

Chapter 7: Caring for children with HIV

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Caring for children with HIV: a personal perspective

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The care of HIV positive patients has undergone significant changes in the past 10 to 15 years. It is very likely to continue to improve over the next 10 years with better understanding of the immunology of the HIV virus, more efficient treatment and reduced pill burden due to new combination therapies.

I came across my first HIV positive children in 1996 during my work as a junior doctor in the Infectious Unit in Great Ormond Street Hospital in London. Highly active antiretroviral treatment (HAART) had been introduced and increasingly more children were treated with this regime. The benefit of HAART was still unknown then and care was primarily provided during inpatient stays. My memory of that time was seeing sick children, malnourished with AIDS defining illnesses, who seemed to be hospitalised for several weeks. It is now well recognised that the introduction of HAART together with a multidisciplinary approach had a major impact on improving survival of HIV infected children. At present their care is mainly delivered on an outpatient basis, as with other chronic diseases, and the hospital admission rate has decreased 3.5 fold from 1996 to 2001.

The next milestone was the introduction of universal antenatal HIV Testing in the late 1990s, which was first introduced in high prevalence areas, such as London and Edinburgh (about 15 HIV infected women per 10,000 pregnancies). Initially this test was voluntary ("opt in") and uptake was as low as 50% or less. In 2001 an "opt out" approach was introduced to improve uptake. During their antenatal care women were automatically tested for HIV following appropriate counselling. This has led to the national target of 90% uptake being reached in most areas within the UK. This improved approach of preventing mother to child transmission (MTCT) has led to a significant reduction of the spread of HIV in the UK. HIV positive families now have the choice to have children in the knowledge that the risk of HIV transmission to their newborn baby can be significantly reduced from 25% to as low as less than 2%. Preventing MTCT of HIV has become the success story in HIV care. It represents a very efficient and cost effective method of preventing the transmission of a life shortening infection, which would require life-long, expensive treatment.

Since my appointment as a Consultant Paediatrician in Manchester (in post since February 2003) I have been the Lead in Paediatric HIV for Greater Manchester and since 2005 I have been Clinical Lead of the Perinatal and Paediatric HIV Network in the North West. Manchester has the second biggest Paediatric HIV centre in the UK outside of London. We have introduced a weekly family centred clinic which consists of: one Paediatric and two adult Infectious Disease Consultants; two middle grade doctors from each specialty; two specialist nurses; one visiting paediatric specialist nurse; and a social worker from Barnardo's. A detailed business plan has been submitted to expand the service further to provide a holistic care for the increasing numbers of HIV infected families in the next 5 to 10 years.

The future challenges for both clinicians and politicians alike with an interest in HIV is to tackle the global burden of HIV in developing countries, particularly in sub-Saharan Africa, the unchanged mortality rates of infants with HIV despite the introduction of HAART, and lastly the overwhelming negative stigma and prejudice of HIV in society.

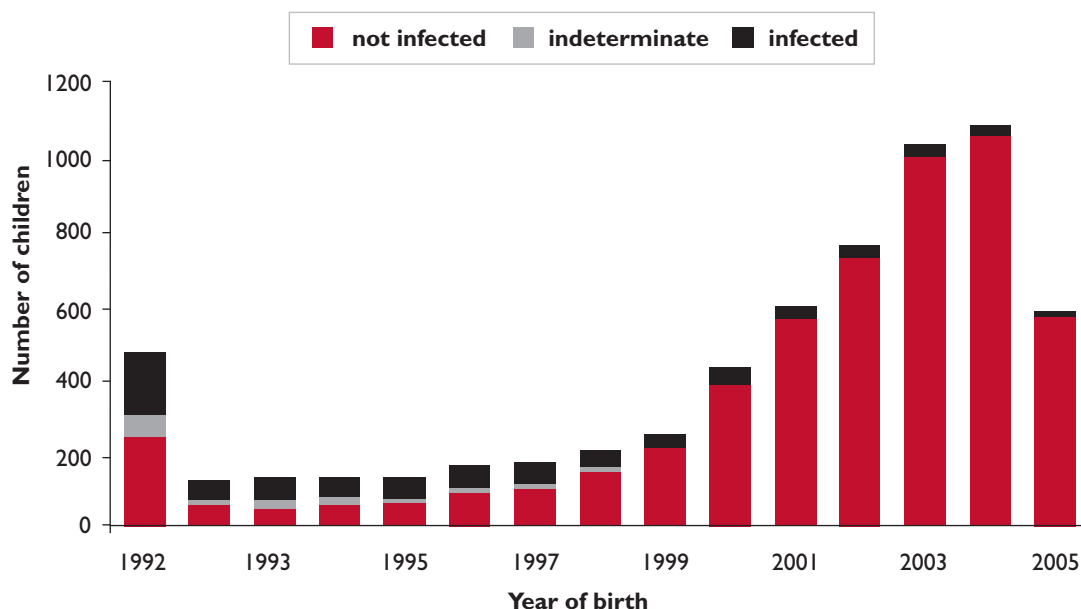
Introduction

Worldwide, around 1,500 children are born with HIV every day, with newly infected children representing 14% of all new infections¹. Nearly 87% of children with the diagnosis of HIV or AIDS worldwide reside in sub-Saharan Africa, where extreme poverty and the lack of health care combine to make their outlook extremely bleak. Less directly, there is also a profound impact of AIDS on children left as orphans when one or both of their parents have died of AIDS. There were an estimated 9.1million double orphans (children who have lost both parents) in sub-Saharan Africa in 2005; in almost 60% of cases, AIDS was the cause of death of at least one of the parents¹.

