Selective cerebral hypothermia for post-hypoxic neuroprotection in neonates using a solid ice cap

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Objective. The main objective of this study was to study the safety and efficacy of a simple, cost-effective method of selective head cooling with mild systemic hypothermia in newborn infants with hypoxic ischaemic encephalopathy.

Design. Ethical approval was obtained for a randomised controlled study in which 20 asphyxiated neonates with clinical signs of hypoxic ischaemic encephalopathy would be randomised into cooled and non-cooled groups. However, after cooling the first 4 babies, it was clear that repeated revisions to the cooling technique had to be made which was inappropriate in the context of a randomised controlled trial. The study was therefore stopped and the data for the 4 cooled infants are presented here in the form of a technical report. Hypothermia was achieved by applying an insulated ice cap to the heads of the infants and replacing it at 2 - 3-hourly intervals, aiming to achieve a target rectal temperature of 35 - 35.5°C and a target scalp temperature of 10 - 28°C.

Setting. This study was carried out between July 2000 and September 2001 in the neonatal units of Groote Schuur Hospital and Mowbray Maternity Hospital, Cape Town.

Subjects. Term infants with signs of encephalopathy were recruited within the first 8 hours of life if they had required resuscitation at birth and had significant acidosis within the first hour of life.

Results. Target rectal temperature was achieved in all infants, but large variations in incubator and scalp temperatures occurred in 3 of the 4 infants. Reducing the target core temperature in a stepwise manner did not prevent excessive temperature variation and resulted in a longer time to reach target temperature. There was least variation in scalp temperature when the ice pack was covered in two layers of mutton cloth before application, but the resulting scalp temperatures were above the target temperature. The maximum scalp temperature variation was reduced from 22°C to 12°C using this method. Nasopharyngeal temperatures varied excessively within less than a minute, suggesting that air cooling via mouth breathing was occurring. The surface site that correlated best with deep rectal temperature was the back, with the infant supine. During cooling, the respiratory rate and heart rate dropped while the mean arterial blood pressure was elevated. There were no irreversible adverse events due to cooling, but infants did become agitated and exhibited shivering which required sedation and analgesia.

Conclusions. Nasopharyngeal temperature monitoring was not reliable as an acute clinical indicator of brain temperature in these spontaneously breathing infants, and the back temperature in supine infants correlated better with deep rectal temperature than did exposed skin temperature. This method of cooling achieved systemic cooling but there were large variations in regional temperatures in 3 of the 4 infants. The variations in temperature were probably due to the excessive cooling effect of the ice cap, coupled with the use of external heating to maintain systemic temperature at 35 - 35.5°C. Variation in temperature was reduced when additional insulation was provided. However, the additional insulation resulted in the loss of the selective cerebral cooling effect. This cooling technique was therefore not an appropriate method of selective head cooling, but did successfully induce systemic hypothermia. This method of insulating an ice cap could therefore be used to induce whole-body cooling but the use of lower core temperatures of 33 - 34°C is recommended as this will probably result in fewer regional temperature fluctuations. Ideally a more uniform method of cooling should be used.

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Hypoxic ischaemic insults during labour remain an important cause of brain injury in term and near-term infants.[1] Brain injury that occurs in this way is an evolving process and the clinical manifestation of this injury is termed hypoxic ischaemic encephalopathy (HIE).[2]

Several animal studies have shown that the evolving brain injury in newborn animals following a hypoxic ischaemic insult is potentially amenable to neuroprotective rescue therapy in the form of cerebral hypothermia.[3-7] Focal cerebral cooling, with mild systemic cooling, achieves neuroprotection with fewer systemic complications than deep whole-body cooling.[8, 9]

In 1998, Gunn *et al.*[10] published a safety study using a cooling coil that circulated water at 10°C around the head. The scalp temperature of the cooled infants fell to 28°C and the rectal temperature was 35.7 ± 0.2°C. In this study, no significant adverse effects of cooling were detected if the core temperature was maintained above 34.2°C. Following the initial safety

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study by Gunn *et al.*,[10] we sought to devise a simpler form of head cooling that could be used in developing countries.

Ice packs have been applied to the heads of neonates during cardiopulmonary bypass surgery[11] and cooling caps at -30°C, covered in cloth, were applied to piglets' heads after cardiac arrest and resuscitation, with no local complications.[12] We therefore designed this study to pilot a simple insulated ice pack, aiming for similar temperatures to those described by Gunn *et al*.[10]

A study of asphyxiated fetal sheep found that prolonged cerebral cooling started within 5.5 hours of birth is associated with neuronal rescue, but delaying the rescue to 8.5 hours results in a loss of the effect.[8] Therefore, we recruited infants as early as possible, but set 8 hours as the maximum recruitment age.

Ethical approval was obtained from the University of Cape Town Medical Research Ethics Committee to conduct a randomised controlled study of selective cerebral hypothermia on 20 infants with HIE. However, after cooling the first 4 babies, it was clear that repeated revisions to the technique had to be made and that the ice cap was not a satisfactory method of inducing selective cerebral cooling. If selective cerebral cooling was not being achieved then lower core temperatures would have to be used in those infants. The study was therefore stopped and the data and observations from the 4 cooled infants are presented here in the form of a technical report.

Method

Setting

This study was done in the neonatal units of Groote Schuur Hospital and Mowbray Maternity Hospital, Cape Town, South Africa.

Patients

From July 2000 to September 2001, infants were recruited during the first 8 hours of life when they met the following entry criteria: a gestational age of 37 or more weeks, a base deficit of 10 or more on arterial cord blood (or infant's arterial blood within the first hour), an Apgar score of 6 or less at 5 minutes after birth or the need for assisted ventilation at delivery, and signs of encephalopathy (with a score of at least 2 on a previously validated scoring system).[13] Written informed consent was obtained from parents or legal guardians.

Exclusion criteria were major congenital abnormalities, active bleeding, obvious sepsis, hypoxaemia requiring more than 50% oxygen to maintain normal oxygen saturation and severe hypoglycaemia or electrolyte abnormality not responding to standard therapy.

Procedures

As soon as infants met the entry criteria, an insulated ice cap was applied and changed as required to maintain the rectal temperature (probe inserted 5 cm into the rectum) at 35 - 35.5°C and a scalp temperature of 10 - 28°C. All infants were nursed in a closed, non-humidified incubator (Airshields, C100).

Temperature was regulated by servo-controlling the back skin temperature on supine infants. This location was chosen because it should approximate the rectal temperature but is technically easier to access. Scalp temperature over the anterior fontanelle, and nasopharyngeal and surface abdominal skin temperatures were also monitored. The probe position for nasopharyngeal temperature monitoring was estimated by measuring the nostril to ear tragus distance but in all cases this resulted in the tip of the probe protruding past the uvula, so it was withdrawn until it was palpable immediately above the uvula.

The temperature probes used in all infants were disposable thermistor probes, equivalent to the Yellow Springs International 400 series (Respiratory support Products, Inc., Smiths Industries Medical Systems, California, USA). Soft silicone size 8 French Foley catheter temperature probes with the same specifications as above were used (not inflated) in the rectum and nasopharynyx. Abdominal skin probes were fixed in position with a reflective disc supplied by the manufacturer and back skin and fontanelle probes were fixed in position using Tegaderm. Temperatures were documented every 5 minutes at all sites except the back temperature which was monitored every 2 hours.

The ice pack that was used for head cooling was a 12 × 12 cm freezable gel pack made by Penguin Manufacturers. This pack is normally used to keep vaccines cool in transit. The pack was covered with mutton cloth and then frozen around an empty 2-litre cooldrink bottle to obtain a suitable curvature. The frozen ice pack was then secured onto the baby's head over the anterior fontanelle.

Following severe fluctuations in incubator and scalp temperatures in the first case (Fig. 1), the optimal timing and method of placement of the ice cap was refined with each subsequent case as shown in Table I.

Restlessness and shivering were noticed in the first case treated. In the subsequent cases, phenobarbitone 20 mg/kg was routinely administered for sedation with the onset of cooling. If discomfort persisted, a second dose of phenobarbitone was administered and if discomfort persisted further, then morphine 0.03 mg/kg was given as a slow intravenous bolus. Apart from the cooling and additional sedation and analgesia, all infants received standard clinical care.

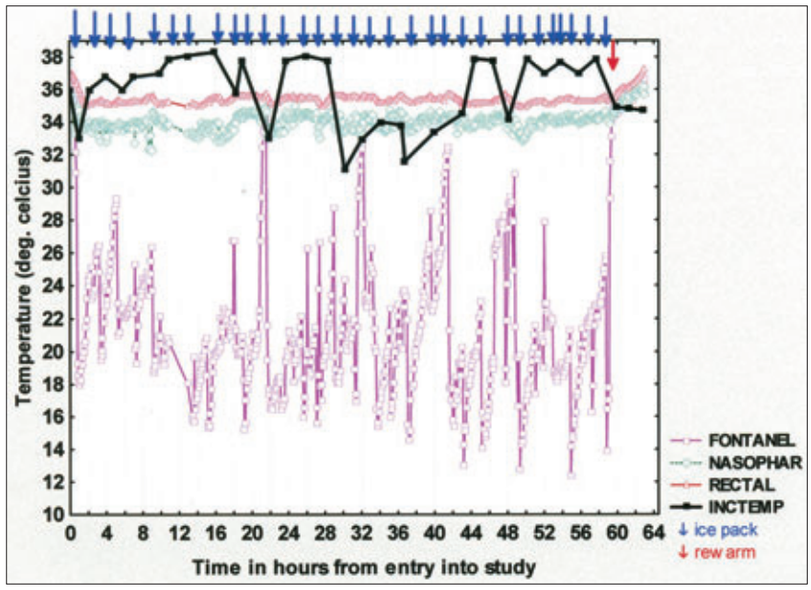

Fig. 1. Temperature variation during cooling in case 1.

