NUTRITION AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN CHILDREN

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Objectives. To review the relationship between nutrition and paediatric HIV infection, and to discuss treatment options and their applicability to situations with scarce resources.

Results. Growth failure and malnutrition are frequent complications of paediatric HIV infection. Intra-uterine growth of infants born to HIV-seropositive mothers is compromised, and paediatric HIV infection causes early and progressive growth failure throughout childhood. Furthermore, micronutrient deficiencies are widespread and may accelerate immunological deterioration. Dysfunctional gastro-intestinal and metabolic processes underpin many of these growth changes. Although nutritional requirements of HIV-infected children have not yet been optimised, certain interventions such as improving energy intake may improve general well-being while vitamin A supplements reduce infectious complications during the early course of the disease.

Conclusion. Further research is needed to optimise the nutritional requirements in children with HIV infection, and to identify specific micronutrient supplements which may further reduce the frequency and severity of secondary infections.

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HIV continues to have a major impact on child health and survival worldwide. Of the more than 1.5 million children who have already developed AIDS, 85% reside in sub-Saharan Africa.[1] Seventy-five per cent of all infected children die before the age of 5 years, the majority because of opportunistic infection or malnutrition. In South Africa the true extent of the problem is unknown. However, if one extrapolates from the Sixth National HIV Seroprevalence Survey conducted among women attending antenatal clinics, approximately 40 000 HIV-infected infants were born in South Africa in 1995.[2]

HIV infection is most prevalent in developing countries, where malnutrition abounds.[3] A study indicated that 56% of child deaths in these countries may be attributed to the

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potentiating effects of malnutrition.[4] Growth failure and malnutrition are frequent concomitants of HIV infection. Nearly everyone with HIV infection will eventually develop growth failure, which shortens survival time. Furthermore, recurrent infections, including diarrhoeal disease and respiratory infections caused by declining immune function, compound growth failure and malnutrition.

The purpose of this article is to review the relationship between HIV infection and nutrition, and to discuss management strategies, and their applicability to situations with scarce resources.

GROWTH FAILURE AND MALNUTRITION IN HIV-INFECTED CHILDREN

Growth and nutritional changes

Several studies indicate that intra-uterine growth of infants born to HIV-seropositive mothers is compromised. A study from Zambia found that the prevalence of low birth weight (< 2 500 g) was higher in infants born to seropositive than in those born to seronegative mothers. The prevalence of prematurity was similar in the two groups.[5] A recent study from Rwanda showed that birth weight, crown-to-heel length, head circumference and placental weight were lower in infants born to seropositive mothers. Maternal HIV-1 infection was significantly associated with intra-uterine growth retardation, but not with prematurity. Furthermore, differences in body mass index and weight/head ratio suggested that the impact on fetal growth was greater towards the end of pregnancy.[6] Another study (from Zaire) showed that the severity of maternal disease influences the degree of growth retardation. Intra-uterine growth of children born to mothers with AIDS was more compromised than that of children born to seropositive mothers without AIDS.[7] However, studies comparing growth at birth of infected and uninfected infants born to HIV-seropositive mothers have shown their growth to be similarly compromised; in particular, there were no significant differences in birth weight and the prevalence of prematurity.[8,9]

Paediatric HIV infection causes early and progressive decrements in attained linear growth and growth of mass, early and sustained decrements in head growth and marked decrements in body mass index. Postnatal growth differences between infected and uninfected children are maintained throughout childhood.[10,11] However, while uninfected children born to seropositive mothers show catch-up growth, infected children fail to catch up.[9]

Changes in body composition reflect changes in water, protein, fat and mineral content. Depletion of total body potassium, intracellular water, and somatic and visceral protein, as well as variable depletion of body fat, occur in adults with AIDS.[12-14] Furthermore, timing of death in adults is related to magnitude of depletion of total body potassium, a

Table I. Growth and nutritional changes in HIV infection

Mean birth weight is lower in infants of seropositive than seronegative mothers.

Growth parameters at birth are similar for infected and uninfected infants born to seropositive mothers.

Mean birth weight is lower in infants born to mothers with AIDS than to seropositive mothers without AIDS.

Postnatal growth is significantly impaired from 3 months of age.

Postnatal growth is compromised throughout childhood.

Preferential muscle wasting over fat wasting occurs.

Somatic and visceral protein depletion occur.

Essential amino acid depletion occurs.

