Severe malnutrition and metabolic complications of HIV-infected children in the antiretroviral era: clinical care and management in resource-limited settings[1–4]

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ABSTRACT

More than 2 million children globally are living with HIV infection and >90% of these reside in sub-Saharan Africa. Severe acute malnutrition (SAM) remains a major problem for HIV-infected children who live in resource-limited settings (RLS), and SAM is an important risk factor for mortality. SAM in HIV-infected children is associated with complications including electrolyte disorders, micronutrient deficiencies, and severe infections, which contribute to the high mortality. Access to antiretroviral therapy (ART) has significantly improved the survival of HIV-infected children, although the response to ART of children with SAM remains undocumented in the literature. Immune and virologic responses to ART in RLS are similar to those of infected children in resource-rich settings, but delays in initiation of therapy have led to a high early mortality. Antiretroviral drug toxicities have been described in children who receive therapy and may affect their quality of life and long-term survival. Metabolic complications of ART include lipodystrophy, dyslipidemia, lactic acidosis, insulin resistance, and osteopenia. These complications have been well described in adults and children from developed countries, but data from RLS are limited, and these complications may be compounded by SAM. In this article we review the epidemiology, clinical presentation, and complications of SAM in HIV-infected children and the metabolic complications of HIV-infected children in the era of ART, and discuss future research priorities for RLS. *Am J Clin Nutr* 2011;94(suppl):1716S–20S.

INTRODUCTION

Approximately 2 million children globally are living with HIV and 95% of these children are found in sub-Saharan Africa (1). Without access to ART[5], 50% of these perinatally infected children die by the age of 2 y (2). An increase in access to ART is critical for improving these children's survival and quality of life. ART has been associated with a significant reduction in the incidence of opportunistic infections and mortality in HIV-infected children from developed countries and resource-poor settings (3, 4). However, improved survival in those who receive ART is associated with toxicities including lipodystrophy, dyslipidemia, lactic acidosis, insulin resistance, and osteopenia (5). The diagnostic resources required to identify these toxicities are not readily available in most RLS, which leads to inadequate documentation.

The prevalence of, and mortality among, HIV-infected children with SAM in RLS are well described; however, the data available are from the pre-ART era (6). The effect of ART on the nutritional rehabilitation of children with SAM in RLS remains undocumented in the literature. Some data on the metabolic complications of ART are available from studies of children in industrialized countries; however, the concurrent malnutrition, multiple opportunistic infections, and limited antiretroviral drug options for children living in RLS may affect the incidence and clinical presentation of metabolic complications. Correct pediatric dosing of ART is also challenging in RLS with a high prevalence of chronic and acute malnutrition, which puts children at increased risk of complications. The metabolic implications of ART are particularly important in children because of their potential lifetime exposure to ART and because of the rapid growth and development that occurs in childhood. This article aims to review the epidemiology, clinical presentation, and complications of SAM in HIV-infected children, discuss the added metabolic complications of ART, and suggest potential areas for future research.

SAM

Malnutrition is a major problem of children who live in RLS and is responsible for >1 million deaths per year in children younger than age 5 y (7). HIV-infected African infants and children commonly present with SAM, and wasting is recognized as an independent risk factor for mortality (8, 9). Lean body mass has been closely associated with, and predictive of,

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[5] Abbreviations used: ART, antiretroviral therapy; BMD, bone mineral density; MAM, moderate acute malnutrition; PI, protease inhibitor; RLS, resource-limited settings; SAM, severe acute malnutrition.

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survival in both adults and children who live with HIV, even when they are receiving ART (10). SAM is defined anthropometrically by the WHO as a weight for height ≤ -3 SD below the mean, or a mid-upper arm circumference $\leq$11.5 cm in children aged 1–5 y old (9). A systematic review and meta-analysis of children who presented with SAM in sub-Saharan Africa reported an HIV seroprevalence of 29% with data from 17 studies. Urban referral hospitals had the highest burden of disease, with HIV prevalence rates as high as 50% and mortality of 30% among HIV-infected children with SAM (6).

