Systematic review of the care of HIV-infected children with severe acute malnutrition

Mark Manary[1]
Indi Trehan[2]
Juana Willumsen[3]

February 2012

[1] Helene B. Roberson Professor of Pediatrics, Washington University in St. Louis;
Senior Lecturer in Community Health, University of Malawi
[2] Assistant Professor of Pediatrics, Washington University in St Louis;
Visiting Lecturer in Paediatrics and Child Health, University of Malawi
[3] Independent Consultant, 360 rue Fontaine, 01220 Divonne-les-Bains, France

Abbreviations

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral treatment
ARV	antiretroviral medication
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAZ	height-for-age z-score
HIV	human immunodeficiency syndrome
IRIS	immune reconstitution inflammatory syndrome
NUGAG	Nutrition Guideline Advisory Group
ORS	oral rehydration salts
PICO	Population, Intervention, Comparator and Outcomes
RCT	randomized controlled trial
RDA	recommended dietary allowance
RUTF	ready-to-use therapeutic food
SAM	severe acute malnutrition
TB	tuberculosis
WAZ	weight-for-age z-score
WHO	World Health Organization
WHZ	weight-for-height z-score

Measurements

g	gram
m^2	square metres
mcg	microgram
mg	milligram
ml	millilitre

Background

Although great advances have been made in the management of childhood severe acute malnutrition (SAM) with the advent of ready-to-use therapeutic foods (RUTFs) (*1*), the heavy burden of HIV/AIDS continues to hamper progress in reducing mortality and morbidity in much of the developing world, particularly sub-Saharan Africa (*2*). Therapeutic protocols for SAM in both inpatient (*3–5*) and outpatient (*1,5,6*) settings have led to marked reductions in mortality and morbidity, yet children with SAM and HIV still have unacceptably poor outcomes (*7*). A large meta-analysis of children with SAM found that those with HIV were nearly three times more likely to die while on nutritional rehabilitation therapy, compared to their HIV-negative counterparts (*8*). For this reason, it is important to consider whether the child with SAM and HIV has different clinical care and nutritional needs, based on a different pathophysiology, compared with the uninfected child, and if therapeutic protocols could be refined and adapted to best meet these specific requirements.

HIV-infected children with SAM have a poorer prognosis than their uninfected counterparts. A number of physiological and social factors that may contribute to the higher rate of nutritional therapy failure have been proposed. These include: (i) altered glucose and lipid metabolism, either as an effect of HIV or antiretroviral treatment (ART); (ii) specific micronutrient deficiencies; (iii) altered pharmacokinetics of antibiotics and antiretroviral medications (ARVs); (iv) gastrointestinal side-effects of ARVs; (v) higher rates of diarrhoea and malabsorption; (vi) perturbations of mitochondrial function; (vii) diminished antioxidant capacity that may be exacerbated by ARVs; (viii) frequent coinfections; and (ix) higher rates of food insecurity and poverty.

Moderate wasting that is unresponsive to therapy is a World Health Organization (WHO) Stage III condition and severe wasting is a Stage IV condition, both of which qualify HIV-infected children for the initiation of lifelong ART (*9*). However, the optimal timing of ART initiation in children with SAM and optimal dosing in these children have not been established. The initiation of ART in children with SAM is complicated by the complex interplay between their unstable and changing physiology related to both HIV and SAM, including numerous oxidative stressors (including malnutrition, ART and the HIV virus itself), alterations in lean body tissue and drug distribution, mitochondrial dysfunction and ARV toxicity, possible hepatic and renal dysfunction, altered intestinal absorption of oral medications, potential interactions with anti-tuberculosis (TB) medications for those coinfected with TB and the possibility of precipitating the immune reconstitution inflammatory syndrome (IRIS).

Given these uncertainties in the case management of HIV-infected children with SAM, and in order to inform guideline development, a systematic review of the available literature on the subject was carried out. The following specific Population, Intervention, Comparator and Outcomes (PICO) questions were identified at the WHO Nutrition Guideline Advisory Group (NUGAG) meeting in June 2010.

1. For HIV-infected children with SAM, what is the optimal timing for initiating and dosing of ARV?

   - What clinical outcomes, including survival and adverse effects associated with ARVs, are associated with either earlier or later initiation of ART?

   - Are there clinical or laboratory markers of metabolic or toxic perturbations that might identify those children most at risk for adverse effects from ARVs?

- Is any specific ARV regimen correlated with better outcomes in malnourished children?

- Are there any measures to limit the effects or improve the treatment of IRIS specifically in malnourished children?

2. For HIV-infected children with SAM, what is the value (effectiveness and safety) of vitamin A supplementation?

3. For HIV-infected children with SAM and acute or persistent diarrhoea, what are the most effective:

- diagnostic strategies for diarrhoea

- therapeutic strategies:
    - antibiotics or antiparasitics
    - oral rehydration salts (ORS)
    - feeding strategies
    - glutamine or zinc supplementation?