Intravenous fluids were provided using potassium-free Neonatalyte at an initial volume of 50 ml/kg. Fluids were then adjusted on a daily basis as judged by the attending paediatrician. Clinical seizures occurred in 1 patient only and these were controlled with a second dose of phenobarbitone 20 mg/kg.

Cooling continued for 72 hours or until the encephalopathy had resolved, but the minimum duration of cooling was 48 hours.

Statistical analysis

Temperature and vital signs data were analysed and graphically displayed using Statistica 6.0.

Results

Baseline characteristics

Birth weights ranged from 2 730 g to 3 100 g and the base deficit in the first hour of life ranged from 12 to 16.5. Cerebral ultrasound was suggestive of cerebral oedema in 3 of the 4 infants at recruitment, but no infant manifested clinical seizures before cooling and all infants were breathing spontaneously in room air at the time.

Table I. Cooling and re-warming strategies in the 4 cooled infants*

	Case 1	Case 2	Case 3	Case 4
Age cooling commenced	5:24	5:50	5:30	7:20
Empiric phenobarbitone pre-cooling	No	Yes	Yes	Yes
Layers of cloth over ice pack	1	1	1	2
Reflective covering over ice cap	No	Yes	No	No
Ice cap change interval	2-hourly	2-hourly	2-hourly	3-hourly
Induction of cooling protocol when ice cap is first applied	Servo-control back temperature to 35.5°C	Servo-control back temperature to 36.5°C for 10 minutes, then reduce by 0.2°C every 15 minutes until 35.5°C	Servo-control back temperature to 35.2°C	Servo-control back temperature to 36.5°C and reduce by 0.2°C every half hour until 35.3°C
Time to reach target rectal temperature	00:45	2:00	4:00	3:00
Duration of cooling	59:20	72:00	71:05	72:05
Warming protocol from the time of removing ice cap	Servo-control back temperature to 36°C then increase by 0.5°C hourly until 37°C	Servo-control back temperature to 35.5°C for 1 hour. Increase by 0.5°C after 1 hour, then by 0.2°C per hour until 37°C	Servo-control back temperature to 35.2°C for 15 minutes, then increase to 35.5°C and continue to increase by 0.5°C per 30 minutes until 37°C	Servo-control back temperature to 35.5°C for 1 hour. Increase to 36.5°C after 1 hour and increase to 37°C after another hour
Duration of re-warming	3:00	7:00	4:00	2:00

*Time shown as hours: minutes.

Regional temperature variation

The target rectal temperature of 35 - 35.5°C was achieved in all cases except case 3 in which the mean rectal temperature was 34.7°C. The only case with an acceptably short time to target rectal temperature of under 1 hour was case 1. The rapid head cooling in this case and case 3 resulted in high incubator temperatures. The longer cooling time in case 3 was the result of manual manipulation of the incubator settings.

The incubator temperature varied by up to 7°C in cases 1 and 3 and by up to 9°C in cases 2 and 4, but in cases 1 and 3, the incubator temperature rose above 37°C on several occasions. Fig. 1 shows the excessive regional temperature variations experienced by case 1 and this is representative of all cases, except case 4, where the maximum scalp temperature variation was reduced from 22°C to 12°C. The incubator temperature in this case only rose above 36°C to 36.5°C on one occasion.

The target scalp temperature was achieved in all infants except in case 4 where the mean nasopharyngeal temperature was 29.7°C. The use of a reflective covering on the ice cap in case 2 prevented adequate monitoring of the ice cap position and did not prevent incubator temperature fluctuation. Rewarming occurred in all infants in proportion to the speed with which the external heating was increased; the fastest rewarming time of 1°C per hour was achieved by increasing the desired temperature by the same rate, as was done in case 4.

Nasopharyngeal temperature monitoring

Although the trend of nasopharyngeal temperatures represented graphically in Fig. 1 suggests an increased nasopharyngeal-rectal temperature gradient during cooling, individual nasopharyngeal temperatures fluctuated rapidly and by several degrees over less than a minute in infants during times of agitation and rapid mouth breathing or crying.

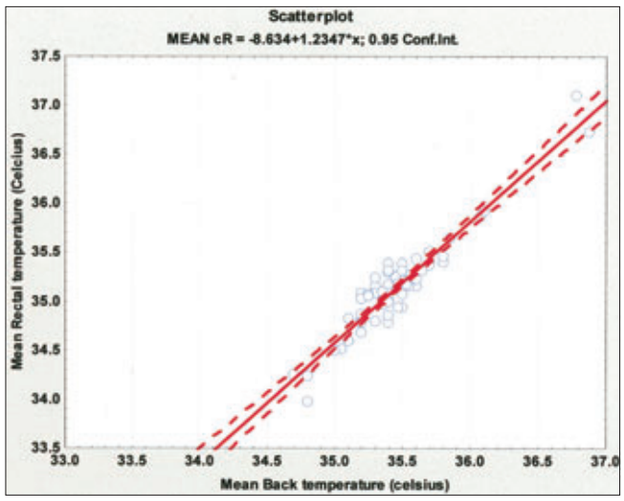

Fig. 2. Mean rectal temperature versus mean back temperature during cooling.

Back temperature (in supine infants) versus surface abdominal temperature

Data from the 4 cooled infants were used to correlate insulated back temperatures and surface abdominal temperatures with rectal temperatures (Figs 2 and 3). The insulated back temperatures correlate much better with rectal temperatures than did the surface abdominal skin temperatures.

Cardiovascular and respiratory observations

The data of all groups were analysed collectively. During cooling, the respiratory rate dropped by an average of 19 breaths per minute, the heart rate dropped by an average of 17 beats per minute, and the mean arterial blood pressure rose by an average of 6 mmHg. During rewarming, these parameters returned to the precooling state and at no time were the infants compromised by these changes.

Biochemical and haematological complications during cooling

Biochemical and haematological monitoring showed no significant irreversible adverse events due to cooling. In case 1, the serum sodium dropped to 125 mmol/l on day 2 and blood sugar rose to 18 mmol/l because of inadvertent administration of excess intravenous fluid. Hypokalaemia was not encountered. Case 3 had transient hypoglycaemia. The metabolic acidosis on admission to the study progressively resolved during cooling and renal failure did not occur. The maximum prothrombin index of 2.5 on day 2 improved to normal limits by day 4 after treatment with intravenous vitamin K. No infant acquired infection during or after the study period.

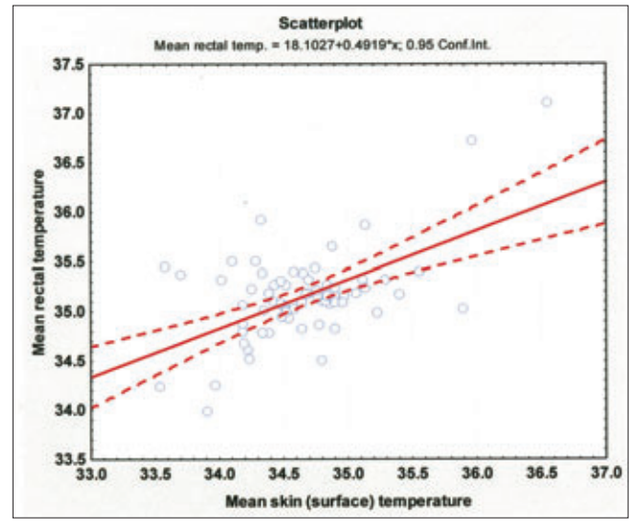

Fig. 3. Mean rectal temperature versus mean surface abdominal skin temperature during cooling.

Physical and short-term neurological outcomes in cooled infants

There were no local side-effects from the ice packs. Two of the cooled infants progressed to moderate encephalopathy but there were no neurological abnormalities at the time of discharge in any of the infants. Full feeds were established between day 5 and day 8.

Discussion

This method of cooling is not simple and there were large fluctuations in regional temperatures. The constant vigilance required to prevent further variation in incubator temperature and the repeated changing of the ice packs was labour intensive. The high incubator temperatures were thought to be due to the excessive cooling effect of the ice cap, coupled with the use of external heating to maintain systemic temperature at 35 - 35.5°C. The strategy of insulating the pack, making it less cool and at the same time prolonging the thaw time, resulted in lower incubator temperatures and less scalp temperature fluctuations but average scalp temperatures were higher than desired. Fluctuations in scalp temperature will not be noticed if scalp temperature is not measured frequently. This is an important finding because large variation in temperature causes variable perfusion and this could potentially exacerbate cerebral injury.

Although the exact depth of cooling required to achieve neuroprotection is not known, a review of several studies14 suggests that the optimal brain temperature to achieve neuroprotection with minimal side-effects is 32 - 34°C. Brain temperature during cooling has been related to scalp temperature using numerical modelling15 which predicts that a scalp temperature of 24°C with a core temperature of 34°C results in a temperature gradient of 32 - 28°C across the cortex. Therefore, in the first two cases with mean scalp temperatures of 21°C, there was probably significant selective cerebral cooling, but the scalp temperatures of 27 and 29.7°C in cases 3 and 4 respectively, suggest that selective cerebral cooling was not achieved in these cases. If significant selective cerebral cooling is not occurring, then deeper core temperatures of 33 - 34°C must be achieved with whole-body cooling.

