Nutritional, immune, micronutrient and health status of HIV-infected children in care centres in Mangaung

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Abstract

Aim: To assess the nutritional, immune, micronutrient and health status of antiretroviral-naïve HIV-infected children.

Method: A cross-sectional descriptive study was undertaken between September 2004 and March 2006 amongst HIV-infected children of which none received antiretroviral therapy, in care centres in Mangaung, Free State.

Results: The study included 37 clinically stable and food-secure HIV-infected children. Their median age was 5.4 years (range 1.2–10.2 years). Fifteen children (41%) were underweight, 30 (81%) were stunted and one (3%) was wasted. The most commonly observed clinical features were lymphadenopathy (84%), skin rashes (51%), hepatomegaly (32%) and pallor (41%). Eight per cent of children had features of TB, while 19% had a lower respiratory tract infection. The median viral load of the group (n = 35) was 117 000 copies/ml, the median $CD4^+$ cell count was 477 cells/mm3 and the median CD4 percentage was 22.5%. A significant negative correlation could be demonstrated between viral load and nutritional indicators. Children had deficient serum levels relative to normal reference values for glutathione (91% of children), albumin (78%), vitamin A (63%), vitamin D (44%), zinc (38%) and vitamin E (13%). Sixty per cent of the children were anaemic and 30% were iron deficient.

Conclusion: A high prevalence of acute and chronic malnutrition and micronutrient deficiencies occurred among HIV-infected children residing in care centres. The study highlights the need to investigate early initiation of antiretroviral therapy and nutrition interventions, including aggressive supplementation, in order to improve the prognosis of these children.

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Introduction

It has been estimated that there are 5.5 million people living with human immunodeficiency virus (HIV) infection in South Africa, 250 000 to 300 000 of whom are children under the age of 15 years.[1] The prevalence of HIV infection is highest among women of reproductive age, that is 20 to 35 years, which places their offspring at particular risk of mother-to-child transmission.[2] In Africa, HIV infection has reversed gains in child survival and lowered life expectancy.[3] In recent years in some provinces in South Africa, prevention of mother-to-child transmission (PMTCT) programmes have impacted on HIV infection prevalence in children by reducing HIV transmission.[4]

In HIV-infected children, acquired immunodeficiency syndrome (AIDS) is associated with an impaired nutritional status, growth failure and weight loss, as well as micronutrient deficiencies.[5] All these factors may further contribute to the already compromised immune system and lead to poor prognostic outcome.

Approximately 25–30% of HIV-infected children in South Africa are underweight and 55–60% are stunted.[6-8] Before the introduction of antiretroviral therapy into the Western Cape, only 7% of 193 symptomatic HIV-infected children in Cape Town weighed above the third weight-for-age percentile.[9] Multiple micronutrient deficiencies have also been found to affect more than 60% of South African HIV-infected children.[6]

A number of nongovernmental organisations in South Africa have been involved in the implementation of care centres for AIDS orphans. Such centres offer children access to care and support. Children are usually admitted on a semi-permanent basis. They usually visit family only during school holidays and/or weekends. At some centres, children receive day care, which includes breakfast, lunch as well as in-between snacks. No information is, however, available regarding the nutritional and micronutrient status of HIV-infected children in these settings.

The purpose of this study was to assess the nutritional, immune, micronutrient and health status of HIV-infected children in selected care centres in Mangaung.

Methods

Study design and sampling

One hundred and fifty-five food-secure, HIV-affected children in selected care centres in Mangaung were screened by enzyme-linked immunosorbent assay (ELISA) to determine their HIV status. All centres in the area that provided care and support to AIDS orphans, with managerial support from and provision of health care by the Department of Health, were included. Most of the children in the centres were from an area within an urban township that includes formal and informal housing areas. All HIV-infected children in the care centres between August 2004 and March 2006 who had either been previously confirmed to be HIV infected (prior to the onset of the study) or had a positive ELISA screening result if older than 12 months were eligible for the study. Thirty-eight children were identified for the study, one of whom was excluded because of hospitalisation due to pneumonia. All these children were admitted to the care centres at least six weeks before the onset of the study. Thirty-seven children entered the cross-sectional descriptive study. Nutrition analysis of menus was done and actual portion sizes served over a three-day period were evaluated before study initiation by a registered dietitian. All the children were food secure and received two to three balanced meals per day, with in-between snacks, at the care centres. The diet and menus were set by a dietitian and the implementation was checked by the Quality Control Committee. The children received their required immunisations, were dewormed less than three months before the study and received regular vitamin A supplementation according to national immunisation guidelines. None of the children received antiretroviral treatment.