4. What are the optimal feeding regimens for HIV-infected children with SAM? Do these differ from those for uninfected children with SAM?

Methodology

A search of computerized databases for all studies from 1985 to 2011 was carried out. Databases searched included Medline, Embase and Google Scholar; clinical trial registers at clinicaltrials.gov, pactr.org and apps.who.int/trialssearch were also searched. Observational and randomized studies published in English, French or Spanish were included.

Initial key words for searches included "HIV", "AIDS", "malnutrition", "severe malnutrition", "kwashiorkor", "marasmus", "antiretroviral therapy", "vitamin A", "zinc", "glutamine", and "antibiotics". A number of outcome measures were sought, including mortality, morbidity, weight gain and nutritional recovery, resolution of diarrhoea, HIV viral load and CD4 count, and improvement in WHO staging of HIV/AIDS.
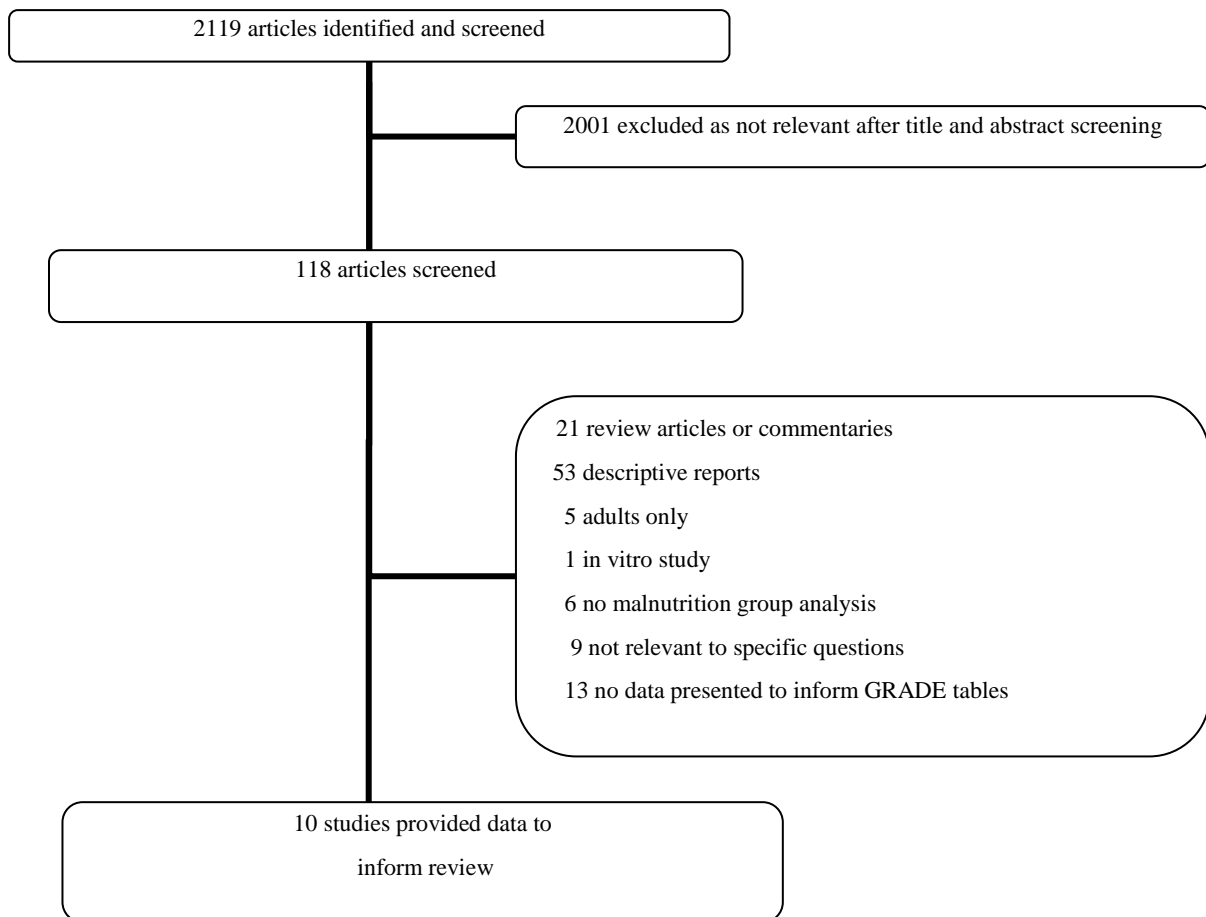

Relevant studies were identified, reviewed and selected for inclusion by one scientific reviewer initially, with a second and third review by two other scientific reviewers. Reference lists and personal literature collections were also evaluated for relevance. Evidence-based Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review tables were created for each of the questions identified above. GRADE provides an evaluation of the quality of evidence and so gives an indication of the confidence that an estimate of effect is correct. In the GRADE approach, randomized controlled trials (RCTs) constitute high-quality evidence. Observational studies without important limitations constitute low-quality evidence. Quality of evidence may be decreased if there are study limitations, inconsistent results, publication bias or the evidence is indirect. Quality of evidence may also be increased if there is a large magnitude of effect, plausible confounding that would reduce the demonstrated effect or a dose-response gradient.

