tolerate or gain weight on enteral supplementation, those who have recurrent or chronic biliary tract or pancreatic disease, and those who have intractable diarrhea with weight loss [21].

9.5.4 Megestrol Acetate

Megestrol acetate is an oral synthetic progesterone used since the early 1990s as an appetite stimulant. Weight gain tends to be associated with increase in body fat rather than muscle. Clarick et al. investigated the effects of megestrol acetate treatment on weight gain and linear growth in 19 children with HIV who had growth failure. The average duration of the study was 7 months. The study concluded that megestrol acetate was associated with weight gain but not linear growth during the treatment period. After the megestrol acetate treatment was discontinued, poor weight gain and weight loss were again noted [39]. Given the dramatic reductions in morbidity and mortality and the improved longitudinal growth in children with HIV in the United States since the widespread implementation of effective cART, megestrol acetate and other therapeutic agents (including growth hormone and the anabolic steroid oxandrolone) are prescribed very rarely, if at all, to subjects with HIV.

9.6 CONCLUSION

In the 1980s and early 1990s, the devastating effects of HIV infection on the health of infants, children, and adolescents became apparent and required a rapid and effective response globally. Over time, in the United States, with the introduction of ARVs, the clinical manifestations associated with HIV infection as well as its treatment were seen to increase,

driven by the short- and long-term toxicities of these new formulations in combination. In children with HIV, these manifestations reflected metabolic changes; wasting and stunting from gastrointestinal dysfunction were most often described in the 1980s, but new clinical concerns in the early 2000s were related to altered body composition, lipid abnormalities, and abnormal regulation of glucose metabolism. These complications were often attributed to the first-generation NRTIs and PIs. The long-term cardiovascular risks of these ARVs on subjects with HIV are still unknown. After 2007, newer PIs and integrase inhibitors became more widely available and appear to have fewer metabolic adverse effects, although ongoing surveillance of these ARVs and tenofovir will be important to evaluate incidences of renal tubular dysfunction and BMD.

In the course of the changes in ART over the previous two decades, optimal nutritional support has continued to be a cornerstone of pediatric and adolescent HIV care, applying the same principles developed from the early 1990s to effectively support infants, children, and adolescents with HIV. These principles include ongoing comprehensive nutritional assessments and follow-up. When cART providing effective viral suppression was unavailable, enteral and parenteral support was associated with improved weight and body composition and overall survival and is still a key part of care for children and adolescents who present with advanced HIV disease. In addition, periodic vitamin A supplementation in children with HIV who are older than 6 months of age is supported by clinical trials in Africa. Children with HIV should also receive zinc supplements in the management of diarrhea and severe acute malnutrition in the same way as uninfected children with the same conditions. Investigators should continue to study the effects of oral hypoglycemic agents, lipid-lowering medications, and lifestyle changes on cardiovascular risk factors in patients with lipodystrophy and hyperlipidemia at this time when obesity has become endemic in many communities in the United States. This unfortunate development on long-term health also has implications for children and adolescents with HIV across the United States.

Nevertheless, the overall outlook for children with HIV has improved significantly since the 1990s, as reflected in the reduced rates of morbidity and mortality and improved quality of life. Perhaps a measure of the latter is the overall medication burden. Figure 9.1 is a child's medications, as shown by Oleske et al. [57]. Figure 9.2 shows the pill burden for a number of adolescent patients in the United States in 2014. The last paragraph of Dr. Oleske's article still relevant for 2014. To quote directly, "Compassionate, comprehensive, and coordinated clinical care services are required for all HIV-infected infants and children through adolescence. We must not underestimate their needs. As we improve their longevity with advances in primary HIV therapies, we must not let quality of life suffer due to a lack of nutritional intervention."
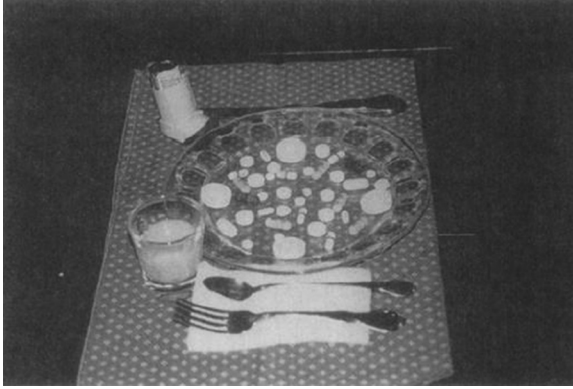
FIGURE 9.1   The slew of daily medications for a 13-year-old long-term surviving patient with perinatally acquired HIV in 1996 included: zidovudine (AZT), didanosine (ddI), trimethoprim/sulfamethoxazole (Tmp/Smx), fluconzol, megase, prednisone, acyclovir, dapsone, biaxin, zalcitabine (ddC), albuterol, isonicotinylhydrazine (INH), rifampin, ranitidine (Zantac); beclomethasone dipropionate (Vancenase) inhaler; nystatin.
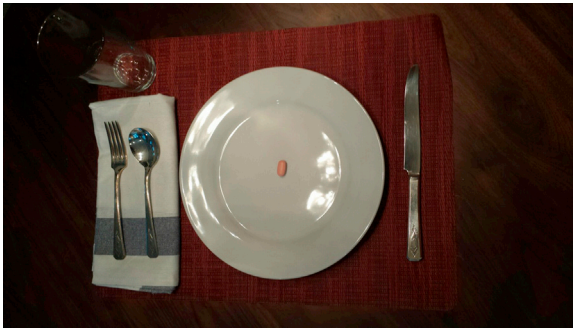

FIGURE 9.2   The high number of medications for an adolescent with HIV in 2014.

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