

Wasting disease in African children: the challenges ahead

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The painful mouth, fever, diarrhea, and purulent foci, in addition to loss of appetite, severely impair the nutritional state of the child existing on a poor diet At the same time, the child whose diet lacks, calories or other essential nutrients may be the child whose skin and other epithelial surfaces are affected by..... in such a way as leads to severe, and at times dangerous, form of the disease with its many "complications"..... David Morley, 1978

Malnutrition is an important contributing factor in 5.6 million children who die annually. Severe acute malnutrition (SAM) is a direct cause in 2.7 million deaths. While the clinical syndrome kwashiorkor has impressed clinician and journalist alike, it are stunting, wasting disease and micronutrient diseases like anaemia, vitamin A and iodine deficiency which contribute most to the large global burden of malnutrition (-related) disease. As discussed in part I of this trilogy, 6 decades of understanding of the pathophysiology of severe malnutrition in children has enabled the world community and WHO to develop evidence-based therapeutic guidelines curing most malnourished children. We tend to have become less dogmatic and in anticipation of the many different, often adverse, environments realise why and how children become malnourished. Jackson and Golden defined the varied clinical presentations of malnutrition as determined by the severity, duration and complexity of interactions of specific macro- and micronutrient deficiencies. Both the impact of the nutrient deficits and susceptibility for infection decrease with age, the young being most vulnerable.

However, 30 years ago the HIV pandemic struck sub-Saharan Africa (s-SA) and its effects are dramatic. One disease altered the epidemiology, aetiology, clinical presentation, pathophysiology, case-management, and survival of severely malnourished children. Like measles, HIV infected children act differently, still incompletely understood and are currently not well served by the paradigm and therapeutic guidelines developed prior to HIV, as described in part 1 of this trilogy. This part II presents recent evidence hereof and describes how the Blantyre Working Group drafted an agenda for research, intervention and education, as published in the Lancets Viewpoint during the MDG Countdown Series.

WHO therapeutic guidelines need revision in the context of HIV co-morbidity

Current guidelines do not deal with the needs of HIV infected malnourished children, neither are these implemented universally in the region of highest need, where health services are severely eroded. In the past Nutrition Rehabilitation Units (NRU) typically admitted sick severely malnourished children during the post-weaning period. We now admit many HIV-infected malnourished children outside this age range and these cannot be managed according to standard guidelines without adaptation. HIV-infected (exposed or affected) young infants admitted with SAM are either perinatally infected with HIV or victims of early

weaning in PMTCT programmes. These infants present with multiple pathology and suffer from diseases like diarrhoea, pneumonia, PCP, extensive skin infections and oral thrush. In addition, older children (2-8 y.) are admitted with persistent and profuse diarrhoea due to HIV-related bacterial and parasitic infections of the gut; their response to therapy is poor and their case fatality is high. Increasingly extremely wasted and -stunted young adolescents, previously rarely admitted outside famines, are now admitted for nutritional recovery and present with HIV related multi-system disease. These include HIV related chronic lung disease, recurrent tuberculosis, HIV related cardiomyopathy, nephropathy, and encephalopathy, and recurrent infections, severe anaemia and Kaposi Sarcoma. Consequently, case-fatality rates still range between 20 and 50% despite the use of the WHO guidelines, SAM complicated by HIV has largely been neglected as an impediment to improving Child Survival. Presently in s-SA, severely malnourished children, within a wider age range, suffer both the synergistic effects of malnutrition and acute, severe infection with the additional complication of HIV infection. Whilst the concept of reductive adaptation in severe malnutrition has assisted us to understand and treat the derangements in malnourished children, whether this is applicable in HIV-infected malnourished children remains to be unresolved. Thus there is an urgent need to reconsider this paradigm in the context of HIV in order to determine the best approach to immediate care and optimal nutritional rehabilitation vii ii.

Changing paradigm of care

In high HIV prevalence communities where poverty, food insufficiency, epidemics and repeated infectious diseases are common, HIV may be the main driver of wasting or one of several co-morbidities in the individual child with SAM. Again this has changed the epidemiology of SAM as previously oedematous malnourished children were the typical sick malnourished ones facing us with therapeutic dilemmas. In addition, SAM and HIV infection often occur in a social milieu of extreme poverty and food insecurity, with the result that a high HIV infectious pressure affects even uninfected children, without infecting them, through all the socio-economic consequences of their caretakers' chronic and lethal disease. Severely HIV infected children presenting with SAM, and acute or chronic co-morbidity present challenging therapeutic and care pathways, also including palliative care. In the Malawian NRUs readmission is common and stands at 10%. In Zambia and Malawi more than half of the admissions to NRUs are HIV infected with up to 40% in hospital mortality in this group, in contrast to HIV uninfected SAM children who have a mortality rate of less than 10%. Under conditions where no early introduction of HAART takes place the fate of these HIV infected, still partially malnourished, children is disastrous. Cumulatively two third of the original sample admitted to hospital don't survive.