The clinical presentation of SAM includes severe visible wasting (marasmus), nutritional edema (kwashiorkor), or a mixed picture (marasmic–kwashiorkor) (11). In sub-Saharan Africa, marasmus occurs more commonly than does kwashiorkor in HIV-infected children (12), and marasmic children have a higher risk of mortality (11). HIV-infected children with SAM are more likely to present with other comorbidities and complications [eg, tuberculosis and acute respiratory infections, persistent diarrhea (usually due to villous atrophy and disaccharide or even monosaccharide intolerance), and oral candidiasis, which contributes to anorexia and poor oral intake]. Concurrent micronutrient deficiencies are common in most children with SAM and may contribute to growth failure and disease progression (13). However, micronutrient supplements alone do not necessarily restore body stores or result in improved weight gain or linear growth. Whereas vitamin A supplements have been shown to lower all-cause mortality in HIV-infected children, systematic reviews have not concluded that multiple micronutrient supplements improve survival of HIV-infected children or adults (14). In the management of SAM, micronutrients including zinc, magnesium, selenium, copper, iodine, and iron are supplemented within the standard high-energy milk formulas (F75 and F100) and ready-to-use therapeutic foods (15).

In the absence of ART for HIV-infected children with SAM, mortality has been reported to be 3 times higher than in those without HIV infection (6). Because of complications and opportunistic infections, HIV-infected children with SAM generally have a prolonged hospital stay, with increased risk of death, especially in the first 2 wk of admission. In Uganda, Bachou et al (16) reported a mortality of 24% in a cohort of 220 infected and uninfected children admitted with SAM. More than 70% of the deaths occurred within the first week of admission. HIV-infected children with nonedematous SAM were shown to have a lower total white count, neutrophil count, and CD4%, when compared with those without edema. The median hemoglobin concentrations did not differ significantly, with 7.3 (6.0–9.1) g/dL in those with nonedematous SAM and 8.2 (6.4–9.6) g/dL in those with edema (17). One study showed that HIV-infected children who survive have a similar rate of weight gain during nutritional rehabilitation when compared with uninfected children with SAM (6). However, in our experience, HIV-infected ART-naive children with SAM who are hospitalized and receive nutritional rehabilitation tend to have a slower weight gain than do HIV-negative children. A study from Zambia showed that infected children with SAM remain severely immunosuppressed after recovery from SAM (18). It is important to document the effect of ART on the nutritional and immune recovery in HIV-infected children with SAM during nutritional rehabilitation.

Complicated SAM is associated with biochemical abnormalities, micronutrient deficiencies, and concurrent infections, which lead to a higher mortality. As acute malnutrition becomes more severe, normal physiologic mechanisms that adapt the organism to low food intake become more pronounced (19). These reductive adaptations affect every physiologic function in the body, mobilize energy and nutrient reserves, and lower energy and nutrient demands. Therefore, inpatient care and hospitalization is recommended by the WHO for the management of the severely malnourished child with complications including hypothermia, hypoglycemia, electrolyte imbalance, micronutrient deficiencies, diarrhea, and severe bacterial infections. Children with complicated SAM have higher mortality than do those with uncomplicated SAM, particularly in high-HIV-prevalence settings (18). Uncomplicated SAM can be managed on an outpatient basis with the use of ready-to-use therapeutic food, and this has improved the survival of SAM in the community (7). The WHO pediatric HIV clinical staging includes SAM that does not respond to nutritional rehabilitation and it is considered a stage 4 event and indication for ART. It is important to ensure that HIV testing and treatment is integrated into care for children with SAM at both the facility and the community level. Clinical staff and community health workers in high-HIV-prevalence settings need training on how to treat HIV and SAM, and this training should include the detection and treatment of metabolic complications.