In developed countries, such as the UK, screening of pregnant women and appropriate treatment for those found to be HIV positive has dramatically reduced the number of children with HIV. In the UK, the key to success has been the introduction of universal antenatal screening of pregnant women in 2000. In 1999 the Department of Health set the targets that by the end of 2002 screening uptake should be at least 90%, with the aim that 80% of the detected women would be offered treatment². Units in the UK achieved the target by introducing a policy of offering HIV testing as an integral part of the antenatal blood testing at booking and offered women the choice to decline the test. This has led to an increase in the number of diagnoses of HIV among pregnant women, but a decrease in the proportion of infants who go on to become infected with HIV, as shown in **figure 7.1**. No increased risk to the child has been found from taking highly active antiretroviral therapy (HAART) during pregnancy³. However, one study has documented an increased risk of foetal abnormality if taking HAART in conjunction with folate antagonists, commonly prescribed for PCP prophylaxis⁴.

Figure 7.1: Number of children born to HIV positive women in UK & Ireland, by likely HIV status

Early cases who were indeterminate have been lost to follow-up. The number is lower for 2005 because data are to September only. Source: National Study of HIV in Pregnancy and Childhood⁵



The successful reduction in the number of babies acquiring HIV from their mothers in the UK has meant that in recent years the majority of new cases of HIV in children are infected abroad, usually from African countries. In the North West in 2005, eight of the total of 11 new cases of children infected from their mothers were infected in African countries⁶.

HAART has been shown to be effective at preventing progression of HIV disease and death from AIDS in children, both in western countries⁷ and in Africa⁸. The UK has seen a drop in crude mortality from 9.3 to 2.0 per 100 child years at risk⁹. Correspondingly, there has been a 26% decline in hospital admissions between 1996 and 2002, and over the same time period the proportion of child time on triple or more therapy increased from 1% to 69%⁹. Indication to commence antiretroviral treatment in children is summarized in the Paediatric European Network of AIDS (PENTA) Guideline 2004¹⁰. In short, treatment is considered depending on severity of symptoms, the compromise to the immune system or the child's development and the child's age. As for adults, the longer survival of children means that problems of drug resistance and antiretroviral therapy (ART) toxicity are more likely. Management of children with HIV therefore focuses on effective use of HAART to minimise these two effects.

There are often limited data to guide the dosage of HAART to children^{11,12}. Drug doses are calculated by extrapolating adult doses for the appropriate surface area (using weight and height measurements). Drug doses need continual modification as children grow, or treatment may be less effective and risk of drug resistant HIV

increases. Data from the collaborative HIV paediatric study (CHIPS) suggest that between 1997 and 2005 significant under dosing of children took place, half of which was as a result of failure to modify doses as children gained in height and weight, or because of rounding down dosage calculations¹¹. Some under dosing was found to be a result of drug toxicity. The authors blamed delays in new dosage information being incorporated into practice, and conflicting guidelines on calculating dose leading to inconsistent dosing. Children have similar side effects to adults taking HAART, for example, development of lipodystrophy syndrome and associated adverse metabolic changes¹⁰. Several studies show increases in low-density lipoprotein (the form of lipoprotein associated with cardiovascular disease) in children on HAART¹³. However, one cohort study also found increases in the protective high-density lipoprotein¹⁴.

In the North West, the number of children (aged under 15) has increased from 14 in 1996¹⁵ to 64 in 2005⁶. In 2005, children were seen in eight centres across the North West. Two thirds of children in 2005 were seen in a joint clinic run by North Manchester General Infectious Disease Unit and Booth Hall Children's hospital (43 children)⁶. A quarter of the children were seen in Alder Hey Children's Hospital (15), and a small number were seen in paediatric departments of other hospitals, as well as adult GUM services. The aim of this chapter is to examine trends in treatment and care of HIV positive children in the North West of England over the last ten years, in order to explore relationships between age and clinical and treatment variables, to identify predictors of disease progression and admission to hospital and to predict future caseload of HIV positive children in the North West.

Methods

Initial exploration of relationships between age and clinical and treatment variables

Initial exploration was carried out on the 2005 dataset, using all individuals (adults and children) to explore how hospital use (number of clinic visits and number of overnight stays in hospital), the proportion of individuals on ART and levels of clinical markers differed between adults and children. The clinical markers used were CD4 count, which measures the status of the immune system (with low counts suggesting more damage to the immune system), and viral load, which measures the quantity of virus in the blood (see chapter 5 for more details of CD4 counts and viral loads).

Analysis of all children since 1996

For the purposes of this analysis, children are defined as those aged 16 years and under. There are relatively few children in total with HIV (71 children were seen in the North West in 2005). Therefore, to create a dataset for analysis, ten years' data on children were accumulated. Data on all children, and their age at the end of that year, were extracted. Individuals are represented in the dataset for each year that they attended services. This gave a dataset of 340 records from 94 individuals, of whom, 18 were represented six or more times, 53 were represented two to five times, and the remaining 23 were represented once. The health status, treatment and use of hospital services in each year were also extracted. Because the dataset included records of children born before 1996, and therefore potentially had a lower chance of benefiting from ART from birth, the individuals were coded as either being in a pre 1996 birth cohort or a 1996 and later cohort. CD4 count and viral load was compared by age and cohort (using Mann Whitney U tests), and logistic regression and chi square tests were used to find which demographic and clinical variables were related to requiring a stay in hospital of at least one night (see the glossary for explanations of statistical and technical terms).

