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Gastrointestinal and Nutritional Complications of HIV Infection:

Working Group for World Congress 2008

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I. INTRODUCTION

A. Epidemiology of Pediatric HIV

As of December 2007, the World Health Organization (WHO) estimated that 2.5 million children had HIV worldwide[1]. Approximately 420,000 children become newly infected with HIV annually, mainly through mother-to-child transmission (MTCT). This makes pediatric HIV a leading cause of morbidity and mortality[1]. Antiretroviral therapy (ART) has prevented MTCT and has lowered the prevalence of perinatal HIV in developed countries. Increased use of prophylactic medications in developing nations is helping to contain the epidemic in those countries as well[1]. However, pediatric HIV in many countries continues to be a widespread public health problem.

Maternal HIV status and death, as well as childhood undernutrition, independently affect childhood mortality. Worldwide, HIV infection is associated with greater child mortality over standard risk by 2 years of age[2]. In developing nations, children with HIV have the same morbidities as non-infected children, yet the rate of disease morbidity is greater with an increased likelihood for progression to AIDS. Increased availability and effectiveness of ART, as well as improved methods of detecting HIV in women and children, will have the greatest impact on outcomes until a vaccine is developed.

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B. Nutritional Problems in Pediatric HIV

i. Nutrition in pregnancy—Maternal undernutrition can have adverse effects on both mother and child and early detection and treatment can minimize these health consequences. For the more than 15.4 million women with HIV infection[1], the prevalence and consequences of maternal malnutrition are further accentuated as a result of concomitant immune compromise and the increased incidence and severity of infectious diseases[3].

Malnutrition is often caused by inadequate protein or energy intake, and results in multiple micronutrient deficiencies[4]. The effects of multivitamins and single vitamin supplementation on HIV pregnancy and neonatal outcomes have been studied extensively. A critical review of this research, as well as the gaps in our understanding, is presented in Section II.B. Highly active antiretroviral therapy (HAART) is associated with improved nutrition, morbidity, and mortality of pregnant women with HIV[5], but it cannot completely alleviate the malnutrition associated with HIV infection in the global setting[6]. In addition, toxicities of *in utero* exposure to ART also need to be closely monitored (Section II.C).

ii. Malnutrition of HIV-infected children—Before HAART, malnutrition was one of the most frequent and devastating complications of pediatric HIV, and it predicted both morbidity and mortality[7]. Malnutrition in HIV-infected children has several causes[8] including: Reduced oral intake, (HIV-induced primary cachexia, opportunistic infections of the upper gastrointestinal tract, and medication side effects); Malabsorption, (HIV alone or infections of the GI tract); Altered metabolic states, (pro-inflammatory effects of chronic HIV infection); and Socioeconomic, (orphans or are cared for by ill parents who may have limited resources).

Although the prevalence of AIDS-associated wasting has declined in the developed world because of of ART, it is still a concern for children in both resource-rich and poor nations[9]. The relationship between protein-energy malnutrition and immunodeficiency is well recognized[10] and similar to HIV effects. Thus protein energy malnutrition may exacerbate the immunologic effects of HIV[11]. Wasting is related to length of survival[11, 12], and weight loss is associated with infectious complications. Conversely, HIV and its complications have also been associated with specific nutritional disorders. Higher HIV viral load, lower CD4 T lymphocyte counts, infections, maternal drug use and zidovudine have been associated with growth problems[9].

iii. Metabolic disorders in HIV-infected children—HAART refers to a combination of antiretroviral agents, generally including a protease inhibitor, that greatly reduces viral replication. The mechanism and indications are described elsewhere[13]. Most children with HIV in developed countries are given these medications. Despite the success of HAART, managing side effects can be challenging. Similarities between host cell proteins and HIV-1 protease may be responsible for protease inhibitors interacting with the proteins responsible for lipid metabolism. Additionally, nucleoside reverse transcriptase inhibitors are associated with mitochondrial DNA toxicity in adipocytes. The aforementioned interactions, and HIV, are linked to metabolic and cardiovascular abnormalities in HIV-infected patients. Altered body composition, lipid abnormalities, and abnormal glucose metabolism—all factors

leading to increased risk of global cardiovascular disease—are manifestations of drug and HIV effects. Metabolic problems, although not as common in resource-poor settings, will emerge as HAART is more widely available[14].