Nutritional status

Growth was assessed by determining weight-for-age, height-for-age and weight-for-height z-scores for all the children and comparing these measurements to the norms for physical growth of the National Centre for Health Statistics data.[10] Anthropometric measurements were done by a trained dietitian using standardised techniques.[11] A SECA electronic scale (model 708) was used to determine the weight of the lightly clothed children to the nearest 0.1 kg. A stadiometer was used to measure the height of the children older than 24 months to the nearest 0.1 centimetre according to standardised techniques. In children younger than 24 months, the recumbent length was measured using a paediatric measuring board.

Immunological, metabolic and micronutrient status

Following the nutritional and clinical assessment, fasting blood samples were collected. The $CD4^+$ cell count, viral load, full blood count, as well as serum levels of cholesterol, albumin, glutathione, vitamin A, vitamin E, vitamin D, ferritin, zinc, folate and vitamin B_{12} were measured. HIV status was classified according to the World Health Organization clinical staging (2006) and $CD4^+$ counts and percentages were used to classify children into immunological categories according to the Centers for Disease Control (CDC) guidelines.[12]

The $CD4^+$ lymphocyte cell count was determined on EDTA-anti-coagulated whole blood samples using a flow cytometer. The plasma viral load (log_{10} HIV-1 RNA copies/ml) was quantified by means of a nucleic acid amplification test on a COBAS AMPLICOR (Roche Diagnostic System Inc).

Plasma chemistry concentrations were quantified using serum prepared from whole blood clotted at room temperature. All the assays were performed by Pathcare, a local private laboratory, according to standardised techniques, and normal reference ranges were thus obtained from that particular laboratory. Serum albumin was measured by direct spectrophotometry, using a colorimetric assay (Beckman; catalogue no. 467858). The serum total cholesterol was measured by means of an enzymatic colorimetric assay (Beckman; catalogue no. 467825). Vitamin A (retinol) and vitamin E were quantified by high-performance liquid chromatography and vitamin D by radioactive binding protein assays. Ferritin (Bayer; catalogue no. 110746), vitamin B_{12} (Bayer; catalogue no. 110748) and folate (Bayer; catalogue no. 118551) were quantified by chem-illuminescence assays and zinc (Randox Laboratories; catalogue no. ZN2341) by flame atomic absorption spectrometry. Blood micronutrient concentrations of the population group were compared with local age-related normal values. Myopathy (proximal weakness) was assessed by asking the children to stand from a sitting position with hands above their heads. Peripheral neuropathy was assessed by asking the children to walk on toes and heels and by evaluating handgrip and/or lower knee and ankle reflexes.

Health status

Health status was determined by means of a clinical examination undertaken by a trained medical doctor. The clinical examination included an assessment of the child's vital signs, for example temperature, pulse rate and respiratory rate, and an examination of all the systems: general, respiratory, cardiovascular, abdominal and neurological.

Ethical aspects

Written consent was obtained from the legal guardian of each child (either the nearest adult family member or if none available, the head of the institution who performed that duty). The study was approved by the Ethics Committee of the Faculty of Health Sciences of the University of the Free State, South Africa (ETOVS 190/00).

Data entry and analysis

Frequencies and percentages were used to summarise the categorical data. The distribution of most numerical variables was skewed. It was therefore decided to use medians and quartiles to summarise these numerical variables. Nonparametric statistical methods (Mann-Whitney and Kruskall-Wallis tests) were used to compare variables between subgroups. All analyses were done using SAS Version 9.1 (2004). Epi Info Version 5 (1990) was used to calculate z-scores and percentiles of anthropometric data. Correlations between variables were determined with the Spearman rank correlation test. A p-value of less than 0.05 was considered to be significant.