Longitudinal analysis to predict disease progression

Finally, to investigate changes in health status at an individual level, the 96 individuals were coded as to whether or not they had progressed in the severity of their disease (e.g. changed from asymptomatic to symptomatic). Viral load and CD4 counts were compared between the two cohorts (Mann Whitney U tests). Individuals were also coded as to whether or not their lowest CD4 count ever was more than 10 cells/mm³ lower than their highest ever CD4 count, and whether the difference between their highest and lowest ever viral load was greater than 100 copies/ml. Then, disease progression was predicted from the demographic factors (sex, ethnicity and cohort) and clinical factors (change in CD4 count and viral load) using backwards stepwise logistic regression.

Future caseload of HIV positive children

The total number of children presenting to services for each year since HIV monitoring began were fitted to a number of models to make predictions as to the caseload of HIV positive children in the North West for future years. The same methodology used in chapter 2 was used on these paediatric data. For this section of the analysis, a cut off age of 14 years or younger was used for comparison with the age bandings used in previous and future annual HIV reports.

Results

Initial exploration of relationships between age and clinical and treatment variables

Figure 7.2 shows the relationship between clinical and treatment variables with age, using the entire 2005 dataset (children and adults). It reveals the expected relationship between CD4 count and age, with the youngest children having the highest average CD4 counts (those aged under 4 years had an average count of 781 cells/mm³). Figure 7.2 also shows that the CD4 count was much more variable in children compared to adults. Adults had a mean count of around 400 cells/mm³.

Figure 7.2: Relationship between CD4 count and age (all people accessing services, 2005)
Bars are 95% confidence intervals

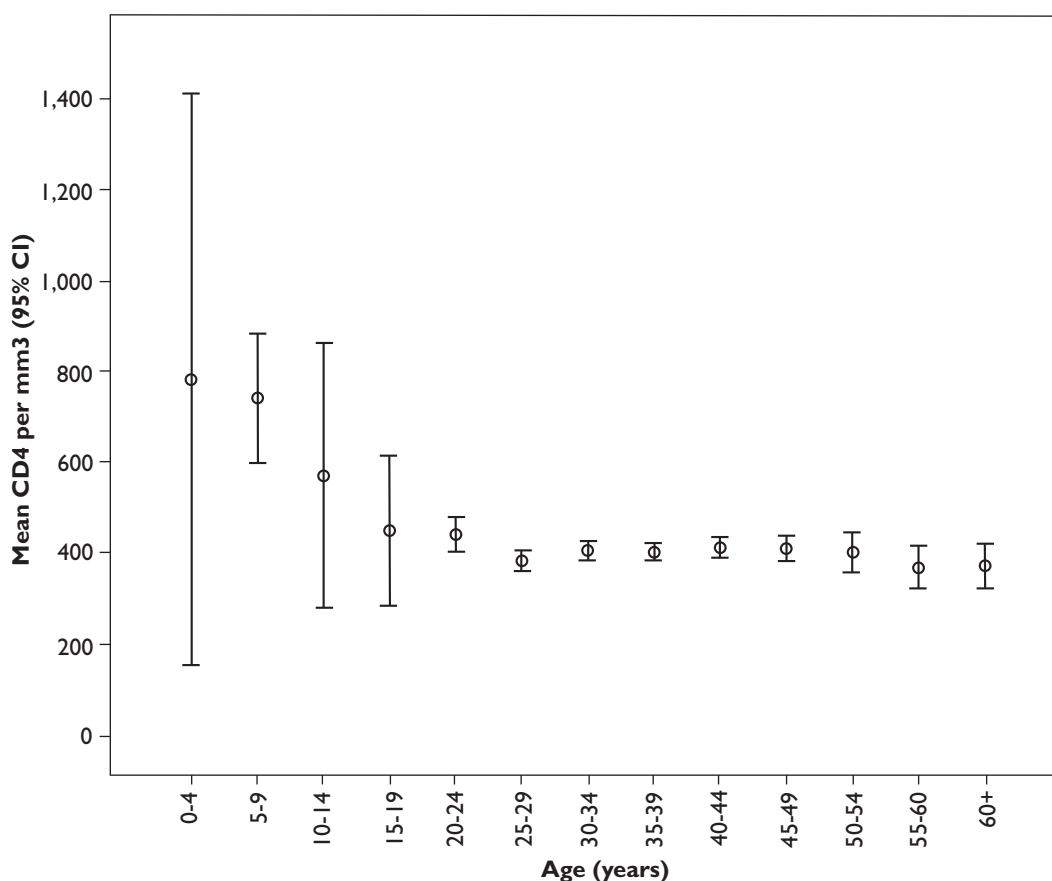


Figure 7.3 illustrates that viral load in children is generally lower than that in adults at under 50,000 copies/ml. There is a high mean viral load (but a lot of variability) in young adults aged 20 to 24 years. **Figure 7.4** shows the relationship between taking ART and age. Whilst approximately 60% of the youngest age category (0 to 4 years) were taking ART, this rose to nearly all those in the 10 to 14 year category. There are fewer individuals taking ART in the young adult age categories, with fewer than 40% on HAART in the 20 to 24 year age group.

Figure 7.3: Relationship between viral load and age (all people accessing services, 2005)
 Bars are 95% confidence intervals

