NUTRITION AND HIV/AIDS

Nutritional Guidelines for HIV-infected Adults and Children in Southern Africa: Meeting the Needs (Sections 3 - 6)

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3. PROVIDING APPROPRIATE NUTRITION TO THE HIV-INFECTED

THE BASIC APPROACH TO PROVIDING NUTRITION TO THE HIV-INFECTED

- Assess whether nutritional support is required
  - History, weight, height, body mass index (BMI) and mid-upper arm circumference (MUAC) and examination. Laboratory tests, e.g. haemoglobin, serum albumin, fasting lipids, etc., where indicated.
  - Where possible, work as a team so as to ensure that the patient's nutritional needs are recognised and acted upon: doctor, nurse, dietician, social worker, patient/parent/caregiver.
- Set goals
  - Improvement in weight and length or height (children).
  - Infants: exclusive breastfeeding for 6 months or formula feeds where this satisfies the UNAIDS/WHO/UNICEF 'AFASS' criteria, viz. acceptable, feasible, affordable, sustainable and safe. If the infant tests HIV positive, breastfeeding is continued. Exclusive breastfeeding is continued where the mother cannot meet the AFASS criteria.
  - Maternal antiretroviral therapy (ART) is continued during the breastfeeding period (and beyond, where appropriate for the control of the mother's infection).
- Advise the patient or caregiver (parent) on how to achieve good nutritional goals.
  - What are the patient's current eating habits? How and what does the child/patient eat?
  - What food is available? What food is eaten in the home: frequency, quantity, quality?
  - Who looks after the infected patient? What practical support is available?
  - Aim at a minimum of three balanced and varied meals a day.
  - Aim at a minimum of two to three portions of fresh vegetables and/or fruit per day.
- Does the patient need nutritional help? Select the appropriate form of support needed
  - Immediate support and action
    - Nutritional supplements
    - Therapeutic feeds
    - Family food support
    - Social support programmes: School feeding programmes, child grants, disability grants, referral to non-governmental organisation (NGO) programmes and faith-based groups in the community.
  - Long-term recovery action
    - Poverty relief and political/social intervention
    - Access to ART and approved HIV management programmes
    - Prevention and rapid control of opportunistic disease, particularly tuberculosis (TB), diarrhoeal illnesses in children and upper respiratory tract disease. Support for appropriate vaccination programmes.

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3.1 PROVIDING NUTRITION, PROVIDING FOOD

To maintain or achieve good health, each person requires energy-providing nutrients (protein, fat and carbohydrates), vitamins, minerals and water. The average minimum daily energy requirement of an adult in the developing world is 2 100 kcal. This is sufficient only for those in good health who are engaged in light physical activity at an ambient temperature of 20°C.[1] Most of this energy comes from carbohydrate. Under normal circumstances protein should comprise 10 - 12% of daily energy, and fat a further 17%.[1,2] However, protein comprises a very small part of the average diet of children in Africa and Asia. Hence these children are vulnerable to protein depletion. The World Health Organization (WHO) recommends that energy intake in asymptomatic HIV-infected adults and children be increased by 10%. During periods of illness or convalescence this should be increased to 20 - 30%.[3] Where possible, this increased energy requirement should be given as food. Where weight loss and malnutrition are severe, the energy needs of HIV-infected children may increase by 100%.[4] Overweight but asymptomatic patients need to be encouraged to lose excess weight, eat a balanced diet and exercise regularly. An improvement in nutrition of the malnourished may enhance immune function, prevent weight loss – particularly the loss of lean mass – and possibly delay disease progression.[5] Exclusive breastfeeding of the infants of HIV-infected mothers has reduced the risk of transmission compared with mixed feeding, and has promoted the survival of such children.[6,7]

INCREASING ENERGY INTAKE[3]

- Asymptomatic HIV-infected adult or child: increase energy intake by 10%. Give extra food.
- During and immediately after an opportunistic disease such as TB, gastroenteritis and chronic lung disease, the body's total energy expenditure increases by 20 - 30%. Both food-based and nutritional supplements can be used to meet these extra needs.
- Severe malnutrition increases basic energy needs by 50 - 100% in children. These needs require therapeutic feeding. This is best managed in conjunction with a dietician who will advise and assist in calculating the amounts of food/special feed required.

3.2 THERAPEUTIC FEEDING

Therapeutic feeding provides the total nutritional needs of a severely malnourished person in the form of a specifically prepared and formulated diet. F100 has been the WHO's standard therapeutic feed and provides severely malnourished children with 150 - 220 kcal/kg/day.[1] A recent addition is the 'ready-to-use therapeutic feed' (RUTF), a mix based on peanut butter, skimmed milk, oil, sugar and micronutrients in a sterile carton that does not require reconstitution with water and therefore avoids potential bacterial contamination. Therapeutic feeds are usually continued for a minimum of 4 - 6 weeks or until the present nutritional crisis is past. These special feeds are often used in famine or warfare situations where acute malnutrition is frequent. South African hospitals and clinics use alternative nutrient supplements.

3.3 FAMILY FOOD SUPPORT

What ought to be done when a patient or family has insufficient food at home? At each clinic visit questions must be asked that check food security, access to food and the quality and quantity of that food. How is it prepared, and who ensures that the child or sick adult is fed? Is assistance needed? Clinic staff can help in the following ways:

- Supplementary feeds are available from government institutions as well as some NGOs. Social workers will assist with accessing financial grants, etc. Those families who can be helped with growing their own vegetables must be referred to local agencies that provide such support.
- The National Strategic Plan provides for food parcels to be available from government clinics.
- Exclusive breastfeeding programmes should be promoted and protected where mothers are unable to provide reliable or safer alternatives to infant feeding. Mothers who are exclusively breastfeeding should be encouraged to continue ART through this period and an attempt should be made to ensure that the maternal viral load is kept well controlled, i.e. by measurement of the mother's viral load at least once during the breastfeeding period.
- Children from 6 months to 5 years ought to receive supplemental vitamin A every 6 months. See below.
- Children experiencing diarrhoea should be given zinc supplementation over this period. See below.
- Lobby government and industry to ensure that staple foods are fortified with appropriate micronutrients: iodised salt, fortified flour and cereals. Take a detailed history from the patient and assess the 'quality' of the food being consumed. Teamwork on the part of the health worker is essential, and where practical, the health worker is encouraged to upgrade his/her skill and knowledge with educational courses in the field. Identify and involve community members or agencies that can provide food, educate the community with regard to nutrition, and promote skills needed in the home production and preparation of food.

3.4 NUTRITION IN THE RELIEF OF HIV-RELATED SYMPTOMS

If symptoms persist for more than a week or are unresponsive to simple home-based care, the child or adult who is HIV positive must be referred to a health practitioner (nurse or doctor) or a clinic or hospital where a diagnosis can be made and corrective treatment instituted (Table 3.I). If the patient is very ill, refer him/her to a doctor immediately. Untreated diseases of the mouth and persistent diarrhoea commonly lead to a loss of appetite and weight loss.[8]

3.5 NUTRITIONAL SUPPLEMENTS: VITAMINS AND OTHER MICRONUTRIENTS

INTERPRETATIONAL DILEMMAS WITH REGARD TO MICRONUTRIENT STUDIES AND HIV[10,11]

- Too few randomised controlled trials (RCTs)
- Studies frequently not standardised with regard to micronutrient amounts or composition
- Studies seldom control for the acute-phase response or the effect of intercurrent inflammatory conditions (e.g. infections)
- Studies seldom control for the basic daily intake of micronutrients in food/diet
- Insufficient regard for the effect of interactions between the varying doses of different micronutrients in an individual supplement

3.5.1 Introduction

Vitamins and minerals are, by definition, essential for life. Do they influence the progression of HIV infection? Micronutrient studies in HIV-infected subjects have been difficult to interpret: the studies differ in the composition and quantities of micronutrients, and few have been randomised and adequately controlled, while in many the effect of the acute-phase response and the effect of the simultaneous intake of micronutrients in food (dietary micronutrients) is seldom taken into account. Nor have the potential interactions between the micronutrients themselves – particularly within the multivitamin cocktail – been assessed *in vivo*.[10] Data from North American and European studies are not immediately applicable to Africa. The staging of HIV is missing from many studies, and the confounding effect of opportunistic disease in subjects is not regularly discussed. Although pre-ARV treatment hospital-based studies from the developed world reported low baseline micronutrient levels in their subjects, selection bias, unknown recruitment criteria and the absence of disease stage have limited the interpretation of these data.[11]

TABLE 3.I. NUTRITIONAL AND 'COMMONSENSE' APPROACHES TO SYMPTOM CONTROL[9]

Symptom	Medical diagnosis	Medical treatment	Dietary and supportive treatments
1. Anorexia, loss of appetite or poor appetite	1. Systemic disease, e.g. TB, lymphoma 2. Local oral disease, e.g. thrush, gingivitis, ulcers 3. Medication: ARVs, TB drugs, antibiotics and chemotherapy 4. Depression, fear and anxiety 5. Malnutrition with apathy and chronic helminth infestation	1. Treat the underlying condition 2.Cyproheptadine (Periactin) 4 mg qd po x 7 - 10 days. 3. Steroids to be used with caution and under supervision: prednisone 0.5 - 1.0 mg/kg/d x 5 - 10 d 4. ARVs: control the underlying viral disease	Small but frequent meals and favourite foods, liquids, soft foods rather than a full meal: high-energy and high-protein drinks and foods. Avoid foods with a strong smell, e.g. fish, cheese and eggs. Snack often, and keep snacks handy e.g. car, handbag. Drink frequently. Emotional support and counselling.
2. Painful mouth and discomfort with swallowing	1. Local causes are usual viral infections: 'flu and the common cold, herpes stomatitis (HSV), cytomegalovirus (CMV), HIV ulcers; bacterial infection: gingivitis and tonsillitis; Fungi: candidiasis 2. Immune: aphthous ulcers 3. Tumour: carcinoma, lymphoma	1. Treat the underlying condition 2. Topical anaesthetic ointments or spray before meals, e.g. amethecaine gel 3. Topical steroid ointment for aphthous sores, e.g. kenolog in orabase 4. Topical antifungal lozenges or cream for angular cheilitis, e.g. amphotericin B, nystatin gel or solution	Avoid acidic foods, e.g. citrus fruit, tomatoes, spicy foods. Drink through a straw. Eat foods at room temp. or well cooled. Suggest thick and smooth foods such as puddings, porridge, mashed potatoes, beans. Clear fluids are more easily aspirated – sit upright when eating and tilt head slightly back. Rinse mouth with boiled, warm salt water after eating.
3. Fever: body temperature persistently >37.4°C	Often a sign of systemic disease 1. Infection: malaria, TB, invasive bacterial dis., pneumonia, bacteraemia 2. Tumour: lymphoma, dissem. Kaposis's 3. Toxins and drugs: ARVs, antibiotics, e.g. co-trimoxazole, penicillin 4. Immune: immune reconstitution syndrome (IRIS), allergy	1. Treat the underlying condition 2. Paracetamol 250 - 500 mg 6-hrly po (prn) 3. Aspirin 300 mg 6-hrly po (prn), non-steroidal anti-inflam. drugs (NSAID, e.g. ibuprofen) Aspirin is not used in children	Encourage rest. Cool bath and/or tepid sponging. Fan and remove warm bedding, Drink lots of fluid. Take high-energy foods, e.g. added oil, margarine, sugar, to enhance caloric value.
4. Nausea and vomiting	1. Local gastrointestinal tract disease: oesophageal lesions, peptic ulcer and gastritis and pancreatitis 2. Systemic infections and medical conditions 3. Medication and toxins: ARVs – zidovudine and ritonavir, TB drugs, antibiotics esp. metronidazole, alcohol and recreational drugs, traditional drugs and potions 4. Metabolic disorders: uncontrolled diabetes, lactic acidosis, renal and liver disease 5. Fear and anxiety	1. Diagnose and treat the underlying cause 2. Anti-nauseants, e.g. metoclopromide 10 mg 8-hrly before meals (prn) 3. Remove the offending cause	Encourage eating even if only small quantities can be taken. Avoid an empty stomach – this will increase the nausea. Small but regular meals of bland food such as soups, porridge, mashed bananas. Dry toast and cream crackers are helpful. Ginger may ease nausea: ginger ale. Herbal teas and lemon juice in hot water. Drink plenty of fluids but not during the meal as this will increase the sense of bloatedness. Avoid spicy and fatty and strong-smelling foods. Avoid fizzy drinks and caffeine.
5. Diarrhoea Defined as a minimum of three soft, unformed stools per day	1. Local GIT disease, HIV enteropathy, Slim disease and opportunistic enteric infections, e.g. cryptosporidiosis 2. Systemic diseases, e.g. TB, lymphoma 3. Drugs and toxins, e.g. ARVs: didanosine, ritonavir, lopinavir, nelfinavir; antibiotics and antibiotic-associated diarrhoea (*C. dificile* enterocolitis); alcohol; traditional medicines and herbs (allovera) 4. Metabolic: uncontrolled diabetes mellitus, hyperthyroidism	1. Diagnose and treat the underlying cause 2. Immodium 1 - 2 tabs po daily or bid in adults. Immodium is NOT given to children 3. Codeine phosphate 10 - 30 ml daily or bid po in adults. Codeine is NOT given to children. 4. Oral rehydration solution (children): 1 litre boiled water, and 8 teaspoons sugar, 1.2 teaspoon salt 5. Zinc (children): 10 mg daily po x 2 wks in those <6 mo. age, or 20 mg daily po x 2 wks in those >6 mo. of age 6. Continue feeding the child 7. Vitamin A: dose as per age in children <5 yrs 8. Refer the child to the clinic if either weight loss is present or diarrhoea continues for >14 d	Lots of fluids such as soup, diluted juices, boiled water, herbal teas. Avoid citrus fruit or citrus drinks e.g. oranges, lemons. Suggest bananas, rice, peeled apples, white toast, oats and lentils (strained), maas and yoghurt. Fruit juices that are acceptable: apple, pear and grape. Leave off bran and fibre from diet: no whole-grain breads, no wheatbix or high-fibre cereals. No fried or fatty foods. Avoid caffeine and alcohol.