Results

The database search as described above identified 2119 articles (Figure 1). Of these, 200 were selected for initial review following screening of titles and abstracts. After an initial review of abstracts, 118 were selected for full review.

Figure 1

Database search process

```
┌─────────────────────────────────────────────┐
│        2119 articles identified and screened │
└─────────────────────────────────────────────┘
                │
                │        ┌──────────────────────────────────────────────────────────┐
                ├────────┤ 2001 excluded as not relevant after title and abstract    │
                │        │ screening                                                 │
                │        └──────────────────────────────────────────────────────────┘
                │
┌─────────────────────────────────────────────┐
│             118 articles screened            │
└─────────────────────────────────────────────┘
                │
                │        ┌──────────────────────────────────────────────────────────┐
                │        │ 21 review articles or commentaries                        │
                │        │ 53 descriptive reports                                    │
                │        │  5 adults only                                            │
                ├────────┤  1 in vitro study                                         │
                │        │  6 no malnutrition group analysis                         │
                │        │  9 not relevant to specific questions                     │
                │        │ 13 no data presented to inform GRADE tables               │
                │        └──────────────────────────────────────────────────────────┘
                │
┌─────────────────────────────────────────────┐
│         10 studies provided data to          │
│              inform review                   │
└─────────────────────────────────────────────┘
```

Question 1: For HIV-infected children with SAM, what is the optimal timing and dosing of ARV?

- What clinical outcomes, including survival and adverse effects associated with ARVs, are associated with either earlier or later initiation of ART?

- Are there clinical or laboratory markers of metabolic or toxic perturbations that might identify those children most at risk for adverse effects from ARVs?

- Is any specific ARV regimen correlated with better outcomes in malnourished children?

- Are there any measures to limit the effects or improve the treatment of IRIS specifically in malnourished children?

Background

Children with severe malnutrition have a number of metabolic and body composition derangements, including less lean body mass, less fat, alterations in hepatic and renal function, diminished mitochondrial integrity and increased oxidative stress (*10*). The contribution of HIV infection itself worsens these factors and there is concern that ART would only further exacerbate these children's perturbed physiology (*11–14*). Standard weight-based ARV dosing for malnourished children may thus be inappropriate, leading to subtherapeutic serum drug levels and potentially the development of viral resistance to ARV, problematic in its own right but especially so in resource-limited settings where second-line therapy may be unavailable. Based on expert opinion, existing WHO guidelines suggest that ART in severely malnourished children should be delayed until their nutritional status has "stabilized" from the acute phase of malnutrition (*9,15*).

Systematic review

The overall quality of data for this PICO question was "Very Low" since there were no prospective randomized trials in the target population. Observational studies were available but only one of these reported on the precise outcomes in relation to the timing of ART initiation.

There was a paucity of studies and data relating to this question. No randomized controlled clinical trials were identified. Nine published observational studies presented data on the nutritional status of children initiated on ART, but none specifically reported on the timing of initiation in relation to nutritional status at baseline. Children initiated on ART with weight-for-age <-3 z-score (WAZ) at baseline had a higher mortality rate than those with WAZ >-3 in a number of different settings (*16–18*). However, Naidoo reported that there was no statistically significant difference in the percentage of children in each WAZ group achieving undetectable viral loads when on ART (*16*). None of these studies reported on the timing of introduction of ARVs with respect to treatment for SAM. One recent retrospective observational study (*19*) reported on 140 HIV-infected, ART-naive malnourished children who were admitted for therapeutic feeding in Malawi. A higher proportion of the 55 who received ART within 21 days of admission, recovered (86% vs 60%, p<0.01), when compared with those who had delayed initiation of ART, or were not considered eligible for ART.