ART IN RLS

Access to ART has had a significant effect on the lives of infected children, with decreased morbidity and mortality (20). However, in resource-constrained countries there still remains a large gap between the number of children who require ART and those who receive treatment. According to the 2009 Joint United Nations Programme on HIV/AIDS ART report, only 28% (350,000) of the 1.27 million children who need ART are receiving treatment (1). Initiation of ART in RLS tends to occur late, and most children initiate treatment with advanced HIV disease. Sutcliffe et al (20) compiled data from multiple cohorts of infected children from RLS who were initiated on ART, and reported a median age and CD4 cell percentage at ART initiation of 5 y and 15%, respectively. After 24–72 wk on ART, 50–80% of infected children were shown to have undetectable viral load ($<$400 copies/mL). Despite late initiation of ART in children from RLS, several treatment outcomes have been similar to those of children in resource-rich settings. The current WHO guidelines for ART initiation state that all infected children under 2 y of age are eligible for ART (18). This policy change should lead to asymptomatic and younger children initiating ART and to better survival and improved quality of life for HIV-infected children if adherence to therapy can be maintained.

IMMUNE, VIRAL, AND GROWTH RESPONSE TO ART

Early initiation of ART improves viral, immune, and growth responses in HIV-infected children (20). However, lack of complete viral suppression on receipt of ART does not preclude adequate growth responses (21). Younger children and those with higher CD4 cell counts at ART initiation are more likely to have a brisk growth response when compared with older children (22). Kekitiinwa et al (23) compared growth, immune, and viral responses to ART in HIV-infected children from Uganda and the

United Kingdom. The major difference was the younger age group and less advanced disease in the UK cohort and a much higher rate of wasting and stunting in the Kampala cohort, similar to that of other African children. Lower CD4 cell counts at ART initiation predicted poor immunologic response in the Kampala cohort but better immune response in the UK cohort. The authors postulate that this difference may have been related to the malnutrition, coinfections, and the older age of the cohort in Kampala. Younger children in both cohorts had better immune, viral, and growth responses to ART, which emphasizes the need to initiate ART early for better overall treatment response (23). A recent comparative meta-analysis of ART responses between children from RLS (n = 17,875) and those from developed countries (n = 1835) showed that viral load suppression was similar after 12 mo on ART but CD4% responses were lower (23 compared with 27, $P = 0.03$). Mortality was 5 times higher in those children from RLS. The median age at initiation of ART was similar in both groups, but the higher mortality and poorer immune responses in children from RLS may have been related to the low CD4% among children from RLS on ART initiation (24). Malnutrition and a high prevalence of opportunistic infections among children in RLS may also be a contributing factor. The majority of infected children present with moderate to severe malnourishment at the time of ART initiation and should receive nutritional assessment and provision of nutritional support in addition to ART.

In a Ugandan cohort of 345 infected children initiated on ART, 21% of the children had moderate or SAM (<-2 SD below mean weight for height). A retrospective analysis was performed to evaluate the mortality among these children in relation to the timing of ART initiation. The median age of the children at ART initiation was 4.7 y and the median time to initiation of ART was 10 wk. Mortality was higher in those children who initiated ART within 10 wk of diagnosis as opposed to those who initiated ART later (OR: 2.8; 95% CI: 1.33–5.90; $P = 0.007$) after adjustment for age, sex, CD4%, and WHO clinical stage. In this cohort early initiation of ART was associated with a higher mortality and may have been related to the concurrent infections and/or complications of SAM. The authors concluded that the optimum time to initiate ART in severely malnourished children needs further evaluation.

MALNUTRITION AND IMMUNE RECONSTITUTION SYNDROME

Recently, there have been reports of children initiating ART and subsequently developing severe edematous malnutrition (23). In the ARROW (Anti-Retroviral Research for Watoto) clinical trial, 3.2% of 1207 African children initiated on ART were hospitalized for SAM within 12 wk of ART initiation. Of the 220 children with severe disease (CD4% and weight-for-age z scores both <-3 SD), 7% (95% CI: 3.8, 10.7) developed kwashiorkor and 3.6% (95% CI: 1.2, 6.1) developed marasmus. Their CD4% rise was similar, but mortality was 32%, 20%, and 1.7% in the children with marasmus, those with kwashiorkor, and those not hospitalized, respectively. The mechanism for this severe malnutrition is not clear, but the authors postulated that this may be a form of immune reconstitution syndrome in those children with severe malnutrition and severe immune suppression who initiate ART (25). Further documentation of this complication in HIV-infected children from other RLS is warranted, including a better understanding of the pathogenesis and interventions to prevent its occurrence.