The Blantyre Working Group's response: a research,

intervention and policy agenda

In 2007, fifty clinical and public health child scientists and practitioners from diverse areas within s-SA gathered in Blantyre-Malawi and established the Blantyre Working Group (BWG). This was the first time that this regional capacity was drawn together. Participants, collectively caring for more than 100,000 severely malnourished children per year, included many who have been trainers on the WHO therapeutic guidelines. As a consequence most NRUs and CTC programs in the region now follow these protocols. However it is clear that, despite all efforts, the disease burden and case-fatality rates remain high and that present WHO therapeutic guidelines should address today's realities in the region. The members of BWG presented and discussed recent experiences, dilemmas and challenges in the management of SAM in the context of HIV and concluded that SAM in the HIV infected individual is genuinely a different clinical entity, and treating them requiring a new paradigm.

The challenges ahead

Despite the widespread availability of HIV diagnostic testing, HAART, the implementation of WHO guidelines and RUTF, the HIV infected child with complicated SAM in s-SA is likely to have slower recovery rate, and case-fatality rates more than 4 times greater than in SAM without HIV xvii. Hence, the results in our region do not approach those suggested by the WHO guidelines and the increased fatality rate is not simply the result of failing to effectively implement WHO standard management guidelines. This was recognised during the WHO consultations 2004 and 2005. Therapeutic options in both SAM and HIV have increased, but many questions have arisen and new therapeutic guidelines are urgently needed based on evidence from the region of high HIV prevalence. The BWG formulated four areas to guide the development of improved treatment recommendations, and one to improve the continuum of care of SAM children infected with HIV. It is anticipated that presentations and deliberations during the 10th CAPGAN conference will strengthen and extend this agenda for improving Child Survival in sub-Saharan Africa.

The management of systemic infections

Severe illness occurring in children with HIV and SAM is often due to the coincidence of multiple infections and the metabolic adaptations of malnutrition, and the case fatality rates remain high. As early in-hospital mortality is high appropriate initial treatment strategies should include both antimicrobial therapies and supportive care. The former depends on knowledge of aetiology and antimicrobial susceptibilities, pharmacokinetics in malnourished children and complex interactions with HAART and/or other anti-infective drugs including TB therapy. Improving supportive care requires rapid identification and correction of life threatening complications, which is the standard recommended for non-malnourished children, but not currently advocated for this group due to fears of adverse outcome in the malnourished child which has adapted to its reduced body mass and -functions. There is evidence that antimicrobial sensitivity to first line antibiotic treatment according WHO guidelines is totally inadequate and second line (usually a combination of ampicillin /

chloramphenicol and gentamicin) varies between centres, and that recommended second line agents may not be ideal. The prevalence of childhood tuberculosis has doubled in the region due to HIV. In South Africa, among children with community acquired lower respiratory tract infection, TB was identified 22 times more commonly among HIV-infected children. New and creative approaches to diagnosis are needed in children with SAM and concurrent HIV infection and tuberculosis as clinical scoring systems perform poorly, tuberculin skin testing is insensitive, radiological appearances are frequently non-specific, lymphocyte stimulation tests yet do not distinguish active- from latent disease, sputum samples are difficult to obtain and often have low numbers of mycobacteria and culture facilities are expensive and rarely available in the region.