An observational study by Pollock et al. presented data on the pharmacokinetics of nevirapine in Malawi (*20*). Treatment naive children who received a divided adult fixed-dose combination tablet containing nevirapine were enrolled. Children were grouped by nutritional status and blood samples taken at various points pre- and post-dose. Of the 37 children recruited, 12 were malnourished (weight-for-height 75–85% of median). Suboptimal dosing (<300 mg/m^2/day), when dosing was estimated using weight band tables compared to dosing requirements estimated on surface area, was not significantly different between malnourished and non-malnourished children. The eight children that did have suboptimal dosing were all in the lightest weight band and were receiving a quarter of a tablet as part of their regimen. An observational study in India of children receiving a generic nevirapine fixed-dose combination (*21*) reported no significant difference in trough or 2-hour nevirapine concentrations, when dosage was based on body weight bands, in children, with WAZ <-2, compared to those >-2. Stunted children with height-for-age <-2 z-scores (HAZ) had significantly lower median (range) 2-hour nevirapine concentrations (5.3 [1.6–14.3] mcg/ml, n=55) than normal children (6.1 [1.5–18.9] mcg/ml, n=32).

One retrospective study (*22*) reported the association between IRIS and some indicators of malnutrition among 91 children receiving ART for more than one year, in Lima, Peru. Of the children, 18 developed IRIS, with median onset 6.6 weeks after treatment initiation. None died and IRIS did not necessitate treatment interruption in any of the children. Children with IRIS were more likely to have had at least one indicator of malnutrition (HAZ <-2, WAZ <-2 and/or WHZ <-2) when starting ART (78%), compared with those who did not develop IRIS (42%, p=0.007). There was no discussion of any measures that might improve treatment or limit the incidence of IRIS among HIV-infected children with SAM.

There were no studies that presented data on markers for toxicity or adverse effects from ARVs among children with HIV and SAM. There were no studies that presented data on the effects of varying ARV regimens on children with HIV and SAM.

No studies were found that provided data to directly answer the PICO question.

Summary

In summary, there is no prospective trial evidence available to guide the optimal timing or dosing of ART in children with SAM. Observational studies indirectly assessing the efficacy of ART in children

with SAM suggest that they are able to respond favourably to ART. There is some suggestion that malnourished children have higher rates of IRIS but the balance of IRIS with possibly increased mortality from delaying ART remains an open question.

Future research evaluating the effects of ARV initiation in children with SAM is necessary. Areas for study should include optimal choice and timing of the initial ARV regimen, the pharmacokinetics of ARV in this population, an evaluation of metabolic (renal, hepatic, mitochondrial, antioxidant) toxicities, and an assessment of short-term clinical outcomes (nutritional recovery, IRIS, etc.) and long-term clinical outcomes (mortality, nutritional relapse, etc.).

Question 2: For HIV-infected children with SAM, what is the value (effectiveness and safety) of vitamin A supplementation?

Background

Vitamin A supplementation is recommended for children who are hospitalized for SAM (*4*). Regular supplements of vitamin A every six months are also recommended for all children between 6 months and 5 years of age to support normal growth and development and to reduce all-cause mortality.

Systematic review

The overall quality of data for this PICO question was "Very Low" since there were no prospective randomized trials in the target population. One randomized trial on multiple micronutrient supplementation comparing two recommended dietary allowances (RDAs) vs one RDA of Vitamin A in HIV-infected children was found.

There were no studies that directly addressed this question. One study by Ndeezi et al. was an RCT trial of multiple micronutrient supplementation of 847 HIV-infected children in Uganda (*23*). In this trial, children aged 1–5 years were randomized to receive six months of supplementation with either an intervention supplement with 14 micronutrients at twice the RDA (including 800 mcg/day vitamin A), or the standard of one RDA of six micronutrients (including vitamin A at 400 mcg/day). After six months, all children received the standard supplement. Children were stratified by ARV and the primary outcome of interest was mortality at 12 months. At baseline 246/847 children had WAZ <-2 and in multivariate analysis this independently predicted early mortality (adjusted hazard ratio 2.6 [1.2–5.8], p=0.02). The intervention group tended towards slightly better anthropometric parameters than the control group, although this was not analysed according to nutritional status at baseline.

A recent Cochrane review (*24*) of micronutrient supplementation in children and adults with HIV similarly reported that there is a paucity of data relating to vitamin A supplementation of HIV-infected children. Five small trials were included in that analysis and the authors concluded that there was strong evidence of clinical benefits of vitamin A supplementation on mortality of HIV-infected children, and moderate evidence of morbidity and growth benefits. Although some adverse effects were reported, it was noted that these were isolated instances, in small sample sizes, in some trials. None of these studies reported specifically on children with HIV and SAM and so have not been included in this analysis.

Summary

Vitamin A supplementation is currently recommended for children with SAM (*4*) and children with HIV infection (*9*). There is currently no data available to directly address the issue of whether HIV-infected children with SAM are more susceptible to adverse effects from vitamin A supplementation, or would benefit from an adapted administration regimen, compared to uninfected children with SAM. For this reason, and until such data become available, it is currently recommended that HIV-infected children be given vitamin A supplements when presenting with SAM in the same manner as uninfected children.