Results

General and nutritional status

The 37 children's median age was 5.4 years (range, from 1.2 to 10.2 years); 16 (43%) were girls. The median (25th and 75th

quartiles) indicators of nutritional status were as follows: weight-for-age z-score -1.97 (-2.48; -1.4), height-for-age z-score -2.59 (-3.35; -2.03) and weight-for-height z-score -0.66 (-0.85; 0.05). Stunting was commoner than underweight, with 81% (n = 30) of the children having a height-for-age z-score < -2, while 41% had a weight-for-age z-score of < -2.

Spearman rank correlation coefficients indicated significant but weak negative correlations between viral load and height-for-age z-score (r = -0.42; p = 0.03) and weight-for-age z-score (r = -0.35; p = 0.04) respectively. No significant correlations could be demonstrated between growth indicators and $CD4^+$ cell counts or percentage. A significant but weak positive correlation could be demonstrated between the weight-for-height z-score (r = 0.42; p = 0.03) and glutathione levels. A weak positive correlation approaching significance (r = 0.31; p = 0.06) was demonstrated between weight-for-age z-score and serum levels of glutathione as well. Apart from glutathione, no significant correlations could be demonstrated between serum levels of vitamin A, D, E and zinc and the z-scores for weight for age, height for age and weight for height.

Health status

The most commonly occurring clinical features were lymphadenopathy (84%), HIV-related skin rashes (51%) and pallor (41%) (See Table I). Signs of lower respiratory tract infection were present in seven (19%) of the children. Three children (8%) were on TB treatment, with crepitations (43%) and hepatomegaly (32%) being the most common respiratory and abdominal pathology present respectively. Symptoms of diarrhoea were identified in six children (16%) during the clinical examination, while splenomegaly, vomiting and oral thrush occurred in less than 10% of the sample. Muscle weakness and peripheral neuropathy was present in 38% and 35% respectively of the sample. No children had neck stiffness or encephalopathy.

Table I: Clinical features of HIV-infected children in care centres

Clinical sign	n = 37	%
Lymphadenopathy	31	84
Skin rash (generalised dermatitis)	19	51
Pallor	15	41
Hepatomegaly	12	32
Ear infection	9	24
Clubbing	9	24
Oedema	8	21
Signs of lower respiratory tract infection	7	19
Mucosal lesions	6	16
Diarrhoea	6	16
Splenomegaly	3	8
Oral thrush	2	5

According to the WHO Clinical Staging of HIV for Infants and Children with Established HIV Infection, only four children could be classified as clinical stage 1, while seven were in stage 2, seven were in stage 3 and 19 were in stage 4. Although trends of decreased serum albumin and haemoglobin (Hb) levels amongst children in stages 3 and 4 could be observed, no significant correlations could be demonstrated between specific clinical features and nutritional, immune and biochemical indicators.

Immunological, metabolic and micronutrient status

The median (quartiles) viral load was 117 000 copies/ml (14 500; 305 000) and the median (quartiles) $CD4^+$ cell count 477 cells/mm^3 (300; 791). The median (quartiles) $CD4^+$ percentage was 22.5% (14.2; 35.8). There was no significant correlation between the age of the children and the viral load (r = -0.12; p = 0.48). As expected, a significant (p = 0.04) but weak negative correlation (r = -0.35) was demonstrated between the total number of T-lymphocytes and the age of the children. According to the 1994 Revised Pediatric HIV Classification System,[12] 40% (14/35) of the group could be categorised as Category 1, with no evidence of immunosuppression; 34.3% (12/35) were moderately immunosuppressed (Category 2) and 25.7% (9/35) were severely immunosuppressed (Category 3). According to the updated Southern African HIV Society guidelines for the management of HIV infection in children,[13] 32% (n = 12) of the children should have been treated with antiretroviral drugs, if these had been available to them at that stage.

The percentage of children with abnormal metabolic indicators, which for the purpose of this study included full blood count, serum albumin, serum cholesterol and certain micronutrient markers, is summarised in Table II. Median serum albumin levels were 32 g/l (28; 35), compared to the normal range of 37 to 52 g/l. Seventy-eight per cent of the group presented with low serum albumin levels. Children in the severely immunosuppressed group had significantly (p = 0.02) lower serum albumin levels than children with no evidence of immunosuppression (See Table III). According to Spearman correlation coefficients, a significant but weak positive correlation was demonstrated between height-for-age z-score and serum albumin (r = 0.44).