Gunn *et al.*[10] used nasopharyngeal temperatures to infer cerebral cooling. However, we found that the nasopharyngeal temperature varied greatly with mouth breathing and therefore has little value in spontaneously breathing infants.

Gunn *et al.*[10] used surface abdominal skin as a site to servo-control temperature of cooled infants but commented that manual adjustment was required intermittently. We also found that the surface abdominal temperature varied greatly and was subject to environmental influence. The covered back temperature showed close correlation with the rectal temperature and in future studies we suggest that this site could be used to servo-control temperature instead of rectal temperature.

The infants that we cooled frequently became agitated and exhibited shivering. In animal studies, unsedated cooled piglets had cortisol levels three times higher than those of their normothermic counterparts16 and neuroprotection was not successful. This supports our finding that sedation and analgesia are necessary during induced hypothermia.

In summary, the salient lessons and recommendations that can be derived from the four infants studied are as follows:

1. Solid ice cap application is not recommended for inducing selective cerebral hypothermia. Increased insulation of the ice cap can be used to successfully induce whole-body cooling but the fluctuation in incubator and scalp temperatures is still not ideal. However, there will probably be less fluctuation if external heating is reduced by accepting a target core temperature of 33 - 34°C which has recently been shown to be safe.17-19 A more uniform method of head or whole-body cooling would be preferable if it were available and simple to use.
2. The ice cap did not result in local complications.
3. Mild systemic cooling did not result in significant systemic or biochemical complications.
4. Nasopharyngeal temperature monitoring is not an accurate reflection of brain temperature in spontaneously breathing infants.
5. The superficial abdominal skin temperature was not a reliable indicator of core temperature, but the covered back temperature closely follows the core temperature and this site may be used as a less invasive alternative to deep rectal temperature monitoring.
6. Sedation and analgesia to control discomfort should be given to infants with induced hypothermia to reduce stress and decrease shivering.

The current international consensus opinion of the National Institute of Child Health and Human Development recommends that results from outstanding trials should be awaited and reviewed before hypothermia becomes a standard of care for infants with HIE, and that care should be taken to prevent inadvertent overheating of these infants.20 We support this statement. If infants with HIE are cooled, parental consent should be sought and there should be a careful audit of the intervention, bearing the above lessons in mind.

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Secular trends in risk behaviour of Cape Town grade 8 students

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Objective. To compare prevalence rates of selected risk behaviours and age of first intercourse of grade 8 students in Cape Town between 1997 and 2004.

Design. Cross-sectional surveys in 1997 and 2004. Survival analysis was used to estimate the cumulative incidence of first intercourse. The log-rank statistic was used to compare the survival distributions. When comparing data from the two studies we used a logistic regression model with the factors year, race and age group to test the difference in reported risk behaviours between 1997 and 2004 within each gender.

Setting. Public high schools in Cape Town.

Subjects. Multistage cluster samples of 1 437 and 6 266 grade 8 students in 1997 and 2004 respectively.

Outcome measures. Ever having had sexual intercourse; for those that had, whether any method was used to prevent pregnancy or disease at last intercourse, and (if so) what was used; use of tobacco, alcohol and marijuana; violence-related behaviours; and suicidal behaviour.

Results. There was a significant delay in first intercourse in 2004 compared with 1997. For males, levels of condom use were lower in 2004 than in 1997, while for females levels of injectable contraceptive use were lower. There were significant increases in past month use of cigarettes for males and marijuana for both genders. Rates of perpetration of violence behaviour remained stable or decreased from 1997 to 2004, while the rate of suicidal behaviour for males increased.

Conclusions. School-based interventions that address sexual risk behaviours should be expanded to include other risk behaviours.

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Risk behaviour can be defined as behaviour that increases one's risk of adverse outcomes in the short or long term, in the psychological, social or physical domains. Several national studies have documented prevalence rates of risk behaviours among South African adolescents, including national household surveys conducted by the Human Sciences Research Council in 2002[1] and 2005,[2] a national household survey of 15 - 24-year olds,[3] and a national survey of risk behaviour among youth in grades 8 - 11 in public high schools.[4] The present report compares risk behaviour of grade 8 students in Cape Town across two time points, 1997 and 2004. This time period is important, as one would expect the consequences of South Africa's transition to a democratic dispensation to become evident in these years. It also coincides with a period of rapid advance of the HIV epidemic, with a corresponding increase in the extent of AIDS prevention activities. Against this background, it is crucial to know whether these profound social changes were accompanied by changes in levels of risk behaviour of high-school students.

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Methods

The data reported in this paper were derived from two studies, conducted in 1997 and 2004. While selected prevalence rates from the 1997 study have been reported previously,[5-7] the prevalence rates from the 2004 study are reported for the first time in this paper.

Populations and samples

In both 1997 and 2004, the study population was grade 8 students attending public schools in Cape Town.

In 1997, we stratified the schools by postal code groupings since these groupings are relatively homogeneous in terms of factors such as social class, racially defined social group, language and culture. We selected 39 schools such that the proportion of schools in a selected stratum was directly proportional to the number of students in that stratum. The selection probability of a school was proportional to the number of students in that school. We selected 40 students from the combined class lists of two randomly selected grade 8 classes.

The 2004 sample consisted of 15 schools randomly selected from the 39 schools selected in 1997 using simple random

sampling. All grade 8 students were selected to participate in the study. Each of these selected schools was matched to another school on a range of demographic characteristics (student population size, socially defined racial group of students, language of instruction, geographical area in which the school was located and the school fee (as a proxy for socio-economic status)). Fifteen matched pairs were formed as a result of this for use in an intervention study of an AIDS prevention strategy. Two pairs of schools were excluded from the study owing to difficulties in obtaining consent to participate in the intervention study.

Procedure

The selected students completed a questionnaire during a normal school period. The seating was arranged to minimise the risk of students seeing the responses of their classmates. No school staff were present during the administration of the questionnaire.

In 1997 the questionnaire was in paper-and-pencil format. In 2004 it was administered using personal digital assistants (PDAs). We have compared the test-retest reliability of the electronic questionnaires with paper-and-pencil questionnaires, and found that it was similar.[8]

In both years, after obtaining permission from the Western Cape Education Department and the participating schools, we sent a letter to parents at all participating schools to introduce the study. If a parent objected to their child participating in the study, they were asked to convey this by contacting the school or the research team or completing a declination form attached to the letter and returning it to the evaluation co-ordinators. All participating learners signed an assent form agreeing to participate.

Instrument

The instrument used in the 1997 study had been used in previous studies[9,10] and has been subject to extensive pilot studies in small groups and classrooms. In addition, the test-retest reliability of the items has been documented, and found to be at least satisfactory.[11,12] Finally, there is considerable evidence of the validity of the items, since they have been shown to be associated with a large number of relevant constructs.[13]

The items in the 2004 questionnaire addressing violence (including suicidality) were identical to those in the 1997 questionnaire. However, the items addressing sexual behaviour and substance use differed slightly in format, in that in 1997 they had stem questions followed by a set of contingent questions. For example, in 1997 the students were asked 'Have you ever had sexual intercourse? This means intimate contact with someone of the opposite sex during which the penis enters the vagina (female private parts)'. Students answering positively were asked a number of further questions, for example whether they or their partner had used anything to prevent pregnancy or disease. However, in 2004 all students were required to answer all questions. If a question involved an issue that was not applicable to a particular student, they were given the option of indicating this (for example, a question involving condom use would have an option indicating that the student had not had sexual intercourse). Likewise, in 1997, for the items involving substance use, the students were asked if they had ever used the substance in question, and then asked contingent questions if they had done so. One such contingent question inquired about how many days in the previous month the substance had been used. In 2004, the respondents were asked whether they had used each of a series of substances in the previous month. For the purposes of this report, the 1997 responses were recorded to form a dichotomous variable indicating use in the previous month or not.

Analysis

For purposes of analysis the schools sampled in 2004 as well as those matched were considered to be a random sample from the public schools in 2004 and comparable to the sample drawn in 1997.

The pooled data for 1997 and 2004 were used for the estimation of the prevalence for the various characteristics by gender and year. An indicator variable for the 65 schools was created. We used the Stata programme to calculate proportions and 95% confidence intervals (CIs) by gender and year taking the sampling of schools at the first stage into account. No sampling weights were used since no 'sensible' weights can be calculated for the 2004 sample. For contingent questions, we calculated the prevalence rates for the number of students who had engaged in the activity to the number of students who answered affirmatively to the main question.