3.5.2 Individual vitamins and micronutrients (Tables 3.II and 3.III)[10]

Vitamin A (retinol, retinoic acid, β-carotene)

Adults: Supplementation of HIV-infected adults with vitamin A is likely to be safe provided dosing does not exceed the daily recommended dietary allowance (RDA), and in cases where deficiency is confirmed[4,12] (see comment and RDA dosing below).

Children: Current evidence supports the use of vitamin A supplementation in under-5-year-olds in Africa and Asia. Supplementation reduces the risk of diarrhoea-related morbidity and mortality and 'all-risk' mortality in HIV-infected and uninfected children.[13-16] Children are supplemented with 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. Further supplementation with 200 000 IU 6-monthly thereafter until the age of 5 years is recommended.[12,13]

Comment: Observational studies in Africa have reported low maternal serum vitamin A levels in pregnant women who also appear to be at an increased risk of perinatal transmission of HIV. Kenyan studies found that low maternal serum retinol predicted increased virus in breastmilk and increased genital shedding of HIV.[10] Vitamin A supplementation of HIV-infected pregnant women has been associated with an increase in birth weight and fewer preterm births.[17] But the perinatal transmission studies have failed to demonstrate any reduction in viral transmission.[18,19] Indeed, a Tanzanian trial of vitamin A supplementation not only failed to show benefit above placebo but reported an increase in viral transmission in breastfeeding mothers.[18,20] Tang *et al.* speculate that vitamin A supplementation promotes cellular differentiation leading to the increased expression of CCR5 co-receptors on CD4 cells, thereby aiding viral entry.[11,21] Retinol levels decrease during the acute-phase response – i.e. low serum levels of vitamin A do not necessarily imply nutritional deficiency.[10,11]

Recommended dietary allowances (RDA) for vitamin A (µg/d) in HIV-uninfected populations[22] (recommendations are expected to apply equally to HIV-infected persons):

Infants 0 - 6 mo. = 400, 7 - 12 mo. = 500; children 1 - 3 yrs = 300, 4 - 8 yrs = 400; males 9 - 13 yrs = 600, 14 - >70 yrs = 900; females 9 - 13 yrs = 600, 14 - >70 yrs = 700; pregnancy ≤18 yrs = 750, 19 - 50 yrs = 770; lactation ≤18 yrs = 1 200, 19 - 50 yrs = 1 300.

Vitamin B group

Adults and children: There are no randomised controlled trials (RCTs) that examine the separate contribution of the individual B-group vitamins to the wellbeing or transmission risk of HIV-infected persons. Supplementation with 1 x RDA is currently recommended until additional data are available.[10,12]

Comment: RCTs in Tanzania and Thailand have shown benefit with multivitamin supplements that have included the following B-group vitamins: thiamine, riboflavin, pyridoxine and vitamin B_{12}.[20,23] The Tanzanian trials noted improved birth outcomes among pregnant HIV-positive women given multivitamin supplements. In particular, CD4+ and CD8+ levels improved and subjects progressed less rapidly to advanced HIV disease and were less likely to die. The design, methodology and the use of extremely high doses of micronutrients in these trials has, however, been questioned.[4,10] Nevertheless, some observational studies have also recorded benefit with vitamin B supplementation including a reduced risk of HIV progression.[10] Benefit in the Thailand RCT was limited to those with CD4 levels below 100 cells/µl. A small placebo-controlled prospective USA-based study of multi-micronutrient supplementation – including high doses of many of the B-group vitamins – reported improved CD4 counts after 12 weeks in patients on ARVs.[24] Tang *et al.'s* comment may have relevance: '[while] a combination of vitamins may provide some benefit to undernourished HIV-infected subjects with advanced disease, the role of individual nutrients is less clear.'[11]

RDA daily intakes for the B-group vitamins:[22]

Thiamine (vitamin B_1, mg/d): Infants 0 - 6 mo. = 0.2 , 7 - 12 mo. = 0.3; children 1 - 3 yrs = 0.5, 4 - 8 yrs = 0.6; males 9 - 13 yrs = 0.9, 14 - >70 yrs = 1.2; females 9 - 13 yrs = 0.9, 14 - 18 yrs = 1.0, 19 - >70 yrs = 1.1; pregnancy and lactation ≤18 - 50 yrs = 1.4.

Riboflavin (vitamin B_2, mg/d): Infants 0 - 6 mo. = 0.3, 7 - 12 mo. = 0.4; children 1 - 3 yrs = 0.5, 4 - 8 yrs = 0.6; males 9 - 13 yrs = 0.9, 14 - >70 yrs = 1.3; females 9 - 13 yrs = 0.9, 14 - 18 yrs = 1.0, 19 - >70 yrs = 1.1; pregnancy = 1.4; lactation = 1.6.

Niacin (vitamin B_3, mg/d): Infants 0 - 6 mo.= 2, 7 - 12 mo. = 4; children 1 - 3 yrs = 6, 4 - 8 yrs = 8; males 9 - 13 yrs = 12, 14 - >70 yrs = 16; females 9 - 13 yrs = 12, 14 - >70 yrs = 14; pregnancy = 18; lactation = 17.

Pyridoxine (vitamin B_6, mg/d): Infants 0 - 6 mo. = 0.1, 7 - 12 mo. 0.3; children 1 - 3 yrs = 0.5, 4 - 8 yrs = 0.6; males 9 - 13 yrs = 1.0, 14 - 50 yrs = 1.3, 51 - >70 yrs = 1.7; females 9 - 13 yrs = 1.0, 14 - 18 yrs = 1.2, 19 - 50 yrs = 1.3, 51 - >70 yrs = 1.5; pregnancy ≤18 yrs = 1.6, 19 - 50 yrs = 1.9; lactation = 2.0.

Folate (µg/d): Infants 0 - 6 mo. = 65, 7 - 12 mo. = 80; children 1 - 3 yrs = 150, 4 - 8 yrs = 200; males 9 - 13 yrs = 300, 14 - >70 yrs = 400; females 9 - 13 yrs = 300, 14 - >70 yrs = 400; pregnancy = 600; lactation = 500.

Vitamin B_{12}: Infants 0 - 6 mo. = 0.4, 7 - 12 mo. = 0.5; children 1 - 3 yrs = 0.9, 4 - 8 yrs = 1.2; males 9 - 13 yrs = 1.8, 14 - >70 yrs = 2.4; females 9 - 13 yrs = 1.8, 14 - >70 yrs = 2.4; pregnancy = 2.6; lactation = 2.8.

Vitamin C

Adults and children: RCT data detailing a specific role for vitamin C are absent apart from multivitamin studies that have included vitamin C together with other micronutrients. Where supplementation is indicated because of malnutrition or where patients wish to take vitamin supplements, it is recommended that doses of 1 x daily RDA be taken.[10,12]

Comment: Vitamin C supplementation formed part of the multivitamin RCTs in Tanzania and Thailand discussed above.[20,23] Observational studies have suggested that vitamin C may reduce HIV progression.[10] Further data suggest

TABLE 3.II. VITAMINS AND IMMUNE/BIOLOGICAL INTERACTIONS		
Vitamin	**Source**	**Described immune and biological effects**
Vitamin A, carotenoids	Full-cream milk when fortified Cheese, butter, red palm oil Fish oils, eggs, liver, carrots, mangoes, papaya, pumpkin, Green leafy vegetables, sweet potatoes	Enhanced phagocytic activity, which is reduced in vitamin A deficiency. Important in vision, the differentiation of cells, cellular recognition, growth, bone development and reproduction.
Vitamin E	Green leafy vegetables, liver, vegetable oils, wheat germ, whole-grain products, butter, peanuts, milk, nuts and seeds, egg yolk and fats	Promotes phagocytosis, adherence and chemotaxis. Supplementation protects natural killer (NK) cell and suppresses the production of toxic oxygen radicals. The most important lipid-soluble antioxidant in cell membranes.
Vitamin C	Citrus fruit: baobab, guava, oranges and lemons. Cabbage, green leaves, tomatoes, yams, peppers, cooking plantains, fresh milk	Supplementation enhances NK cell activity, phagocytosis, adherence and chemotaxis. Acts as an antioxidant within the cell. NB: The activity of vitamin C is lost when food is cut, heated or left standing after cooking.
Vitamin B_{12}, cyanocobalamin	Green leafy vegetables, liver, meat	Deficiency leads to decreased bacterial killing. A coenzyme that is needed for the maintenance of neural tissue and for folate-dependent red cell synthesis.

TABLE 3.III. TRACE ELEMENTS AND IMMUNE/BIOLOGICAL INTERACTIONS		
Trace element	**Source**	**Described immune/biological action**
Selenium	Meat, eggs, seafood, whole grains and plants provided their soil is rich in selenium	An antioxidant that is active within the glutathione peroxidase enzyme system. Supplementation increases macrophage phagocytic and cytotoxic activity. Deficiency leads to reduced antibody production.
Zinc	Meat, fish, poultry, shellfish, whole-grain cereals, legumes, peanuts, milk and cheese	Zinc is a cofactor in enzymes systems and is active in cell growth. It is an antioxidant. Zinc is necessary to thymus development, the production of superoxide dismutase. Supplementation results in the production of cytokines and the major histocompatibility complex (MHC) class 1 proteins.
Iron	Liver, chicken, beef, egg yolk Beans, nuts, green leafy vegetables, fortified cereals	Is a pro-oxidant. Iron-containing cellular components, e.g. haemoglobin, myoglobin, permit oxygen delivery to tissues. Deficiency appears to inhibit TH-1 cellular immune activity and reduce neutrophil function.

that vitamin C may behave as an antioxidant in HIV-positive subjects, though the clinical value of this is unknown. Baseline levels of vitamin C have been reported to be low in some studies of HIV-infected patients, including children.[25,26]

RDA daily intake for vitamin C (mg/d):[22]

Infants 0 - 6 mo. = 40, 7 - 12 mo. = 50; children 1 - 3 yrs = 15, 4 - 8 yrs = 25; males 9 - 13 yrs = 45, 14 - 18 yrs = 75, 19 - >70 yrs = 90; females 9 - 13 yrs = 45, 14 - 18 yrs = 65, 19 - >70 yrs = 75; pregnancy ≤18 yrs = 80, 19 - 50 yrs = 85; lactation ≤8 yrs = 115, 19 - 50 yrs = 120.