II. CURRENT CONTROVERSIES OR ISSUES

A. Intestinal Dysfunction and Novel Gastrointestinal Therapies

i. Intestinal Dysfunction—The intestine is a primary target organ for HIV and is also important in the pathogenesis of HIV infection. In developing countries, persistent diarrhea from known or unknown pathogens is a frequent problem and may be the initial manifestation of HIV infection. In untreated HIV-infected children, as many as 80% will have one or more intestinal abnormalities at a given time, with iron malabsorption prevalent as much as 45% of the time[15]. The pattern of intestinal dysfunction may change with time and can occur without evident cause or change in clinical HIV stage or immunologic status. Endoscopic and histologic findings show a wide pattern of abnormalities and without clear origins[16].

AIDS-related pathogens, such as *Cryptosporidium parvum*, can induce intestinal damage but may not cause intestinal dysfunction. A direct effect of HIV has been proposed (HIV enteropathy). The transactivator transfer factor, Tat, may be involved because it can impair enterocyte proliferation by targeting its L-type calcium sodium-glucose symporter. This pathway may explain many features of intestinal dysfunction, such as intestinal atrophy, carbohydrate malabsorption, and diarrhea, that are frequently observed. Direct involvement by gp-120, a putative HIV-1 virotoxin, has also been hypothesised[17]. The direct involvement of HIV on intestinal dysfunction is supported by the observation that function improves after HAART is started, viral load decreases and CD4 counts increase[18]. Residual intestinal dysfunction is often detected[19], although there is little follow up data in children treated long-term with HAART. ART, including protease inhibitors, can contribute to diarrhea.

ii. Novel drug and nutritional therapies for intestinal dysfunction—Effective treatments for persistent diarrhea include ART, anti-infectious drugs, or an aggressive nutritional approach. Opportunistic infections, such as enteric cryptosporidiosis, pose little threat to HIV-infected children on HAART who have improved immune function[20]. However, as CD4 counts drop (from resistance to or the unavailability of ART), HIV-infected children become susceptible.

Enteral supplementation can treat children who are not able to consume food orally (for example, because of esophageal candidiasis), have severe intestinal dysfunction, or who have AIDS-related wasting. Gastrostomy tube feedings have improved the nutritional and gastrointestinal symptoms in HIV-infected children[21] and can improve immunologic function[22]. In countries where ART is largely available, enteral supplementation is rarely needed.

Specialized nutritional supplements, such as nucleotides, polyamines, probiotics, and zinc, can improve gastrointestinal absorption. In animal studies, nucleotides promote cell

replication, disaccharidase concentrations, modulate the intestinal repair and regeneration and stimulate intestinal mucus. The polyamines, such as spermine, spermidine, and putrescine, can modulate intestinal maturation. Probiotics, such as *Saccharomyces boulardii*, target the gastrointestinal tract and have antioxidant, antibacterial, enzymatic, anti-infective, metabolic, and anti-inflammatory activity. However, their effectiveness is not well established[23].

Few new drugs help manage diarrhea in HIV-infected children. The effects of nitazoxanide on diarrhea caused by *Cryptosporidia* and rotavirus infection has been conflicting. A recent Cochrane review concluded that there are no effective agents against cryptosporidiosis[24]. Oral administration of immunoglobulins for cryptosporidial diarrhea has been proposed and it is effective for rotavirus infection[25]. Rotavirus infections can be serious in the HIV-infected child. Safety and efficacy trials for the rotavirus vaccine are ongoing in HIV-infected children, but administering the vaccine to immunocompromised children is not yet recommended. However, because the vaccine is administered before 6 weeks of age, it may be indicated in HIV-infected children before immune suppression. The new ESPGHAN guidelines may be helpful[26].