Therapeutic diets composition, timing and long-term effects

The introduction of evidence based therapeutic diets, like F75, F100, ReSoMal and Ready to Use Therapeutic Food (RUTF) has improved the rehabilitation process and shortened admission times of non-HIV infected severely malnourished children and contributed to a continuum of care within district child health systems. They have become vehicles to adequately address micro- and macronutrient deficiencies, despite the fact that the use of F100 and RUTF in the transition phase is still not well established due to frequently occurring diarrhoea resulting from their increased osmolality. However, with the advent of young HIV-infected infants suffering from SAM the question of requirements and formulations needs further consideration and investigation. The metabolic requirements and -system in the HIV infected child suffering from SAM is altered, but we are not yet fully aware to which extent and how to remedy this. RUTF and its local production has revolutionised the management of children suffering from SAM and assisted African child health services to use their limited (human) resources more effectively and efficiently. However, dietary advice during recovery from severe malnutrition in HIV infected children is almost certainly inadequate which warrants further studies. What are the optimal diets? We perceive that the metabolic needs are different, but in what way? Is there a problem with the damaged gut and traditional therapeutic foods? Is there a need for a new food, in the acute resuscitation phase of the management of SAM, and/or diets that can be used in transition to RUTF? Do SAM HIV-infected children always enter a phase of reductive adaptation and why do they more often present with marasmus than with kwashiorkor? Are diets with higher energy and nutrient densities tolerated in the reductive adapted phase, and will their use result in higher intakes? Is appetite still a useful guide to recovery in HIV infected severely malnourished children? Which supplementary micronutrients do in HIV infected SAM children reduce morbidity and mortality, and at which stage of recovery should these be given? Feeding regimes during the occurrence of purging diarrhoeas in the different rehabilitative stages in severe malnourished children pose a problem, as presented from Lusaka where unmanageable diarrhoea, mainly caused by *C. parvum* is often associated with an increased case fatality irrespective of HIV status. Suitable diets for use in children under 6 months of age are needed as the present F 75 and F100 are inadequate for them. However, the low resourced environments in which our

patients live contra-indicates the use of existing commercial formulae, also for HIV exposed HIV negative infants post-weaning after 6 months exclusive breastfeeding .

Management of diarrhoea, hypovolaemia and dehydration

One of the most striking observations made in the HIV infected SAM population is the prevalence, severity and protracted nature of diarrhoeal episodes on admission and during its attempted nutritional rehabilitation process. Preceding the HIV epidemic high purging rates and persistent diarrhoea in SAM have shown to be associated with gram-negative infections and zinc deficiency, malabsorption or differences in intestinal flora and adequate treatment regimes were developed to reduce diarrhoeal incidence and increase catch-up growth rates. However, co-morbidity and chronic multiple pathology has unpredictably altered metabolic processes and electrolyte- and water balances in severely malnourished children. The spectrum of HIV enteropathy remains incompletely defined. In children hospitalised with diarrhoea positive HIV status and carbohydrate malabsorption were strongly associated with septicaemia . Carbohydrate malabsorption may be a marker of impaired gut integrity and thus predisposition to bacterial translocation. The spectrum of organisms (i.e. *K. pneumonia*, *E. coli*, *Salmonella* species and *P. aeruginosa*) associated with septicaemia episodes in this and other studies further supports the role of bacterial translocation in the pathogenesis of systemic sepsis. Interventions to maintain mucosal integrity and/or prevent bacterial translocation need further study in HIV-infected children with persistent diarrhoea. The efficacy of empiric management of small bowel bacterial overgrowth in children with persistent diarrhoea as extrapolated from the pre-HIV epidemic may not be generalisable to HIV-infected children with SAM and persistent diarrhoea. Fluid and nutritional management in HIV-infected children with SAM is challenging, severe wasting makes clinical assessment of dehydration difficult so that presence of metabolic acidosis and lethargy often alert one to the need for resuscitation .

Management, timing and impact of anti retroviral therapies

There are few prospective studies on the long term outcomes of children with SAM, and almost none on SAM complicated by HIV. Before the advent of HAART, body composition studies found weight gain predominantly represented fat deposition rather than lean body mass; suggesting altered recovery of body composition in HIV . The role of HAART in improving nutritional status is increasingly recognised, yet wasting can resolve in children on nutritional therapy alone, probably reflecting background food insecurity or a complicating, treatable co-morbidity. The use of high energy therapeutic feeds (e.g. F100 or RUTF) for HIV-infected children with SAM remains part of the nutritional standard care at least until recovery from acute wasting. However mortality within 4-6 weeks remains high (38%) in SAM complicating HIV viii , and the optimal timing for addition of HAART is unknown or how to coordinate with TB treatment. Current practice is to start ART after acute malnutrition and opportunistic infections have been successfully treated. However, with some infections (e.g. CMV), it is recognised that control of viral load, and initial immunological recovery will be necessary before, nutritional and overall, recovery can occur. Similarly, those children in whom nutritional therapy fails to cause weight gain -despite energy intakes double normal requirements- will not recover without HAART. HAART in these children

will control viral replication and allow some immunological contribution to infection resolution. A lack of response to antimicrobials and feeding would suggest a more proactive approach appropriate. As the effect of ARTs are not rapid, these children will still need to be supported for some weeks before the benefits of HAART occur, and mortality in this high risk 'salvage' group is substantial.