Vitamin D

Adults and children: Currently there are no data directly assessing the role of vitamin D supplementation in HIV-infected adults and children. However, standard recommendations apply to pregnant women, infants including exclusively breastfed infants, and older children. Where osteoporosis is present, vitamin D 200 IU daily for adults aged <50 years, 400 IU daily for those aged 51 - 70 years and 600 IU daily for those aged ≥71 years is recommended for the general population.[27]

Comment: Bone loss is a frequent complication of HIV infection and may accompany ARV treatment. Both adults and children are at risk. A preventive role for vitamin D and calcium is not yet established.[28] Despite plenty of sunshine, rickets remains a problem in developing countries where the diet may be low in vitamin D or where children are kept indoors. There is little vitamin D in human milk. Sunlight and supplementation of exclusively breastfed infants (irrespective of HIV status) is recommended.[29] An association between vitamin D and the activation of Toll-like receptors on macrophages infected with *Mycobacterium tuberculosis* has been noted. However, there are currently no data to suggest that vitamin D supplementation of dual HIV/TB-infected patients should be recommended.[30]

RDA for vitamin D (µg/d):[22]

Infants, children and adults 0 mo. - 50 yrs = 5; adults 51 - 70 yrs = 10, >70 yrs = 15; pregnancy and lactation = 5.

Vitamin E, α-tocopherol

Adults and children: Daily supplementation with not more than 1 x RDA is acceptable.

Comment: The North American Multicenter AIDS Cohort Study (MACS) found a reduced risk of progression to AIDS or death during 9 years of follow-up in those subjects with high levels of vitamin E, but whether this is an acute-phase epiphenomenon, a reflection of the stage of infection or a direct effect of vitamin E remains uncertain.[10] Vitamin E is a major lipid-soluble antioxidant in cell membranes, where it functions as a scavenger of free radicals. It interacts with several other antioxidants and micronutrients – zinc, selenium, copper and vitamin C – and its activity is dependent upon sufficient levels of these other nutrients within the cell.[11] It is suggested that daily requirements of vitamin E ought to be increased during the simultaneous use of the pro-oxidant, iron.[10] There are no RCTs using vitamin E alone in HIV-positive patients, although both the Tanzanian and Thailand studies of multivitamin supplementation contained vitamin E in large doses.[20,23]

RDA of vitamin E (mg/d, α-tocopherol):[22]

Infants 0 - 6 mo. = 4, 7 - 12 mo. = 5; children 1 - 3 yrs = 6, 4 - 8 yrs = 7; males 9 - 13 yrs = 11, 14 - >70 yrs = 15; females 9 - 13 yrs = 11, 14 - >70 yrs = 15; pregnancy = 15; lactation = 19.

Iron

Adults and children: There is no evidence that iron supplementation is required for HIV-infected patients apart from periods of increased physiological need such as pregnancy and periods of identified iron deficiency.

Comment: High iron stores (increased serum ferritin levels and increased marrow iron) have been associated with shortened survival of HIV-positive patients. This relationship probably reflects advanced HIV disease itself, so-called reverse causality: serum levels of ferritin increase during the acute-phase response and thus mark advancing disease.[10] Anaemia in the setting of HIV infection is not invariably associated with iron deficiency and iron studies must be checked before supplementing with iron. Iron supplementation trials in non-HIV-infected children in developing regions caution against the generalised provision of iron to children where infectious diseases such as malaria and TB are rife. Mortality may be enhanced.[31,10]

RDA of iron (mg/d)[22]

Infants 0 - 6 mo. = 0.27, 7 - 12 mo. = 11; children 1 - 3 yrs = 7, 4 - 8 yrs = 10; males 9 - 13 yrs = 8, 14 - 18 yrs = 11, 19 - >70 yrs = 8; females 9 - 13 yrs = 8, 14 - 18 yrs = 15, 19 - 50 yrs = 18, 51 - >70 yrs = 8; pregnancy = 27; lactation ≤18 yrs = 10, 19 - 50 yrs = 9.

Selenium

Adults and children: There are no definitive data to guide the HIV clinician or treater. Daily supplementation with not more than 1 x RDA is prudent.

Comments: A study from Kenya indicated that low selenium levels were a predictor of vaginal HIV shedding, and in prospective cohort studies in both developed and developing countries, low selenium levels have been associated with an increased risk of death. Unfortunately these studies failed to exclude confounding from an acute-phase response. Tanzanian pregnancy data linking low selenium to increased HIV mortality falter for the same reasons.[10] Nevertheless, selenium is a major constituent of glutathione peroxidase, an important cellular antioxidant, and is believed to guard against damage to proteins, lipids, lipoproteins and DNA itself.[32] A recent report from North America indicated improvement in viral load and CD4 levels in an intention-to-treat RCT involving 450 subjects. High doses of selenium, 200 µg/d, were used, and only 174 patients completed the 9-month follow-up.[33] Clearly more data from African studies are needed.

RDA of selenium (µg/d):[22]

Infants 0 - 6 mo. = 15, 7 - 12 mo. = 20; children 1 - 3 yrs = 20, 4 - 8 yrs = 30; males 9 - 13 yrs = 40, 14 - >70 yrs = 55; females 9 - 13 yrs = 40, 14 - >70 yrs = 55; pregnancy = 60; lactation = 70.

Zinc

Adults: There is currently insufficient evidence to recommend zinc supplementation of all HIV-infected adults. If daily supplementation is considered, it is advised that standard 1 x RDA doses are used.

Children: Zinc supplementation during episodes of chronic diarrhoea is recommended: a daily dose of 10 mg zinc for 2 weeks in HIV-positive children under 5 years.[4,12] A daily supplement dose of 3 mg zinc for 6 months has also been shown to be safe in this age group.[12]

Comment: Zinc supplementation of children in developing regions is associated with fewer episodes of watery diarrhoea and a reduced mortality from both diarrhoea and pneumonia. This applies to both HIV-infected and uninfected children.[34,35] The provision of zinc to children with diarrhoea has been helpful: see doses below (box, p. 41). USA studies found baseline levels of copper to be higher and zinc lower in HIV-infected subjects with progressive disease, but toenail concentrations and levels of dietary intake of these trace elements were actually the same in both subjects and controls. The alterations in the serum levels probably reflect advancing HIV infection. Serum zinc levels fall in response to the acute-phase phenomenon.[10] HIV requires zinc in its structural proteins and its enzymic activity: 'zinc-fingers' are part of the reverse transcriptase enzyme. Excessive zinc intake may be harmful. At least one American study found zinc intake to be associated with more rapid progression to AIDS and death.[10] Furthermore, large doses of zinc have also been found to be immunosuppressive.[36]

RDA of zinc (mg/d):[22]

Infants 0 - 6 mo. = 2, 7 - 12 mo. = 3; children 1 - 3 yrs = 3, 4 - 8 yrs = 5; males 9 - 13 yrs = 8, 14 - >70 yrs = 11; females 9 - 13 yrs = 8, 14 - 18 yrs = 9, 19 - >70 yrs = 8; pregnancy ≤18 yrs = 12, 19 - 50 yrs = 11; lactation ≤18 yrs = 13, 19 - 50 yrs = 12.

Calcium

Adults and children: There are no data specific to the HIV-infected population. Standard recommendations apply.

Comment: A low calcium intake has been described in South African schoolchildren.[37-39] During the 1999 National Food Consumption Survey, 21.6% of 1 - 9-year-olds were found to have stunted growth. The diet of these children was noted to be broadly deficient in many nutrients.[40] While many HIV-infected adults and children demonstrate reduced bone mineral density, a role for calcium deficiency and the value of its replacement needs further study in African HIV-positive populations. Osteopenia and osteoporosis in patients with HIV is multifactorial in cause and frequently associated with underlying disease progression or to the therapy employed in viral control.

RDA for calcium (mg/d):[22]

Infants 0 - 6 mo. = 210, 7 - 12 mo. = 270; 1 - 3 yrs = 500, 4 - 8 yrs = 800; males 9 - 18 yrs = 1 300, 19 - 50 yrs = 1 000, 51 - >70 yrs = 1 200; females 9 - 18 yrs = 1 300, 19 - 50 yrs = 1 000, 51 - >70 yrs = 1 200; pregnancy ≤18 yrs = 1 300, 19 - 50 yrs = 1 000; lactation ≤18 yrs = 1 300, 19 - 50 yrs = 1 000.

3.6 CONCLUSIONS

A recent Cochrane review of 15 micronutrient trials in HIV-infected subjects noted no effect of vitamin A or β-carotene on mortality, morbidity or viral load or CD4 cell levels. The authors remark that 'there is no conclusive evidence at present to show that micronutrient supplementation effectively reduces mortality and morbidity among HIV-infected adults though there is evidence of benefit of vitamin A supplementation in children'.[41] These authors agree that it is reasonable to support the WHO's recommendations to promote the adequate dietary intake of micronutrients at RDA levels and to provide vitamin A supplementation to children.

Many HIV-infected patients are poor and unemployed and malnutrition is common, particularly among children. The national strategic plan provides for the supplementation of those in need. The HIV-infected must be identified and offered assistance before malnutrition becomes overt. Randomised controlled micronutrient studies are needed in the HIV-infected of southern Africa. Currently huge gaps in knowledge remain. Adequate nutrition must be provided together with ARVs. Controlling the virus without providing food and micronutrients will not restore weight or correct metabolic and cellular function in the malnourished.

MICRONUTRIENTS IN THE MANAGEMENT OF THE HIV-INFECTED

- Malnourished HIV-infected adults and children must be assured of food with or without daily supplements.
- Where micronutrient requirements cannot be met adequately with food, give supplements.
- If micronutrients are needed, daily individual supplementation at not more than 1 - 2 times the RDA is permissible.
- Malnutrition is common in the developing world. Micronutrient supplementation is therefore likely to be beneficial to most of Africa's HIV-infected people.
- The micronutrient fortification of food is essential in developing regions. Countries and their food industries must be made aware and held accountable.
- Vitamin A supplementation of all children aged under 5 years is mandatory in developing regions. See text for dosing details. Note that high doses of vitamin A have been associated with an increased risk of HIV disease progression in adults. High doses should be avoided.
- Supplementation with zinc improves the clinical outcome in HIV-infected children with diarrhoea. A daily dose of 10 mg for 2 weeks in children below the age of 12 and 20 mg for those above this age is recommended. Severely malnourished children with diarrhoea should continue with zinc supplementation for 2 - 4 weeks.

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4. NUTRITION AND PREGNANCY, LACTATION AND THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION (PMTCT)

4.1 INTRODUCTION

Pregnancy and infancy are vulnerable periods in human life. In sub-Saharan Africa, 1 in 16 women dies in pregnancy or childbirth. This risk is 175 times higher than that in developed countries.[1] Of the 136 million babies born every year, 3.2 million are stillborn and 4 million die in the first month of life: 98% of these babies live in low-income and middle-income countries.[1] Health may be compromised by a variety of factors including maternal malnutrition, age, poverty, social disruption and chronic disease such as HIV/AIDS and tuberculosis (TB). During pregnancy, the absence of specific nutrients, e.g. folate (neural tube defects), and the presence of dietary toxins, e.g. alcohol (the fetal alcohol syndrome), may directly affect the weight and well-being of the newborn. However, in developing countries intrauterine growth restriction is mainly due to poor maternal nutrition and infections including HIV.[2] Increased infant mortality and morbidity correlate strongly with low birth weight.[3] Premature birth is more common in the context of maternal HIV infection, a risk that has not been altered by the introduction of antiretroviral therapy (ART).[4] Low birth weight (<2 500 g at ≥37 weeks) or small for gestational age (SGA) newborns remain at risk for significant morbid events such as hypertension, obesity, glucose intolerance and cardiovascular disease later in life;[5-6] 11% of births in developing countries fall into this category.[2] Nutritional requirements increase in pregnancy and lactation. HIV infection increases the energy needs of both the asymptomatic and the symptomatic.[2,7] HIV-infected women generally gain less weight during pregnancy than uninfected women, particularly in the third trimester[8] (Table 4.I).