Question 3: For HIV-infected children with SAM and acute or persistent diarrhoea, what are the most effective:

- diagnostic strategies

- therapeutic strategies:

    o antibiotics or antiparasitics

    o ORS

    o feeding strategies

    o glutamine or zinc supplementation?

Background

Acute diarrhoeal disease is the second leading cause of death among children worldwide and children with HIV suffer a disproportionate mortality when suffering from an acute episode of diarrhoea. HIV-infected children with SAM are at particularly high risk for a range of opportunistic pathogens. Increased malabsorption during and following diarrhoeal episodes (25) also hinders their recovery from SAM, further complicating their nutritional recovery.

Systematic review

The overall quality of data for this PICO question was "Very Low" since there were no prospective randomized trials in the target population. One randomized trial of different therapeutic diets in HIV-infected children with persistent diarrhoea-malnutrition and one randomized trial of micronutrient supplements were found.

No studies were identified to address the question of the most effective diagnostic, antibiotic, antiparasitic or ORS therapeutic strategies for HIV-infected children with SAM and diarrhoea.

One single-blind RCT was identified (26), which randomized HIV-infected and uninfected children admitted with persistent diarrhoea-malnutrition in Zambia, aged 6–24 months, to receive either an elemental diet or the standard nutritional rehabilitation diet. The improvement in WAZ and WHZ in both the intervention and control groups was similar for both HIV-infected and uninfected children: the amino acid-based elemental feed was associated with greater weight gain than the standard nutritional rehabilitation (skimmed milk followed by soya) group. This single study with a relatively small number of children does not adequately address the question of whether specific feeding regimens are better suited to the treatment of HIV-infected children with SAM and diarrhoea. Given the concerns regarding malabsorption and metabolic disturbances due to HIV infection, further research is warranted to elucidate the effect of therapeutic diets on the recovery from diarrhoea and malnutrition in this specific group of children. Until such data is available, children with HIV infection, SAM and diarrhoea should continue to receive the same therapeutic feeds as those without HIV.

An RCT by Mda et al. (*27*) was identified in which HIV-infected children admitted with diarrhoea in South Africa were given short-term multiple micronutrient supplements, including 300 mcg/day of vitamin A and 8 mg/day of zinc, during hospitalization. Not all children were malnourished, although the group mean WAZ at baseline was <-2. However, no subgroup analysis was presented for children with WAZ <-2. The primary outcome of interest was the duration of hospitalization, and there was no significant difference between the placebo and supplementation group. It should be noted that both groups included fewer than 25 children.

In a recent Cochrane review (*24*) of micronutrient supplementation in children and adults with HIV, two trials of zinc supplementation of HIV-infected children were identified. In children without HIV infection, zinc supplementation has been shown to reduce the risk and severity of diarrhoea and pneumonia. A placebo-controlled equivalence trial to determine the safety of zinc supplementation in HIV-infected children found that 10 mg/day zinc for up to six months did not increase viral load but did decrease the incidence of watery diarrhoea (*28*), however, a subsequent study in 32 children did not show any benefit of prophylactic zinc supplementation on diarrhoeal morbidity (*29*).

Summary

Zinc supplementation is recommended for children with SAM and diarrhoea and is not considered unsafe for HIV-infected children (*30*). For this reason, and until such data become available, it is currently recommended that HIV-infected children with SAM and diarrhoea be given zinc supplements in the same manner as uninfected children (*31*).

Question 4: **What are the optimal feeding regimens for HIV-infected children with SAM?**

Do these differ from those for uninfected children with SAM?

Background

Given the relatively poor recovery rates of HIV-infected children with SAM and the fact that HIV adds a heavy catabolic burden to a malnourished child's metabolism, it is reasonable to explore whether the standard therapeutic feeding regimens recommended for malnourished children (*1,4*) are sufficient for malnourished children with HIV.

Systematic review

The overall quality of data for this PICO question was "Very Low" since there were no prospective randomized trials that directly addressed this question in the target population.

Two studies were identified that investigated the duration and pattern of recovery among HIV-infected and uninfected children with SAM. The study by Barker (*32*) presented observational data on 10 HIV-infected children and 48 matched controls, recruited between 1988 and 1999. No significant difference was found in the duration of phase 1 and phase 2 of treatment. The study by Fergusson (*8*) was a prospective cohort study of 79 HIV-infected children and 375 uninfected children with SAM. The primary outcomes investigated were weight gain and mortality. All children were given the same nutritional rehabilitation diet and there was no significant difference in nutritional recovery among HIV-infected children who survived, compared to uninfected children. However, mortality was higher in infected children.

Two further studies were identified that addressed the issue of probiotic, prebiotic or dietary supplements added to the diets of children undergoing SAM treatment. The RCT by Simpore investigated the addition of 10 g/day of spirulina to the traditional diet of HIV-infected and uninfected children being treated for SAM in Burkina Faso (*33*). This study did not present any statistical analysis of the difference between the two treatment groups.