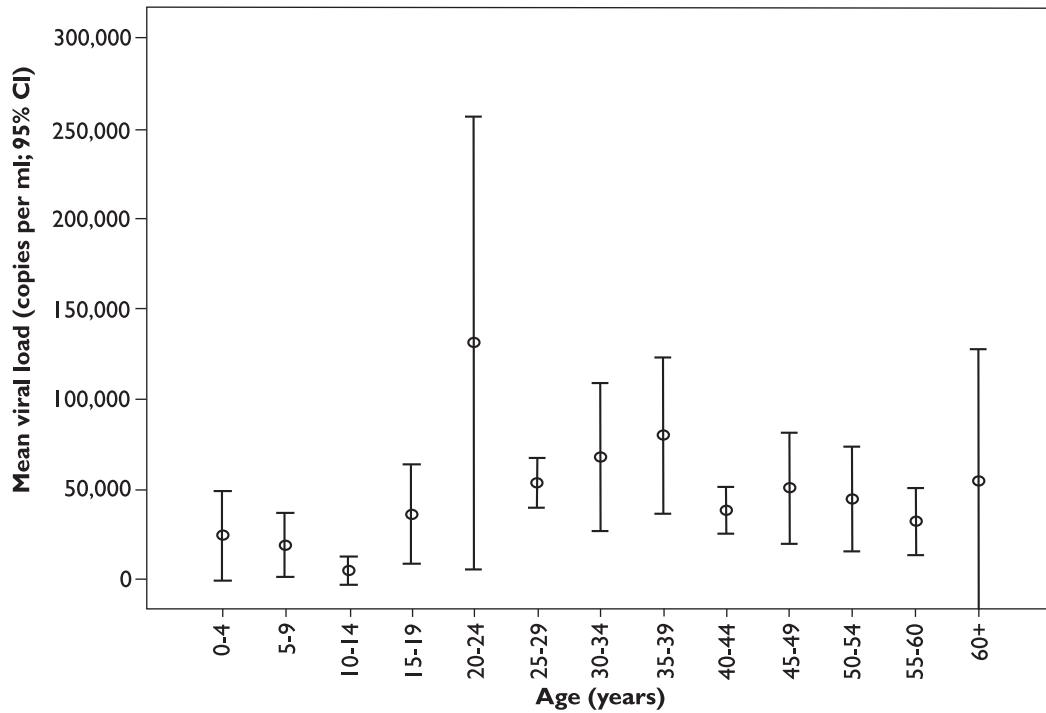
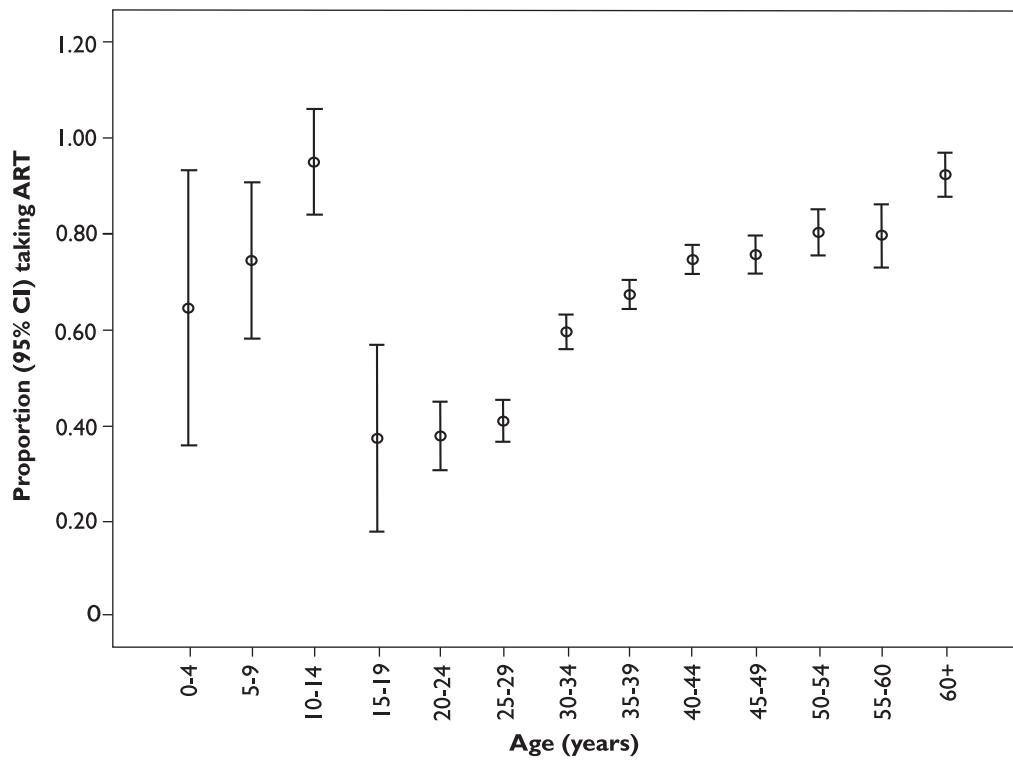


Figure 7.4: Relationship between the proportion of individuals taking ART and age (all people accessing services, 2005)
 Bars are 95% confidence intervals



Analysis of all children since 1996

Figure 7.5 shows the greater breakdown of the relationship between CD4 count and age that was possible using the dataset of all children at all ages who have presented to treatment since 1996 (340 records). CD4 count declined with age, with those aged two years or younger having had an average count of nearly 1,000 cells/mm³, while those aged 15 years or older had counts of nearly half that, at just over 500 cells/mm³.

Because children born in 1996 or later may have benefited at an earlier age from ART, the dataset was split into those born in 1995 or earlier and were compared to the later birth cohort. The later cohort comprises children up to the age of nine years, while the early cohort is represented by children of all ages. **Figure 7.6** shows the relationship between age and CD4 count by cohort. The earlier cohort in general had a lower CD4 count. The difference was significant even after excluding those in the older cohort aged nine years or more (to make the cohorts more comparable, since this age range was not represented in the more recent cohort) (Mann Whitney U test: Z=2.5, P=0.013). There was no such difference in viral loads (Z=0.8, P=0.406).