TABLE 4.I. GENERALLY ACCEPTABLE INCREMENTS OF WEIGHT DURING PREGNANCY[51]

Body mass index (BMI), pre-pregnancy (kg/m²)	Total weight gain (kg)
Underweight (<20)	12.5 - 18 kg
Normal (20 - 25)	11.5 - 16 kg
Overweight (25 - 30)	7 - 1.5 kg
Obese (>30)	≤7 kg

Where antiretroviral (ARV) drugs are not available, rates of mother-to-child transmission (MTCT) are high at 25 - 45%. Intrauterine and intrapartum transmission account for 5 - 10% and 10 - 20% of this figure, respectively.[9,10] Depending upon its duration, the introduction of mixed feeds, maternal viral load, etc., breastfeeding may carry an additional 12 - 16% risk.[11] Contaminated maternal fluids – amniotic fluid, vaginal secretions, blood and breastmilk – ingested before birth, at birth or during breastfeeding, transmit virus to the baby. Maternal virus has been recovered from cells in the newborn's mouth shortly after birth.[12] The infant's punctured skin may be a further site of transmission: scalp electrodes, suction and forceps should be avoided during delivery.[13] Do micronutrients slow the natural progression of HIV infection? Can they reduce perinatal transmission? MTCT of HIV can be prevented, but in 2005 only 9% of pregnant women in low-income and middle-income countries received services to prevent transmission to their newborn babies, and only 9.2% of HIV-positive pregnant women received prophylactic ARVs.[14] Can improved maternal nutrition enhance the survival of the infected mother and her child?

4.2 VITAMINS, MICRONUTRIENTS AND THE PREVENTION OF PERINATAL HIV TRANSMISSION

Vitamin and micronutrient supplementation during pregnancy has not uniformly led to a reduction in MTCT. The Tanzanian vitamin intervention trials indicated reduced child mortality, improved pregnancy outcome and reduced transmission to the children of malnourished mothers with low lymphocyte counts. These studies have not been duplicated elsewhere, and the reported benefit was restricted to the use of micronutrients, excluding vitamin A.[14-18] Data from additional sites are needed to support these results.

Prophylaxis with vitamin A in South Africa did not reduce MTCT.[19] Behind these results has been the observation that women with low serum retinol levels appear to transmit HIV more readily to their babies.[20-21] Kenyan reports correlate low serum retinol with increased viral shedding in vaginal/cervical fluids and in breastmilk.[22,23] Unfortunately these studies did not exclude an 'acute-phase/active inflammatory' response as the cause of low retinol levels: the low vitamin A levels may have had little direct relationship with the findings, and may have reflected advanced HIV disease itself, and a resulting increased risk of transmission.[24] In Zimbabwe a large single dose of vitamin A (400 000 IU) given to women after delivery had no protective effect against their subsequent acquisition of the virus. During the 2-year follow-up those with low baseline serum retinol levels and anaemia (haemoglobin <7 g/dl) were more likely to seroconvert. But the authors admit that confounding variables had not been adequately excluded.[25] Maternal viral load and severe maternal immunodeficiency – in particular a CD4 count below 200 cells/µl – remain the major determinants of risk of transmission.[26-28] Only ART has been consistently shown to reduce maternal viral load and reduce perinatal HIV transmission.[29] Where malnutrition and HIV infection coexist, providing food and correcting specific nutritional deficiencies remains the appropriate response.

4.3 BREASTFEEDING AND THE RISK OF HIV TRANSMISSION

When deciding on a preventive strategy for Africa, one needs to take into account the importance of breastfeeding for child survival.[30] Breastfeeding protects infants from malnutrition, gastrointestinal and respiratory infections.[31] Mortality from these conditions is common in developing countries, where babies who are not breastfed in the first 2 months of life experience a 6-fold increase in death rate.[32] Breastmilk provides optimal nutrition for an infant – the milk is economical and safe, it fulfils the infant's total nutritional needs for the first 6 months of life, and it is an important component of the child's intake until 2 years of age.[33] It is important to note that iron supplementation may be given from 6 months onward to exclusively breastfed children who come from low-income areas.[34] On the other hand, the HIV-infected mother who breastfeeds has a 4 - 16% risk of transmitting virus to the child, depending on the duration and type of breastfeeding.[11,35,36] In rural KwaZulu-Natal, HIV prevalence rates in newborns increased from 14% at 6 weeks to 24% at 3 - 6 months in a mixed breastfeeding population.[33] Risk persists throughout the breastfeeding period and returns upon subsequent re-exposure to breastmilk with an increased risk relative to the duration of exposure.[35] Among exclusively breastfed infants, a transmission rate of 2 - 4% has been recorded at 6 months.[36,37] If an infected mother is to breastfeed her infant, the technique of exclusive breastfeeding must be followed.

Virus is present in both the cell-associated and cell-free components of breastmilk.[38] Direct viral invasion of the infant's gastrointestinal cells may alter the permeability of the child's gastrointestinal tract.[33] Childhood vitamin A deficiency is widespread in the developing world. This might further contribute to poor epithelial repair. Mixed feeds – breastmilk with a combination of water, formula, solids, teas, yoghurts, etc. – theoretically present the immature gastrointestinal tract with a variety of bacterial and food antigens. The resulting inflammatory activity is believed to promote viral penetration and facilitate viral entry into the infant's immune (gastrointestinal lymphatic) system.[33] In addition, mixed feeding is associated with sub-clinical mastitis, and with increased viral concentrations in breastmilk. Exclusive breastfeeding – offering the infant only breastmilk and no other source of nutrition – may present the infantile gastrointestinal tract with less inflammatory stress and less opportunity for viral transmission.[11,39-40]

Public health authorities recommend feeding choices on the basis of local infant mortality rates (IMRs). South Africa has a different IMR in each province, so a blanket policy is inappropriate. A recent model recommends that if the IMR is <25/1 000 live births, replacement feeding will give the best HIV-free survival. However where the IMR is >25/1 000 live births, exclusive breastfeeding produces the best outcomes. Indeed, where the IMR is >101/1 000 live births, replacement feeding results in a lower HIV-free survival than no intervention.[30]

Several factors may increase the risk of viral transmission through breastfeeding[41] (Table 4.II).

4.3.1 Breastfeeding: Exclusive or mixed?

ART through pregnancy, good viral suppression and the avoidance of breastfeeding have almost eradicated MTCT in the developed world.[4] For a minority of women in the developing world this approach can be followed provided formula feeds can be given in an acceptable, feasible, affordable, sustainable and safe manner.[42] But for the majority of mothers in southern Africa these 'AFASS' criteria cannot be met and the baby will need to be breastfed (see boxes, p. 44). Can transmission be prevented, or at least reduced, despite breastfeeding? Data suggest that exclusive breastfeeding for the first 6 months of life will reduce transmission risk and vulnerability to life-threatening childhood infections.[11,39-40] A 3- to 4-fold decrease in risk of transmission has been achieved when compared with non-

TABLE 4.II. RISK FACTORS FOR THE TRANSMISSION OF HIV THROUGH BREASTFEEDING[41]

Strong evidence	Limited evidence
High plasma viral load	High breastmilk viral load
Advanced disease/ low CD4 count	Sub-clinical mastitis as evidenced by increased breastmilk sodium levels
Breast pathology – mastitis, abscesses, cracked bleeding nipples	Low maternal levels of vitamins B, C, E
Primary infection/new infection: high plasma viral load	
Prolonged duration of breastfeeding (>6 mo.)	
Non-exclusive breastfeeding, mixed feeding and oral lesions[55]	

AFASS: ACCEPTABLE, FEASIBLE, AFFORDABLE, SUSTAINABLE AND SAFE

Acceptable
This means that the mother does not see any barrier to formula feeding. In some cultures, refusal to breastfeed may result in stigma, discrimination and rejection on cultural or social grounds or the tacit acknowledgement of being HIV positive. Mothers who choose to formula feed must be able to do so without fear of repercussions.

Feasible
Formula feeding requires adequate time, knowledge, skill and resources to feed an infant up to 12 times a day. The mother will need to mix formula adequately within the constraints of her work and family schedule.

Affordable
The mother and her family must be in a position to purchase and prepare formula feeds. This requires sufficient money to cover fuel costs and that of clean water, soap and the equipment needed (sterile bottles, cleaning agents, etc.). There must be no compromise of the family's finances with regard to their nutrition and medical needs.

Sustainable
There must be a continuous, uninterrupted and dependable system that ensures that the infant always has milk. Where the mother is absent, another caregiver must be able to prepare the formula feed reliably.

Safe
Replacement/formula feed must always be correctly, hygienically handled and stored. In addition, sufficient quantities must always be available for the child.

(World Health Organization[43])

exclusively breastfed cohort studies.[43] Congolese children born to both HIV-infected and uninfected mothers were at greater risk from death when not exclusively breastfed in the first 6 months of life.[44] Stopping breastfeeding before 6 months or at 4 months in studies in Malawi, Kenya, Uganda and Zambia all appear to increase the risk of infant mortality, often from diarrhoea.[43] Despite some earlier anxiety, breastfeeding does not increase maternal mortality.[45-46]

4.3.2 Is exclusive breastfeeding for 6 months possible in the South African context?

In a study looking at the HIV-1 transmission risk and survival associated with exclusive breastfeeding and other types of infant feeding, it was found that a much higher rate of exclusive breastfeeding was achieved through counselling and support for the mothers.[47] Facility-based or community-based antenatal and postnatal clinic support is associated with an increase in exclusive breastfeeding rates.[30]

A facility-based programme with increased rates of exclusive breastfeeding is the Mother Baby Friendly Hospital Initiative (MBFHI). This international programme aims to improve mother and child survival by changing hospital practices and by supporting, promoting and protecting breastfeeding. In South Africa there is a drive to make all health care facilities 'mother-baby friendly'.[30]

IS EXCLUSIVE BREASTFEEDING POSSIBLE IN SOUTH AFRICA?

Yes, but it requires the support of lactating mothers. Pre- and postnatal counselling is essential to ensure the mother's attempts at breastfeeding are successful. Counselling would include guidance on the following:

- Good lactation management (early initiation, attachment, positioning, frequent feeds, learning to express) to avoid mastitis, cracked nipples, etc.
- Condom use during lactation period
- Avoidance of feeding from breasts with cracked, bleeding nipples or abscesses (express and discard milk from affected side and continue feeding from unaffected side)
- Prompt treatment of infant oral thrush
- Heat treatment of expressed breastmilk
- The promotion of exclusive breastfeeding for up to 6 months
- Nutritional support for breastfeeding mothers irrespective of CD4 count

In the context of preventing mother-to-child HIV transmission, health workers need to be 'agents of change'.

Mothers need to be assisted in making the best decision with regard to infant feeding. The following are some of the choices:

- **Exclusive breastfeeding:** an infant only receives breastmilk and no other liquids or solids, not even water, with the exception of drops or syrups consisting of vitamins, minerals, supplements or medications.
- **Commercial infant formula:** a breastmilk substitute formulated industrially in accordance with international standards to satisfy the nutritional requirements of infants during the first months of life and up to the introduction of complementary foods.

Mixed breastfeeding is feeding with breastmilk, other fluids and pureed solids. The enhanced risk of HIV transmission is thought to result from maternal breast and nipple infections (mastitis) that result in an increase in the viral load of the milk, and the introduction of multiple foreign 'antigens', including bacteria, that compromise the integrity of the infant's gastrointestinal tract.[42] Mixed feeding is not a choice: Mothers do this by default. Where formula feeding cannot be provided within the AFASS guidelines, exclusive breastfeeding for a minimum of 6 months is recommended (Table 4.III).[43]

WHO/UNICEF recommends that women who do not know their HIV status should exclusively breastfeed for the first 6 months of the child's life with continued breastfeeding and complementary feeding until 2 years of age.[30]

4.3.3 When should breastfeeding be stopped?

When alternative choices are 'acceptable, feasible, affordable, sustainable and safe'. This is generally at or just before 6 months: maternal milk supplies are insufficient to cope with the energy and nutrient needs of children beyond this age, and additional food sources need to be introduced.[47]

TABLE 4.III. WORLD HEALTH ORGANIZATION 2006 BREASTFEEDING RECOMMENDATIONS[43]

- The most appropriate infant feeding option will depend upon the mother's circumstances but ought to consider local health care services, counselling and practical support available to the mother.
- Exclusive breastfeeding is recommended for HIV-infected women for the first 6 months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS criteria).
- At 6 months, if replacement feeding still does not satisfy AFASS criteria, breastfeeding must continue with the addition of complementary feeds. The mother and baby must be regularly assessed. All breastfeeding must stop once a nutritionally adequate and safe diet without breastmilk can be provided.
- Whatever the decision, health services must continue to follow up and support women and HIV-exposed infants offering counselling and assistance when feeding decisions are being reconsidered.
- Breastfeeding mothers and infants who are known to be HIV-positive should be encouraged to continue to breastfeed.
- Governments and other stakeholders are encouraged to revitalise breastfeeding protection, promotion and support. They are asked to actively support women who choose to exclusively breastfeed and to ensure that replacement feeding is safer for women who choose that option.
- National health programmes are asked to provide all HIV-exposed infants and their mothers with a total package of interventions that will promote survival and the prevention of transmission. Those women in the antenatal clinic who test HIV negative ought also to have access to primary prevention programmes for themselves and their infant.
- Governments are urged to ensure that all the above interventions, including those dealing with exclusive breastfeeding, are available before distribution of free commercial infant formula is considered.
- Governments and donors are requested to increase their commitment and resources to ensure the implementation of the Global Strategy for Infant and Young Child Feeding and the UN HIV and Infant Feeding Framework for Priority Action in order to prevent postnatal HIV transmission, improve HIV-free survival and achieve relevant UNGASS goals.

