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 2100 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
In increasing energy intake:

- 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. 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 quantity of that food. How is it prepared, and sufficient food at home? At each clinic visit questions must be asked that check food security, access to food and the quantity of that food. How is it prepared, 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.

3.4 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 3.1). 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.

3.5 Nutritional supplements: vitamins and other micronutrients

Interpretational dilemmas with regard to micronutrient studies and HIV

- 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. 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.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medical diagnosis</th>
<th>Medical treatment</th>
<th>Dietary and supportive treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia, loss of appetite or poor appetite</td>
<td>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 helmint infestation</td>
<td>1. Treat the underlying condition 2. Cyleprophedrine (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</td>
<td>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.</td>
</tr>
<tr>
<td>Painful mouth and discomfort with swallowing</td>
<td>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</td>
<td>1. Treat the underlying condition 2. Topical anaesthetic ointments or spray before meals, e.g. amethocaine 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, myristin gel or solution</td>
<td>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. 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.</td>
</tr>
<tr>
<td>Fever: body temperature persistently &gt;37.4°C</td>
<td>Often a sign of systemic disease 1. Infection: malaria, TB, invasive bacterial dis., pneumonia, bacteremia 2. Tumour: lymphoma, disease. Kaposis’s 3. Toxins and drugs: ARVs, antibiotics, e.g. co-trimoxazole, penicillin 4. Immune: immune reconstitution syndrome (IRIS), allergy</td>
<td>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-inflammatory drugs (NSAID, e.g. ibuprofen) 4. Aspirin is not used in children</td>
<td>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.</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>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</td>
<td>1. Diagnose and treat the underlying cause 2. Anti-nauseants, e.g. metoclopramide 10 mg 8-hrly before meals (prn) 3. Remove the offending cause</td>
<td>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 wheat-bix or high-fibre cereals. No fried or fatty foods. Avoid caffeine and alcohol.</td>
</tr>
<tr>
<td>Diarrhoea Defined as a minimum of three soft, unformed stools per day</td>
<td>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 difficile enterocolitis); alcohol; traditional medicines and herbs (allovera) 4. Metabolic: uncontrolled diabetes mellitus, hyperthyroidism</td>
<td>1. Diagnose and treat the underlying cause 2. Immunod 1 – 2 tabs po daily or bid in adults. Immunod 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 teaspoon salt 5. Zinc (children): 10 mg daily po x 2 wks in those &lt;6 mo. age, or 20 mg daily po x 2 wks in those &gt;6 mo. of age 6. Continue feeding the child 7. Vitamin A: dose as per age in children &lt;5 yrs 8. Refer the child to the clinic if either weight loss is present or diarrhoea continues for &gt;14 d</td>
<td>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.</td>
</tr>
</tbody>
</table>
3.5.2 Individual vitamins and micronutrients (Tables 3.II and 3.III)\textsuperscript{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\textsuperscript{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.\textsuperscript{11-16} 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.\textsuperscript{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.\textsuperscript{12} Vitamin A supplementation of HIV-infected pregnant women has been associated with an increase in birth weight and fewer preterm births.\textsuperscript{12} But the perinatal transmission studies have failed to demonstrate any reduction in viral transmission.\textsuperscript{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.\textsuperscript{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.\textsuperscript{12,21} Retinol levels decrease during the acute-phase response – i.e. low serum levels of vitamin A do not necessarily imply nutritional deficiency.\textsuperscript{12,11}

**Recommended dietary allowances (RDA) for vitamin A (µg/d) in HIV-uninfected populations**\textsuperscript{22} (recommendations are expected to apply equally to HIV-infected persons):

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RDA (µg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0 - 6 mo.</td>
<td>400</td>
</tr>
<tr>
<td>7 - 12 mo.</td>
<td>500</td>
</tr>
<tr>
<td>Children 1 - 3 yrs</td>
<td>300, 4 - 8 yrs = 400</td>
</tr>
<tr>
<td>Males 9 - 13 yrs</td>
<td>600, 14 - &gt;70 yrs = 700</td>
</tr>
<tr>
<td>Females 9 - 13 yrs</td>
<td>600</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>800</td>
</tr>
<tr>
<td>Lactation</td>
<td>770</td>
</tr>
<tr>
<td>Pregnancy &amp; lactation</td>
<td>18 yrs = 1 200, 19 - 50 yrs = 1 300</td>
</tr>
</tbody>
</table>