In the RCT by Kerac (*34*), there was no significant difference in nutritional cure rates among HIV-infected children with SAM given RUTF with or without the addition of a combination prebiotic and probiotic (symbiotic).

Summary

Although HIV-infected children who survive SAM may achieve similar growth parameters as those who fail therapy, mortality rates remain higher compared to their uninfected counterparts. Trials of dietary supplements added to therapeutic feeds failed to demonstrate significant differences in recovery rates. Studies of different feeding regimens for HIV-infected children with SAM are warranted.

Conclusions

There is a paucity of evidence in the form of clinical trials involving HIV-infected severely malnourished children to answer these four questions. However, clinicians must continue to manage and care for HIV-infected severely malnourished children despite this lack of high-quality evidence. Clinicians must, therefore, rely on general principles of medicine and on clinical studies and experience from other groups of patients to guide them in the management of these children. Given this background, evidence and practices among other populations may be useful to clinicians and policy-makers. These include:

- A number of studies in various contexts have demonstrated that early initiation of ARV in infants and children correlates with decreased mortality and decreased rates of progression to advanced AIDS stages (*35,36*). Growth faltering among HIV-infected children can also be ameliorated with earlier initiation of ART (*37*), providing further motivation for starting ART early in young children (*9*).

- The concern for potential toxicity due to ARV exacerbating the already perturbed physiology in children with HIV and SAM is worrisome and has led international guidelines and some clinicians to delay the initiation of ARV in this population. However, no prospective trials or observational data are available to corroborate these concerns or to demonstrate that the rate of this toxicity is any higher in children with SAM than in those without SAM. In the absence of such data, therefore, it seems prudent to treat HIV-infected children with SAM as one would those without SAM, and to modify therapy based on the clinical progress of the individual patient.

- Similarly, there is no clear evidence to suggest that children with SAM are more susceptible to IRIS than children without SAM. Recent observational evidence, in fact, suggests that delaying ARV in children coinfected with TB may be associated with a poorer virological response and a higher mortality rate (*38*). Children with SAM who develop IRIS after the initiation of ARV also should be managed generally similar to children with IRIS and without

SAM, with treatment options ranging from simple treatment of the unmasked infection to the use of corticosteroids to decrease the inflammatory cascade to the stopping of ARV.

Acute diarrhoeal disease is the second leading cause of death among children worldwide and children with HIV experience a disproportionate mortality when suffering from an acute episode of diarrhoea. Not only does their doubly immunocompromised state place them at high risk for a range of opportunistic pathogens, but increased malabsorption (25) also hinders their recovery from SAM, further compounding the problem. The transitional nature of the feedings that often precipitates SAM (weaning from breast milk, introduction of complementary foods, etc.) can lead to further disturbances of the enteric microbiome and worsen intestinal absorptive function.

Children with HIV suffer from an increased burden of bacterial, parasitic and viral enteropathogens and the vast majority also suffer from some degree of HIV enteropathy, which contributes to diarrhoea, malabsorption of macronutrients and micronutrients, and increased gut permeability (39–41). The pathogens most frequently responsible for diarrhoea are generally similar in children with or without HIV (42), although those with HIV especially suffer from chronic *Cryptosporidium* colonization (41). *Microsporidia* and *Giardia* are also known to occur in high frequency among those with HIV. The roles of astrovirus, rotavirus and other enteric viruses in HIV-associated diarrhoea and enteropathy are likely to be further elucidated as nucleic acid methods of diagnosis become more sophisticated and are applied to this problem (39).

Clinicians need to be aware of the high risk of diarrhoea in children with HIV and that this can be particularly problematic in those with SAM as well, in whom optimal gut integrity is especially important to the process of nutritional rehabilitation. At this time, no unique treatment recommendations can be made for HIV-infected children with SAM and diarrhoea. Usual treatment options for malnourished children with diarrhoea (e.g. zinc supplementation, antibiotics for bloody diarrhoea, low-osmolarity ORS) also will likely be applicable to children with HIV, although the rate of cotrimoxazole-resistant pathogens is likely to be higher in HIV-infected children (43) and this needs to be considered when planning antibiotic therapy. Given the high rates of *Cryptosporidium* observed in this population, nitazoxanide may be considered for children with prolonged diarrhoea (44–46). The key goals for clinical care should be the timely and accurate assessment of dehydration and appropriate rehydration, whether this is with ReSoMal or crystalloid intravenous fluids. Empiric antimicrobial therapies for children with prolonged diarrhoea (e.g. seven days or more) can be considered, as they would for children without HIV. These could include metronidazole or, in refractory cases, ciprofloxacin. Given that a fair percentage of prolonged diarrhoea in these children may be related to AIDS enteropathy (47), it would be prudent to consider prolonged diarrhoea as a specific indication to begin ARV (48).