For comparing the crude prevalence of the gender and year combinations for a specific characteristic, one can use the reported 95% CIs. If the CIs do not overlap, there is a significant ($p < 0.05$) difference between the groups. If they overlap to the extent that the point estimate of one group is contained within the CI of the other group, the two estimates are not significantly different ($p > 0.05$). If the CIs overlap, but not to the extent that the point estimate of one group is contained within the CI of the other group, no definite conclusion can be made and a formal test has to be performed. For this purpose a formal comparison was done for a specific characteristic between the prevalences for 1997 and 2004 for each gender using a logistic regression model with adjustment for the factors age group and race. The clustering due to the sampling of schools was taken into account as well. The gender-specific analysis was done because gender was an important differentiating factor in the 1997 study.[6]

We used survival analysis to estimate the cumulative incidence over a limited age interval of the event first intercourse by gender and year. This approach enabled us to provide estimates of the age of first intercourse that were

not biased by the current ages of the study participants. The reported age at first intercourse was used as the time to the event in the survival analysis. Students who had not yet experienced sexual intercourse were censored at their reported current age. The Kaplan-Meier product limit method was used to estimate the incidence curves and the corresponding confidence limits. The log-rank statistic was used to compare the survival distributions.

Table I. Demographic description of the samples in 1997 and 2004*

	1997 (*N* = 1437)		2004 (*N* = 6266)	
	N	%	*N*	%
Gender				
Males	625	43.5	3 026	48.3
Females	812	56.5	3 240	51.7
SDRG				
Black	399	28.5	2 314	42.0
Coloured	737	52.6	2 214	40.2
Indian	9	0.6	34	0.6
White	256	18.3	908	16.5
Other	0	0.0	37	0.7
Age category				
13 years or less	514	35.2	1 752	20.0
14 years	542	37.1	2 761	44.5
15 years	231	15.8	1 225	19.7
16 years or less	174	11.9	983	15.8

* Column totals for demographic categories are less than the total sample sizes owing to missing values for these categories.
SDRG = self-denoted race group.

Results

The details of the samples are presented in Table I, and the results of the survival analysis of age of first intercourse are presented in Table II and Fig. 1. For both males ($\chi^2 = 21.97$, $p < 0.00$) and females ($\chi^2 = 44.93$, $p < 0.00$), there was a significant delay in first intercourse in 2004 compared with 1997. For example, in 2004 12.9% of male students aged 14 years had experienced their sexual debut whereas the equivalent figure in 1997 was 17.4%. The duration of the relative delay was about 1 year. Furthermore, for both years there was a significant delay in first intercourse for females compared with males.

The protection used by students who had experienced intercourse is presented in Table III. For use of any method, females were significantly more likely to use protection than males in 1997. However, in 2004 the converse finding was obtained, with males being more likely to use protection than females. For both males and females, use of protection was significantly less likely in 2004 compared with 1997. In both 1997 and 2004, males were significantly more likely to use condoms than females. Males were significantly less likely to use condoms in 2004 compared with 1997, while for females

Table II. Estimated cumulative incidence of debut sexual intercourse

	Percentage who have had intercourse (95% confidence interval)			
	2004		1997	
Age (years)	Males	Females	Males	Females
10	2.7 (2.1 - 3.4)	0.1 (0.1 - 3.5)	4.8 (3.0 - 6.3)	0.3 (0.1 - 0.9)
11	4.6 (3.8 - 5.4)	0.2 (0.1 - 0.4)	5.7 (4.1 - 7.8)	0.4 (0.1 - 1.2)
12	8.0 (7.1 - 9.2)	0.6 (0.4 - 0.9)	8.1 (6.2 - 10.6)	0.8 (0.3 - 1.7)
13	10.8 (9.6 - 12.1)	1.5 (1.1 - 2.0)	12.8 (10.4 - 15.8)	2.5 (1.6 - 3.9)
14	12.9 (11.7 - 14.3)	2.9 (2.3 - 3.6)	17.4 (14.5 - 20.9)	7.5 (5.6 - 10.0)
15	17.1 (15.4 - 19.0)	6.6 (5.3 - 8.2)	27.9 (23.1 - 33.5)	18.5 (14.2 - 23.9)
16	19.6 (17.4 - 22.0)	14.5 (11.6 - 18.2)	37.3 (30.3 - 45.4)	29.8 (22.3 - 39.0)
17	22.6 (19.5 - 20.4)	19.7 (15.2 - 25.4)	37.3 (30.3 - 45.4)	34.8 (24.1 - 48.5)

Table III. Estimated prevalence (95% confidence interval) for protection used at last intercourse for students who had experienced sexual intercourse

	Males			Females		
	1997 (*N* = 133) % (CI)	2004 (*N* = 815) % (CI)	*p*	1997 (*N* = 83) % (CI)	2004 (*N* = 326) % (CI)	Adjusted *p**
Any method	50 (40.5 - 59.5)	37.9 (33.9 - 42.1)	0.01	64.6 (53.6 - 74.2)	23.8 (20.1 - 27.9)	0.00
Condom	67.2 (59.4 - 74.1)	44.2 (40.2 - 48.3)	0.00	34.6 (21.8 - 50.0)	35.1 (30.4 - 40.0)	0.96
Oral contraceptive	8.6 (5.0 - 14.5)	11.7 (9.1 - 14.8)	0.17	7.6 (3.7 - 15.0)	7.1 (4.8 - 10.3)	0.79
Injection	9.5 (4.4 - 19.2)	8.0 (6.3 - 10.1)	0.10	53.1 (39.0 - 66.7)	17.7 (12.8 - 24.0)	0.00

**p*-value from gender-specific logistic regression model of protection indicator on year adjusted for age group and socially defined racial group.

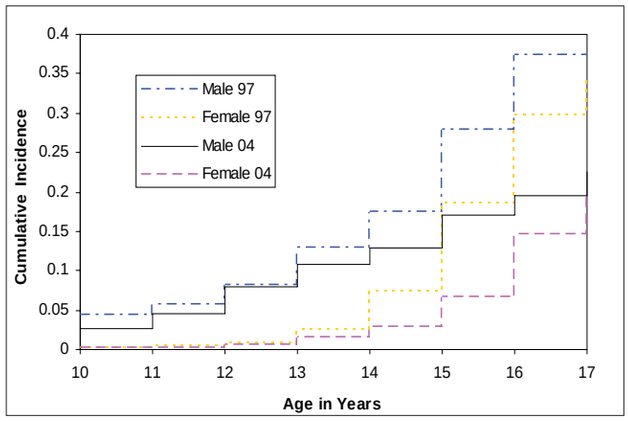

Fig. 1. Cumulative incidence of debut of sexual intercourse by year and gender.

there were no significant differences in condom use between the two years. Females were significantly more likely than males to use injections in both years. While there was no significant difference in the proportion of males whose partners used injections between the two years, there was a large and significant decline in the proportion of females who used them (from 53.1% to 17.7%). There were no significant differences between the genders or the years in the proportion who used oral contraceptives.

In terms of substance use (Table IV), we observed significant increases for past month use of cigarettes for males and marijuana for both males and females. There were no significant differences for past month use of alcohol. In terms of violence-related behaviours, there were significant increases for carrying a knife to school to be used as a weapon (males and females) and causing serious damage to property (males only). However, there were significant decreases for going out at night beyond the neighbourhood and walking home alone (both genders), stealing (both genders), bullying (females only) and being bullied (both genders). There was a significant and large increase in suicidal behaviour for males (from 7.0% to 20.7%), but no difference for females.

Discussion

We found that there was a significant and substantial delay in first intercourse from 1997 to 2004. There are two possible explanations for this change. First, it could be due to the effects of intervention efforts that were implemented in these years. Second, the effects of the HIV epidemic may have become more evident in these years, as more people display symptoms of HIV infection or die. This could contribute to behaviour change through making it more difficult to deny the existence of the disease or to attribute it to other groups.[14] Whatever the reason for the change, it is encouraging that age of sexual debut among grade 8 students in Cape Town occurred later in 2004 than in 1997, especially given the relatively short period of time involved. However, these findings are not consistent with the trends inferred from the Human Sciences Research Council household surveys, which concluded that in 2005 young people aged 15 - 24 years were engaging in sexual intercourse at a younger age than in 2003 or 2002.[2]

The findings for use of protection against pregnancy and disease were, however, discouraging. The proportion of both males and females who used any form of protection declined significantly between 1997 and 2004. One possible explanation for this finding is that young people might have been more likely to have sexual encounters in the context of longer and more stable relationships in 2004 compared with 1997. This is relevant for protection use, since young people may be less likely to use protection in such relationships. If further research confirms this explanation, the implication for prevention activities is that the necessity for protection should be emphasised, whether the relationship in which the sexual activity takes place is ongoing or not.

For males, the reduction in the proportion who used contraception between 2004 and 1997 can be attributed to a reduction in the proportion who used condoms, since the proportion whose partners used oral or injectable contraceptives remained stable in this time period. The reduction in the proportion who used condoms implies that increased numbers were at risk both of contracting sexually transmitted infections (including HIV infection) and of impregnating their partners. This finding contradicts data from the Human Sciences Research Council national household surveys which show a substantial increase in reported condom use at last sexual encounter among young men (and young women) aged 15 - 24 years between 2002 and 2005.[2] However, for females the decline in contraception use can be attributed to a large reduction in the proportion who used injectable contraceptives (from 53.1% to 17.7%). There was no change in the proportion who used oral contraceptives, or in the proportion whose partners used condoms. The reduction in the proportion who used injectable contraceptives may be a consequence of personnel at clinics encouraging the use of condoms owing to their beneficial effects on risk of HIV infection, even though the policy is that 'dual protection' (against risk of sexually transmitted infections and pregnancy) should be promoted. Another explanation is that concern about the adverse consequences of injectable contraceptives has resulted in decreased demand by service users and decreased promotion by service providers. Whatever the explanation for the decrease in use of injectable contraception, it is a source of concern that this decrease has placed large numbers of young women at risk for pregnancy.