Median serum ferritin and white blood cells were within the normal ranges for these variables, but median haemoglobin (10.8 g/dL) and haematocrit (0.33 l/l) concentrations were lower than the age-specific normal ranges. Of the total sample, 60% (n = 21) were anaemic (Hb < 11 g/dl for children below five years; Hb < 11.5 g/dl for children between five and 11 years) and 30% (n = 11) were iron depleted (serum ferritin less than 12 ng/mL).[14] Of the anaemic group 38% (n = 8) were iron depleted. Red blood cell morphology was not available to determine iron deficiency anaemia. No significant differences could be demonstrated between serum levels of haemoglobin, folate, vitamin B_{12} and ferritin in the various immune categories.

As summarised in Table II, low levels in relation to the normal reference range for micronutrients were found in 91.2% of children for glutathione, 62.5% for vitamin A, 43.8% for vitamin D, 38.2% for zinc and 12.5% for vitamin E. Sixty-nine per cent of the children suffered from two or more micronutrient deficiencies. Significant (p < 0.05) weak to moderate negative correlations were shown between viral load and the following micronutrient serum levels: vitamin A (r = -0.46), vitamin D (r = -0.39) and zinc (r = -0.36).

Table II: Percentage of HIV-infected children with micronutrient concentrations and metabolic parameters below or above the normal age-related range

Variable	Samples analysed	Normal range	Median concentration (quartiles)	Values ↓ normal range (frequency)		Values ↑ normal range (frequency)	
	n			n	%	n	%
Zinc µmol/l	34	12–17	12 (11; 14)	13	38	-	-
Glutathione mg/dl	34	24–37	18 (15; 20)	31	91	-	-
Vitamin A µg/dl	32	20–43	18.15 (15.3; 22.35)	20	63	-	-
Vitamin D ng/ml	32	20–60	20 (16; 24.5)	14	44	-	-
Vitamin E mg/dl	32	3–9	8.05 (6.7; 9.65)	4	13	-	-
Serum cholesterol mmol/l	37	3–5	3 (2.5; 3.3)	18	49	-	-
Serum albumin g/l	37	37–52	32 (28; 35)	29	78	-	-
Serum ferritin ng/ml	37	12–55	24 (16; 40)	11	30	5	14
Vitamin B_{12} pmol/ml	37	156–672	482.9 (424.7; 617.9)	-	-	7	19
Serum folate nmol/ml	37	> 12.19	36.2 (28.4; 54.4)	-	-	-	-
Haemoglobin g/dl	37	11.5–13.5	10.8 (9.4; 11.9)	21	60	-	-
Haematocrit l/l	37	0.35–0.4	0.33 (0.3; 0.35)	22	67	-	-
WBC x 10^9/l	35	5–15.5	7.54 (5.97; 10.87)	2	6	4	11
Platelets x 10^9/l	35	140–420	316 (285; 443)	2	5.7	11	31

*Laboratory error resulted in missing values of some of the variables

Glutathione levels showed a nonsignificant weak negative (r = -0.33, p = 0.06) correlation with viral load. Assessing the micronutrient levels between the different groups (see Table III), classified according to the CDC CD4% classification, a significant difference could be demonstrated between the group with no evidence of suppression and the group with severe immunosuppression, in relation to levels of serum zinc ($p < 0.01$) and vitamin A ($p = 0.05$).

Children with low serum zinc levels had a significantly lower median $CD4^+$ count (300 vs 736 cells/mm^3, p = 0.002). Although not significant, a similar tendency occurred for median viral load (250 500 [5.39 log] vs. 43 400 [4.63 log], p = 0.06). Children with abnormally low vitamin A levels presented with significantly (p = 0.01) higher viral loads and lower $CD4^+$ cell counts (p = 0.05). Both of these indicators could have been influenced by the acute phase response. Despite similar trends in relation to glutathione, vitamin D and vitamin E status, no significant differences could be demonstrated.