**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.\textsuperscript{20,12}

**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\textsubscript{12}.\textsuperscript{20,22} 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.\textsuperscript{4,10} Nevertheless, some observational studies have also recorded benefit with vitamin B supplementation including a reduced risk of HIV progression.\textsuperscript{11} 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.\textsuperscript{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’.\textsuperscript{11}

**RDA daily intakes for the B-group vitamins:**\textsuperscript{22}

- **Thiamine** (vitamin B\textsubscript{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\textsubscript{2}, mg/d): Infants 0 - 6 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\textsubscript{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\textsubscript{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\textsubscript{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.\textsuperscript{10,12}

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

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**TABLE 3.II. VITAMINS AND IMMUNE/BIOLOGICAL INTERACTIONS**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Source</th>
<th>Described immune and biological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A, carotenoids</td>
<td>Full-cream milk when fortified Cheese, butter, red palm oil Fish oils, eggs, liver, carrots, mangoes, papaya, pumpkin, Green leafy vegetables, sweet potatoes</td>
<td>Enhanced phagocytic activity, which is reduced in vitamin A deficiency. Important in vision, the differentiation of cells, cellular recognition, growth, bone development and reproduction.</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Green leafy vegetables, liver, vegetable oils, wheat germ, whole-grain products, butter, peanuts, milk, nuts and seeds, egg yolk and fats</td>
<td>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.</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Citrus fruit: baobab, guava, oranges and lemons. Cabbage, green leaves, tomatoes, yams, peppers, cooking plants, fresh milk</td>
<td>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.</td>
</tr>
<tr>
<td>Vitamin B₁₂, cyanocobalamin</td>
<td>Green leafy vegetables, liver, meat</td>
<td>Deficiency leads to decreased bacterial killing. A coenzyme that is needed for the maintenance of neural tissue and for folate-dependent red cell synthesis.</td>
</tr>
</tbody>
</table>

**TABLE 3.III. TRACE ELEMENTS AND IMMUNE/BIOLOGICAL INTERACTIONS**

<table>
<thead>
<tr>
<th>Trace element</th>
<th>Source</th>
<th>Described immune/biological action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium</td>
<td>Meat, eggs, seafood, whole grains and plants provided their soil is rich in selenium</td>
<td>An antioxidant that is active within the glutathione peroxidase enzyme system. Supplementation increases macrophage phagocytic and cytotoxic activity. Deficiency leads to reduced antibody production.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Meat, fish, poultry, shellfish, whole-grain cereals, legumes, peanuts, milk and cheese</td>
<td>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.</td>
</tr>
<tr>
<td>Iron</td>
<td>Liver, chicken, beef, egg yolk Beans, nuts, green leafy vegetables, fortified cereals</td>
<td>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.</td>
</tr>
</tbody>
</table>
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. 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. It is suggested that daily requirements of vitamin E ought to be increased during the simultaneous use of the pro-oxidant, iron. 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.

**RDA of vitamin E (mg/d, α-tocopherol)**

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 = 15; females 9 – 13 yrs = 11, 14 – >70 yrs = 15; pregnancy = 27; 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. 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.

**RDA of iron (mg/d)**

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 = 15; females 9 – 13 yrs = 11, 14 – >70 yrs = 15; 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. 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. 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. Clearly more data from African studies are needed.

**RDA of selenium (µg/d)**

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. A daily supplement dose of 3 mg zinc for 6 months has also been shown to be safe in this age group.

**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. 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. 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. Furthermore, large doses of zinc have also been found to be immunosuppressive.

**RDA of zinc (mg/d)**

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.
Reduced mortality among Mother-to-child transmission of HIV-infected population. Standard recommendations apply.