The rate of recent tobacco use increased for males only, and there were no significant differences for recent alcohol use (although there was a trend ($p = 0.08$) for the rate among females to decrease). There were significant and large increases in the rates of marijuana use for both males (from 3.1% to

Table IV. Estimated prevalence (95% confidence interval) for non-sexual risk behaviours for all students

	Males			Females		
	1997 (*N* = 625) % (CI)	2004 (*N* = 3 026) % (CI)	Adjusted *p**	1997 (*N* = 812) % (CI)	2004 (*N* = 3 240) % (CI)	Adjusted *p**
Smoke a whole cigarette (4 weeks)	23.0 (18.2 - 27.9)	31.5 (28.5 - 34.6)	0.00	21.3 (15.2 - 27.4)	18.2 (14.5 - 21.9)	0.11
Use alcohol (including wine and beer), other than a few sips (4 weeks)	22.0 (17.3 - 26.8)	25.9 (23.1 - 28.7)	0.23	18.0 (13.4 - 22.6)	14.8 (13.0 - 16.7)	0.08
Smoke marijuana (4 weeks)	3.1 (1.7 - 4.5)	17.2 (13.8 - 20.6)	0.00	1.9 (0.9 - 2.9)	5.2 (3.7 - 6.6)	0.01
Carry a knife at school to be used as a weapon (4 weeks)	9.7 (6.9 - 12.5)	18.0 (14.2 - 21.7)	0.01	1.3 (0.4 - 2.1)	4.6 (2.9 - 6.2)	0.00
Go out at night beyond the neighbourhood and walk home alone (4 weeks)	37.7 (33.3 - 42.0)	29.0 (26.5 - 31.3)	0.00	17.1 (13.9 - 20.2)	12.1 (10.2 - 14.0)	0.00
Stealing anything from anybody (12 months)	37.9 (33.3 - 42.5)	32.5 (29.2 - 35.7)	0.04	23.2 (19.4 - 26.9)	15.6 (13.5 - 17.6)	0.00
Cause serious damage to property (12 months)	14.4 (11.5 - 17.2)	22.7 (20.8 - 24.7)	0.00	6.8 (4.6 - 9.0)	7.8 (6.5 - 9.0)	0.75
Bully anybody at school (12 months)	28.4 (23.6 - 33.3)	26.2 (24.4 - 28.1)	0.19	15.7 (12.7 - 18.7)	12.6 (11.0 - 14.3)	0.01
Been bullied at school (12 months)	41.1 (35.8 - 46.4)	31.4 (29.0 - 33.7)	0.00	30.3 (25.6 - 34.9)	15.7 (14.4 - 16.9)	0.00
Been involved in any physical fights (12 months)	36.4 (31.8 - 41.1)	32.8 (30.3 - 35.2)	0.25	16.9 (13.8 - 19.9)	15.9 (14.1 - 17.7)	0.41
Try to put an end to one's life (12 months)	7.0 (4.6 - 9.4)	20.7 (17.3 - 24.1)	0.00	16.9 (13.2 - 20.6)	16.9 (14.6 - 19.2)	0.67

**p*-value from gender-specific logistic regression model of non-sexual risk behaviour indicator on year adjusted for age group and socially defined racial group.

17.2%) and females (from 1.9% to 5.2%). Furthermore, the rates in 1997 were almost double those observed in a 1990 study that included grade 8 students.[10] Although the sampling strategies differed in the two studies, both studies aimed to produce samples that were representative of students in Cape Town in the selected grades. There is therefore robust evidence of a secular trend of an increase in marijuana use among grade 8 students in Cape Town from 1990 to 2004. This may be due to more vigorous enforcement of laws that aim to reduce drug use in developed countries such as the USA, or increased access to cannabis because the borders have become more open in recent years. The effects of an increase in marijuana use will be amplified by the current epidemic of crystal methamphetamine ('tik') in Cape Town. Urgent steps are necessary to address use of illicit drugs among young people in Cape Town.

The rates of stealing, exposure to bullying as perpetrator or victim, and involvement in physical fights decreased or remained stable for both males and females in the period under study. However, the proportion who had gone out at night beyond their neighbourhood and walked home alone decreased for both genders. This could reflect an increased sense of vulnerability to interpersonal violence. The increased rate of carrying a knife to school to be used as a weapon could also reflect such increased vulnerability, in that the young people may have carried knives to protect themselves if attacked.

There was a large increase in the proportion of boys who had attempted suicide in the previous year (from 7.0% to 20.7%), while the rate for girls remained stable. When comparing the 1997 data with those from the 1990 study cited above,[10] there

were no significant changes for either gender. An analysis of nationally registered mortality data showed an increase in the suicide rate for young white males only from 1968 to 1990.[15] However, the increase for males in the current study was not evident only for white males, since socially defined racial group was included as a covariate in the multiple logistic regression analyses. It is an urgent research priority to ascertain whether this increase is also present in other age groups and other places in South Africa, and to identify the reasons for the increase. Such reasons are necessarily applicable only to males.

It is important to mention the limitations of the study. First, it was limited to students who were present at school on the day the study was undertaken, thus excluding dropouts and absentees who may have higher rates of risk behaviour.[9] However, for this to bias the findings about secular trends, the relationship between risk behaviour and dropout or absenteeism would need to be different between the two time periods. There is no reason to think that this might be the case. Also, the data for those who attend school are applicable for school-based interventions. Second, the study was confined to grade 8 students attending public high schools in Cape Town, which limits the extent to which the findings can be generalised to other populations. Third, the study relied on self-report data. Although we went to great lengths to ensure anonymity and confidentiality, it is possible that the data are biased, probably in the direction of providing falsely low prevalence estimates for the risk behaviours. Again, for this to bias the findings about secular trends, the extent and/or direction of the bias would need to vary between the two time periods, and again there is no reason to think that this might be the case. Finally, there were some methodological differences between the two studies. A different means of data collection was employed at the two stages. In 1997, we collected data using paper and pencil questionnaires, while in 2004 we used PDAs. However, our pilot work concluded that there were no significant differences in the prevalence rates obtained using the two methods.[8] In addition, if this were a relevant bias, one would expect that the differences between the time periods would all be in the same direction, which was not the case. Other methodological differences between the studies include the differences in question format and the absence of weighting in the 2004 study.

In conclusion, the study confirms that large numbers of grade 8 students in Cape Town engage in risk behaviour. It is necessary to replicate the findings regarding secular trends, as they may be attributable to the methodological differences between the studies mentioned above. However, if they are valid, there are some positive findings regarding secular trends for postponement of sexual debut and involvement in behaviours that are associated with interpersonal violence. These findings indicate that it is possible for risk behaviour to change in a relatively short period of time. However, the rates of selected risk behaviours among boys and/or girls changed in a direction that is associated with increased risk of adverse outcomes, such as use of protection against pregnancy of sexually transmitted infections, tobacco use, marijuana use, and suicidal behaviour. There are a number of school-based interventions in Cape Town high schools that have as their main aim to reduce the prevalence of sexual risk behaviours, including two cluster randomised control trials,[16,17] the loveLife groundBREAKER intervention,[18] and a peer education intervention[18] that is funded by the Department of Health in the Western Cape and implemented by various non-profit organisations. There is an urgent need to disseminate interventions that effectively reduce sexual risk behaviour. In addition, such interventions should increase their scope to address other the risk behaviours (such as substance use, interpersonal violence and suicidal behaviour) with which involvement in sexual risk behaviour is correlated and with which it shares common aetiological roots.[19,20]

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Antiretroviral treatment for children

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Objective. To describe the response of children during their first year on highly active antiretroviral therapy (HAART).

Design. Retrospective, descriptive.

Setting. Tertiary, referral hospital.

Subjects. All HIV-infected children commenced on HAART from 1 August 2002 until 31 December 2004.

Outcome measures. Children were retrospectively restaged using the WHO 4-stage clinical classification and CDC immunological staging system. After commencing HAART, patients were assessed at monthly intervals for the first 6 months and thereafter mostly 3-monthly. Baseline and 6-monthly CD4 counts and viral loads were performed.

Results. Of 409 children commenced on HAART, 50.6% were < 2 years old, 62.7% had severe clinical disease and 76.6% had severe immune suppression. After 1 year, 65.8% were alive and continued HAART at the hospital, 11.2% had been transferred to another antiretroviral site, 15.4% had died, 4.6% were lost to follow-up and treatment had been discontinued in 2.9%. Kaplan-Meier survival estimate for 407 children at 1 year was 84% (95% confidence interval (CI) 80 - 87%). On multivariate analysis, survival was adversely affected in children with WHO stage 4 v. stage 2 and 3 disease (adjusted hazard ratio (HR): 5.26 (95% CI 2.25 - 12.32), $p = 0.000$), age < 12 months (adjusted HR: 2.46 (95% CI 1.48 - 4.09), $p = 0.001$) and CD4 absolute count (per 100 cell increase) (adjusted HR: 0.93 (95% CI 0.88 - 0.98), $p = 0.013$). In a separate multivariate model including only children with an initial viral load ($N = 367$), viral load ≥ 1 million copies/ml (adjusted HR: 1.84 (95% CI 1.03 - 3.29)) and taking a protease inhibitor (PI)-based regimen (adjusted HR: 2.25 (95% CI 1.10 - 4.61)) were additionally independently associated with poorer survival; however, young age was not a significant predictor of mortality, after adjusting for viral load ($p = 0.119$). After 1 year of HAART 184/264 (69.7%) of children had a viral load < 400 copies/ml. Comparative analysis showed significant improvements in growth, immunological status and virological control.