Table III: Median viral load, biochemical indicators and micronutrient levels according to CD4% – age-corrected CDC immunologic classification

Parameter	Normal range	Median values	Median in Category 1 No evidence of suppression (n; LQ; UQ)	Median in Category 2 Moderately suppressed (n; LQ; UQ)	Median in Category 3 Severely suppressed (n; LQ; UQ)	Difference (p-value; Kruskall-Wallis)
Viral load copies/ml		117000	5 630 (n = 14; 400; 43 400)	205 000 (n = 11; 102 000; 480 000)	247 000 (n = 9; 167 000; 294 000)	0.001
Albumin g/l	37–52	32	34 (n = 14; 33; 43)	31 (n = 12; 29; 33)	28 (n = 9; 25; 32)	0.02
Cholesterol mmol/l	3–5	3	3.15 (n = 14; 2.8; 3.9)	2.9 (n = 12; 2.6; 3.2)	2.8 (n = 9; 2; 2.8)	0.09
Haemoglobin g/dl	11.5–13.5	10.8	11.6 (n = 14; 10.5; 12.5)	10.4 (n = 12; 9.7; 11.6)	9.8 (n = 9; 8.7; 11,.8)	0.21
Ferritin ng/ml	12–55	24	22.5 (n = 14; 18; 29)	25 (n = 12; 9; 41.5)	25 (n = 9; 22; 55)	0.45
Folate nmol/ml	> 12.19	36.2	44.6 (n = 14; 36.1; 54.4)	29.2 (n = 12; 25.1; 54.4)	33.1 (n = 9; 29.7; 45.1)	0.22
Vitamin B_{12} pmol/ml	156–672	483	505 (n = 14; 436; 581)	452 (n = 12; 412; 636)	502 (n = 9; 349; 674)	0.96
Vitamin A µg/dL	20–43	18.15	22.7 (n = 13; 17.7; 24.8)	16.7 (n = 11; 14.6; 20.8)	16.65 (n = 8; 12.15; 18.65)	0.05
Vitamin D ng/ml	20–60	20	24 (n = 13; 20; 26)	19 (n = 11; 16; 21)	17 (n = 8; 16; 22.5)	0.1
Vitamin E mg/dl	3–9	8.05	8.2 (n = 13; 6.7; 9.6)	7.6 (n = 11; 6.3; 10.3)	8.25 (n = 8; 7; 9.05)	0.97
Zinc µmol/l	12–17	12	14.5 (n = 14; 12; 15)	12 (n = 12; 11; 12.5)	11 (n = 8; 10.5; 11)	0.001
Glutathione mg/dl	24–37	18	19.5 (n = 14; 17; 23)	17 (n = 12; 11.5; 19.5)	17 (n = 8; 13.5; 19.5)	0.12

Discussion

Paediatric HIV infection is associated with growth failure in most settings, even in children receiving antiretroviral drugs.[6,15] HIV-infected children in developing countries, and specifically South Africa,[6,8] experience more severe growth retardation than observed in HIV-infected children in developed countries.[13] Data from an earlier study[16] amongst preschool children from informal settlements in Mangaung showed figures for underweight and stunting of below 20% and 30% respectively. In this study, figures for HIV-infected children in the same area were 41% for underweight and 81% for stunting, indicating that HIV infection further compromises the nutritional status of this socio-economically deprived group of children. Even access to regular, balanced meals in the care centres (managed by a quality control committee) could not improve the nutritional status of these AIDS orphans in the absence of antiretroviral drugs. Without any available data on quality control of diets and the implementation thereof in similar centres in other parts of the country, it is not possible to determine unique risk factors in this group of HIV-infected children. It can, however, be assumed that AIDS orphans, especially during the period before acceptance into a care centre, have less access to health care, while basic needs, for example for sufficient nutrition, may have been denied as well.

A higher HIV-1 viral load has been associated with a greater risk of growth failure as well as poor linear growth in children.[17-19] In this study, a similar trend could be observed with significant correlations between viral load and nutritional indicators. However, no significant correlations could be demonstrated between nutritional indicators and median $CD4^+$ cell counts. Several factors may contribute to growth failure in HIV-infected children. In more than one study,[19,20] growth failure has been linked to a decreased resting energy expenditure (REE) and total energy expenditure (TEE), most likely as a result of deficient energy intake and a lower fat-free mass. As HIV-infected infants with growth failure have as much as a five-fold increase in the risk of early death,[21,22] efforts to reverse growth failure in children attending care centres should receive priority, preferably by providing antiretroviral drugs and aggressive nutrition support with energy-dense nutrition supplements to supplement the meals these children currently receive.