Multiple trace element, vitamin and electrolyte deficiencies occur.

measure of body cell mass.[15] Similar body composition changes occur in HIV-infected children. Findings indicate that preferential muscle wasting over loss of fat stores occurs (Table I).[8]

In developing countries the burden of malnutrition among HIV-infected children is usually greater and more severe than in the general paediatric population. A local study of 240 infected children showed that at diagnosis (median age of 6 months) 64% were below 80% of expected weight for age (EWA) and 18.5% were below 60% EWA.[16] This contrasts with national figures indicating that about 10% of all South African children aged 6 - 71 months are below 80% EWA.[17] Similarly, a study conducted in Zimbabwe showed that of 219 HIV-infected children, 52% were below 80% EWA and 26% were below 60% EWA. In contrast, of 485 non-infected children assessed, 21% were below 80% EWA and 6% below 60% EWA.[18] Two smaller descriptive studies from South Africa have confirmed the high prevalence of failure to thrive and malnutrition among infected children.[19,20]

Micronutrient status

A number of studies of infected adults have documented many micronutrient deficiencies. In 100 patients, low blood levels of vitamin A (18%), vitamin E (27%), riboflavin (26%), vitamin B_6 (53%), vitamin B_{12} (23%), copper (74%) and zinc (50%) were documented. With exception of riboflavin, zinc and copper, a similar prevalence of abnormalities among seronegative controls was not observed.[21] In another study 87% of patients sampled had at least one micronutrient deficiency. More than 10% of these patients had vitamin A, vitamin B_6, vitamin C, vitamin E, b-carotene, zinc, calcium and magnesium deficiencies.[22] Furthermore, a study of 70 patients with HIV infection documented deficiencies of vitamin A (5%), vitamin E (27%), vitamin C (7%) and selenium (10%).[23] In children a number of micronutrient deficiencies, including retinol and tocopherol, have been documented early in the course of infection.[24] The significance of micronutrient deficiencies in HIV infection is discussed below.

MALNUTRITION AND IMMUNITY

Malnutrition affects immunity adversely and predisposes to opportunistic infections. Most host defences are breached in protein-energy malnutrition, particularly cell-mediated immunity. Immunological changes include decreased total and helper T-cell counts, reversal of helper/suppressor cell ratio, cutaneous energy, decreased lymphokine production and decreased alloreactivity. Similar abnormalities are found in HIV infection.[25] Deficiencies of many nutrients have been documented in HIV infection, including those essential for normal immune function such as copper, zinc, iron, selenium, magnesium, folic acid, vitamin C, vitamin B_6, vitamin B_{12}, β-carotene and vitamin E.[26,27] Therefore, micronutrient deficiencies may compound immune dysfunction in HIV infection. A study showed that vitamin A concentration correlated significantly with natural killer cell counts, and with IgG concentration. Furthermore, vitamin C and selenium levels correlated with IgM concentration, but vitamin E concentration did not correlate with any immune parameter.[23] Of 75 children with HIV infection, 50% had marginal vitamin A status, and 12% were vitamin A deficient. A positive correlation between vitamin A concentration and CD4+ T-lymphocyte count, and a negative correlation between vitamin A concentration and IgG concentration were documented. Vitamin A supplementation increased vitamin A, total lymphocyte, CD4+ lymphocyte and natural killer cell concentrations significantly.[28] A study of 11 adults with HIV infection showed that β-carotene supplementation increased the percentage of natural killer cells and activated lymphocytes.[29] Furthermore, vitamin B_6-deficient patients with HIV infection had significantly decreased lymphocyte responses to phytohaemagglutinin and pokeweed mitogen, and reduced natural killer cytotoxicity compared with subjects with adequate vitamin B_6 status.[30] Growth failure often precedes the onset of opportunistic infections.[31] Therefore growth monitoring and appropriate interventions are necessary to limit nutritional deterioration in HIV infection.

PATHOGENESIS OF GROWTH AND NUTRITIONAL DISTURBANCES

Several mechanisms are responsible for growth failure and malnutrition in HIV infection. These include decreased dietary intake, intestinal malabsorption and increased excretion of nutrients, abnormal energy utilisation and increased requirements. Weight loss usually follows one of two general patterns, either cachexia or malnutrition. In HIV infection features of both cachexia and malnutrition commonly coexist.[32]

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Gastro-intestinal dysfunction

The gastro-intestinal tract is a common target for disease in HIV infection. Diminished oral intake may result from oral, pharyngeal and oesophageal diseases, neuropsychiatric disorders, and conditions associated with anorexia. The results of adult studies lend support to the view that reduced intake is

an important cause of growth failure and malnutrition. One study found that while calorie intake was similar in HIV infection, AIDS and seronegative controls, patients with AIDS and secondary infections caused by *Pneumocystis carinii*, cytomegalovirus (CMV) and bacterial organisms experienced a 36% reduction in calorie intake. Anorexia caused these patients to consume 17% fewer calories than their required resting energy expenditure (REE).[33] Another study documented reduced food intake and significant weight loss in adults with asymptomatic HIV infection or AIDS-related complex.[34]