- Mother must be counselled on the need to stop at 6 months.
- Prepare baby for weaning and plan other forms of comfort apart from breast. Crying is very distressing and is a reason why mothers revert to breastfeeding.
- Prepare family for weaning of child. Counsel re disclosure and the need for help.
- Plan how to feed. Get supply of formula feed ready and demonstrate.
- Plan for any breast difficulty, such as engorgement.

4.3.4 Where highly active antiretroviral therapy (HAART) is affordable or available, should HAART be continued after delivery and/or for the duration of breastfeeding?

ART for the mother

Women who require indefinite HAART will continue with ARVs after childbirth. Those with baseline CD4 counts above 200 - 350 cells/µl and asymptomatic HIV infection will currently discontinue ARVs once their child is born. Continuing with ARVs for the duration of breastfeeding seems a reasonable approach provided adherence is reliable and viral suppression can be maintained. Two recent studies, the AMATA and MITRA trials from Rwanda and Tanzania, provided ARVs for the duration of breastfeeding and showed a transmission rate at 6 months of 1.4% and 5%, respectively.[48,49] These studies confirm reduced transmission to the infant. ARV drugs consumed by lactating women appear in breastmilk at levels that reduce breastmilk viral load.[50,51] Whether stopping therapy at the cessation of breastfeeding will lead to an increased risk of maternal viral resistance is currently unknown.[48,49,52]

ARV prophylactic therapy for the infant

The Botswana 'Mashi' study revealed that breastfed infants given only monotherapy with zidovudine (ZDV, AZT) as preventive therapy while being breastfed (not exclusive, usually 6 months) were not adequately protected. (Nevertheless, 7-month mortality was actually greater in the formula-fed infants. But by 18 months HIV-free survival was the same in both formula and breastfed groups. The children died of pneumonia and diarrhoea.) Few mothers commenced HAART before delivery (71 of a total of 1 200 women randomised), and few (only 82) started on ARVs during the 7 postpartum study months. The women were given zidovudine monotherapy from 34 weeks until delivery. Some also received intrapartum single-dose nevirapine.[53] In essence, the mothers were taking inadequate ARV therapy themselves while breastfeeding their infants. Giving ZDV monotherapy to these children during the breastfeeding period was inadequate post-exposure preventive therapy.

4.3.5 Weaning

Weaning is a difficult time for both the mother and the child. Apart from the distress experienced by both, newly weaned infants frequently develop diarrhoea and anorexia. Mothers may experience breast engorgement, mastitis and abscess formation. Women need counselling and support during this time. The success of weaning is often dependent on prior contact with clinic staff and access of the mother to support. The weaning period is variable: 2 - 3 days in some cases, 2 - 3 weeks in others. In the context of maternal HIV infection, replacement feeds need to be introduced rapidly and the period of 'mixed' feeding kept as short as possible (A Coutsoudis, personal communication, June 2007).

Heat treatment of expressed breastmilk. Pasteurisation and 'flash-heating' decrease both the bacterial contamination and the HIV viral content of breastmilk. Loss of nutritional value is minimal.[54-55] Is heat treatment feasible in urban and informal settlements and rural situations in southern Africa? Pasteurisation requires heating the milk to 62.5°C for 30 minutes. With flash-heating, milk is rapidly

brought to the boil and then immediately removed to cool to 37°C. Mothers who take this option need to be able to set aside time. A supportive domestic and social environment is essential. A recent Zimbabwean report notes that education and community discussion will improve the social acceptance of this modification to breastfeeding.[56]

4.3.6 Alternatives to breastfeeding

When infants are exclusively formula fed, the risk of postnatal HIV transmission is eliminated. This method of feeding is mainly chosen by women in developed countries.[30] From a meta-analysis of women in developing countries but of unknown HIV status, it was found that infants who were not breastfed and who received formula or replacement feeds have a 6-fold increase risk of death in the first 2 months of life. Between 2 and 3 months, the risk is 4-fold and 2.5-fold between 4 to 5 months.[30]

Formula or replacement feeds are only given when these are 'acceptable, feasible, affordable, sustainable and safe': the AFASS criteria.[43] Mothers who take this route must also be supported and counselled. It is imperative that the mother clearly understands the need for clean utensils, hygienic preparation and the correct measurement of the infant's feeds.[44] The International Code of Marketing of Breast Milk Substitutes discourages the promotion or recommendation by health professionals of a specific milk substitute. Being HIV positive does not automatically bar the mother from breastfeeding her infant. Mothers must decide for themselves which formula to use should they reject the free formula provided by the state.[44] No commercial product is a complete replica of breastmilk. Each has been modified for unique reasons and there is no 'best' formula: each is produced with the nutritional needs of all infants in mind.[33] The formula must be prepared in a clean environment and all equipment – bottles, nipples, mixers, lids (including that of the formula container) – must be thoroughly washed before use. Most children begin with a cow's milk-based formula feed.

In the South African PMTCT programme, mothers who so choose are supplied with free formula for the first 6 months of their child's life. Those mothers who exclusively breastfeed are given free formula for 6 months after weaning.[33] Table 4.IV outlines the recommended amount of formula appropriate to the age of the infant. These quantities provide sufficient energy for normal growth: keep in mind that HIV-infected infants will require at least 10% extra energy per day. These children will therefore need additional formula each day.

Since lactating mothers lose weight, in particular fat but not muscle, it is prudent to encourage increased nutrition during both pregnancy and lactation. Furthermore, it has been noted that CD4 cell counts decrease during lactation and hence good nutrition is imperative at this time.[57-58]

4.4 CONCLUSIONS

The energy and nutritional needs of pregnant and lactating women, particularly the malnourished and the HIV-infected, are increased. Limited data suggest that some multivitamins – vitamins B, C and E – may delay progression of infection, reduce the relative risk of dying from AIDS and improve CD4 counts and decrease viral loads.[17,59] In this context, the use of vitamin A has sometimes had conflicting results, including the possible promotion of MTCT.[17,19,59] With regard to the prevention of transmission, a beneficial role for other micronutrients – zinc, iron and selenium – in pregnancy has not been established.[24] Good maternal health is necessary for the welfare of the entire family. A sick mother increases the likelihood of death, stunted growth and poor development of her children.[1] While children remain vulnerable to vertical infection from their mothers, interventions aimed at reducing this risk are necessary. In addition to ART, exclusive breastfeeding now appears to offer some protection. But women find it difficult to do: it was seldom done in the studies from Zimbabwe and Uganda.[11,60] Health workers must be convinced and motivated if their patients (mothers and children) are to be protected from the virus and breastfeeding carried out successfully.[33] A considerable amount of effort is required by mothers, and the team of health workers around them, to ensure that exclusive breastfeeding is continued through to 6 months. Chen *et al.* make the perceptive remark that health workers 'are active agents of

KEY MESSAGES

- Mother-to-child transmission is preventable.
- There is no evidence that micronutrients prevent HIV transmission.
- Where malnutrition and HIV infection coexist, providing food and correcting specific nutritional deficiencies remains the appropriate response.
- Antiretroviral drugs are the only consistent means to reduce maternal viral load and reduce perinatal HIV transmission.
- Exclusive breastfeeding has been shown to reduce mother-to-child transmission.
- Exclusive breastfeeding should be encouraged for the first 6 months of life.

TABLE 4.IV. AMOUNTS FOR INFANT FEEDING UNTIL 6 MONTHS OF AGE

Age of infant	Milk feed: Previously boiled water	Milk feed: No. of scoops	No. of feeds per 24 hours	No. of tins required for 1 infant per month (varies with the individual)
1 - 2 wks	100 ml	4	6	7 tins
3 - 4 wks	125 ml	5	5	7 tins
2nd mo.	150 ml	6	5	9 tins
3 - 4 mo.	175 ml	7	5	10 tins
5 - 6 mo.	200 ml	8	4	9 tins

change'.[61] In the context of preventing MTCT, health workers need to be these 'agents of change'.

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5. HIV/AIDS IN INFANTS AND CHILDREN: NUTRITION

5.1 CHARACTERISTICS OF HIV INFECTION IN CHILDREN

- Children are not small adults.
- HIV infection in childhood differs from that in adults with regard to transmission, viral dynamics, the 'immaturity' of the immune system and clinical manifestations.
- More than 90% of infected children acquire their virus vertically, from an infected mother.[1] Most infections occur in the peri- or intrapartum periods.[2]
- Transmission via transfusion, sexual activity and drug abuse is infrequent in children.
- Depending upon whether it is mixed or exclusive and its duration, breastfeeding carries an additional postpartum risk of 4 - 16%.[3,4]
- Without antiretroviral therapy (ART), clinical disease in the vertically infected child takes a bimodal course: rapid progression with AIDS-defining symptoms and life-threatening complications in the first year of life in 10 - 25%. The natural course is slower in the remainder with a mean duration of more than 8 years until AIDS-defining symptoms occur.[5]
- Where infection is acquired at birth, the viral load rises rapidly in the first few months of life. If left untreated, these levels fall slowly in children surviving beyond the age of 4 - 5 years. These viral dynamics are significantly different to those of newly infected and untreated adults.[6]

Approximately 2.3 million children worldwide have HIV infection. Globally, only 115 000 of the 700 000 children requiring ART receive it. Just 15% of the need is actually being met. The vast majority of infected children live in Africa. In sub-Saharan Africa, only 80 000 children are currently receiving ART.[7]

5.2 UNDER-NUTRITION IN HIV-INFECTED CHILDREN

5.2.1 Introduction

Under-nutrition is frequent in the children of Africa.[8-10] Many are also HIV-infected.[11,12] Growth stunting, an indicator of malnutrition, was present in 21.6% of South African children aged between 1 and 9 years; 10.3% of 1 - 3-year-olds were underweight.[13,14] Unemployment, poverty, food insecurity, malnutrition and vulnerability to infectious diseases define the cycle in which millions of Africans – adults and children – live their lives.[15] Most parents lack any formal nutritional education, and have inadequate skills to grow, purchase, prepare and provide food in sufficient variety to promote the growth of their children and ensure their own health. The child's survival is closely dependent on the health of the parent(s). In Malawi maternal mortality has risen 3-fold since 1990,[16] and in Botswana, Swaziland and Zimbabwe AIDS now causes more than half of the childhood deaths.[17] Africa's families are no longer the stable centre of communal life. Migratory labour, advancing urbanisation and the disappearance of traditional roots and values together with the social impact of the AIDS epidemic have shifted this centre.[18] For some 11 - 17 million South Africans the supply of food is unreliable; 38% of households report regular absence of meals.[17,18] Rural children and those in informal settlements around the cities are particularly at risk.[19,20] In addition, farming communities weakened by AIDS are likely to find it difficult to produce sufficient food for themselves or their surrounding region. With a reduced capacity to produce food, food insecurity is expected to persist into the future.[21] Africa's children may also be at risk from climate change: malnutrition, diarrhoea and malaria will increase should global warming affect the continent's weather patterns in the 21st century.[21,22]

5.2.2 Acute and chronic malnutrition in HIV-infected children

THE WHO DEFINITION OF SEVERE ACUTE MALNUTRITION (SAM)[10]

Any of the following criteria:

- Weight-for-length/height <3 Z-scores below reference range (or)
- Bilateral pitting oedema (or)
- Severe visible wasting (or)
- Mid-upper arm circumference (MUAC) ≤110 mm for children 6 months - 5 years.

NB: The proposed WHO Draft Malnutrition MUAC Guideline range for the following ages:
Age 6 - 9 years <135 mm
Age 10 - 14 years <160 mm.*

*Source: Nigel Rollins, Durban, KwaZulu-Natal, August 2007.