The position in the majority of HIV infected children with SAM who respond to nutrition care is less clear. Where CD4 counts and DNA-PCR are available, these can guide who requires earlier initiation treatment. About a quarter (unpublished, Bunn 2008) will have a CD4% above that indicated for treatment, possibly representing food insecurity rather than advanced disease. Those without other stage 3 or 4 disease should be commenced on co-trimoxazol and may be watched. In those requiring HAART, the timing of this is a balance between any advantage on survival, and any adverse effects. Commencing ARTs in children where reductive adaptation will have reduced renal and hepatic function, and where micronutrient status is initially poor, may predispose to greater toxicity. In addition some ART compromise mitochondrial function and enhance oxidative stress; both implicated in the pathogenesis of oedematous malnutrition, and therefore could potentially precipitate oedema in vulnerable children. Immune reconstitution syndromes are recognised on recovery from SAM, TB and HIV these syndromes are as yet poorly defined clinical entities, as these present with a clinical deterioration within a few weeks of treatment, and there is no confirmatory laboratory test yet. The combination of SAM and HIV treatment concurrently might be associated with this, and might contribute to the high mortality within a few months of starting ARTs.

The optimal drug doses for HAART in SAM children are unknown, and it is expected that markedly altered drug absorption, distribution, metabolism and excretion occur in these children, particularly in the first weeks following presentation with SAM. This will change with nutritional recovery, as cellular and organ function recover. There is a need for pharmacokinetic studies of ART drugs in SAM, and during recovery, to confirm or establish the correct ART doses for children recovering from SAM. However, the more important question (which cannot be resolved before pharmacokinetic data is available), will be the optimal timing of HAART in SAM, and this will require an RCT of early (after initial stabilisation), versus later (after discharge) HAART in HIV related SAM. The outcome of interest would be long term survival and nutritional status after 6-12 m. of treatment. Until this is addressed we are unable to advise on the optimal timing to start HAART.

A Continuum and Synergy of Care

A particular advantage of CTC is the smaller number of staff that is needed to run CTC programmes and that compliance is higher. In order to develop regionally appropriate and local child health specific programs maintaining this continuum of care for these children - who often are orphans and thus without direct caretakers - the roles and functions of the entire child health system need to be transparent and clear, the triage, admission and discharge criteria of these children at each level of care need to be unambiguous, and adequate numbers of staff need to be present and educated to understand and handle these hitherto incompletely understood clinical syndromes. Latter is an important task

of medical schools and nursing colleges which hitherto do not avail as yet over up to date learning materials, texts or textbooks. Local production of weaning foods and a variety of therapeutic foods in Malawi has offered affordable and appropriate infant feeding solutions to child health systems. Can operational projects be translated into more programmatic child health systems approaches in the region? Operational studies should explore the indications for use, the delivery chain, local manufacturing options of these commodities and the role of governments and non-governmental organisations.

The way ahead: moving the agenda and ownership to the area of high prevalence

Ideally, major curative medical advances are based on careful clinical observations framed within a pathophysiological paradigm, followed by hypothesis generation and testing. Resulting research data should inform improved management protocols that are then introduced to the operational settings. The BWG is convinced this will be true for childhood SAM and HIV. Randomized controlled trials exploring the timing and dosing of ART in SAM, the therapeutic feeding of individuals with SAM and HIV, and the management of acute infection and diarrhea based on successful pilot projects are urgently needed. There is a critical mass of thoughtful clinician scientists engaged to address the issue with the will to succeed. Young clinical scientists from s-SA need to be recruited to this body and talented young physicians need to be supported. The synergism between HIV/AIDS, malnutrition and (opportunistic) infections, contributing to much of the child mortality in s-SA, makes it morally imperative to utilise -with the limited human resources available in s-SA- the large sums presently available for Maternal Neonatal Child Health Initiatives and for HIV/AIDS in a joint manner. Only then are we able to develop and drive effective interventions, operational research in a manner which guarantees ownership locally and support to educational institutions and health systems which are so neglected.

Funding agencies need to better understand the context in which such conditions are treated and the operational conditions in which research will be undertaken. Support is needed, not just in providing funds, but to optimise the design and implementation of studies that are patently tackling the right issues. This will not only address the research questions but will also serve to build the scientific base and competency within the region. Operational support is needed for facilities and national programs committed to treated these children in accordance with the best available evidence and systematically document lessons and insights.

A call to action is in order - that the international scientific, health and donor communities join together to defeat the devastating scourge HIV and malnutrition, which was barely acknowledged in national AIDS plans and the 2003 Child Survival Series.

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