Comment: A low calcium intake has been described in South African schoolchildren. 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. 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): 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; 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.' 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.

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

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 women of reproductive age in high-income 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, eg. folate (neural tube defects), and the presence of dietary toxins, eg. 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 morbidity events such as hypertension, obesity, glucose intolerance and cardiovascular disease later in life,5-7 11% of births in developing countries fall into this category.6 Nutritional requirements increase in pregnancy and lactation. HIV infection increases the energy needs of both the asymptomatic and the symptomatic.7-8 HIV-infected women generally gain less weight during pregnancy than uninfected women, particularly in the third trimester (Table 4.1).

Where antiretroviral (ARV) drugs are not available, rates of mother-to-child transmission (MTCT) are high at 25 – 45%. Intratubal 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?

**TABLE 4.1. GENERALLY ACCEPTABLE INCREMENTS OF WEIGHT DURING PREGNANCY**

<table>
<thead>
<tr>
<th>Body mass index (BMI), pre-pregnancy (kg/m²)</th>
<th>Total weight gain (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;20)</td>
<td>12.5 – 18 kg</td>
</tr>
<tr>
<td>Normal (20 – 25)</td>
<td>11.5 – 16 kg</td>
</tr>
<tr>
<td>Overweight (25 – 30)</td>
<td>7 – 1.5 kg</td>
</tr>
<tr>
<td>Obese (&gt;30)</td>
<td>≤7 kg</td>
</tr>
</tbody>
</table>

Where antiretroviral (ARV) drugs are not available, rates of mother-to-child transmission (MTCT) are high at 25 – 45%. Intratubal 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. ¹³ 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.³⁵-³⁷-³⁸ 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.³⁹ Risk persists throughout the breastfeeding period and returns upon subsequent re-exposure to breastmilk with an increased risk relative to the duration of exposure.⁴⁰ Among exclusively breastfed infants, a transmission rate of 2 - 4% has been recorded at 6 months.⁴¹-⁴³ 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.³⁹ 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.³⁵ 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.³⁵,⁴⁰-⁴¹

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.⁴²

Several factors may increase the risk of viral transmission through breastfeeding (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.⁴‡ 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.⁴¹,⁴³-⁴⁵ 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 BREASTFEEDING⁴⁷

<table>
<thead>
<tr>
<th>Strong evidence</th>
<th>Limited evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High plasma viral load</td>
<td>High breastmilk viral load</td>
</tr>
<tr>
<td>Advanced disease/ low CD4 count</td>
<td>Sub-clinical mastitis as evidenced by increased breastmilk sodium levels</td>
</tr>
<tr>
<td>Breast pathology – mastitis, abscesses, cracked bleeding nipples</td>
<td>Low maternal levels of vitamins B, C, E</td>
</tr>
<tr>
<td>Primary infection/new infection: high plasma viral load</td>
<td></td>
</tr>
<tr>
<td>Prolonged duration of breastfeeding (&gt;6 mo.)</td>
<td></td>
</tr>
<tr>
<td>Non-exclusive breastfeeding, mixed feeding and oral lesions⁵⁵</td>
<td></td>
</tr>
</tbody>
</table>

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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. Facility-based or community-based antenatal and postnatal clinic support is associated with an increase in exclusive breastfeeding rates.

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’.

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.

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.

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

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’.

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 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.
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. In essence, 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. These studies confirm reduced transmission to the infant. ARV drugs consumed by lactating women appear 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. These studies confirm reduced transmission to the infant. ARV drugs consumed by lactating women appear to be transmitted in breastmilk at levels that reduce breastmilk viral load. Whether stopping therapy at the cessation of breastfeeding will lead to an increased risk of maternal viral resistance is currently unknown.