The two cohorts were compared in terms of the likelihood of requiring a stay in hospital of at least one night. While 26% of the records from the more recent cohort documented a stay in hospital, only 8% of the records from the earlier cohort when at the equivalent age did so (Chi square=10.3, df=1, P=0.001; excluding records of the older cohort when they were aged nine years or more). However, further inspection of the data revealed that the highest inpatient attendance rates are found in the youngest children, a group under represented in the earlier (pre 1996) cohort. **Table 7.1** takes into account age and cohort, and shows that older children in the earlier cohort are less likely to stay in hospital compared to a reference category of those in the later cohort aged three years or under. Age and cohort was a stronger predictor of requiring a hospital stay than was severity of HIV disease, CD4 count or viral load. Those taking ART were also more likely to have been admitted to hospital.

Figure 7.7 shows that in the older cohort taking anti-HIV therapy was most common in children aged 9 to 14 years, while the proportion taking therapy in the younger cohort peaked at a younger age, at 6 to 8 years old.

Figure 7.5: Relationship between children’s age and CD4 count (all children at all ages, 1996 to 2005)
Bars are 95% confidence intervals

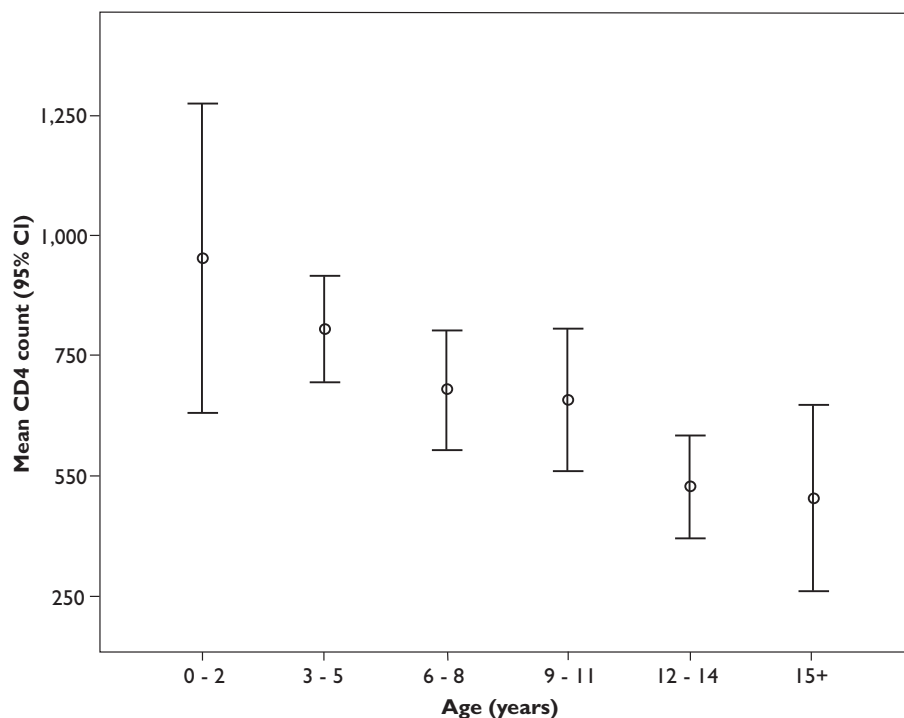


Figure 7.6: Relationship between age and CD4 count, by cohort

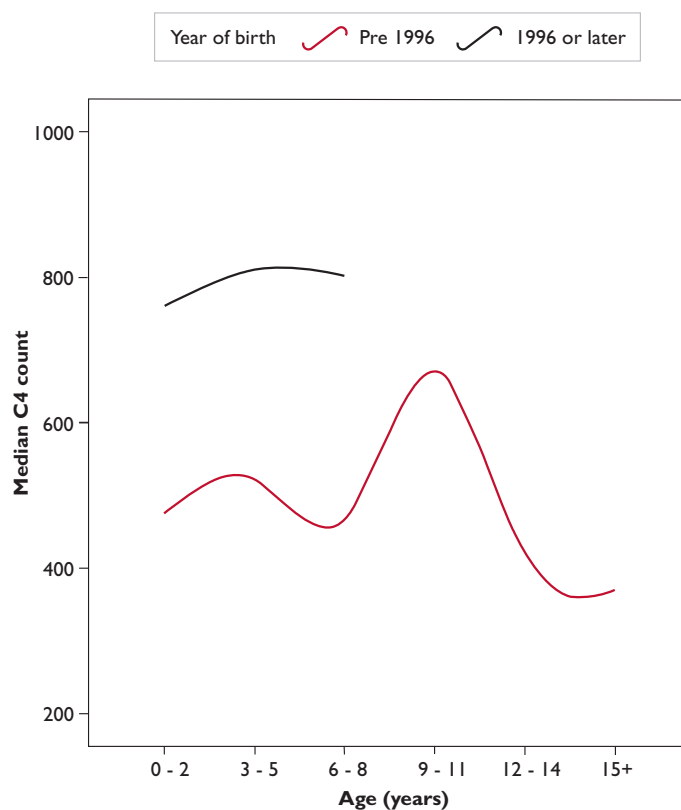
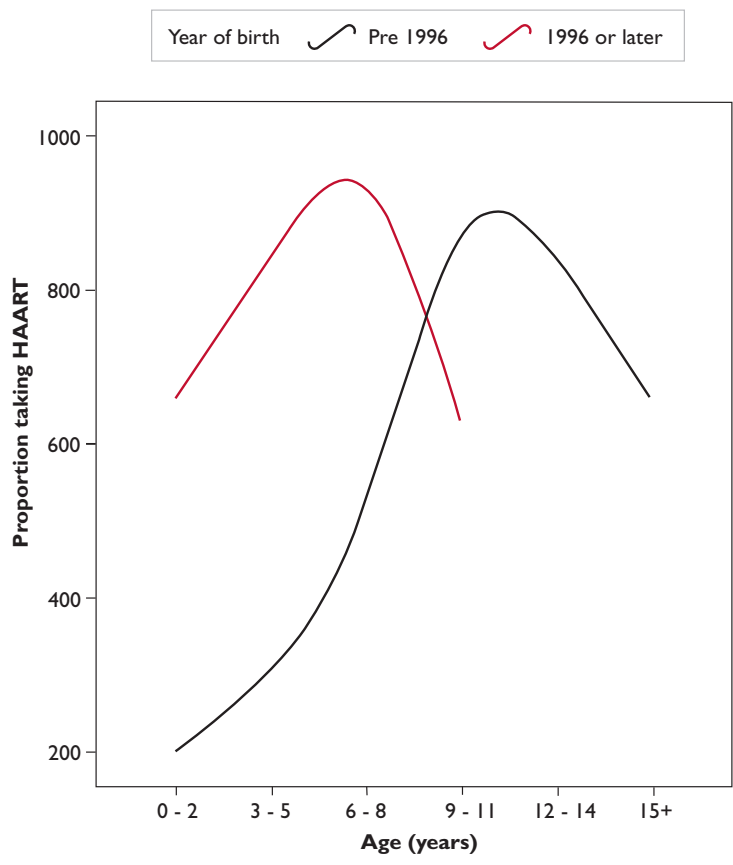