Persistent or recurrent diarrhoeal disease and malabsorption have been implicated in the pathogenesis of growth failure.[35] A review of 210 children showed that 43% had had diarrhoea during the course of their disease.[16] Pathogens may be identified in about 50% of infected patients with chronic diarrhoea. In patients without an identifiable secondary organism, HIV has been directly implicated.[35,36] Sugar malabsorption, steatorrhoea and faecal protein loss were detected in 26%, 36% and 17% of symptomatic HIV-infected children, respectively.[37] Other studies have documented a strong association between persistent diarrhoea and lactose malabsorption.[38] Iron and vitamin B_{12} malabsorption have also been described.[37,39] Furthermore, gastric acid hyposecretion may decrease the absorption of iron and other micronutrients, and facilitate enteric infection.[40,41]

Metabolic dysfunction

Increased REE has been documented in adults with HIV infection,[33,42,43] but is not a consistent feature. Decreased REE was reported in stable patients with AIDS.[13] Another study showed that while most subjects were hypermetabolic, 32% were either normometabolic or hypometabolic.[43] The extent to which increased REE influences weight loss remains unresolved. While weight trend correlated with calorie intake, it did not correlate with REE.[33] Although REE may be increased in HIV infection, activity energy expenditure is likely to be reduced, particularly in the latter stages of HIV infection. This should compensate for the increased REE, except where secondary infections cause increased anorexia and catabolism, aggravating lean tissue loss.[44]

Altered lipid metabolism occurs in HIV infection. In advanced disease, plasma triglyceride (TG) and free fatty acid levels, and *de novo* hepatic lipogenesis are increased, while plasma cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol are decreased. TG clearance is slower, and total, hepatic and lipoprotein lipase activities are significantly depressed. Hypertriglyceridaemia, however, does not correlate with the degree of wasting.[45-47] Some researchers have argued that elevated lipogenesis causes hypertriglyceridaemia and retards fat oxidation, facilitating lean body mass attrition. Increased lipogenesis is therefore maladaptive, because preservation of lean body mass would be expected to assume precedence in HIV infection. Metabolic

costs associated with lipogenesis may contribute to hypermetabolism.[47] Others have proposed that futile cycling causes increased energy expenditure and growth failure in HIV infection. The metabolic costs associated with cyclical lipolysis and lipogenesis, i.e. fatty acids being shuttled from adipose tissue to the liver and back again, result in hypermetabolism and weight loss.[48]

Attrition of somatic and visceral proteins are features of HIV-associated malnutrition.[12-15] Studies of protein turnover have yielded conflicting results. One study documented significantly decreased whole-body protein synthesis and breakdown, and reduced fibrinogen synthetic rates in adults with AIDS.[49] Another study suggested that protein turnover is increased.[50] More recently, increased protein turnover with no change in protein balance was reported in advanced HIV infection.[51]

Pro-inflammatory mediators have been implicated in the genesis of wasting and growth failure in HIV infection. Cytokines may induce anorexia, alter lipid metabolism, accelerate protein breakdown and elevate energy expenditure.[48] Lipid metabolism may be altered by interferon-α. Interferon-α concentration correlates with TG concentration and TG clearance in patients with asymptomatic HIV infection or AIDS.[46,52] Furthermore, antiretroviral therapy is associated with improved nutritional status and reduced levels of interferon-α and TGs in patients with AIDS.[53] Other cytokines including tumour necrosis factor, interleukin-1 and interleukin-6 may be involved in HIV-related wasting.[48]

Endocrine dysfunction may also cause growth failure. A study suggested that partial growth hormone (GH) resistance occurs in HIV infection.[54] Short-term administration of recombinant human GH to HIV-seropositive adults resulted in progressive weight gain, increased protein anabolism and increased protein-sparing lipid oxidation.[55] However, a multicentre trial showed that patients given insulin-like growth factor I and GH had similar weight and lean body mass changes compared with control subjects 12 weeks after commencing therapy. Initial weight gain was due to increased body water and not to increased lean body mass.[56] Subnormal thyroid, adrenal and testicular function have been documented in HIV infection,[57-60] but whether endocrine abnormalities are significant in HIV-related growth failure remains unresolved.

NUTRITIONAL MANAGEMENT

Breast-feeding and HIV infection

HIV infection may be transmitted postnatally from breast-milk to the developing infant. An analysis of five studies showed that for mothers infected antenatally, the additional risk of transmission from breast-feeding is 14%.[61] Although the accuracy of this meta-analysis has been questioned, a cohort study, based on serial polymerase chain reaction testing, produced a similar estimate.[62] Furthermore, the risk of breast-milk transmission from mothers who become infected with

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HIV-1 postnatally is 26%.[61] In ideal situations, HIV-seropositive mothers should be encouraged to bottle-feed.