Apart from wasting, HIV infection also causes micronutrient deficiencies, which can further compromise the immune system, resulting in a poorer outcome.[23] Especially in Africa, deficiencies of a number of these micronutrients are more prevalent among children infected with HIV than among HIV-negative children.[24] This study confirmed that micronutrient deficiencies frequently occurred in the majority of children, with the highest prevalence of deficiencies relating to glutathione, vitamin A, zinc and vitamin D, which are all essential in maintaining the immune function. However, only glutathione levels correlated with growth indicators. Our results seem to be in accordance with a study by Arpadi[25] that found that the plasma glutathione levels in HIV-infected children were decreased by 24% if compared to HIV-negative controls. HIV-infected children with growth failure had glutathione levels that were further reduced by 35%.

These results should, however, be treated with caution, as they are affected by the acute-phase response and thus are susceptible to changes in binding proteins.[26] Serum zinc and vitamin A levels normally decrease during the acute phase response, while serum levels of ferritin increase. A small number (14%) of children had increased ferritin levels and as C-reactive protein levels were not available, serum levels of micronutrients in some children may not accurately reflect true micronutrient levels. This is supported by the fact that the children with increased ferritin levels had significant decreases in both $CD4^+$ cell counts and serum zinc levels.

Previous studies amongst HIV-infected children in South Africa indicated a significant relationship between immunological status and Hb levels.[6] In this study, children with higher viral loads had significantly lower Hb levels as well. A similar trend could be observed between CD4% and Hb levels whereby the median Hb value in the Category 3 group (9.8 g/dl) was lower than in the Category 1 group (11.6 g/dl). There was no correlation between the prevalence of iron depletion and immune suppression in this particular sample.

Decreased serum levels of albumin and cholesterol significantly correlated with higher viral loads, lower CD4%, lower CD4:CD8, as well as stunting. Unlike HIV-infected children in developed countries in whom abnormal protein levels could not be demonstrated,[27] the majority of children in this study not only had abnormally low values but these correlated with a compromised immune system as well. Stunted HIV-infected children in care centres are therefore more likely to have anaemia and decreased serum levels of albumin and cholesterol.

Children with abnormally low vitamin A and zinc levels had significantly higher viral loads and lower $CD4^+$ cell counts. Though no significant differences could be demonstrated in relation to vitamins D and E, a trend could be observed whereby children with abnormal low levels of these antioxidants had higher viral loads and lower $CD4^+$ cell counts. If indeed these deficiencies are related to immune status rather than growth, it remains to be seen whether these deficiencies can be reversed by nutritional supplementation and whether that can impact on the immune status as well. Unfortunately, other than vitamin A and zinc, no randomised trials have examined the impact of micronutrient supplementation in children born to HIV-infected mothers. In developing countries, vitamin A supplementation showed reductions in child morbidity and mortality, also in HIV-infected children.[28,29]

The limited sample size and the lack of a control group in terms of HIV-negative children were the biggest limitations of the study. All care centres initially earmarked for the study indicated that their main focus was the care and support of HIV-infected children. However, of the more than 150 children in six centres, only 38 had a positive ELISA. It is therefore evident that the majority of children who are currently receiving care and support from institutions in this part of the country are affected by HIV/AIDS and not infected as assumed before the commencement of the study. It may be very valuable to determine the nutritional and health status of these HIV-affected children to ensure timely intervention if needed.

The correlation demonstrated in this study between viral loads and stunting is in accordance with international data that have shown that compromised statural growth is superior to weight-based criteria as an indicator of disease progression.[30,31] In the absence of viral loads being performed routinely in HIV-infected children living in care centres in South Africa, the severity of stunting may be a more easily accessible indicator of disease progression. Although the deprived socio-economic background these children originate from cannot be ignored as contributing factor to the underlying malnutrition observed, the nutritional problems regarding underweight and stunting as well as the widespread micronutrient deficiencies emphasise the need for early initiation of antiretroviral therapy, especially in the case of children qualifying for it. The impact of aggressive macro- and micronutrient supplementation in addition to the high-quality food they currently receive should also be investigated to determine whether rehabilitation of growth and micronutrient deficiencies is possible at all in HIV-infected children in these relatively controlled settings. This may have critical long-term implications for these children with respect to their future development, school achievement and economic productivity.

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Disclosure

L Steenkamp is an independent nutrition consultant and has in the past provided consultancy services for Diva Nutritional Products.

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