Table 7.1: Numbers, percentages and odds ratios for admission to hospital, by demographic and clinical variables (all children at all ages, 1996 to 2005)

	n	Univariate			Multivariate		
		Number (%)	Chi	df	P	Adj OR (95% CI)	P
Cohort/age			23	5	<0.001		0.002
Pre 96, age <7 years	6	1 (16.7%)				0.440 (0.043-4.544)	0.490
Pre 96, age 7-11 years	61	4 (6.6%)				0.112 (0.035-0.355)	0.000
Pre 96, age 12+ years	71	10 (14.1%)				0.290 (0.123-0.683)	0.005
96/after, age 0-3 years	73	26 (35.6%)				Reference category	
96/after, age 4-7 years	79	18 (22.8%)				0.472 (0.222-1.005)	0.051
96/after, age 8+ years	19	1 (5.3%)				0.115 (0.014-0.939)	0.044
Stage			9.1	1	0.003		NS
Asymptomatic	219	33 (15.1%)					
Symptoms/AIDS/Death	90	27 (30%)					
Viral load			7.7	2	0.021		0.076
Undetectable	42	6 (14.3%)				Reference category	
Detectable	136	36 (26.5%)				2.632 (0.972-7.13)	0.057
Missing	131	18 (13.7%)				1.487 (0.516-4.288)	0.463
CD4 count			9.1	2	0.011		NS
CD4 over 200	154	29 (18.8%)					
Low CD4	27	11 (40.7%)					
CD4 missing	128	20 (15.6%)					
Therapy			10.4	1	0.001		0.001
No ART	118	12 (10.2%)				Reference category	
ART	191	48 (25.1%)				3.476 (1.668-7.244)	
Total	309	60 (19.4%)					

NS Not significant ($P > 0.05$); not included in final logistic regression model

Figure 7.7: Relationship between taking antiretroviral therapy and age, by cohort



Longitudinal analysis to predict disease progression

Figure 7.8a shows that those whose HIV disease became more severe over their years of treatment had on average lower CD4 counts (lowest ever count, Mann-Whitney U test $Z=2.0$, $P=0.044$), while **figure 7.8b** shows that the highest ever viral load was not a good indication of whether HIV disease advanced ($Z=1.2$, $P=0.240$). **Table 7.2** shows the predictors of progression to more serious HIV disease: the only significant predictor of disease progression was experiencing greater than 10 cells/mm³ decrease in CD4 count at some point during treatment history. There was no difference between the cohorts in terms of the probability of advancing HIV disease. Only two children have been recorded as having died since data collection began in 1996. Since this number of deaths is low, no attempt was made to find associations between death and any other factor.

Future caseload of HIV positive children

Figure 7.9 shows observed and predicted numbers of children in treatment for HIV using the same methods that were used to generate the trends in chapter 2. A cubic equation was the best fit to the historical data on the number of children aged 14 years or under in the North West in treatment for HIV ($r^2=0.992$; $F_{3,6}=240$, $P<0.001$). The model was an extremely good fit, explaining nearly all of the variance (99.2%) in the historical data with the equation $y = 19.9 - 0.09x^3 + 2.01x^2 - 7.2x$ (where x is the year number, with 1996 being 1, and y is the number of children). The model predicts a lower rate of increase in paediatric cases than has been seen historically, with the caseload going up to 71 in 2006 and 76 in 2007, followed by a levelling off in 2008 at 80 cases. However, caution must be exercised when extrapolating the line too far into the future. Fitting a straight line to the linear section of the historical trend (i.e. after 1998) generates predictions of 72 for 2006, rising to 80 in 2007 and 88 in 2008 ($y = 8.04x + 7.57$; where x is the year number, with 1999 being 1, and y is the number of children). This model was also a good fit, explaining 98.8% of the variance in the historical data ($F_{1,5}=423$, $P<0.001$).