However, universal breast-feeding is advocated as it is associated with reduced paediatric morbidity and mortality. Because of socio-economic circumstances, many mothers cannot afford to bottle-feed. Expenditure needed to implement formula feeding schemes for all infants of HIV-seropositive mothers is prohibitive. Cost considerations include subsidisation of formula milk, development of laboratory services to undertake comprehensive HIV antibody testing, provision of test kits, education to promote the service and counselling facilities. Furthermore, domestic expenditure is appreciable. In 1994 the cost of feeding a 3-month-old infant with 800 ml formula milk per day ranged from 27% (Zimbabwe) to 900% (Uganda) of the daily wage of a hospital cleaner.[63] Breast-feeding policy is therefore unlikely to change in developing countries in the immediate future.

South Africa currently abides by the 1992 WHO/UNICEF consensus statement on HIV transmission and breast-feeding, which advocates universal breast-feeding.[64] Interim results of a study to determine the effect of breast-feeding on vertical transmission of HIV-1 in Soweto recently showed that significantly more breast-fed than formula-fed infants were infected in the first 18 months of life (53/114 (46%) v. 4/49 (8%); $P = 0.002$).[65] In the light of these findings, and the statement formulated at the recent 'Breastfeeding choices for the HIV-seropositive mother' conference in Durban indicating that policy for this country should take into consideration settings where the risk of HIV transmission is greater than the protective effect of breast-milk, national policy should be critically reappraised.[66] Although a formula-feeding policy for infants of HIV-seropositive mothers may unwittingly discourage healthy mothers from breast-feeding, if implemented as part of a comprehensive programme to reduce vertical transmission, it would undoubtedly help reduce the burden of paediatric HIV infection in South Africa and limit any negative effect on breast-feeding by seronegative mothers.

Treatment of HIV infection

Antiretrovirals are able to alter the natural history of paediatric infection. Zidovudine causes appreciable weight gain in children.[67] Current evidence suggests that combination antiretroviral therapy is superior.[68] Prophylactic intravenous immunoglobulin therapy, particularly in children with peripheral CD4+ counts of ±200/mm³, decreases the frequency of minor infections and delays the development of serious bacterial infections, thereby slowing nutritional deterioration.[69] Vigorous treatment of opportunistic infections prevents deterioration of nutritional status. Patients with untreated CMV infection experience progressive decline in nutritional status, while those treated with ganciclovir gain weight, and experience repletion of body cell mass and body fat and increased serum albumin concentrations.[70] Furthermore,

wasting illnesses such as CMV and *Mycobacterium avium-intracellulare* infections cause depletion of body cell mass.[15] Although HIV-associated diarrhoea often responds poorly to conventional therapy, investigation is necessary to identify those patients with treatable conditions.[35] Many drugs used in the management of HIV infection are expensive, and beyond the health budgets of most developing countries, including South Africa.

Nutritional support

Regular clinical assessment should include a history of feeding problems, gastro-intestinal symptoms and intercurrent infections; serial recording of growth parameters; examination for signs of overt malnutrition; and frequent monitoring of haemoglobin and other red blood cell indices to detect anaemia. Children with evidence of growth failure should, in addition, be screened for gastro-intestinal infections, malabsorption and micronutrient deficiencies, and have a detailed dietary assessment.[71,72] Acute severe malnutrition should be managed according to standard clinical practice (Table II).[73]

Table II. Treatment principles of acute severe malnutrition

Prevent and treat hypoglycaemia and hypothermia.
Prevent and treat dehydration.
Prevent overhydration.
Correct electrolyte imbalances.
Treat infections.
Correct micronutrient deficiencies.
Introduce feeds slowly.
Allow for catch-up growth during convalescence.
Provide emotional and intellectual stimulation.
Provide adequate follow-up after discharge.

Nutritional recommendations for HIV-infected children are largely based on theoretical considerations. Age-related macro- and micronutrient requirements have not been optimised. Recommended daily allowances (RDAs) applicable to normal children are used as guidelines, but those who fail to thrive require additional nutrition for catch-up growth.[72] Extra calories may be provided by glucose polymer, medium-chain TG or vegetable oil preparations, or high-energy foodstuffs.[71] A recent study cautioned against widespread use of dietary fish oil as it was associated with a trend towards decline in CD4+ cell numbers.[74] Daily vitamin and trace element supplements are recommended, provided that dosages do not exceed RDAs.[72] Dietary modifications such as lactose-free diets for lactose intolerance, and enteral or parenteral alimentation for patients who fail to thrive despite adequate oral feeds, should also be considered.[38,75] Enteral alimentation in HIV-infected children causes weight and arm fat area gains, but not height or arm muscle area changes.[75] Intravenous alimentation may be considered if enteral alimentation proves ineffective. Adult

AIDS patients gain weight, and increase body fat and body cell mass in response to parenteral nutrition.[76,77] Studies indicated that the risk of infection from central venous catheters is not increased in HIV infection. Practical constraints, however, prevent widespread use of parenteral nutrition.[77,78]