Conclusion. HAART can improve the health of many HIV-infected children with advanced disease, including those aged less than 2 years in resource-limited settings.

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The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched their '3 by 5' initiative in December 2003. The principal aim was to mobilise the world to provide highly active antiretroviral therapy (HAART) to 3 million people living with HIV/AIDS in low- and middle-income countries by the end of 2005.[1] By June 2005 approximately 1 million people were receiving HAART in these countries, giving an estimated average coverage rate of 15%. Of an estimated 600 000 children in sub-Saharan Africa who required HAART, less than 5% were receiving therapy.[2] Consequently, the United Nations Children's Emergency Fund (UNICEF) along with the WHO and UNAIDS have begun to mobilise global forces to intensify perinatal prevention programmes, and extend care, particularly in the provision of co-trimoxazole prophylaxis to HIV-exposed children and HAART to all infected children in poor countries.[3]

From 1996 onwards triple combination antiretroviral (ARV) therapy has been used to treat HIV-infected children.[4,5] Since then a large body of research has been published attesting to the benefits of HAART in children. Although in general virological control has been more difficult to achieve in children compared with adults, the risks of progression to end-stage disease or AIDS and death have been significantly attenuated in children treated with HAART.[4,5] Furthermore, improvements in growth and body composition parameters, reduced frequency and severity of infectious complications, decreased hospitalisation rates and reversal or prevention of organ-specific damage have been achieved.[6-9] Long-term survival is possible and some perinatally infected children have already reached their second or third decade of life.[10,11] Research has also documented some concerns associated with HAART including the overall negative impact of HIV infection on quality of life among children, emergence of viral resistance, long-term metabolic complications, and the challenges of managing these problems.[10,12]

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Several studies on paediatric ARV treatment programmes in middle- and low-income countries have documented favourable responses to HAART.[13-16] At Red Cross War Memorial Children's Hospital (RCH) a donor-funded ARV treatment programme for children was started in August 2002. Initial experience of this programme was reported on in 2004.[17] Between February and November 2004, after the Western Cape province of South Africa began providing HAART to public sector patients, the donor-funded programme was fully integrated with the provincial programme. At the end of March 2006 RCH was therefore one of 37 accredited public sector institutions in the Western Cape managing children on HAART. At the time, 16 300 patients were receiving HAART in the province of whom 2009 (12.3%) were children. In this report we describe the response of children during their first year on HAART at our institution.

Methods

This retrospective study describes a public sector ARV treatment programme for HIV-infected children. The study took place at Red Cross War Memorial Children's Hospital, a tertiary referral hospital affiliated to the University of Cape Town. All children who started treatment between 1 August 2002 and 1 December 2004 were included. The study documented the outcomes of children during their first year on HAART. The Research Ethics Committee of the University of Cape Town approved the study.

Children were selected to start HAART according to established clinical and immunological criteria. The first 122 children were enrolled according to criteria derived from the Paediatric European Network for the Treatment of AIDS (PENTA) recommendations. Briefly, children with Centers for Disease Control (CDC) clinical category C or immune category 3 disease and those with CDC clinical category B disease plus a low CD4 percentage (< 20% if < 12 months old or < 15% if > 12 months old) qualified for treatment and were considered for enrolment.[18] The remaining 287 children were enrolled according to criteria derived from the WHO's 2003 recommendations for children. Children with modified WHO clinical stage 2 or 3 disease *or* a low CD4 percentage irrespective of disease stage (< 20% if < 18 months old or < 15% if > 18 months old) qualified for HAART.[19] In addition to the clinical and/or immunological criteria all children were required to have an identifiable caregiver who could take responsibility for the administration of the medication.

Triple combination ARV therapy comprising of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) was administered according to conventional paediatric dosing recommendations.[20] The choice of individual drugs was determined by funding constraints, availability of home refrigeration required to store temperature-sensitive drug formulations, and previous exposure to perinatal nevirapine. Children who had been exposed to perinatal nevirapine were given a PI-based regimen in keeping with the national treatment guidelines of South Africa.[21] The monitoring plan included monthly clinical assessments for the first 6 months of therapy and thereafter mostly 3-monthly reviews, baseline and 6-monthly CD4 counts and viral loads (due to financial constraints, the viral load at 6 months was omitted in the first 122 children unless they were enrolled in parallel research studies), and regular biochemical and haematological evaluations.

For the purpose of this analysis, all children were retrospectively re-staged at the time of starting HAART according to the latest WHO 4-stage clinical classification and the CDC immunological staging system.[22,23] Weight-for-age, height-for-age and weight-for-height z-scores were calculated using EpiInfo 2000, version 1.0, Division of Surveillance and Epidemiology, CDC, Atlanta, Georgia. Moderate underweight, stunting and wasting were defined as weight-for-age z-score (WAZ) < -2, height-for-age z-score (HAZ) < -2 and weight-for-height z-score (WHZ) < -2 respectively. Severe underweight, stunting and wasting were defined as WAZ < -3, HAZ < -3 and WHZ < -3 respectively.[24] Data were analysed using Stata version 8.0, College Station, Texas, USA and StatsDirect software, version 2.5.5, 2006, Cheshire, UK. The probability of survival was determined using Kaplan-Meier analysis and log-rank tests were used to compare survival times between strata. The Cox proportional hazards model was used for multivariate analysis. Patient characteristics found to be associated with mortality ($p < 0.1$) on univariate analysis were included in the multivariate model, and removed by a backward selection procedure if $p > 0.05$. Separate models were estimated for all children, and on the subset on whom initial viral load was measured. The regimen variable (PI v. NNRTI) was then added to both models to assess whether regimen was independently associated with survival. The Wilcoxon signed ranks test was used to compare continuous data. The chi-square test was used to compare categorical data. A p-value of < 0.05 was regarded as statistically significant.

Results

By the end of December 2004, 409 children had been enrolled on the ARV treatment programme. The median age (interquartile range) at enrolment was 23 months (8.9, 54.6), 207/409 (50.6%) were less than 24 months old and the female-to-male ratio was 182:227. Baseline clinical staging was available for 407 children: 3 (0.7%) had WHO stage 2 disease, 149 (36.6%) WHO stage 3 disease and 255 (62.7%) WHO stage 4 or advanced clinical disease. CD4 percentages and/or absolute counts were available for 406 children at the start of ARV therapy. The median CD4 percentage (interquartile range) was 11.7% (7, 17.3), 266/402 (66.2%) had a CD4 percentage < 15%

and 41/402 (10.2%) had a CD4 percentage ≥ 15%. According to the CDC classification 18/406 (4.4%) had no immune suppression (immune category 1), 77/406 (19%) moderate immune suppression (immune category 2) and 311/406 (76.6%) severe immune suppression (immune category 3). At baseline the median viral load (interquartile range) was 380 000 copies/ml (140 000, 1 292 000), and 111/367 (30.2%) had an initial viral load > 1 million copies/ml. The nutritional status of the children at the start of ARV therapy showed that 116/408 (28.4%) were moderately underweight, 116/408 (28.4%) severely underweight, 129/406 (31.8%) moderately stunted, 142/406 (35.2%) severely stunted, 55/390 (14.1%) moderately wasted and 26/390 (6.7%) severely wasted. The children were initiated on an ARV treatment regimen comprising two NRTIs plus either a PI (208/409 (50.9%)) or an NNRTI (201/409 (49.1%)).

After 1 year on ARV therapy, 269/409 (65.8%) were alive and continued to be managed at RCH, 46/409 (11.2%) had been transferred to another ARV treatment site for continuation of HAART, 63/409 (15.4%) had died, 19/409 (4.6%) were lost to follow-up and treatment had been discontinued in 12/409 (2.9%) because of sub-optimal adherence. The Kaplan-Meier survival estimate for all children (N = 407) at 1 year was 84% (95% confidence interval (CI) 80 - 87%). Survival for WHO clinical stage 2 (N = 3), stage 3 (N = 149) and stage 4 (N = 255) was 100%, 96% (95% CI 91 - 98%) and 77% (95% CI 71 - 82%) respectively (Fig. 1). On univariate analysis, survival was adversely affected in children with WHO stage 4 v. stage 2 and 3 disease (hazard ratio (HR): 6.19 (95% CI 2.67 - 14.36), p = 0.000), age < 12 months (HR: 2.81 (95% CI 1.71 - 4.61), p = 0.000), those with a viral load ≥ 1 million copies/ml (HR: 2.80 (95% CI 1.63 - 4.80, p = 0.000) and those on a PI regimen (HR: 3.84 (95% CI 2.12 - 6.96), p = 0.000). Survival was unaffected by gender, CDC immunological category, absolute CD4 count and CD4 percentage. On multivariate analysis of all children, after adjusting for WHO clinical stage and age, the absolute CD4 count did affect survival. In a separate multivariate model including only children on whom an initial viral load was done (N = 367), more severe WHO clinical stage, lower absolute CD4 count, viral load ≥ 1 million copies/ml and taking a PI-based regimen were independently associated with poorer survival; however, age was no longer a significant predictor of mortality (p = 0.119) (Table I).