Figure 7.8: Mean lowest CD4 count ever (a), and mean highest viral load ever (b), categorised by advancement in HIV disease severity (change: n=11; no change: n=61)

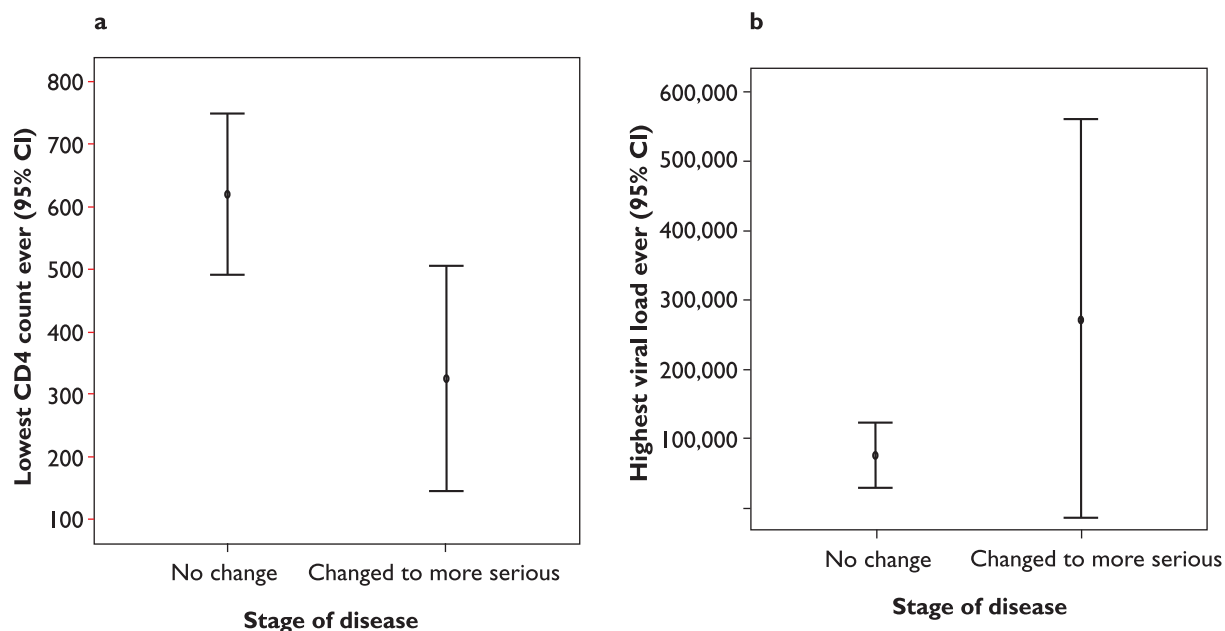
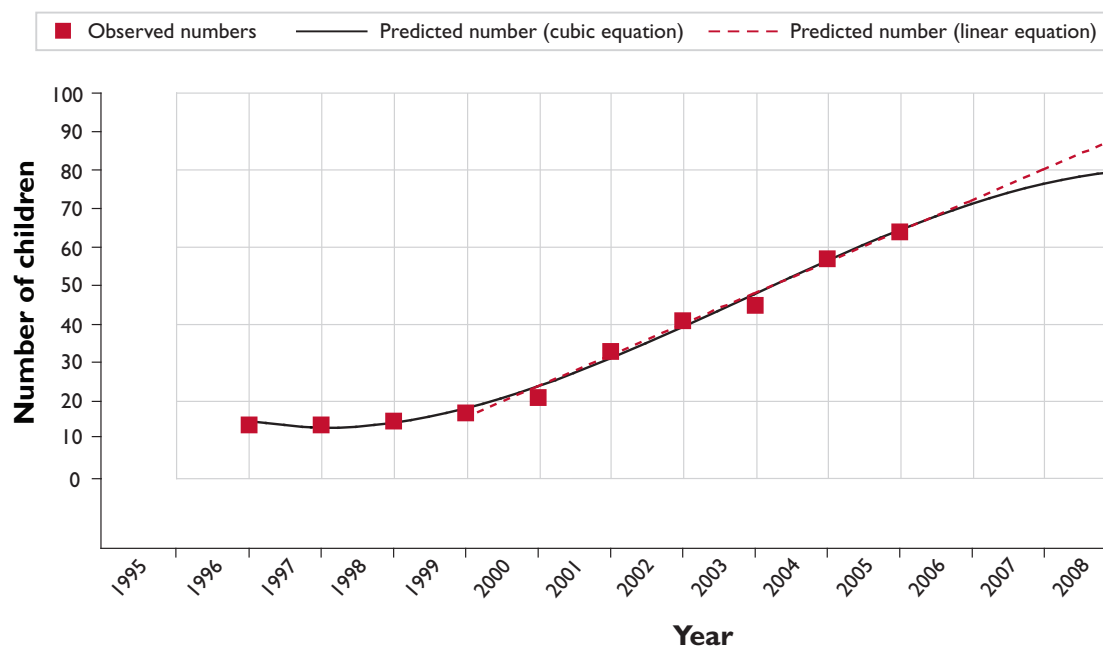


Table 7.2: Number, percentage and odds ratios of progression to more serious HIV disease by demographics and changes in viral load and CD4 count

	n	Univariate			Multivariate		
		Number (%)	Chi	df	P	Adj OR (95% CI)	P
Viral load			6.1	2	0.046		NS
VL same or decreased	39	3 (7.7%)					
Increase in VL	33	8 (24.2%)					
VL unknown	22	1 (4.5%)					
CD4			11.8	2	0.003		0.014
CD4 same or increased	36	1 (2.8%)				Reference category	
Decrease in CD4	36	10 (27.8%)				13.5 (1.6-111.9)	0.016
CD4 unknown	22	1 (4.5%)				1.7 (0.1-28.1)	0.723
Sex			0.5	1	0.489		NS
Male	40	4 (10.0%)					
Female	54	8 (14.8%)					
Ethnicity			0.3	1	0.555		NS
BME/unknown	72	10 (13.9%)					
White	22	2 (9.1%)					
Cohort			0.5	1	0.469		NS
Pre 96	38	6 (15.8%)					
96 or later	56	6 (10.7%)					
Total	94	12 (12.8%)					