Dietary supplements, such as medium-chain TGs and parenteral feeding, are expensive. However, regular dietary supplementation may be possible in many HIV-infected children in developing countries. A study from Zimbabwe indicated that regular use of a commercial substitute which provided protein, energy and micronutrient supplements resulted in appreciable weight gain in HIV-infected children.[79] A study from Cape Town showed that vitamin A supplementation resulted in significant short-term increases in total lymphocyte, CD4+ and natural killer cell counts.[28] Furthermore, a study from Durban indicated that regular vitamin A supplementation resulted in reduced morbidity, particularly morbidity associated with diarrhoeal disease. In this study, HIV-infected children received 50 000 IU of vitamin A at 1 and 3 months, 100 000 IU at 6 and 9 months, and 200 000 IU at 12 and 15 months of age.[80] Whether these and other relatively inexpensive measures are able to produce sustained benefits such as improved quality of life and reduced infectious complications remains to be corroborated by or established in further clinical trials.

Pharmaceutical preparations

Therapies to improve nutritional status and prevent wasting are being evaluated. Megestrol acetate, a synthetic derivative of progesterone, is able to increase weight by stimulating appetite and increasing calorie intake. Weight gain is primarily due to increased body fat. The results of a pilot study of 7 children with HIV infection showed that significant weight gain occurred in all patients over the first month of therapy and sustained weight gain occurred in 5 and 3 patients over 3 and 5 months, respectively.[81] Although therapy appears to improve general well-being, it does not prolong survival in adults.[82] Results of clinical trials in children are awaited with interest.

Other drugs that are being considered include:
(i) dronabinol (delta-9-tetrahydrocannabinol), the psycho-active substance of marijuana; (ii) pentoyfilline, an inhibitor of tumour necrosis factor; (iii) cyproheptidine, an antihistamine with appetite-stimulant properties; and (iv) glucocortico-steroids.[32,83]

CONCLUSION

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The majority of HIV-infected children live in impoverished circumstances with limited access to health care. Growth failure and malnutrition often complicate the course of HIV infection and influence outcome. Therefore, improved nutritional support may reduce morbidity, particularly during the early stages of the disease. Nutritional interventions are currently

based on guidelines applicable to normal children. Optimisation of RDAs for children with HIV infection may result in further benefits, particularly in developing countries where access to antiretrovirals and other drugs is constrained by socio-economic circumstances.