ARV prophylactic therapy for the infant

The Botswana ‘Mashe’ 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 diarrhea.) 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. 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. 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.59 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.23 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.23 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.57-58 In this context, the use of vitamin A has sometimes had conflicting results, including the possible promotion of MTCT.11,13,59 With regard to the prevention of transmission, a beneficial role for other micronutrients – zinc, iron and selenium – in pregnancy has not been established.44 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.3 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.11,16 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.23 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}

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

<table>
<thead>
<tr>
<th>Age of infant</th>
<th>Milk feed</th>
<th>No. of feeds per 24 hours</th>
<th>No. of tins required for 1 infant per month (varies with the individual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 2 wks</td>
<td>100 ml</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>3 – 4 wks</td>
<td>125 ml</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2nd mo.</td>
<td>150 ml</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>3 – 4 mo.</td>
<td>175 ml</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>5 – 6 mo.</td>
<td>200 ml</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

**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.

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change. In the context of preventing MTCT, health workers need to be these ‘agents of change’.

REFERENCES


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. Most infections occur in the peri- or intrapartum periods. 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%. 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.
- 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.

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.

5.2 UNDER-NUTRITION IN HIV-INFECTED CHILDREN

5.2.1 Introduction

Under-nutrition is frequent in the children of Africa. Many are also HIV-infected. 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. Unemployment, poverty, food insecurity, malnutrition and vulnerability to infectious diseases define the cycle in which millions of Africans – adults and children – live their lives. 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, and in Botswana, Swaziland and Zimbabwe AIDS now causes more than half of the childhood deaths. 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. For some 11 - 17 million South Africans the supply of food is unreliable; 38% of households report regular absence of meals. Rural children and those in informal settlements around the cities are particularly at risk. 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. Africa’s children may also be at risk from climate change: malnutrition, diarrhea and malaria will increase should global warming affect the continent’s weather patterns in the 21st century.

5.2.2 Acute and chronic malnutrition in HIV-infected children

THE WHO DEFINITION OF SEVERE ACUTE MALNUTRITION (SAM)

<table>
<thead>
<tr>
<th>Any of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-for-length/height &lt;3 Z-scores below reference range (or)</td>
</tr>
<tr>
<td>Bilateral pitting oedema (or)</td>
</tr>
<tr>
<td>Severe visible wasting (or)</td>
</tr>
<tr>
<td>Mid-upper arm circumference (MUAC) ≤110 mm for children 6 months - 5 years.</td>
</tr>
</tbody>
</table>

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


Up to 2% of under-5s in developing countries are acutely and severely malnourished. Of Malawian children with severe acute malnutrition (SAM), 34% tested HIV-positive. Fatality rates and slower recovery were frequent in these children. Despite this, successful feeding programmes can be implemented in resource-poor communities. These interventions reduce hospital admissions and enhance public awareness. 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). Growth stunting is a frequent manifestation of chronic malnutrition. 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. 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. Similar changes have been reported in malnourished children. 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.

Poor growth is a sensitive indicator of the progression of HIV infection and is a strong and independent risk factor for death. Indeed, linear growth faltering (loss of height/length) frequently anticipates the onset of new
opportunistic disease in HIV-infected children. Both the increased daily energy requirements of children infected with HIV and inadequate energy intake contribute to the accompanying loss of weight (Table 5.1). 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. 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.

Assess the HIV infection: Clinical stage, CD4 count and viral load. Does the child need antiretrovirals (ARVs)? Control the virus. Exclude opportunistic disease.

5.2.4 Major management goals

The management of acutely and chronically malnourished children

5.2.4.1 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. MUAC reflects lean body mass and not body fat. 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.

5.2.4.2 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. ‘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. 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. Children need a balanced diet. Protein requirements remain at 12 - 15% of total energy intake. ARVs may need to be considered as these will improve the child’s appetite, promote weight gain and provide control of the underlying infection.