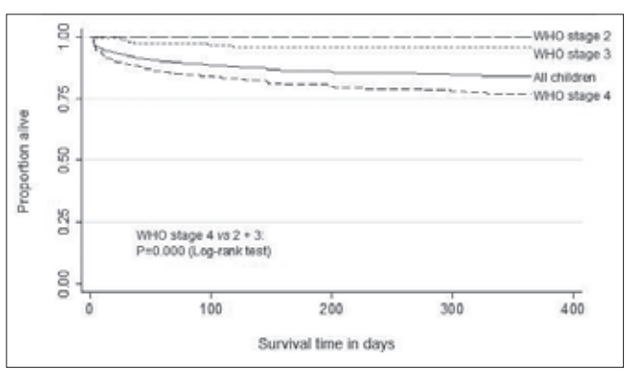

Fig. 1. Kaplan-Meier survival estimates by WHO clinical stage.

One-year viral load results were available for 264/269 children who continued their management at RCH throughout the first year on HAART. The proportion of these children with a viral load less than 400 copies/ml was 184/264 (69.7%). A further 26/264 (9.8%) had a viral load between 400 and 5 000 copies/ml. A more detailed analysis of the cohort after 1 year of HAART is presented in Table II. This analysis is confined to children with complete results at both baseline and 1 year, for each parameter evaluated.

Discussion

The treatment programme at RCH is an integral component of a complex network of primary, secondary and tertiary ARV treatment sites that was established by the HIV/AIDS Directorate of the Western Cape from March 2004 onwards to respond to the HIV epidemic among children in the province. Through donor funds several institutions, including RCH, began treating children before 2004 but all have since been incorporated into the provincial network.[17] Central to the provincial response to the paediatric epidemic is a successful perinatal prevention programme. The perinatal programme has undergone significant improvement in the last few years and could in the foreseeable future reduce the absolute perinatal transmission rate to less than 5%. This should decrease the paediatric HIV burden and ultimately lead to improved care for children with established infection. The development of treatment sites for children has generally lagged behind adult care. However, this problem has largely been corrected and at

Table I. Predictors of death in children receiving HAART

	Adjusted HR	95% CI	p-value
Cox-proportional hazards model for all children (N = 407)			
WHO stage 4	5.26	2.25 - 12.32	0.000
Age < 12 months	2.46	1.48 - 4.09	0.001
CD4 absolute count (per 100 cell increase)	0.93	0.88 - 0.98	0.013
Cox-proportional hazards model for children on whom initial viral load was measured (N = 367)			
WHO stage 4	3.84	1.45 - 10.20	0.007
CD4 absolute count (per 100 cell increase)	0.90	0.84 - 0.96	0.002
Viral load ≥ 1 million	1.84	1.03 - 3.29	0.041
PI-based regimen	2.25	1.10 - 4.61	0.026

Adjusted HR = adjusted hazard ratio; 95% CI = 95% confidence interval; PI = protease inhibitor.

Table II. Comparison of status at baseline and 1 year after commencing HAART

Parameter	Baseline	1 year	*p*-value
Median WAZ; IQR	-2.17; -3.09, -1.12	-0.93; -1.66, -0.13	0.000
Moderate underweight	76/266 (28.6%)	42/266 (15.8%)	0.000
Severe underweight	73/266 (27.4%)	9/266 (3.4%)	0.000
Median HAZ; IQR	-2.51; -3.41, -1.72	-1.92; -2.67, -1.14	0.000
Moderate stunting	89/264 (33.7%)	77/264 (29.2%)	0.3
Severe stunting	89/264 (33.7%)	46/264 (17.4%)	0.000
Median WHZ; IQR	-0.63; -1.77, 0.4	0.43; -0.37, 1.14	0.000
Moderate wasting	34/254 (13.4%)	3/254 (1.2%)	0.000
Severe wasting	18/254 (7.1%)	3/254 (1.2%)	0.000
Median CD4%; IQR	12.0; 7.2, 17.2	24.0; 18.74, 30.0	0.000
CD4% < 15%	173/261 (66.3%)	28/261 (10.7%)	0.000
CD4% ≥ 25%	26/261 (10.0%)	118/261 (45.2%)	0.000
Median log10 VL; IQR	5.54; 5.15, 6.08	2.6; 2.6, 3.27	0.000
VL > 10^6 copies/ml	69/241 (28.6%)	3/241 (1.2%)	0.000
VL < 400 copies/ml	0/241	168/241 (69.7%)	0.000

IQR = interquartile range; WAZ = weight-for-age z-score; HAZ = height-for-age z-score; WHZ = weight-for-height z-score; VL = viral load.

the end of March 2006, 37/43 (86%) ARV treatment sites in the province were treating children.[25]

This retrospective study addressed the effectiveness of HAART in a setting characterised by high unemployment and low rates of secondary school completion among caregivers.[26] As with many retrospective studies some of the data were not available for analysis. Furthermore, children were retrospectively restaged using the latest WHO clinical staging system and the CDC immunological staging system. While immunological classification is based on objective criteria, retrospective clinical staging is dependent on the quality and availability of the clinical records. The latest WHO staging guidelines include clinical case definitions for each staging criterion, which does improve the objectivity of staging.[22] Furthermore, the impact of HAART on the frequency and severity of infectious complications and on hospitalisation rates was not evaluated. Despite these limitations, we believe that the results of this study are an accurate reflection of the response to HAART at our institution.

Baseline characteristics described the clinical condition of the children at the time of starting HAART. Striking features were the high frequency of advanced, WHO clinical stage 4 disease (62.7%), advanced immune suppression (76.6%) and pervasive nutritional deficiencies. The median age of 23 months, the high proportion of children below 2 years of age and the adverse survival associated with an age of less than 1 year reflect the high burden of severe disease among young children treated at our institution. These findings are consistent with natural history studies of paediatric HIV infection in Africa that have reported mortality rates in excess of 50% by the age of 2 years.[27] In contrast, previous publications on paediatric ARV treatment programmes from low- and middle-income countries have documented limited experience with treating children less than 2 years of age.[13,15,16] Treating young infected children may be particularly challenging as they often have complex medical problems, the state of knowledge of the use of ARVs in the very young is incomplete and obtaining blood samples for monitoring may be technically challenging. For these reasons health professionals have generally been reluctant to treat young children with HIV infection.[28] Special attention is needed to ensure that health institutions in resource-limited settings are adequately capacitated to address the medical needs of this vulnerable group.

Given the severity of the clinical and immunological status of the children at baseline and the high proportion of young children in the programme, the overall estimated survival after 1 year of 84% (95% CI 80 - 87%) was reasonable. The probability of survival on HAART after 1 year in a study conducted in Côte d'Ivoire was 91% (95% CI 82.1 - 95.6%). In that study 107 children were enrolled, hence the wider 95% confidence interval, the median age at enrolment was 7.2 years, which was higher than in our study, and severe clinical disease was present in only 12.8%, suggesting that children enrolled in that study were relatively less ill at the start of HAART.[13] The marked, but expected, predictable pattern of decline in 1-year survival between children with WHO stage 2 and 3 disease (96% (95% CI 91 - 98%)) compared with those with WHO stage 4 disease (77% (95% CI 71 - 82%)) and the adverse effect of viral load ≥ 1 million on survival in our study suggests that the high proportion of children enrolled with severe disease adversely affected overall survival rates. While the Côte d'Ivoire study showed significantly lower survival in children with a CD4 percentage < 5%, interestingly in our study survival was not associated with CD4 percent or CDC immunological category.[13] However, on multivariate analysis higher absolute CD4 counts were independently associated with improved survival, with a 7% (95% CI 2 - 12%) reduction in mortality for every 100-cell increase in CD4 count. In the present study, univariate

analysis and the multivariate model on all children suggest that children under 1 year of age experience adverse survival. However, the separate multivariate model in children in whom an initial viral load was measured showed that after adjusting for viral load, age does not affect survival. This suggests that poorer survival in very young children is due to their more severe disease rather than their age *per se*. While univariate analysis and the multivariate submodel including viral load showed greater mortality in children receiving a PI-based regimen, this was not confirmed in the main multivariate model for all children in the study. The apparent adverse effect of a PI-based regimen may therefore largely be due to preferential administration of PIs to younger children who tended to have more severe disease. Alternatively, regimen and age were co-linear variables, which may explain why age was excluded and replaced with regimen in the multivariate submodel analysis.

Table II summarises the effect of 1 year of HAART on growth, immune reconstitution and viral replication in children for whom complete data existed. Notably, of 264 children who remained on HAART at RCH 69.7% had a viral load below 400 copies/ml. This result is consistent with published efficacy studies where the percentage of children with viral loads < 400 copies/ml varied between 63% and 87%.[29] The future management of the 30.3% of children with detectable viral loads is of concern. Current national treatment guidelines have made provision for two rounds of ARV therapy. Beyond second-line therapy there is no specific recommendation for the provision of salvage regimens.[21] This particular issue has to be confronted in South Africa and other middle-income countries where resources exist to manage patients beyond second-line therapy and where a sizeable proportion of children are likely to fail second-line therapy in the near future.