References

1. The status and trends of the global HIV/AIDS pandemic: Final Report. XI International Conference on AIDS, Vancouver, 5 - 6 July 1996.
2. Department of Health and Population Development. Sixth national HIV survey in women attending antenatal clinics of the public health services in Republic of South Africa. *Epidemiological Comments* 1996; **23:** 3-14.
3. Merson MH. Slowing the spread of HIV: Agenda for the 1990s. *Science* 1993; **260:** 1266-1268.
4. Pelletier DL, Frongillo EA jun, Schroeder DG, Habicht J-P. The effects of malnutrition on child mortality in developing countries. *Bull World Health Organ* 1995; **73:** 443-448.
5. Hira SK, Kamanga J, Bhat GJ, et al. Perinatal transmission of HIV-1 in Zambia. *BMJ* 1989; **299:** 1250-1252.
6. Bulterys M, Chao A, Munyemena S, et al. Maternal human immunodeficiency virus 1 infection and intrauterine growth: a prospective cohort study in Butare, Rwanda. *Pediatr Infect Dis J* 1994; **13:** 94-100.
7. Ryder RW, Nsa W, Hassig SE, et al. Perinatal transmission of the human immunodeficiency virus type 1 to infants of seropositive mothers in Zaire. *N Engl J Med* 1989; **320:** 1643-1648.
8. Miller TL, Evans SJ, Orav EJ, Morris V, McIntosh K, Winter HS. Growth and body composition in children infected with the human immunodeficiency virus-1. *Am J Clin Nutr* 1993; **57:** 588-592.
9. Saavedra JM, Henderson RA, Perman JA, Hutton N, Livingston RA, Yolken RH. Longitudinal assessment of growth in children born to mothers with human immunodeficiency virus infection. *Arch Pediatr Adolesc Med* 1995; **149:** 497-502.
10. Moye J, Rich KC, Kalish LA, et al. Natural history of somatic growth in infants born to women infected by human immunodeficiency virus. *J Pediatr* 1996; **128:** 58-69.
11. McKinney RE, Robertson JW. Duke Paediatric AIDS Clinical Trials Unit. Effect of human immunodeficiency virus infection on the growth of young children. *J Pediatr* 1993; **123:** 579-582.
12. Kotler DP, Wang J, Pierson RN jun. Body composition studies in patients with acquired immunodeficiency syndrome. *Am J Clin Nutr* 1985; **42:** 1255-1265.
13. Kotler DP, Tierney AR, Brenner SK, Couture S, Wang J, Pierson RN jun. Preservation of short-term energy balance in clinically stable patients with AIDS. *Am J Clin Nutr* 1990; **51:** 7-13.
14. Kotler DP, Gaetz HP, Lange M, Klein EB, Holt PR. Enteropathy associated with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **101:** 421-428.
15. Kotler DP, Tierney AR, Wang J, Pierson RN jun. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *Am J Clin Nutr* 1989; **50:** 444-447.
16. Burgess J, Reynhard R, Strebens A, Potgieter S, Schaaf S, Hussey G. The natural history of human immunodeficiency virus infection in Cape Town children (Abstract). Presented at 1995 Annual Research Day, Department of Paediatrics and Child Health, University of Cape Town.
17. South African Vitamin A Consultative Group. Anthropometric, vitamin A, iron and immunisation coverage status in children aged 6-71 months in South Africa, 1994. *S Afr Med J* 1996; **86:** 354-357.
18. Nathoo KJ, Nkrumah FK, Ndlovu D, Nhembe M, Pirie DJ, Kowo H. Acute lower respiratory tract infection in hospitalised children in Zimbabwe. *Ann Trop Paediatr* 1993; **13:** 253-261.
19. Friedland IR, Snipelisky M. Vertically transmitted HIV-1 infection in children: A report of 23 cases. *S Afr Med J* 1991; **79:** 157-159.
20. Friedland IR, McIntyre JA. AIDS — the Baragwanath experience: Part II. HIV infection in pregnancy and childhood. *S Afr Med J* 1992; **82:** 90-94.
21. Beach RS, Mantero-Atienza E, Shor-Posner G, et al. Specific nutrient abnormalities in asymptomatic HIV-1 infection. *AIDS* 1992; **6:** 701-708.
22. Bogden JD, Baker H, Frank O, et al. Micronutrient status and human immunodeficiency virus (HIV) infection. *Ann NY Acad Sci* 1990; **587:** 189-195.
23. Javier JJ, Fordyce-Baum MK, Beach RS, Gavancho M, Cabrejos C, Mantero-Atienza E. Antioxidant micronutrients and immune function in HIV-1 infection (Abstract). *FASEB J* 1990; **4:** A940.
24. Periquet BA, Jammes NM, Lambert WE, et al. Micronutrient levels in HIV-1-infected children. *AIDS* 1995; **9:** 887-893.
25. Timbo BB, Tollefson L. Nutrition: A cofactor in HIV disease. *J Am Diet Assoc* 1994; **94:** 1018-1022.
26. Chandra RK. 1990 McCollum award lecture. Nutrition and immunity: Lessons from the past and new insights into the future. *Am J Clin Nutr* 1991; **53:** 1087-1101.
27. Kelleher J. Vitamin E and the immune response. *Proc Nutr Soc* 1991; **50:** 245-249.
28. Hussey G, Hughes J, Potgieter S, et al. Vitamin A status and supplementation and its effect on immunity in children with AIDS (Abstract). Presented at 1995 Annual Research Day, Department of Paediatrics and Child Health, University of Cape Town.

29. Garewal HS, Ampel HM, Watson RR, Prabhala RH, Dols CL. A preliminary trial of beta-carotene in subjects infected with the human immunodeficiency virus. *J Nutr* 1992; **122:** 728-732.

30. Baum MK, Mantero-Atienza E, Shor-Posner G, *et al.* Association of vitamin B6 status with parameters of immune function in early HIV-1 infection. *J Acquir Immun Defic Syndr* 1991; **4:** 1122-1132.

31. Brettler DB, Forsberg A, Bolivar E, Brewster F, Sullivan J. Growth failure as a prognostic indicator for progression to acquired immunodeficiency syndrome in children with hemophilia. *J Pediatr* 1990; **117:** 584-588.

32. Gorbach SL, Knox TA, Roubenoff R. Interactions between nutrition and infection with human immunodeficiency virus. *Nutr Rev* 1993; **51:** 226-234.

33. Grunfeld C, Pang M, Shimizu L, Shigenaga JK, Jensen P, Feingold KR. Resting energy expenditure, caloric intake, and short-term weight change in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *Am J Clin Nutr* 1992; **55:** 455-460.

34. McCorkindale C, Dybevik K, Sucher KP. Nutritional status of HIV-infected patients during the early disease stages. *J Am Diet Assoc* 1990; **90:** 1236-1241.

35. DuPont HL, Marshall GD. HIV-associated diarrhoea and wasting. *Lancet* 1995; **346:** 352-356.

36. Yolken RH, Li S, Perman J, Viscidi R. Persistent diarrhoea and faecal shedding of retroviral nucleic acids in children infected with human immunodeficiency virus. *J Infect Dis* 1991; **164:** 61-66.