B. Role of Macro and Micronutrients

i. In mother-to-child HIV transmission—Pregnancy is a period of increased metabolic demands and micro or macronutrient deficiencies can have adverse effects on the HIV-infected mother and fetus[27]. Impaired fetal immune function and fetal growth because of maternal malnutrition may make the young infant more vulnerable to HIV. Deficiencies or surpluses in micronutrients can affect the fetus in several ways, including stillbirth, intrauterine growth restriction, congenital malformations, preterm delivery, and decreased immunocompetence. Furthermore, poor nutrition during pregnancy may impair the integrity of the placenta, the genital mucosal barrier, and the GI tract. Each of these circumstances may facilitate MTCT. Data confirming these relationships, independent of maternal HIV disease progression, are limited[28]. No trials on the role of macronutrients in MTCT of HIV have been published.

Maternal vitamin A deficiency might increase the risk of MTCT. Evidence exists that serum retinol concentration is strongly and negatively associated with the risk of vertical HIV transmission[28]. Vitamin A deficiency impairs innate and adaptive immunity; such defects could increase intrauterine, intrapartum, or breast-milk transmission. In three trials evaluating the effect of maternal vitamin A supplementation on MTCT, none found reduced transmission and one showed increased transmission[28].

A trial in Tanzania found daily supplementation (with vitamins B, C, and E) during pregnancy and breast-feeding reduced MTCT among nutritionally and immunologically vulnerable women[28]. Selenium reduced the virulence of HIV and slowed disease progression. Selenium deficiency may increase the risk of MTCT[29]. No clinical trials on selenium supplementation in vertical transmission of HIV have been published, but some are underway.

There is a dual role of zinc in HIV infection: zinc has a fundamental impact in sustaining cellular immunity, but it is also necessary for HIV assembly and infectivity. The only randomized trial examining the effect of zinc supplementation on early MTCT in HIV-infected pregnant women[28], found no effect on transmission or mortality by 6 weeks. There is no evidence to support additional zinc for HIV-infected women in pregnancy.

ii. In maternal and perinatal outcomes—Micronutrients (and deficiencies) can be beneficial (or detrimental) in pregnancy and in the perinatal period. Vitamin A deficiency in pregnant women is associated with night blindness, anemia, wasting, malnutrition, reproductive, infectious morbidity and increased risk of mortality up to 2 years after delivery[28]. In HIV infection, daily multivitamin supplementation in pregnancy has been associated with: a reduction in maternal mortality from AIDS-related causes; a reduced risk of disease progression; fewer adverse pregnancy outcomes; less diarrheal morbidity; and a reduction in early child mortality among immunologically and nutritionally compromised women[30]. Vitamin A supplementation did not lower the risk of stillbirths, preterm births, low birth weight, or death by 24 months[28]. Vitamin A supplementation (both preformed retinol and high-dose [30 mg] beta-carotene) reduced the benefits of the multiple micronutrient supplement[30], possibly because the beta-carotene acted as a pro-oxidant rather than as an antioxidant. The long-term clinical benefits, adverse effects, and optimal formulation of micronutrient supplements have not been established. The reported reduced morbidity for some of these micronutrients may not be strictly HIV-specific as HIV-negative, nutritionally depleted women may also benefit from similar supplementation.

iii. In pediatric HIV disease progression and nutritional rehabilitation—Deficiencies of ß carotene, lycopene, retinol, vitamin E, and glutathione have been reported and often relate to disease status[28]. Low blood concentrations of vitamins A, E, B6, zinc, and copper were found in a significant number of South African HIV-infected children[31]. Most studies are cross-sectional and do not indicate the causality between HIV infection and micronutrient deficiencies. Observational micronutrient studies are limited by the challenge of separating the effects of the acute-phase response (depresses serum micronutrient concentrations) from true nutritional deficiencies.

Limited data from randomized controlled studies provide some support for micronutrient supplementation in children with HIV. Among HIV-infected Tanzanian children hospitalized with acute respiratory tract infections, high-dose vitamin A supplementation (400,000 IU at baseline and at 4 and 8 months after discharge) was associated with a 63% reduction in all-cause mortality over 2 years of follow-up[28]. Vitamin A supplementation improved weight gain in HIV-infected infants and decreased the risk of stunting[32].

Zinc can prevent and treat diarrhea in healthy children and may be effective in HIV-positive children. Although zinc may potentially increase HIV replication, a randomized controlled trial in South African children yielded reassuring results[33]. Zinc may control diarrhea in HIV-infected children because it specifically counteracts Tat-induced intestinal ion secretion[34]. Zinc's spectrum of efficacy, safety, compatibility with drugs and nutrients, availability, and cost make it a good option for both preventing and treating diarrhea[33], but confirmatory studies are needed.