Up to 2% of under-5s in developing countries are acutely and severely malnourished.[15] Of Malawian children with severe acute malnutrition (SAM), 34% tested HIV-positive.[23] Fatality rates and slower recovery were frequent in these children.[17,23] Despite this, successful feeding programmes can be implemented in resource-poor communities. These interventions reduce hospital admissions and enhance public awareness.[24,25] A low mid-upper arm circumference (MUAC) is a rapid and useful measurement of the severity of malnutrition, though reduced height-for-weight scores and the presence of pitting oedema are also important clinical signs (see box).[10,26] Growth stunting is a frequent manifestation of chronic malnutrition.[27] This may begin very early, even during fetal development or soon after birth, and if not addressed, growth faulting will persist through childhood into adulthood.[28,29] In animals, early under-nutrition, iron deficiency, environmental toxins, poor stimulation and poor social interaction affect brain structure and function. Lasting cognitive and emotional defects result.[27] Similar changes have been reported in malnourished children.[29,30] Of children in developing regions, 39% are believed to be 'disadvantaged' in this way – stunted and/or living in poverty. Sub-Saharan Africa has the highest prevalence of such children, and is the only region where growth stunting and food insecurity are increasing.[30]

Poor growth is a sensitive indicator of the progression of HIV infection and is a strong and independent risk factor for death.[31,32] Indeed, linear growth faltering (loss of height/length) frequently anticipates the onset of new

opportunistic disease in HIV-infected children.[31] Both the increased daily energy requirements of children infected with HIV and inadequate energy intake contribute to the accompanying loss of weight[31] (Table 5.I). In addition to providing nutrition, these children require control of their HIV infection. ART has been shown to enhance the child's gain of weight and height and to facilitate catch-up weight gain.[33,34] The child at risk must be identified before he/she becomes severely malnourished. Regular measurement of the child's weight and height/length is essential – as is the appropriate response of the health worker.

Poor growth of the HIV-infected child is a strong and independent predictor of death. Failure to achieve expected height or length goals in children may occur before the onset of clinical disease in infected children.

5.2.3 The assessment and measurement of nutritional status in children

Nutritional assessment should be routine and viewed as an 'early-warning system'. The assessment starts with a detailed history and is followed by a thorough examination. Though it is important to recognise wasting, it is a late sign. Action needs to be taken before wasting is clinically obvious. The response to interventions such as ART and nutritional supplements can be objectively measured. But the child who is responding will also take more interest in play activities and perform better at school. He/she will be happier and more contented.

Measurement: height/length, weight, head circumference and MUAC. In children the measurement of weight and height (length) is expressed as a Z-score – a comparison of the child to an international median or growth standard appropriate to age.[35] MUAC reflects lean body mass and not body fat.[36] Skinfold measurements provide information on subcutaneous fat but not visceral fat. Skinfold measurement is generally restricted to academic and referral centres. Similarly, whole body dual-energy X-ray absorptiometry (DEXA) scans have a limited role in Africa. Expense and expertise restrict this measurement to very few sites on the continent.

5.2.4 The management of acutely and chronically malnourished HIV-infected children

5.2.4.1 Major management goals

- Define the cause of the malnutrition: insufficient food, anorexia, opportunistic diseases such as tuberculosis and gastrointestinal infections (chronic diarrhoea), co-morbid disease such as diabetes, overwhelming and untreated HIV-infection. Correct the cause.
- Assess the HIV infection: Clinical stage, CD4 count and viral load. Does the child need antiretrovirals (ARVs)? Control the virus. Exclude opportunistic disease.
- Strengthen the long-term support of the child:
  - Identify the primary and/or other caregiver(s): parent, aunt, sibling, etc.
  - What are the nutritional and economic needs of the family and will the child be adequately cared for at home?
  - Implement counselling and support. Access social and child grants. Work as a team: utilise social workers and local non-governmental organisations (NGOs) or train community workers to assist in counselling and with obtaining grants and support.
  - Set targets: define the child's ideal weight and height and set a follow-up time-frame for achieving these targets. Ensure reliable follow-up: diarise dates, use phones (cell phone) and local community contacts. Ensure that the child has someone at home or in the community, to support him/her.
  - Admit the severely malnourished child. Provide therapeutic feeding where needed. Plan long-term nutritional support: note that the energy needs of the HIV-infected are significantly higher than the uninfected. The World Health Organization (WHO) recommends meeting the increased resting energy needs by an additional 10% above usual requirements in asymptomatic adults and children and by an additional 20 - 50% during and immediately after severe illness.[31]

5.2.4.2 What food/supplementation should be used?

Increased energy and protein intake can best be achieved by using locally available foodstuffs and developing a locally appropriate, sustainable food-based intervention. Various supplements are available from the government clinics and hospitals of South Africa; their general acceptability awaits further evaluation.[37,38] 'Ready-to-use' therapeutic food (RUTF) is an energy-dense feed enriched with minerals and vitamins. This is provided for children with severe acute malnutrition. Therapeutic foods may also be prepared from local food sources and crops.[10] A variety of specialised nutritional products are also available from South African public health services. Nevertheless many children still do not have routine nutritional assessments, nor are all provided with supplements when needed.[38] Children need a balanced diet. Protein requirements remain at 12 - 15% of total energy intake.[31] ARVs may need to be considered as these will improve the child's appetite, promote weight gain and provide control of the underlying infection.[39]

TABLE 5.I. WEIGHT LOSS IN HIV-INFECTED CHILDREN – CAUSES AND RELATIONSHIPS[31]

Increased energy requirements	Inadequate energy intake
Energy needs increase by 10% from time of acquiring virus	Anorexia and poor dietary intake: oral candidiasis, gingivitis, oral sores, oesophageal candidiasis and dysphagia, loss of taste, insufficient food, poverty
Energy needs increase by 20 - 30% during and after illness	
Energy needs may increase to 50 - 100% in severely malnourished children	Opportunistic infections and cancers: chronic lung disease (lymphoid interstitial pneumonitis, LIP), chronic diarrhoea, tuberculosis, recurrent respiratory infections, lymphoma
NB. Protein requirements remain at 12 - 15% of total energy intake provided diet is well balanced	Advanced HIV infection and untreated, end-stage HIV infection

5.2.4.3 Is micronutrient supplementation required?

Daily access to a diet that provides the full range of essential micronutrients is important. Randomised controlled trials (RCTs) indicate that **vitamin A supplementation** benefits young HIV-positive children: a single large oral dose of 50 000 IU before 6 months is followed by another single dose of 100 000 IU between 6 and 11 months and a further 200 000 IU every 6 months thereafter until the age of 5 years.[40,41]

Similarly **zinc supplementation** in HIV-infected and uninfected **children with diarrhoea** is recommended: zinc 10 mg daily × 2 weeks in those under 6 months of age and 20 mg daily × 2 weeks in those over 6 months.[42,43] Irrespective of HIV status, the WHO recommends a daily intake of 1 × the Recommended Nutrient Intake (RNI) of each essential vitamin and mineral.[31] Micronutrient deficiencies are endemic to many developing countries. Diversified diets, fortified foods and micronutrient supplements assist in preventing these deficiencies. Although two randomised controlled multivitamin trials incorporating among others large doses of the B-, C- and E-group vitamins have demonstrated benefit in HIV-infected Tanzanian and Thai adults, no similar paediatric data are currently available.[44,45] Iron supplementation is recommended for children with iron deficiency anaemia, but giving iron to children who are iron-replete may increase their risk of infections and should be avoided.[46,47]

5.3 THE METABOLIC SIDE-EFFECTS OF ART AND ITS MANAGEMENT IN CHILDREN

The benefits of ART outweigh its potential to cause harm. Drug-related metabolic side-effects are common but can be minimised or avoided with close supervision. In this regard the child on ART or his/her parent will often have noticed changes in body shape and appearance before these changes are observed by the doctor or nurse. The examination must take note of the child's general appearance, weight and height/length; particularly look for loss of fat on the face, upper and lower limbs and buttocks, an increase of abdominal fat and/or breast enlargement, a fat pad or 'buffalo hump' between the shoulders and firm non-tender enlargement of the liver. Fasting blood glucose and lipids, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides may be abnormal. These are measured annually or bi-annually or more frequently if abnormal. An isolated elevation of the alanine aminotransferase (ALT) level may suggest a fatty liver or hepatic steatosis. Fat in the liver may also be confirmed with a hepatic ultrasound or abdominal CT scan.[48]

The fat redistribution or lipodystrophy that complicates ARV drug use in adults occurs in children too. Various paediatric studies report a prevalence of 1 - 43%, though a recent review of children with a mean exposure to ARVs of 5.9±2.4 years noted a considerably higher prevalence, viz. 73%.[49-52] The syndrome follows the use of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), in particular stavudine, didanosine and zidovudine, and the use of stavudine and didanosine together.[53-55] Children are at risk throughout childhood.[56] Insulin resistance is frequent, though overt hyperglycaemia and diabetes remain rare.[49] Serum lipids – cholesterols and triglycerides – are often elevated and an increase in the thickness of the wall of the carotid vessels has been noted in these children. While the actual risk of heart disease and stroke is currently unknown, it is likely to be significant over time.[57,58] All ethnic groups, including those living in Africa, appear to be at risk.[59,60] Metabolic abnormalities have also been reported in the absence of exposure to ART, though this is rare.[49,54]

Depleted levels of mitochondrial DNA and a variety of related abnormalities have been described in the cord blood of HIV-uninfected newborns exposed *in utero* to ARVs.[61,62] Mitochondrial DNA depletion and the inhibition of mitochondrial DNA polymerase-γ are known consequences of NRTI therapy.[63] The PIs inhibit the activity of the glucose transporter protein 4 (GLUT 4), alter the degradation of the sterol regulatory element-binding protein 1 (SREBP-1) and apolipoprotein B, and inhibit the function of the low-density lipoprotein receptor-related protein (LPR), leading to increased lipid production and reduced triglyceride clearance from the circulation.[64]

5.3.1 Management of metabolic abnormalities

5.3.1.1 Switching of ARVs

Adult 'switch' studies support the replacement of stavudine and zidovudine with abacavir and/or tenofovir. Bone demineralisation in children and infant monkeys exposed to tenofovir suggest caution in its use in this age group.[65] However, a recent study that switched children from a stavudine and PI-based ART to tenofovir and efavirenz noted improved biochemical parameters of bone resorption on tenofovir.[66] The NRTIs abacavir, lamivudine and emtricitabine carry little risk of either metabolic or mitochondrial toxicity and are safe in children.[67-69] Children switched from PI-based regimens to a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen (efavirenz) improved total and LDL cholesterols and triglycerides.[49] The adult DAD study noted a similar effect, viz. lower serum lipid levels and fewer myocardial infarcts in patients on NNRTI- versus PI-based regimens.[70] Apart from atazanavir, most of the PIs are associated with lipid abnormalities and insulin resistance. Both boosted and un-boosted atazanavir may be less likely to cause fat abnormalities in adults, but there are no confirmatory data in children.[71-73] Adult studies suggest that nevirapine, an NNRTI, is less likely than efavirenz to elevate serum cholesterol.[74] Future antiretroviral classes – the fusion inhibitors, the CCR5 and the integrase inhibitors – hold out the hope of improved metabolic outcomes, but adult and paediatric data are limited and these agents are not currently registered for paediatric use in southern Africa.[75]

5.3.1.2 Diet and exercise

Obesity, high serum lipids and the lipodystrophy syndrome may all improve following a combination of resistance (mild weight training) and aerobic exercise. Exercise helps to maintain lean body mass and to restore lost lean tissue in children and adults.[76,77] Children enjoy playing and having fun: exercise strengthens relationships between parents and their children and is extremely important in the overall wellbeing of the child. In adults, regular high-frequency aerobic exercise – a minimum of 4 hours per week – has been accompanied by a decrease in intra-

abdominal fat, increased HDL cholesterol levels and a small decrease in triglyceride levels.[78] Obese children need to lose weight. Those with elevated serum lipids need to reduce their total daily intake of fats, particularly saturated fats. However, carbohydrate loading from high-glycaemic foods such as ready-to-eat cereals, white bread and snack foods should be avoided. Diets that are low in fat but high in carbohydrates may reduce LDL but also HDL cholesterols.[78] High serum triglycerides may respond to diets rich in n-3 polyunsaturated fats such as canola or olive oil, soy and flaxseed oils, nuts (almonds, peanut, walnuts and pecans) and cold-water fish (salmon and mackerel),[79] but for many in Africa these foods are expensive and unobtainable, and a recent meta-analysis of n-3 fatty acid supplementation or dietary modification has not confirmed any cardiovascular benefit in adults.[78] Dietary advice must be simple and practical. Fish, poultry (without the skin) and lean red meat are recommended. Refer malnourished and obese children to a dietician wherever possible. Lifestyle modification programmes have been successful in adults, improving physical activity and reducing lipodystrophy scores and waist circumference and systolic blood pressures.[80] These programmes could be modified for use in children.