After 1 year on HAART, 11.3% of the children had been transferred to another ARV treatment site for ongoing care. Most were referred to their local community clinics in the greater Cape Town region. This development represents another important component of the provincial paediatric programme, namely the provision of treatment for infected children at the most appropriate level within the health care system. Referral of clinically stable children on HAART to community institutions accompanied by the transfer of appropriate paediatric clinical skills is a necessary strategy in countries with high HIV prevalence rates. This approach will alleviate the congestion experienced at referral hospitals, allowing them to address the more technically challenging aspects of the disease, including children with complex pathology, serious infectious complications, adverse events including immune reconstitution inflammatory syndrome, and many of the younger children. The success of this initiative, which has gained momentum over the last year, is best illustrated with the official provincial statistics. At the end of March 2004, 78.4% (537/685) of all children treated with HAART in the province were managed at the three paediatric referral hospitals in Cape Town namely RCH, Groote Schuur Hospital and Tygerberg Hospital.[30] At the end of March 2006, this figure had declined to 49.5% (995/2009) of the total number of children on treatment.[25] Furthermore, the referral hospitals in Cape Town have been actively involved in developing the clinical capacities of health professionals at community institutions and providing telephonic and on-site consultation support to these institutions.

In conclusion, while this study has demonstrated that HAART is able to improve the health of many HIV-infected children with advanced disease, including those less than 2 years of age in a middle-income country, it has generated concern about treatment beyond second-line therapy.

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Determining the prevalence of malnutrition in hospitalised paediatric patients

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Aim. To determine the prevalence of malnutrition in hospitalised paediatric patients at Red Cross War Memorial Children's Hospital.

Method. A 1-day cross-sectional survey was completed in all medical and surgical wards and some specialist outpatient clinics.

Results. A total of 227 children participated in the study. Thirty-five per cent of patients were moderately malnourished (≤ -2 z-score), of whom 70% had no road to health card with them. Thirty-four per cent of children under 60 months of age received supplements in addition to a normal ward diet, 7.8% were enterally fed and less than 1% were parenterally fed. Almost 14% of children were found to be overweight/obese, which is higher than the national average of 6%. The prevalence of HIV infection on the day of the audit was 18% across all age groups compared with the Western Cape antenatal prevalence of 15.7% (2005).

Conclusion. The overall prevalence of undernutrition was 34%, which is comparable with similar studies. However, the proportion of overweight children (14%) was greater than the national average. In view of the level of malnutrition seen, a nutrition risk-screening tool, identifying risk factors for malnutrition such as food access and vulnerability, should be developed. The tool should be used to assess nutrition status and risk during the course of hospitalisation, in addition to planning appropriate nutrition care plan interventions for discharge.

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Over the last 20 years studies focusing on malnutrition have helped to define the benefits of nutrition intervention. Malnutrition remains a widespread and largely unrecognised problem.[1-2]

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Malnutrition may be defined as a nutrition disorder resulting from reduced nutrient intake or impaired metabolism. There is currently no 'gold standard' or single measure of malnutrition.[3]

Malnutrition impacts on the length of hospital stay (LOS), cost of stay, morbidity, mortality, infectious complications and quality of life, and deprives the patient of participating in usual family or social dynamics.[4]

Malnutrition is associated with children who are going through periods of rapid growth. Surveys of hospitalised patients in developed and developing countries have found a prevalence of 35 - 60% of patients nutritionally at risk with a further 25% of patients documented as having overnutrition.[1,2,5]

It has been argued by some that increased hospital stay may not be a result of malnutrition but rather underlying pathology.[6] Despite improvements in nutritional therapy, in

some hospitalised paediatric groups many of the strategies remain ineffective in dealing with malnutrition and/or identifying it timeously.[7]

Growth failure and malnutrition are commonly seen in children with HIV, and are recognised as poor prognostic factors for short-term survival in addition to being sensitive markers for disease progression.[8]

Aim

The aim of this study was to determine the prevalence of malnutrition of children at Red Cross War Memorial Children's Hospital via a 1-day cross-sectional survey.

Methods

The 1-day cross-sectional survey was undertaken in September 2005 at Red Cross War Memorial Children's Hospital. It included patients in all medical and surgical wards and in some specialist outpatient clinics. Ethical approval was obtained from the Ethics Committee, University of Cape Town.

Dietitians were responsible for collecting anthropometric, biochemical, clinical and dietary information using a standardised proforma.

Results

Two hundred and twenty-seven children were surveyed, of whom 52% were male, and 44% (N = 90) were less than 1 year of age. The LOS varied from < 24 hours to 295 days, with the overall average being 19.4 days (standard deviation (SD) 36.7).

Table I indicates a comparison between the prevalence of malnutrition in a survey completed in 1999 versus the current 2005 survey. Although the trends in respect of moderate to severe malnutrition with regard to height-for-age z-scores (HAZ) and weight-for-height z-scores (WHZ) are similar (28% v. 34% (HAZ) and 19% (WHZ)), there is a trend towards increasing prevalence of malnutrition.

Eighty per cent (80%) of malnourished children (≤ -2 z-scores) had an albumin level of < 35 g/l. No correlation could be found between haemoglobin (Hb) and malnutrition. On average those with an Hb of > 10 g/l had a WHZ of -1.6 z-scores.

Thirty-four per cent of children between the ages of 13 and 60 months received nutrition supplementation, 7.8% were enterally fed and < 1% were parenterally fed. According to the national surveillance figures from the Department of Health 7% of all infants are exclusively breastfed; the incidence of exclusive breastfeeding on the day of the audit was 12%.

Of particular interest is the double disease burden (Table I) evident among the population surveyed. While the national average for overweight/obesity ≥ +2 z-scores is 7.6%, the average of ≥ +2 z found among the participants at Red Cross War Memorial Children's Hospital was as high as 13.5%. The concern regarding this trend is the early rebound adiposity seen in the 13 - 60-month age group.

Discussion

In order to promote good nutrition status it is essential to develop and implement nutrition guidelines and support algorithms to assist with early appropriate interventions, which should ideally be planned by a dietitian.[6] A nutrition risk-screening tool may determine the extent of malnutrition within a population and is associated with a decrease in LOS, morbidity and mortality and improved nutrition status.[3,9]

The results from this survey mirror findings by other centres with regard to malnutrition and LOS. However, limitations of the study should be noted, e.g. that it was only a 1-day sample, conducted during springtime. The overall prevalence of malnutrition in the population surveyed at Red Cross War

Table I. Over- and undernutrition

Prevalence of moderate malnutrition > -2 z-scores	< 12 months	13 - 60 months	> 60 months	1999 survey Waterlow criteria
WAZ	40% (N = 39)	27% (N = 17)	29% (N = 22)	
HAZ	33.5% (N = 35)	31% (N = 20)	31% (N = 19)	28%
WHZ	27% (N = 27)	21% (N = 13)	14% (N = 19)	19%
WHZ ≥- 2 Z scores & LOS	> 7 days p = 0.0093 (95% CI = 1.17 - 3.4)			
Overall	34%	32%	19%	
Prevalence of overweight/obesity ≥ +2 z-scores	< 12 months	13 - 60 months	All ages	
WAZ	13.5% (N = 13)	11% (N = 7)	6.6% (N = 20)	
WHZ	9% (N = 7)	9.5% (N = 6)	7% (N = 16)	

WAZ = weight-for-age z-score; HAZ = height-for- age z-score; WHZ = weight-for-height z-score; LOS = length of hospital stay.

Memorial Children's Hospital was 34% (including weight for age). Twenty per cent (20%) were wasted (weight for height) and 34% were stunted (height for age), compared with the national average of 10% wasting and 22% stunting respectively.[10]

Despite an active dietetic department in addition to each ward having a dedicated dietitian, the prevalence of malnutrition is still unacceptably high, with no discernable improvement over the last 7 years. Confounding factors such as HIV/AIDS obviously play a role in the increasing disease burden. But can all findings be related to an increase in disease prevalence or are our strategies at treating malnutrition becoming less effective, especially as many of the HIV-infected children are receiving antiretrovirals?

The HIV prevalence rate on the day of the study was 18% among all age groups, compared with the Western Cape antenatal prevalence of 15.7% (2005).[11] While this figure may contribute to the prevalence of malnutrition seen among our population group, it does not entirely explain the continued high incidence recorded. This would suggest that other factors are contributing to the high prevalence of malnutrition, such as issues surrounding food security and vulnerability.

The Integrated Nutrition Programme has a targeted Nutrition Supplementation Programme (NSP) indicated for growth-faltering children. The programme is successful in providing nutrition products targeted at the individual for a period of 6 months. The NSP is currently unable to tackle issues around food security and vulnerability, so while disease-related malnutrition may be successfully treated in a few, malnutrition as a result of socio-economic causes is unlikely to result in successfully rehabilitated patients unless socio-economic issues are addressed.

The results from this survey also indicate the evidence of a double disease burden among the population surveyed. The national average for overweight/obesity ≥ +2 z-scores is 7.6%. The average found among the survey participants was as high as 13.5%. Most of this was seen in children under the age of 5 years indicating that they had experienced early rebound adiposity. Early rebound adiposity is associated with an increased risk of chronic diseases of lifestyle later in life. While it is outside of the scope of this audit to link those patients to disease profiles, it raises the question regarding the practice of aggressive 'catch-up growth' past the age of 2 years and whether or not we should be recommending concurrent linear growth in addition to weight gain alone.[12]

To date effective ways of treating malnutrition in this patient population group have remained elusive. Perhaps it is time to question strategies around malnutrition and nutrition supplementation in relation to food security and vulnerability to accommodate a sustainable access to food in vulnerable households.

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