5.2.3 The assessment and measurement of nutritional status in children

TABLE 5.1. WEIGHT LOSS IN HIV-INFECTED CHILDREN – CAUSES AND RELATIONSHIPS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition/cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased energy requirements</td>
<td>Energy needs increase by 10% from time of acquiring virus</td>
</tr>
<tr>
<td></td>
<td>Energy needs increase by 20 - 30% during and after illness</td>
</tr>
<tr>
<td></td>
<td>Energy needs may increase to 50 - 100% in severely malnourished children</td>
</tr>
<tr>
<td></td>
<td>NB. Protein requirements remain at 12 - 15% of total energy intake provided diet is well balanced</td>
</tr>
<tr>
<td>Inadequate energy intake</td>
<td>Anorexia and poor dietary intake: oral candidiasis, gingivitis, oral sores, oesophageal candidiasis and dysphagia, loss of taste, insufficient food, poverty</td>
</tr>
<tr>
<td></td>
<td>Opportunistic infections and cancers: chronic lung disease (lymphoid interstitial pneumonitis, LIP), chronic diarrhoea, tuberculosis, recurrent respiratory infections, lymphoma</td>
</tr>
<tr>
<td></td>
<td>Advanced HIV infection and untreated, end-stage HIV infection</td>
</tr>
</tbody>
</table>
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 \(\times\) 2 weeks in those under 6 months of age and 20 mg daily \(\times\) 2 weeks in those over 6 months.\(^{42,43}\) Irrespective of HIV status, the WHO recommends a daily intake of 1 \(\times\) 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%\(^{49}\), 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%.\(^{49,50}\)

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.\(^{51,52}\) Children are at risk throughout childhood.\(^{53}\) Insulin resistance is frequent, though overt hyperglycaemia and diabetes remain rare.\(^{54}\) Serum lipids – cholesterol 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.\(^{55,56}\) All ethnic groups, including those living in Africa, appear to be at risk.\(^{57,58}\) 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.\(^{49,59,60}\) Mitochondrial DNA depletion and the inhibition of mitochondrial DNA polymerase-\(\gamma\) are known consequences of NRTI therapy.\(^{61}\) 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.\(^{44}\)

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.\(^{62}\) 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.\(^{63}\) The NRTIs abacavir, lamivudine and emtricitabine carry little risk of either metabolic or mitochondrial toxicity and are safe in children.\(^{64-66}\) Children switched from PI-based regimens to a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen (efavirenz) improved total and LDL cholesterols and triglycerides.\(^{67}\) 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. 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 cholesterol. 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), 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. 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. 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. However, lovastatin has been approved for use in American adolescents with familial hypercholesterolaemia, its use – and that of simvastatin – in HIV-infected adults is discouraged. Pravastatin, rosvastatin, atorvastatin and fluvastatin are used in adults and appear to be safe. 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 acute rhabdomyolysis. While lovastatin has been approved for use in children, it may reduce the efficacy of the fibrates. 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 acute rhabdomyolysis. While lovastatin has been approved for use in children, it may reduce the efficacy of the fibrates. Likewise, 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 acute rhabdomyolysis. While lovastatin has been approved for use in children, it may reduce the efficacy of the fibrates.

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. Insulin resistance in children is a risk factor for subsequent cardiovascular disease. A fasting blood glucose and/or an oral glucose tolerance test should be checked as part of the diagnostic workup. 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 thiazolidinediones (e.g. rosiglitazone) have demonstrated sufficient efficacy and safety in adult studies to be recommended currently in HIV-infected children.

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. Studies indicate a loss of bone mineral density (BMD) in HIV-infected adults and after starting ART. Children with HIV infection demonstrate a similar decrease in BMD. 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. Mitochondrial toxicity has been suggested as the cause of ARV-related bone loss. The nucleotide tenofovir has been associated with a significant decrease in BMD compared with stavudine. Its use in osteopenic adults, in those at risk for osteoporosis and in children requires a regular review of BMD where feasible.

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 (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 bisphosphonates 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 bisphosphonate compared with those given only calcium and vitamin D. 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>
<thead>
<tr>
<th>Age or ‘life-stage’ group</th>
<th>Estimated adequate daily calcium intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1 - 3 yrs</td>
<td>500 mg daily</td>
</tr>
<tr>
<td>Children 4 - 8 yrs</td>
<td>800 mg daily</td>
</tr>
<tr>
<td>Adolescents and young adults 9 - 18 yrs</td>
<td>1 300 mg daily</td>
</tr>
<tr>
<td>Men and women 19 - 50 yrs</td>
<td>1 000 mg daily</td>
</tr>
<tr>
<td>Men and women &gt;51 yrs</td>
<td>1 200 mg daily</td>
</tr>
</tbody>
</table>

*Lindsay and Cosman,* 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.