Although there is a lack of specific evidence that HIV-infected children with SAM benefit from vitamin A supplementation, there is no reason to believe that their response to this therapy should be any different than the response in uninfected children.

As with vitamin A, there is no reason to believe HIV-infected children should respond differently to zinc compared to uninfected children when suffering from SAM and diarrhoea.

Further research

Research is needed to:

- Evaluate the effects of ART initiation in children with SAM. Areas for study should include optimal choice and timing of the initial ARV regimen, the pharmacokinetics of ARV in this population, an evaluation of the metabolic (renal, hepatic, mitochondrial, antioxidant) toxicities and an assessment of clinical outcomes including the development of IRIS.

- Evaluate the risks and benefits of vitamin A and zinc supplementation in HIV-infected children with SAM, including whether an adapted administration regimen would be beneficial. Studies should also be performed on the risks and benefits of newer adjuncts such as glutamine and arginine in this context.

- Identify optimal therapeutic diets in HIV-infected children with SAM, particularly in those with significant malabsorption and diarrhoea. The etiologies of and treatment for prolonged diarrhoea in this population also need further study. In particular, the development and evaluation of empiric management protocols of chronic diarrhoea in circumstances where extensive diagnostic are not available would be of value in the management of SAM in the HIV-infected child.

References

1. A Joint Statement by the World Health Organization, the World Food Programme, the United Nations System Standing Committee on Nutrition and the United Nations Children's Fund. *Community-based management of severe acute malnutrition*. Geneva, WHO/WFP/UN/UNICEF, 2007.

2. You D et al. Levels and trends in child mortality, 1990–2009. *Lancet*, 2010, 376:931–933.

3. *Management of severe malnutrition: a manual for physicians and other senior health workers*. Geneva, WHO, 1999.

4. *Guidelines for the inpatient treatment of severely malnourished children*. Geneva, WHO, 2003.

5. *Clinical guidelines: diagnosis and treatment manual for curative programmes in hospitals and dispensaries*. Paris, Médecins sans Frontières, 2010.

6. *Community-based therapeutic care: a field manual*. Oxford, Valid International, 2006.

7. Heikens G et al. Case management of HIV-infected severely malnourished children: challenges in the area of highest prevalence. *Lancet*, 2008, 371:1305–1307.

8. Fergusson P et al. Nutritional recovery in HIV-infected and HIV-uninfected children with severe acute malnutrition. *Archives of Disease in Childhood*, 2009, 94:512–516.

9. *Antiretroviral therapy for HIV infection in infants and children: towards universal access*. Geneva, WHO, 2010.

10. Manary M, Leeuwenburgh D, Heinecke J. Increased oxidative stress in kwashiorkor. *Journal of Pediatrics*, 2000,137:421–424.

11. Pace G, Leaf C. The role of oxidative stress in HIV disease. *Free radical biology and medicine*, 1995, 19:523–528.

12. Gil L et al. Contribution to characterization of oxidative stress in HIV/AIDS patients. *Pharmacology Research*, 2003, 47:217–224.

13. Stephensen C et al. Glutathione, glutathione peroxidase and selenium status in HIV-positive and HIV-negative adolescents and young adults. *American Journal of Clinical Nutrition*, 2007, 85:173–181.

14. Jareno E et al. Serum malondialdehyde in HIV-seropositive children negatively correlates with CD4+ lymphocyte count. *Biofactors*, 1998, 8:129–132.

15. *Manual on paediatric HIV care and treatment for district hospitals*. Geneva, WHO, 2011.

16. Naidoo R et al. The influence of nutritional status on the response to HAART in HIV-infected children. *Pediatric Infectious Diseases Journal*, 2010, 29:511–513.

17. Callens S et al. Mortality and associated factors after initiation of pediatric antiretroviral treatment in the Democratic Republic of the Congo. *Pediatric Infectious Diseases Journal*, 2009, 28:35–40.

18. Taye B, Shiferaw S, Enquselassie F. The impact of malnutrition in survival of HIV-infected children after initiation of antiretroviral treatment (ART). *Ethiopian Medical Journal*, 2010, 48:1–10.

19. Kim M et al. Prompt initiation of ART with therapeutic food is associated with improved outcomes in HIV infected Malawian children with malnutrition. *Journal of Acquired Immune Deficiency Syndromes*, 2012, 59:173–176.

20. Pollock L et al. Pharmokinetics of nevirapine in HIV-infected children with and without malnutrition receiving divided adult fixed-dose combination tablets. *Journal of Antimicrobial Chemotherapy*, 2009, 64:1251–1259.

21. Swaminathan S et al. Factors influencing plasma nevirapine levels: a study in HIV-infected children on generic antiretroviral treatment in India. *Journal of Antimicrobial Chemotherapy*, 2011, 66:1354–1359.