METABOLIC COMPLICATIONS AND LIPODYSTROPHY

Metabolic complications are well recognized in HIV-infected adults and children who receive ART, including lipodystrophy, dyslipidemia, lactic acidosis, insulin resistance, and osteopenia (26, 27). These complications may occur in the absence of fat redistribution but they tend to be worse when fat redistribution is present (28). Fat redistribution can affect between 30% and 70% of children with HIV who receive ART, depending on the method of detection (29). In one study in New York City researchers used a sensitive dexa scan and showed that HIV-infected children who were receiving ART had increased fat redistribution when compared with HIV-negative control subjects (30). Most of the published data are from developed countries, with a dearth of data from RLS. Further information on metabolic complications for HIV-infected children in sub-Saharan Africa is urgently needed, particularly because of the high prevalence of acute malnutrition and the possible interactions. Children should have their height and weight measured and plotted at each visit to monitor growth and to assist with accurate dosing of ART. Blood lipid profiles should be measured regularly where feasible (26).

Lipodystrophy is associated with the duration of ART and is related to specific antiretroviral drugs. ART-associated peripheral lipoatrophy, central lipohypertrophy, dyslipidemia, and insulin resistance have been well described in developed countries (31). As access to ART in RLS has increased, the complication of lipodystrophy has also been reported, albeit to a limited degree (32, 33). In a cohort of 90 children from Thailand, the incidence of lipodystrophy increased with the duration on a non-PI-based antiretroviral regimen, and 9%, 47%, and 65% of the children developed lipodystrophy after 48, 96, and 144 wk on ART, respectively. Only 12% and 4% of the children had concurrent dyslipidemia and increased plasma glucose, respectively, at 144 wk. Female children (61% compared with 39%, $P = 0.04$) and those with advanced disease (73% compared with 51%, $P = 0.04$) were more likely to develop lipodystrophy (32). Similar findings were shown in a Brazilian cohort in which 53% of the children who had received ART for a median of 28 mo developed lipodystrophy. However, 30% of the children were on a PI-based regimen and 60% of the children were shown to have concurrent dyslipidemia (29).

The preliminary data from RLS also show that lipodystrophy is associated with older age and longer duration on therapy. Stavudine was the main nonnucleoside reverse transcriptase inhibitor associated with lipoatrophy, but zidovudine was also associated with the lipodystrophy syndrome. In those cohorts in which children were on a PI regimen there were higher rates of dyslipidemia. Most clinicians who work in RLS have identified infected older children on ART who have extreme lipoatrophy of the face and limbs with prominent veins of the upper limbs and loss of cheek fat. These changes lead to further stigmatization and poor adherence to ART. Clinicians should conduct a physical examination of children on ART at each visit to look for evidence of lipodystrophy and they should ask parents if they have noticed any changes in their child's fat stores. There have been some

successes in industrialized countries in the treatment of lipodystrophy with growth hormone; however, the costs are prohibitive for use in a RLS (34). Strategies to prevent and manage lipodystrophy are urgently needed in RLS.

For children with severe lipodystrophy or elevated blood lipid concentrations, a change in nucleoside reverse transcriptase inhibitor agents (from stavudine, didanosine, or zidovudine) to abacavir or tenofovir may help decrease the cosmetic appearance of lipodystrophy and regulate blood lipids. A switch of the PI agent to atazanavir may also have a beneficial effect (26). However, these changes may not be feasible in RLS, where a limited range of ART regimens is available. In RLS a switch from stavudine to zidovudine or abacavir has been beneficial in some children with lipoatrophy, but other children fail to reverse the lipoatrophy, despite the switch in ART.

Where there are no facilities to measure blood lipids, clinicians should have a high index of suspicion for dyslipidemia because it is not always associated with fat redistribution. Skinfold thickness and hip and waist circumferences ratios can also be used as screening tools for identification of children with lipodystrophy (35). Children on PIs are more likely to have dyslipidemia than those on nonnucleoside reverse transcriptase inhibitors. Referral to centers of excellence for an annual lipid profile or collection of blood samples for testing in a reference laboratory would be useful. Because of the limited number of reference laboratories in most countries, it may be difficult to send blood for lipid profile measurements from distant centers. Therefore, the use of dried blood spots for measurement of blood lipids in children on ART in RLS should be evaluated and, if feasible, implemented in areas where there is limited access to reference laboratories (36).