Maternal supplementation may improve infant outcomes. Maternal supplementation with vitamins B, C, and E were associated with increased infant CD4 counts and lower incidence of diarrhea in the first 2 years of life[6]. Multivitamin supplementation in pregnant Tanzanian women improved hemoglobin levels of both mother and child[35]. Non-HIV children undergoing nutritional rehabilitation generally receive high-dose micronutrients[36], and this approach may be applicable to HIV-infected children, but efficacy data are lacking.

C. Antiretroviral Therapies

i. HIV-exposed children—A number of large studies have compared growth of HIV-infected children to non-infected, but HIV-exposed children[10, 15]. In general, these studies show significant differences in growth between the two groups. However, results from large cohort studies conflict as to whether HIV-exposed children are growing along expected parameters, given their socioeconomic status[9, 37]. Exposures *in utero* can contribute to impaired growth. Thus, unique and potentially mutagenic *in utero* exposures, such as ART, should be considered. ART, especially nucleoside reverse transcriptase inhibitors, can induce mitochondrial DNA abnormalities[38]. Altered mitochondrial function could potentially be responsible for growth and other organ abnormalities and studies are underway to evaluate this. Because HIV disease among women of child-bearing age will increase in both developed and developing nations, care providers should be made aware of potential toxicities related to ART exposure *in utero*.

ii. Initiation in HIV-infected children—The majority of children with HIV in developed countries are given ART. In resource-poor settings, current guidelines for initiating HAART are also based on CD4 cell counts. Yet, in the severely malnourished child, these guidelines suggest initiation of HAART after the child is clinically stable[39]. What constitutes “clinical stability” is not always well defined. In theory, when the child is nutritionally “stable,” ART may be better metabolized with improved gastrointestinal absorption - factors that could improve the effectiveness of ART. Yet, earlier initiation of ART may rapidly control the virus and prevent or reverse many of the metabolic and nutritional derangements. Few studies have evaluated the effects of early versus late initiation of ART in severely malnourished children.

D. Nutritional Interventions

i. Adequate and effective substitutes for breast milk in older infants—Up to 83% of HIV-infected women in resource-poor settings breastfeed[40]. The WHO and UNICEF recommend that HIV-infected women breastfeed *unless* replacement feeding is: acceptable, feasible, affordable, sustainable, and safe. However, it is unknown whether these guidelines have been implemented effectively in developing countries. One recent study found that piped water; electricity, gas, or paraffin for fuel; and disclosing HIV status were important factors in insuring the safety of formula feedings and improved survival of infants born to HIV-infected women[41]. Another study revealed there was greater transmission of HIV and worse survival of infants who were both breastfed and received supplemental feedings[40] compared to exclusively breastfed infants. Thus, individual and environmental exposures should be carefully considered when infant feeding choices are determined. In a case-control study in Botswana, infants weaned from breast milk were significantly more

likely to suffer infectious morbidities[42], and in Zambia, exclusive breastfeeding was associated with significantly lower rates of HIV-infection by 4 months[43].

Nutritional goals for HIV-infected children should include preservation of normal growth and development, provision of adequate amounts of all nutrients, prevention of malabsorption and deficiencies of nutrients that alter immunological function, all while improving quality of life. Current recommendations are to increase the caloric density to more than 0.67 kcal/mL while maintaining the standard macronutrient ratios (10% - 15% protein, 30% - 35% fat and 55% - 65% carbohydrate), and the standard RDAs of micronutrients, trace elements**,** vitamins, and minerals[15].