REFERENCES

APPENDIX A


Feed the Child. (www.gautengonline.gov.za)

1. Regular small meals 5 - 6 times a day
2. Add to porridge: milk, oil, sugar, peanut butter, bean or sovbean powder.
3. Bread, pap, samp, meales, other cereals
   Give as much as the child wants but mix with one of the items in 2 (adjacent) or use sour milk to improve nutritional value.
4. Fruit and vegetables
   Give 1 fruit and 1 vegetable every day, e.g. mashed bananas, avocados, pumpkin.
5. Home-cooked food is better than pre-cooked or take-out food
6. Milk
   After 6 months the child can drink boiled fresh milk: cows or goat’s milk. Children over 1 year should drink 2 - 3 glasses of fresh milk or full-cream powdered milk daily.
7. Increase protein intake
   At least one portion every-day of fish or chicken or meat or dry beans or eggs or peanut butter. Vary the protein.
8. Sweets, chocolates and crisps
   Allowed as a treat and in limited amounts, but not as a food substitute.
9. Dry beans
   Sugar beans and brown beans are a good protein source.

APPENDIX B


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

TC = total cholesterol; TG = triglycerides; IR = insulin resistance; LDL = low-density lipoprotein; HDL = high-density lipoprotein.
TABLE 6.I. FOOD INTERACTIONS AND THE ARVs

<table>
<thead>
<tr>
<th>ARV medication</th>
<th>Food effect and interactions with other drugs</th>
<th>Dietary recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI/ NRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC, Ziagen) 300 mg bd po (Trisivir: ZDV + 3TC + ABC; Kivexa: ABC + 3TC)</td>
<td>No effect. Alcohol increases the area under the curve (AUC) by 41%.</td>
<td>Can be taken without regard to meals. Avoid alcohol.</td>
</tr>
<tr>
<td>Didanosine (ddI, Videx; Videx EC) 400 mg/d po if weight &gt;60 kg or 250 mg if &lt;60 kg</td>
<td>Food decreases absorption: approx 55% reduction in AUC. Avoid magnesium and aluminum containing antacids: these decrease absorption.</td>
<td>Take on an empty stomach at least 30 minutes before a meal or 2 hours after. Take only with water. Alcohol increases toxicity: avoid.</td>
</tr>
<tr>
<td>Emtricitabine (FTC) 200 mg daily po (Truvada, TVD: TDF + FTC; Atripla: TDF + FTC + EFV)</td>
<td>Food has little effect on absorption or metabolism.</td>
<td>Can be taken without regard to meals.</td>
</tr>
<tr>
<td>Lamivudine (3TC, Epivir) 150 mg bd po (Combivir: ZDV + 3TC; Kivexa: ABC + 3TC; Triomune, Stalinev: d4T + 3TC + NVP)</td>
<td>Food has little effect on absorption or metabolism.</td>
<td>Can be taken without regard to meals. But Combivir is taken on an empty stomach. Avoid alcohol.</td>
</tr>
<tr>
<td>Stavudine (d4T, Zerit) 30 mg bd po irrespective of weight (Triomune, Stalinev: d4T + 3TC + NVP)</td>
<td>Food has little effect on absorption or metabolism.</td>
<td>Can be taken without regard to meals.</td>
</tr>
<tr>
<td>Tenofovir (TDF, Viread) 300 mg daily po (Truvada: TDF + FTC; Atripla: TDF + FTC + EVF)</td>
<td>Administration with a high-fat meal increases AUC by 40%.</td>
<td>Take with food.</td>
</tr>
<tr>
<td>Zalcitabine (ddC, Hivid) 0.75 mg 8-hrly po</td>
<td>Food has little effect on absorption. Avoid antacids containing magnesium or aluminum. Do not take together with metoclopramide: decreases the AUC.</td>
<td>Can be taken without regard to meals. Avoid alcohol.</td>
</tr>
<tr>
<td>Zidovudine (AZT, ZDV, Retrovir) 300 mg bd po (Combivir: ZDV + 3TC; Trisivir: ZDV + 3TC + ABC)</td>
<td>AUC decreased by 25 - 50% with food.</td>
<td>Preferably take on an empty stomach. Otherwise, a low-fat meal. Avoid alcohol.</td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFV, Stocrin, Sustiva) 600 mg/d (nocte) po (Truvada and Atripla)</td>
<td>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.</td>
<td>Can be taken without regard to meals. Avoid a high-fat meal. Alcohol may increase unpleasant side-effects.</td>
</tr>
<tr>
<td>Nevirapine (NVP, Viramune) 200 mg bd po (Triomune and Stalinev)</td>
<td>Absorption not affected by food. Care with drugs that induce or inhibit CYP450 activity. Avoid St John’s Wort.</td>
<td>Can be taken with food. Avoid alcohol.</td>
</tr>
<tr>
<td><strong>Protease inhibitors (PIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir (APV, Agenerase) 1 200 mg bid po (Fosamprenavir)</td>
<td>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.</td>
<td>Can be taken without regard to meals but avoid a high-fat meal.</td>
</tr>
<tr>
<td>Atazanavir (ATZ, Reyataz) 400 mg daily or 300 mg + ritonavir 100 mg (boosted) daily po</td>
<td>Absorption is enhanced with food.</td>
<td>Given with meals.</td>
</tr>
</tbody>
</table>
Garlic. Garlic is an inducer of CYP3A4 and its use together with the protease inhibitor, saquinavir, has led to decreased blood levels of the latter. 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. 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. As with the herbs, danshen, dong quai and papaya, garlic has been noted to interfere with platelet function. 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. 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. However, the ginkolides inhibit platelet activating factor. Spontaneous subarachnoid hemorrhage and subdural haematoma have been reported and therefore caution is advised in any patient with a bleeding diathesis. Mania has been reported in patients taking Asian ginseng. Caution is advised in any confused patient.