5.3.1.3 Lipid-lowering agents in children

Children with elevated fasting lipids unresponsive to ARV-switching regimens, diet and exercise may require lipid-lowering agents, statins and fibrates. These should be used with caution as paediatric data are limited and the concomitant use of a PI with a statin may increase the risk of acute rhabdomyolysis.[49] While lovastatin has been approved for use in American adolescents with familial hypercholesterolaemia, its use – and that of simvastatin – in HIV-infected adults is discouraged.[81] Pravastatin, rouvastatin, atorvastatin and fluvastatin are used in adults and appear to be safe.[81] Similarly, fibrates may be required to bring down the triglycerides if modifications to diet, exercise and drug switches fail. Paediatric data are limited: interaction of the fibrates and the statins increases the risk of rhabdomyolysis and hepatitis, and interactions with the PIs may reduce the efficacy of the fibrates.[49]

5.3.1.4 Insulin resistance and hyperglycaemia in children on ARVs

Insulin resistance and elevated glucose levels have been reported in HIV-infected children, particularly those with lipodystrophy.[49] Insulin resistance in children is a risk factor for subsequent cardiovascular disease.[82] A fasting blood glucose and/or an oral glucose tolerance test should be checked as part of the diagnostic workup.[81,82] With regard to management there are very few paediatric data available. However, ARV-switch regimens and attention to dietary changes and exercise should be tried. In particular, obese children should be assisted to lose weight. Neither metformin nor the thiazolidenediones (e.g. rosiglitazone) have demonstrated sufficient efficacy and safety in adult studies to be recommended currently in HIV-infected children.[49,83]

5.3.1.5 Decreased bone mineral density in HIV-infected children

Bone mass increases in childhood and adolescence, peaks in early adult life and then declines slowly through adulthood.[84] Studies indicate a loss of bone mineral density (BMD) in HIV-infected adults before and after starting ART. Children with HIV infection demonstrate a similar decrease in BMD.[49,66] While the use of NRTIs and PIs has been incriminated, loss of bone mass may occur independent of exposure to the ARVs. The latter is probably a consequence of cytokine up-regulation within the bone and bone marrow following chronic activation of the immune system.[66,85,86] Mitochondrial toxicity has been suggested as the cause of ARV-related bone loss.[81,86] The nucleotide tenofovir has been associated with a significant decrease in BMD compared with stavudine.[87] Its use in osteopenic adults, in those at risk for osteoporosis and in children requires a regular review of BMD where feasible.[66,86] Malnutrition, weight loss and a background deficiency of vitamin D and calcium are common in the developing world and may further contribute to bone loss and weakness[88] (Table 5. II). The diagnosis and management of reduced BMD in HIV-infected children is currently unclear. DEXA scans are the best means of diagnosing subclinical osteopenia and osteoporosis. These scans are not widely available in sub-Saharan Africa. Discussion with a local paediatric expert is recommended. Where poor nutrition and specifically vitamin D and calcium deficiency have been confirmed or are likely, these nutrients must be replaced. The role of biphosphonates in children with documented loss of BMD remains ill defined. Alendronate has been used together with calcium and vitamin D in HIV-infected adults. BMD improved significantly in the group of adults on a biphosphonate compared with those given only calcium and vitamin D.[89] Discussion with a local metabolic specialist is recommended.

5.4 CONCLUSION

Children in Africa continue to be drawn into the HIV epidemic. Inadequate screening of at-risk mothers and failure to prevent mother-to-child-transmission permit this appalling situation to continue. Inadequate linear growth and failure to gain weight are important markers of malnutrition and of uncontrolled infection – HIV itself or an opportunistic disease such as tuberculosis. Small children frequently go without meals. Childhood stunting leads to restricted neurological development. This has consequences that follow the child into adulthood. Food security is expected to worsen as the HIV epidemic expands

TABLE 5.II. ADEQUATE CALCIUM INTAKE*

Age or 'life-stage' group	Estimated adequate daily calcium intake
Children 1 - 3 yrs	500 mg daily
Children 4 - 8 yrs	800 mg daily
Adolescents and young adults 9 - 18 yrs	1 300 mg daily
Men and women 19 - 50 yrs	1 000 mg daily
Men and women >51 yrs	1 200 mg daily

*Lindsay and Cosman,[90] adapted from the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, Washington, DC, 1997, National Academy Press. Note that for pregnancy and lactation needs are the same as for non-pregnant women.

across southern Africa and as climate 'change' reduces the productivity of agricultural land. Many children on ART will develop the metabolic complications of ARV. Can lifestyle modification – exercise and diet – prevent these complications? Answers will require close surveillance. Adequate care demands the regular assessment of HIV-infected children and their assured access to a sympathetic and competent health system. Such children deserve the broadest participation and commitment of multiple sectors within society: a trained and functional health care system, a willing and supportive government, and a community that owns the epidemic and believes in the future of these children.

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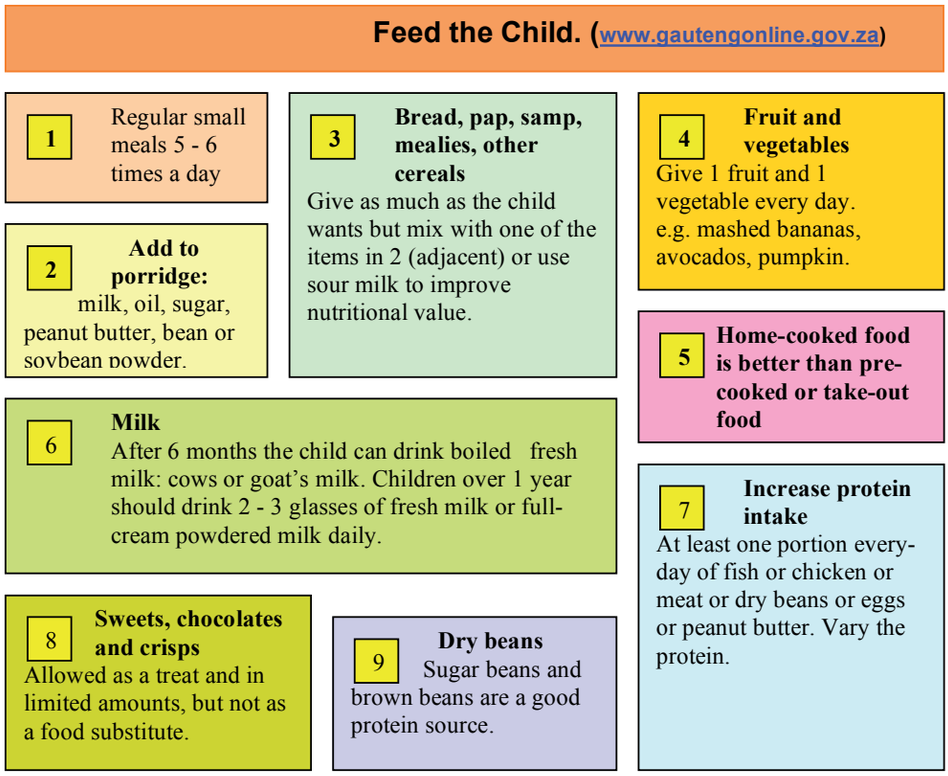
APPENDIX A

Feeding the HIV-infected child. (Draft of Food-based Support for HIV and AIDS Affected households and Communities, South African Department of Health: www.gautengonline.gove.za, accessed 25 October 2007.)



APPENDIX B

Antiretroviral Therapy: Lipid and Glucose Side-Effects. (Tebas P. Cardiovascular Disease Prevention in Patients with HIV Infection. Expert column, CME, Medscape, http:www.medscape.com/viewarticle/548184, accessed March 2007.)

Drug class and individual ARVs	Changes in serum lipids	Changes in serum glucose and insulin
Nucleoside/nucleotide reverse transcriptase inhibitors (N/NtRTIs)		
Zidovudine	Increase in TC and TG	IR: increased insulin levels
Stavudine	Increase in TC and TG	IR
Didanosine	Increase in TC and TG	IR
Tenofovir, abacavir, lamivudine and emtricitabine	No significant effect	No significant effect
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz	Increase in TC, HDL, LDL cholesterols, no effect on TG	No significant effect
Nevirapine	Increase in HDL, no effect on TC, LDL or TG	No significant effect
Protease inhibitors (PIs)		
Atazanavir	No significant effect	No significant effect
Fosamprenavir	Increase in TC and TG, increase in HDL	No significant effect
Indinavir	Increase in TC and TG	IR
Lopinavir/ritonavir (Kaletra)	Increase in TC and TG	IR
Nelfinavir	Increase in LDL cholesterol and TG, decrease in HDL	No significant effect
Ritonavir: full dose	Increase in TC and TG	IR
Saquinavir	No significant effect	No significant effect
Tipranavir	Increased TC and TG	Unknown

TC = total cholesterol; TG = triglycerides; IR = insulin resistance; LDL = low-density lipoprotein; HLD = high-density lipoprotein.

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6. FOOD, DRUGS, HERBS AND HIV INFECTION

6.1 FOOD AND DRUG INTERACTIONS

Food and drug interactions are important in the management of HIV-infected patients. Table 6.I sets out several of the known interactions with the antiretroviral (ARV) class of medicines.

6.2 WEBSITES WITH INFORMATION ABOUT DRUG AND DRUG INTERACTIONS

Food and drug interactions:
www.foodmedinteractions.com

Liverpool HIV Pharmacology Group:
www.hiv-druginteractions.org

HIV/AIDS Treatment Information Service:
www.hivatis.org

Johns Hopkins AIDS Service:
www.hopkins-aids.edu

International Association of Physicians in AIDS Care:
www.iapac.org

Medscape:
www.medscape.com

6.3 HERBS, FOOD, TRADITIONAL MEDICINES AND ARV INTERACTIONS

African potato (*Hypoxis hemerocallidea*, and Hypoxis sp.). Common names for the African potato are 'magic muthi, yellow stars, star-lily, sterblom, gifbol, lotsane and molikharatsa'.[2] Plant sterols and sterolins and a glycoside, hypoxoside (rooperol) are present in the root of this plant. The African potato has been shown to induce activity of the nuclear pregnane X receptor (PXR) and to inhibit cytochrome P3A4 (CYP3A4). PXR activation promotes a P-glycoprotein dependent drug-efflux mechanism. Enhanced efflux and elimination may therefore reduce the bioavailability of other intestinally absorbed drugs such as the ARVs. This system also operates in the nervous system and its activation may decrease drug concentrations in the brain and spinal cord.[3,4] Clinical studies with the African potato were discontinued prematurely after its use led to bone marrow failure in HIV-infected patients. These subjects also experienced a significant fall in total lymphocyte and CD4 cell counts.[5,6] There is no scientific basis for its use in HIV patients at this time.

Aloe vera (*A. barbadensis*). Dried exudate from the aloe leaf contains anthranoids that behave as laxatives.[7] Although the gel or juice made from the aloe plant itself does not contain anthranoids, contamination during preparation is not unusual. A rapid intestinal drug transit time and/or overt diarrhoea may result in diminished absorption of medication such as the ARVs. Patients should be cautioned.

Beetroot. This vegetable is a food source. There is no scientific support for a role as an 'immune booster' or as an antiviral agent. Beetroot is not a significant source of dietary iron.