With adequate resources, energy, carbohydrate, protein, and fat intake and composition density should be adjusted according to the child's nutritional needs (which are often greater than the RDAs). For older children in resource-poor nations, ready-to-use foods (RUTF) can be administered by caregivers without formal medical training and can provide a more calorically dense diet than traditional foods (such as maize or soy flour). Other specialized supplements, such as spirulina, can correct anemia and improve weight[41]. There is increased recognition that community-based interventions, that include the use and redirection of existing household food resources through maternal nutrition education, are proven and sustainable strategies to improve childhood nutritional status[44].

ii. Role of ART—HAART, especially with protease inhibitor therapy, improves weight, weight-for-height, and muscle mass of HIV-infected children[45]. Cross-sectional studies of HIV-infected children on HAART estimate the prevalence of lipodystrophy to be up to 43%[46]. Simultaneous features of lipoatrophy and lipohypertrophy are more prevalent in older children, supporting the association with puberty. In developed nations, little is known of the long-term effects of HAART on cardiovascular and metabolic risk in children, and even less is known with its use in resource-poor nations where environmental influences are much different. Health care providers should anticipate metabolic and cardiovascular problems in developed nations, as well as a different nutritional profile when HAART is used in resource-poor nations.

III. RESEARCH AGENDA

A. Intestinal Dysfunction and Therapies in HIV-Infected Children

The GI tract is central to the overall health of the child with or who is exposed to HIV. First, the GI tract is one of the first barriers to HIV infection and can also be the largest reservoir of HIV. Second, optimal nutrient absorption is critical, especially in children who are at high risk for malnutrition. Lastly, the proper functioning of the GI tract is essential for appropriate absorption and processing of life-saving ART. Thus, important next steps and research topics that address gaps in understanding the GI tract in HIV-infected children include the need to: 1). Investigate the direct pathogenic effects of HIV or any of its components on GI absorption; 2). Explore therapies (i.e., novel drugs, vaccines, nutrients) to improv GI dysfunction and treat pathogens; and 3). Explore the effects of GI malabsorption on ART pharmacodynamics and pharmacokinetics.

B. Role of Macro and Micronutrients

Macro and micronutrients can potentially impact HIV and its targets at several levels. From pregnancy, to MTCT, to prevention of progression of HIV in the infant and child, the clinical effects of these nutrients are potentially broad. However, rigorous and controlled studies of both macro and micronutrients are limited and current findings are often conflicting. Future research in this field should include attempts to determine: 1). Whether maternal micronutrient supplementation reduces the likelihood of vertical transmission; 2). Whether other micronutrients, in addition to vitamin A, improve health outcomes and HIV disease progression in children; and 3). The role of micronutrients on effectiveness of ART.

C. Antiretroviral Therapies in HIV-infected and HIV-Exposed Children

With the advent of ART (and subsequently HAART), the natural history of HIV has changed markedly in developed nations and, although less rapidly, is also changing the face of HIV in resource-poor countries. Nutrition can impact the therapeutics of drugs by either altering GI absorption or overall metabolism. Furthermore, metabolic problems are increasing in scope as children are exposed to HAART. Important research topics should include efforts to determine: 1). The long-term effects of ART in HIV-exposed children. Long-term studies need to continue to track clinical outcomes (e.g., growth and the function of mitochondrial-rich organs such as the brain and heart) and growth of these ART-exposed children; 2). The appropriate timing of nutritional therapy and initiation of ART; to determine whether HIV-infected children will have a better clinical response if ART is started earlier or later after some nutritional rehabilitation; and 3). Appropriate drug dosing and regimens as nutritional status improves.

D. Nutritional Interventions

It is clear that good nutrition improves clinical outcomes. Important current and potential research topics include the need to: 1). Identify effective substitutes for breast milk in HIV-negative children with HIV-infected mothers; 2). Understand the implications of concurrent infections on nutritional rehabilitation of HIV-infected children; 3). Determine how ART can improve nutritional status and to use the experience in developed nations to understand the emerging metabolic complications associated with ART in poorer nations; to understand how ART differentially affects the nutritional and metabolic status of HIV-infected children in resource-rich versus resource poor nations.

IV. CONSENSUS AND CONCLUSION

HIV became a clinical concern in the early 1980s, and its fulminant and devastating effects on health rapidly demanded medical and social attention worldwide. Over the past 2 decades, the clinical manifestations of this virus have changed, often driven by the resources of nations and their ability to deliver effective preventative strategies, care, and treatments. The GI and nutritional manifestations of HIV have been central to most aspects of prevention and care of children with HIV and are evolving with time. Since HIV is a chronic illness in many areas of the world, the GI and nutritional issues facing children with HIV will become even more important in preventing transmission and mitigating the adverse clinical effects of both the virus and its therapies. There is clearly more work to be done.

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