22. Wang M et al. Immune reconstitution inflammatory syndrome in human immunodeficiency virus-infected children in Peru. *Pediatric Infectious Diseases Journal*, 2009, 28:900–903.

23.   Ndeezi G et al. Effect of multiple micronutrient supplementation on survival of HIV-infected children in Uganda: a randomized, controlled trial. *Journal of the International AIDS Society*, 2010, 13:18.

24.   Irlam J et al. Micronutrient supplementation in children and adults with HIV infection (review). *Cochrane Database of Systematic Reviews*, 2007, (12):Art No. CD003650.

25.   Carbonnel F et al. Macronutrient intake and malabsorption in HIV infection: a comparison with other malabsorptive states. *Gut*, 1997, 41:805-810.

26.   Amadi B et al. Improved nutritional recovery on an elemental diet in Zambian children with persitant diarrhoea and malnutrition. *Journal of Tropical Pediatrics*, 2005, 51:5–10.

27.   Mda S et al. Short-term micronutrient supplementation reduces the duration of pneumonia and diarrheal episodes in HIV-infected children. *Journal of Nutrition*, 2010, 140:969–974.

28.   Bobat R et al. Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial. *Lancet*, 2005, 366:1862–1867.

29.   Luabeya K et al. Zinc or multiple micronutrient supplementation to reduce diarrhea and respiratory disease in South African children: a randomized controlled trial *PLoS ONE*, 2007, 2:e541.

30.   *Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months–14 years): handbook, chart booklet and guideline for country adaptation*. Geneva, WHO, 2009.

31.   *WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children*. Geneva, WHO, 2010.

32.   Barker D et al. HIV serostatus and recovery from severe childhood malnutrition: a retrospective matched case-control study. *West Indian Medical Journal*, 2004, 53:89–94.

33.   Simpore J et al. Nutritional rehabilitation of HIV-infected and HIV-negative undernourished children utilizing Spirulina. *Annals of Nutrition and Metabolism*, 2005, 49:373–380.

34.   Kerac M et al. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi. *Lancet*, 2009, 374:136–144.

35.   Violari A et al. Early antiretroviral therapy and mortality among HIV-infected infants. *New England Journal of Medicine*, 2008, 359:2233–2244.

36.   Purchase S, van der Linden D, McKerrow N. Feasibility and effectiveness of early initiation of combination antiretroviral therapy in HIV-infected infants in a government clinic of Kwazulu-Natal, South Africa. *Journal of Tropical Pediatrics*, 2011, 24 June (Epub ahead of print).

37.   McGrath C et al. Younger age at HAART initiation is associated with more rapid growth reconstitution. *AIDS*, 2011, 25:345–355.

38.   Yotebieng M et al. Effect on mortality and virological response of delaying antiretroviral therapy initiation in children receiving tuberculosis treatment. *AIDS*, 2010, 24:1341–1349.

39.   Liste M et al. Enteric virus infections and diarrhea in healthy and human immunodeficiency virus-infected children. *Journal of Clinical Microbiology*, 2000, 38:2873–2877.

40.   Rossit A et al. Bacterial, yeast, parasitic and viral enteropathogens in HIV-infected children from São Paulo State, Southeastern Brazil. *Diagnosis of Microbioligical Infectious Diseases*, 2007, 57:59–66.

41.   Ford A, Duke T, Campbell H. Evidence behind the WHO guidelines: hospital care for children: what is the aetiology and treatment of chronic diarrhoea in children with HIV? *Journal of Tropical Pediatrics*, 2009, 55:349–355.

42.   Amadi B et al. Intestinal and systemic infection, HIV and mortality in Zambian children with persistent diarrhea and malnutrition. *Journal of Pediatric Gastroenterology and Nutrition*, 2001, 325:550–554.

43.   Musiime V et al. Enteric bacterial pathogens in HIV-infected children with acute diarrhea in Mulago referral and teaching hospital, Kampala, Uganda. *Journal of the International Association of Physicians in AIDS Care*, 2009, 8:185–190.

44.   Amadi B et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet*, 2002, 360:1375–1380.

45. Abubakar I et al. Treatment of cryptosporidiosis in immunocompromised individuals: systematic review and meta-analysis. *British Journal of Clinical Pharmacology*, 2007, 63:387–393.

46. Amadi B et al. High-dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infectious Diseases*, 2009, 9:195.

47. Cello J, Day L. Idiopathis AIDS enteropathy and treatment of gastrointestinal opportunistic pathogens. *Gastroenterology*, 2009, 136:1952–1965.

48. Foudraine N et al. Improvement in chronic diarrhoea in patients with advanced HIV-1 infection during potent antiretroviral therapy. *AIDS*, 1998, 12:35–41.