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.

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

<table>
<thead>
<tr>
<th>TABLE 6.I. FOOD INTERACTIONS AND THE ARVs (CONTINUED)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indinavir (IDV, Crixivan)</strong> 800 mg 8 hourly po or 800 mg bid + ritonavir 100 mg (boosted) bd po</td>
</tr>
<tr>
<td><strong>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</strong></td>
</tr>
<tr>
<td><strong>Nelfinavir (NLF, Viracept) 750 mg td or 1 250 mg bd po</strong></td>
</tr>
<tr>
<td><strong>Ritonavir (RTV, Norvir) 600 mg bd po or in ‘boosted’ combinations with other PIs</strong></td>
</tr>
<tr>
<td><strong>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</strong></td>
</tr>
<tr>
<td><strong>Tipranavir (TPV, Aptivus) 500 mg + ritonavir 200 mg bd po</strong></td>
</tr>
</tbody>
</table>

(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. 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. 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.

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. 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. 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. As with the herbs, danshen, dong quai and papaya, garlic has been noted to interfere with platelet function. 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. 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. However, the ginkolides inhibit platelet activating factor. Spontaneous subarachnoid hemorrhage and subdural haematoma have been reported and therefore caution is advised in any patient with a bleeding diathesis. Mania has been reported in patients taking Asian ginseng. Caution is advised in any confused patient.

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.

Grapefruit juice. Grapefruit contains the flavonoids, naringenin and furanocoumarin bergamottin – inhibitors of intestinal CYP3A4. 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. 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.6

**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.7

**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.9 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.10 SJW has no place in the management of HIV-positive patients.

**Sutherlandia (Sutherlandia fructescens sp. Microphylla).** 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.5,6,13 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.5 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.'13 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-malficence, 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.

**REFERENCES**


5. The Nutritional Information Center (NICUS), Stellenbosch University, Cape, SA. [www.san.ac.za/nicus] (accessed October 2004)