Dagga (marijuana, hashish). The psychoactive components of dagga are the cannabinoids. Oral cannabinoids

TABLE 6.I. FOOD INTERACTIONS AND THE ARVs[1]

ARV medication	Food effect and interactions with other drugs	Dietary recommendation
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI/ NtRTIs)		
Abacavir (ABC, Ziagen) 300 mg bd po (Trisivir: ZDV + 3TC + ABC; Kivexa: ABC + 3TC)	No effect. Alcohol increases the area under the curve (AUC) by 41%.	Can be taken without regard to meals. Avoid alcohol.
Didanosine (ddI, Videx; Videx EC) 400 mg/d po if weight >60 kg or 250 mg if <60 kg	Food decreases absorption: approx 55% reduction in AUC. Avoid magnesium and aluminum containing antacids: these decrease absorption.	Take on an empty stomach at least 30 minutes before a meal or 2 hours after. Take only with water. Alcohol increases toxicity: avoid.
Emtricitabine (FTC) 200 mg daily po (Truvada, TVD: TDF + FTC; Atripla: TDF + FTC + EFV)	Food has little effect on absorption or metabolism.	Can be taken without regard to meals. Avoid alcohol. If on Atripla or Truvada, take with a light meal as food increases the absorption of tenofovir.
Lamivudine (3TC, Epivir) 150 mg bd po (Combivir: ZDV + 3TC; Kivexa: ABC + 3TC; Triomune, Stalinev: d4T + 3TC + NVP)	Food has little effect on absorption or metabolism.	Can be taken without regard to meals. But Combivir is taken on an empty stomach. Avoid alcohol.
Stavudine (d4T, Zerit) 30 mg bd po irrespective of weight (Triomune, Stalinev: d4T + 3TC + NVP)	Food has little effect on absorption or metabolism.	Can be taken without regard to meals. Avoid alcohol
Tenofovir (TDF, Viread) 300 mg/d po (Truvada: TDF + FTC; Atripla: TDF + FTC + EFV)	Administration with a high-fat meal increases AUC by 40%.	Take with food.
Zalcitabine (ddC, Hivid) 0.75 mg 8-hrly po	Food has little effect on absorption. Avoid antacids containing magnesium or aluminum. Do not take together with metoclopromide: decreases the AUC.	Can be taken without regard to meals. Avoid alcohol.
Zidovudine (AZT, ZDV, Retrovir) 300 mg bd po (Combivir: ZDV + 3TC; Trisivir: ZDV + 3TC + ABC)	AUC decreased by 25 - 50% with food.	Preferably take on an empty stomach. Otherwise, a low-fat meal. Avoid alcohol.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz (EFV, Stocrin, Sustiva) 600 mg/d (nocte) po (Truvada and Atripla)	Low-fat meals improve tolerability: high-fat meals increase AUC by 50%. Care with drugs that induce or inhibit cytochrome P-450 (CYP450) activity. Avoid St John's Wort.	Can be taken without regard to meals. Avoid a high-fat meal. Alcohol may increase unpleasant side-effects.
Nevirapine (NVP, Viramune) 200 mg bd po (Triomune and Stalinev)	Absorption not affected by food. Care with drugs that induce or inhibit CYP450 activity. Avoid St John's Wort.	Can be taken with food. Avoid alcohol.
Protease inhibitors (PIs)		
Amprenavir (APV, Agenerase) 1 200 mg bid po (Fosamprenavir)	High-fat diet decreases absorption and decreases AUC. Avoid grapefruit juice. Increase daily fluid intake. Avoid vitamin E supplements, antacids and St John's Wort.	Can be taken without regard to meals but avoid a high-fat meal.
Atazanavir (ATZ, Reyataz) 400 mg daily or 300 mg + ritonavir 100 mg (boosted) daily po	Absorption is enhanced with food.	Given with meals.

TABLE 6.I. FOOD INTERACTIONS AND THE ARVs[1] (CONTINUED)

Indinavir (IDV, Crixivan) 800 mg 8 hourly po or 800 mg bid + ritonavir 100 mg (boosted) bd po or 400 mg bd + 400 mg ritonavir (boosted) bd po	Presence of high-fat, high-protein meal decreases serum levels by 84% and AUC by 77%. Drink 2 litres of fluid daily to avoid renal stones. Avoid grapefruit juice and St John's Wort and take care with other drugs (inducers and inhibitors) that use the CYP450 system.	Taken on an empty stomach at least 1 hour before or 2 hours after a meal unless taken with ritonavir. If taken with ritonavir (i.e. boosted), can be taken with a light low-fat meal.
Lopinavir (LPV/r: Kaletra capsules: lopinavir 133.3 mg + ritonavir 33.3 mg), 3 capsules bd po; Aluvia tablets: LPV + RTV, 2 tablets bd po	Absorption improved with a high-fat meal. Interacts with medication that use CYP450 system. Avoid St John's Wort.	Take with meals of a high fat content. Kaletra is stored in a refrigerator. Aluvia does not require refrigeration.
Nelfinavir (NLF, Viracept) 750 mg td or 1 250 mg bd po	AUC and plasma concentrations increase after a meal. Increase fluid intake. Avoid acidic foods and St John's Wort.	Take with meals or a light snack that includes food of high protein content to enhance absorption. Diarrhoea, a common side-effect, may be improved with lactose-free dairy products.
Ritonavir (RTV, Norvir) 600 mg bd po or in 'boosted' combinations with other PIs	Absorption increased with food. Multiple drug-drug interactions: uses CYP450 enzyme system. Avoid St John's Wort.	Take with a meal. Store in the refrigerator.
Saquinavir (SQV, Invirase, the hard-gel formulation) 600 mg td or in combination with ritonavir e.g. SQV 400 mg/ RTV 400 mg bd po	Absorption increased with food and with grapefruit juice. Latter inhibits intestinal CYP3A4 system. Avoid St John's Wort.	Take with a meal: high fat and high calorie content enhances absorption. Avoid alcohol.
Tipranavir (TPV, Aptivus) 500 mg + ritonavir 200 mg bd po	Utilises the CYP450 system: care needs to be taken with the co-administration of drugs that activate the P-glycoprotein drug transport (efflux) mechanism and CYP enzyme systems.	Should be taken together with food: fewer gastric side-effects.

(dronabinol) and dagga/marijuana (smoked) are sometimes used to stimulate appetite and control nausea. Weight gain has been inconsistent in clinical trials. When gain is achieved, this has been predominantly fat. Dronabinol use is therefore not generally recommended for the purpose of weight gain in HIV-positive patients.[8] With regard to drug interactions, animal studies suggest an inhibitory effect involving the CYP3A and CYP2C families of liver enzymes. This does not appear to result in significant alterations of plasma concentrations of the PIs, indinavir and nelfinavir.[9] Caution is recommended.

Echinacea (*E. augustifolia, E. purpurea*). Although this herb is sometimes taken as an 'immune booster', there is no scientific support for this. It is an inhibitor of CYP3A4 *in vitro* but an effect on ARVs has not been studied. It does not have any role in the management of HIV-infected patients.[4]

Garlic (*Allium sativum*). Garlic is an inducer of CYP3A4 and its use together with the protease inhibitor, saquinavir, has led to decreased blood levels of the latter.[10] Levels of saquinavir remained 30 - 40% below baseline even after a 10-day post-administration washout period. Two case reports indicate that co-administration of garlic and ritonavir may enhance the gastrointestinal toxicity of garlic, i.e cause abdominal discomfort, nausea and pain.[4,11] Garlic may increase the risk of bleeding: Patients with clotting abnormalities (e.g. low platelets, haemophilia), those on anticoagulants and those awaiting surgery are advised to stop taking garlic.[7] And as with the herbs, danshen, dong quai and papaya, garlic has been noted to interfere with platelet function.[7] Randomised controlled trials of garlic in non-HIV-infected subjects have shown small, short-term benefit to some lipid and antiplatelet factors. These findings have been disputed.[12] There is no evidence that garlic has any role in the management of the HIV-infected patient.

Ginkgo (*Ginkgo biloba*) and Siberian ginseng (*Eleutherococcus senticosus*). These compounds are unlikely to cause significant interactions with the ARVs.[4] However, the ginkolides inhibit platelet activating factor. Spontaneous subarachnoid haemorrhage and subdural haematoma have been reported and therefore caution is advised in any patient with a bleeding diathesis.[7] Mania has been reported in patients taking Asian ginseng. Caution is advised in any confused patient.[12]

Goldenseal (*Hydrastis canadensis*) inhibits CYP3A4. Studies with the PI, indinavir, indicated no change in drug pharmacokinetics, though midazolam levels increased significantly. Caution is recommended in patients taking ARVs.[4]

Grapefruit juice. Grapefruit contains the flavonoids, naringenin and furanocoumarin bergamottin – inhibitors of intestinal CYP3A4.[4] Orally administered medications thus

bypass intestinal metabolism when given together with grapefruit juice. This results in greater intestinal absorption of these medications. Saquinavir's area under the curve (AUC) – though not that of indinavir or amprenavir – is increased by 50 - 150% when given simultaneously with grapefruit juice. Concentrations of flavonoids in an individual grapefruit and related products (fruit juice) vary. Consequently individual drug interactions are therefore difficult to predict.[13] Patients are generally warned against the use of grapefruit juice if taking ARVs.

Milk thistle (*Silybum marianum*). There appear to be no important interactions between this herb and the ARVs.[4]

Olive oil. There is no scientific support for the use of virgin olive oil as an 'immune booster' in HIV-positive people. However the use of a monounsaturated fat instead of polyunsaturated fats in patients on PIs and NRTIs with lipid-related metabolic side-effects is prudent.

Senna and laxative herbs (*Cassia senna, C. angustifolia*), cascara sagrada (*Rhamnus purshiana*), frangula (*Rhamnus frangula*), yellow dock (*Rumex crispus*), Chinese rhubarb *(Rheum officinale).* These are anthranoid-containing herbs and will cause diarrhoea. This may compromise gastrointestinal absorption of drugs. These herbs are not recommended.[7]

Skullcap utilises the CYP3A4 pathway for its metabolism and may influence the HIV drugs. This herb is not recommended for use in HIV-positive patients.

St John's Wort, SJW (*Hypericum perforatum*). This herb is used as an antidepressant and anxiolytic, though this indication is not supported by evidence-based studies.[12] A major constituent, hyperforin, induces hepatic CYP3A4 production. Substrates of CYP3A4 are rapidly metabolised. Consequently, plasma concentrations of both the NNRTIs and the PIs decrease significantly – to levels that permit the failure of viral control. Use of SJW with nevirapine, efavirenz and all the PIs is therefore contraindicated. A further constituent, hypericin, induces the production *in vitro* of the drug-efflux protein, P-glycoprotein.[12] This may cause medication to be more rapidly eliminated from the body. SJW also interferes with the biokinetics of other commonly prescribed drugs, e.g. amitriptyline, oral contraceptives, the statins (simvastatin) and warfarin.[12] SJW has no place in the management of HIV-positive patients.

Sutherlandia (*Sutherlandia fructens* sp. *Microphlylla*). Compounds derived from this flowering shrub are used throughout southern Africa and are known by a variety of names: *unwele, insiswa, mukakana, phetola, lerumo-lamadi,* cancerbush (*kankerbos*). Sutherlandia activates PXR, inhibits CYP3A4, and enhances the activity of the efflux protein, P-glycoprotein. As these metabolic pathways are shared by the ARV drugs, adverse interactions can be expected.[2,3] Controlled clinical trials with Sutherlandia are currently underway (Wilson D, personal communication, July 2007). Results are not yet available, and at this time this herb has no proven role in the HIV clinic.

6.4 COMMENT AND CONCLUSION

For many in Africa, traditional medicine and local herbs constitute the most accessible form of health care.[6] Notwithstanding their widespread availability and use over many decades, African traditional medicines have yet to be given a clear role in the management of HIV and AIDS. No single traditional agent either cures or in some way controls HIV infection. Are there alternative remedies? Is there better treatment? ARV therapy addresses this hope. What if any, is the role of herbs and traditional medicines in the HIV epidemic? A traditional healer comments: 'In the African traditional setting, the question, "Why am I ill?" is more important than, "What is the nature of my illness? It follows therefore, that a detailed biomedical explanation based on the germ theory is foreign and irrelevant to African concepts of illness.'[14] The AIDS epidemic points to the need to resolve the deep impasse between Western medicine and the traditional healing systems of Africa. Where the virus is denied, who needs to be counselled and tested? Who will use a condom when engaging in sex? Why bother to prevent the spread of the virus?

Truth, the assembly of facts that can be scrutinised, reproduced and verified, forms the basis of modern scientific medicine. A similar evidence-based examination of traditional medicine must occur if its claims to success are to be believed. Ethical principles underlie the practice of modern medicine: *'Primum non nocere'* (first do no harm), autonomy, beneficence, non-malificence, and justice. All Africa's people ought to be assured that these rights operate irrespective of the healing system they follow.[15] Where both traditional and scientific systems subscribe to these ethical values, there is hope that the two may find common ground – and possibly the way forward to future collaboration. At this time no traditional 'remedy' can be recommended without an adequate assessment of its efficacy and toxicity. These data are still awaited with regard to herbs and traditional approaches to HIV care and management.

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