BMD

HIV infection is associated with decreased BMD in children (37, 38). Infected children on ART have been shown to have lower BMD when compared with ART-naive and HIV-negative children (39). Decreased BMD leads to osteopenia and osteoporosis, with a higher risk of pathologic fractures. In Italy, Zuccotti et al (39) showed decreased bone mineral content in HIV-infected youth (aged 4.8–22 y) who were receiving a PI (full-dose ritonavir)–based regimen compared with healthy HIV-negative youth. In addition, those on a stavudine-based regimen were shown to have decreased BMD. Diets that are deficient in micronutrients such as calcium and vitamin D can lead to decreased BMD in children, even if the children are exposed to adequate sunshine (33). The concurrent malnutrition and micronutrient deficiencies shown in HIV-infected children from RLS may lead to a higher risk of osteopenia on ART. However, severe malnutrition and the chronic inflammation of HIV may lead to severe osteopenia without exposure to ART. The current WHO ART guidelines, which recommend Tenofovir as first-line therapy for adults in RLS may lead to a larger number of adolescents on Tenofovir, with the potential for decreased bone density in these adolescents (34). The lack of modern radiologic equipment such as dexa scans has limited the documentation of BMD in HIV-infected children from RLS.

The underlying nutritional deficiencies and toxicities from ART in HIV-infected children may lead to higher rates of decreased BMD and pathologic fractures. This has not been documented in RLS but will require additional vigilance from clinicians to report pathologic fractures in infected children on ART. Clinical monitoring and documentation of fractures would be important to determine the prevalence of pathologic fractures and associated factors. Infected children on ART may have decreased BMD without bone fractures. Therefore, ensuring adequate vitamin D and intake of calcium may help mitigate the effects of ART on bone (26).

RESEARCH PRIORITIES FOR RLS

There is still an urgent need to determine whether the pharmacokinetics of antiretroviral drugs are affected by SAM, so that appropriate dosing adjustments can be made in severely malnourished children who initiate ART. In addition, the appropriate timing of ART initiation in children with SAM remains unknown because severe malnutrition is associated with impaired absorption from the gut, which may lead to inadequate antiretroviral drug concentrations. However, the delay in initiation of ART in SAM may lead to further immune suppression and the development of complications, which may increase overall mortality. Therefore, studies to determine the pharmacokinetics of antiretroviral drugs in SAM and to identify the best time to initiate ART are urgently needed in RLS. The more recent observation of edematous SAM after initiation of ART requires further study to determine the risk factors and possible pathogenesis so as to decrease the mortality in this subset of children.

Although children with SAM and HIV remain an important group because of their high risk of mortality, there is a much larger proportion of HIV-infected children with MAM, and yet there are limited data on the effect of MAM on the success of ART. Research into the effect of the treatment of MAM in children with HIV is needed to explore the potential of a reversal in MAM and a halting of the progression of MAM to SAM, and thus a reduction in complications and mortality.

The documentation and follow-up of infected children on ART, to establish the incidence of lipodystrophy, hyperlipidemia, and insulin resistance in different cohorts of children, is still needed. In view of the stigmatizing effects of lipodystrophy and the potential increased risk of children with HIV to develop cardiovascular disease or diabetes, it is critical to ensure that children on ART are monitored and that appropriate management is provided to prevent and treat these complications.

Identification of the risk factors for, and effect of, metabolic complications in RLS is critical. Although data from developed countries can provide some guidance the concurrent malnutrition, multiple opportunistic infections, and limited antiretroviral drug options for children who live in RLS may increase the incidence and severity of metabolic complications. Studies are urgently needed to determine the incidence, risk factors, and effect of the metabolic complications of ART in HIV-infected children in RLS. Clinicians already face the challenges of identification and treatment of metabolic complications in children on ART in RLS, and these challenges are intensified by SAM. The authors call for evidence-based guidance on the clinical care and management of metabolic complications in children on ART in RLS.

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