37. Castaldo A, Tarallo L, Palomba E, *et al.* Iron deficiency and intestinal malabsorption in HIV disease. *J Pediatr Gastroenterol Nutr* 1996; **22:** 359-363.

38. Yolken RH, Hart W, Oung I, Shiff C, Greenson J, Perman JA. Gastrointestnal dysfunction and disaccharide intolerance in children infected with human immunodeficiency virus. *J Pediatr* 1991; **118:** 359-363.

39. Remacha AF, Cadafalch J, Gimferrer E. Vitamin B-12 abnormalities in HIV-infected patients. *Eur J Haematol* 1991; **47:** 60-64.

40. Lake-Bakaar G, Quadros E, Beidas S, *et al.* Gastric secretory failure in patients with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988; **109:** 502-504.

41. Belitsos PC, Greenson JK, Yardley JH, Sisler JR, Bartlett JG. Association of gastric hypoacidity with opportunistic enteric infections in patients with AIDS. *J Infect Dis* 1992; **166:** 277-285.

42. Hommes MJT, Romijn JA, Endert E, Sauerwein HP. Resting energy expenditure and substrate oxidation in human immunodeficiency virus (HIV)-infected asymptomatic men: HIV affects host metabolism in the early asymptomatic stage. *Am J Clin Nutr* 1991; **54:** 311-315.

43. Melchior J-C, Salmon D, Rigaud D, *et al.* Resting energy expenditure is increased in stable, malnourished HIV-infected patients. *Am J Clin Nutr* 1991; **53:** 427-441.

44. Bell SJ, Mascioli EA, Forse RA, Bistrain BR. Nutrition support and the human immunodeficiency virus (HIV). *Parasitology* 1993; **107:** S53-S67.

45. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson RN. Hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med* 1989; **86:** 27-31.

46. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1992; **74:** 1045-1052.

47. Hellerstein MC, Grunfeld C, Wu K, *et al.* Increased de novo hepatic lipogenesis in human immunodeficiency virus infection. *J Clin Endocrinol Metab* 1993; **76:** 559-565.

48. Grunfeld C, Feingold KR. Metabolic disturbances and wasting in the acquired immunodeficiency syndrom. *N Engl J Med* 1992; **327:** 329-337.

49. Stein TP, Nutinsky C, Condoluci D, Schluter MD, Leskiw MJ. Protein and energy substrate metabolism in AIDS patients. *Metabolism* 1990; **39:** 876-881.

50. Lieberman SA, Buttersfield GE, Harrison D, Hoffman AR. Anabolic effects of recombinant insulin-like growth factor-I in cachectic patients with the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1994; **78:** 404-410.

51. Macallan DC, McNurlan MA, Milne E, Calder AG, Garlick PJ, Griffen GE. Whole-body protein turnover from leucine kinetics and the response to the nutrition in human immunodeficiency virus infection. *Am J Clin Nutr* 1995; **61:** 818-826.

52. Grunfeld C, Kotler DP, Shigenaga JK, *et al.* Circulating interferon-a levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med* 1991; **90:** 154-162.

53. Mildvan D, Machado SG, Wilits I, Grossberg SE. Endogenous interferon and triglyceride concentrations to access response to zidovudine in AIDS and advanced AIDS-related complex. *Lancet* 1992; **339:** 453-456.

54. Lieberman SA, Butterfield GE, Harrison D, Hoffman AR. Anabolic effects of recombinant insulin-like growth factor-I in cachectic patients with the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1994; **78:** 404-410.

55. Mulligan K, Grunfeld C, Hellerman MK, Neese RA, Schambelan M. Anabolic effects of recombinant human growth hormone in patients with wasting associated with human immunodeficiency virus infection. *J Clin Endocrinol Metab* 1993; **77:** 956-962.

56. Bukar JG, Lee PDK, Pivarnik JM, *et al.* A double-blind, placebo-controlled, multicentre study of insulin-like growth factor-I (IGF-I) and growth hormone (GH) in HIV-1 (Abstract). *J Parenter Enter Nutr* 1996; **20:** suppl 18,10.

57. Laue L, Pizzo PA, Butler K, Cutler GB jun. Growth and neuroendocrine dysfunction in children with acquired immunodeficiency syndrome. *J Pediatr* 1990; **117:** 541-545.

58. LoPresti JS, Fried JC, Spenser CA, Nicoloff JT. Unique alterations of thyroid hormone indices in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989; **110:** 970-975.

59. Membreno L, Irony I, Dere W, Klein R, Biglieri EG, Cobb E. Adrenocortical function in acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1987; **65:** 482-487.

60. Croxson TS, Chapman WE, Miller LK, Levit CD, Senie R, Zumoff B. Changes in the hypothalamic-pituitary-gonadal axis in human immunodeficiency virus-infected homosexual men. *J Clin Endocrinol Metab* 1989; **68:** 317-321.

61. Dunn DT, Newell ML, Ades AE, Peckham CS. Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet* 1992; **340:** 585-588.

62. Van de Perre P. Postnatal transmission of human immunodeficiency virus type 1: The breastfeeding dilemma. *Am J Obstet Gynecol* 1995; **173:** 483-487.

63. Cutting WAM. Breast-feeding and HIV — a balance of risks. *J Trop Pediatr* 1994; **40:** 6-11.

64. Consensus statement from the WHO/UNICEF constitution on HIV transmission and breast-feeding, Geneva. *Wkly Epidemiol Rec* 1992; **67:** 177-184.

65. Gray GE, McIntyre JA, Lyons S. The effect of breastfeeding on vertical transmission of HIV-1 in Soweto, South Africa (Abstract). Presented at conference 'Breastfeeding choices for the HIV seropositive mother,' May 1996, University of Natal, Durban.

66. Statement on HIV transmission and breastfeeding. Formulated at conference 'Breastfeeding choices for the HIV seropositive mother,' May 1996, University of Natal, Durban.

67. McKinney RE, Maha MA, Conner EM, *et al.* A multicentre trial of oral zidovudine in children with advanced human immunodeficiency virus disease. *N Engl J Med* 1991; **324:** 1018-1025.

68. Corey L, Holmes KK. Therapy for human immunodeficiency virus infection — what have we learned? *N Engl J Med* 1996; **335:** 1142-1144.

69. Mofenson LM, Moye J. Intravenous immune globulin for the prevention of infections in chidren with symptomatic human immunodeficiency virus infection. *Pediatr Res* 1993; **33:** suppl, S80-S89.

70. Kotler DP, Tierney AR, Altilio D, Wang J, Pierson RN. Body mass repletion during ganciclovir treatment of cytomegalovirus infections in patients with acquired immunodeficiency syndrome. *Arch Intern Med* 1989; **149:** 901-905.

71. Henderson RA, Saavedra JM, Yolken RH, Perman JA. Nutritional management of HIV infection in childhood. *Annales Nestlé* 1993; **51:** 87-97.

72. Nicolas SW, Leung J, Fennoy I. Guidelines for nutritional support of HIV-infected children. *J Pediatr* 1991; **119:** S59-S61.

73. Ashworth A, Jackson A, Sultana K, Schofield C. Ten steps to recovery. *Child Health Dialogue* 1996; Issues 3-4: 10-12.

74. Bell SJ, Chavali S, Bistrian B, Connolly CA, Utsunomiya T, Forse RA. Dietary fish oil and cytokine and eicosanoid production during human immunodeficiency virus infection. *J Parenter Enter Nutr* 1996; **20:** 43-49.

75. Henderson RA, Saavedra JM, Perman JA, Hutton N, Livingston RA, Yolken RH. Effect of enteral tube feeding on growth of children with symptomatic human immunodeficiency virus infection. *J Pediatr Gastroenterol Nutr* 1994; **18:** 429-434.

76. Kotler DP, Tierney AR, Culpepper-Morgan JA, Wang J, Pierson RN. Effect of home total parenteral nutrition on body composition in patients with acquired immunodeficiency syndrome. *J Parenter Enter Nutr* 1990; **14:** 454-458.

77. Melchior J-C, Chastang C, Gelas P, *et al.* Efficacy of 2-month total parenteral nutrition in AIDS patients: a controlled randomised prospective trial. *AIDS* 1996; **10:** 379-384.

78. Gleason-Morgan D, Church JA, Bagnall-Reeb H, Atkinson J. Complications of central venous catheters in paediatric patients with acquired immunodeficiency syndrome. *Pediatr Infect Dis J* 1991; **10:** 11-14.

79. Choto R-G. Clinical evaluation of nutrition mix — 1. A dietary supplement in sick and undernourished children. *Centr Afr J Med* 1994; **40:** 29-32.

80. Coutsoudis A, Bobat RA, Coovadia HM, Kuhn L, Tsai W-Y, Stein ZA. The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. *Am J Public Health* 1995; **85:** 1076-1081.

81. Brady MT, Koranyi KI, Hunkler JA. Megestrol acetate for treatment of anorexia associated with human immunodeficiency virus infection in children. *Pediatr Infect Dis J* 1994; **13:** 754-756.

82. Hellerstein MK, Kahn J, Mudie H, Viteri F. Current approach to the treatment of human immunodeficiency virus-associated weight loss: pathophysiologic considerations and emerging management strategies. *Semin Oncol* 1990; **17:** suppl 9, 7-33.

83. Coodley GO, Loveless MO, Merrill TM. The HIV wasting syndrome: a review. *J Acquir Immun Defic Syndr* 1994; **7:** 681-694.