NS Not significant (P>0.05); not included in final logistic regression model

Figure 7.9: Observed and projected numbers of paediatric cases being seen for treatment in the North West



Discussion

Predictions of the number of children who will require treatment for HIV in the North West by 2008 ranged from around 80 (a 25% increase on 2005's figures) to 88 (an 38% increase), depending on the mathematical model used (figure 7.9). Whilst this is not as substantial as the predicted increase of 63% in the total number of people with HIV (adults and children) predicted in chapter 2 (figure 2.5), it will require a substantial increase in resources for paediatric care, which is a highly specialised area. As explained in chapter 2, the lines generated by these simple algebraic formulae fitted to historical data must be interpreted with caution, and probably only give reliable estimates for the next two or three years. It is worth noting that a prediction made on data from 1996 to 2004, presented at the North West Paediatric HIV Network conference, used the same method (a cubic equation) to accurately predict that 64 children aged 14 years or less would be seen in 2005¹⁶.

As expected from previous national and international research¹⁰, the CD4 count in children was higher, and more variable, than that in adults. These higher and more variable counts are the reason why CD4 counts are not considered to be a reliable indicator of when to start therapy in children¹⁰. While CD4 count percentage is the preferred indicator for very young children¹⁰, recent research suggests that absolute CD4 counts are useful indicators in children from the age of 5 years¹⁷. This is supported by findings in this chapter, where a drop in CD4 count was the only significant predictor of disease progression (adjusted odds ratio=13.5, 95% CI=1.6-111.9, P=0.016, table 7.2).

In general, children had lower viral loads than adults. Viral load is known to be generally high in babies, peaking at nearly 300,000 copies per ml in the first few months of life¹⁸. However, most infants in the dataset were over one year old, by which time viral loads would have stabilised¹⁸. The very high, but variable, viral load in young adults aged 20 to 24 years may be due to a subset of these individuals being recently sexually infected with HIV (since viral load will be higher in recently infected individuals, and this subset of individuals is less likely to be on ART). Increase in viral load was significantly associated with disease progression, but was not significant after controlling for the other variables, probably because of its high correlation with CD4 count (table 7.2).

Comparing the proportion of those taking ART across the whole age spectrum of adults and children in the 2005 dataset, the proportion of children taking ART increased with age, until by the age of 14 years almost all were on therapy (figure 7.4). Among those in the 15 to 19 year age group there was a drop in the proportion taking therapy, presumably because some of these individuals were young adults recently sexually infected and yet to commence therapy. The ten-year dataset used multiple records for each child to explore patterns of prescription of ART. The records from the older cohort (those born prior to 1996) show that taking therapy was most common in children when they were aged 9 to 14 years, while the proportion taking therapy in the younger cohort peaked when they were at a younger age. Although ART has been available since the outset of the years captured in these analyses, these results suggest that its use in children has changed over the years. The change in prescribing practice, in common with UK data¹¹, reflects increased knowledge about use and dose of antiretrovirals in children and increased licensing of drugs for children.

The results presented here suggest that children born in the post ART era have an increased likelihood of being admitted to hospital. However, this is likely to reflect a lack of data on hospital admissions in the early years of HIV

monitoring. National data show a reduction in hospital admission by 26% over the period 1996 to 2002⁹. Nonetheless, the high hospital attendance recorded in the younger age groups of the recent cohort (36% of under 4 year olds and 23% of 4 to 7 year olds: table 7.1) suggests that despite the improvements in outcomes for children with HIV significant resources will continue to be needed for paediatric care in the North West. This, coupled with the predictions of increasing paediatric caseload in the North West, suggest that increasing investment in services for HIV positive children over the coming years will be necessary.

The small sample size limited the analyses that were possible. Over the ten years' of data collection, 94 children had attended hospitals for HIV treatment for one or more years. Since individuals advance in age, and age was a variable of interest, we deemed it valid to use the records for each year, and the age that the children were in each year, so that multiple records for each child were used. However, the statistical analysis assumes that these are independent data points, so the findings should be interpreted with caution.

Studies on larger cohorts of children in the UK with HIV⁹ have the statistical power to demonstrate some of the relationships suggested by the North West data. However, it is worth bearing in mind that these large UK cohorts are largely drawn from major centres of HIV care and are biased towards centres where expertise and resources are concentrated. The published studies show a bias in sampling from the south/London area and therefore over represent HIV services that have received a disproportionately greater funding over the years compared to the less well resourced North West¹⁹. The major advantage of the North West data source is that it includes all children with HIV (from both large and small treatment centres) and thus represents an important resource to monitor the care of the growing number of HIV positive children.

References

- ¹ UNICEF (2006) Africa's orphaned and vulnerable generations: Children affected by AIDS. United Nations Children's Fund (UNICEF), New York, www.unicef.org.
- ² NHS Executive. Reducing mother baby transmission of HIV. Health Service Circular, HSC 1999/183.
- ³ Patel D, Thorne C, Fiore S, Newell ML for the European Collaborative Study. Does highly active antiretroviral therapy increase the risk of congenital abnormalities in HIV-infected women? *Journal of Acquired Immune Deficiency Syndrome*. 2005;40(1):116-8.
- ⁴ Jungmann EM, Mercey D, DeRuiter A, Edwards S, Donoghue S, Booth T, Mohan D, Lyall H, Taylor GP. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sexually Transmitted Infections* 2001;77:441-443.
- ⁵ National Study of HIV in Pregnancy and Childhood. Obstetric and paediatric HIV surveillance data from the UK and Ireland, data to the end of September 2005. Slide set available from: http://www.hpa.org.uk/infections/topics_az/hiv_and_sti/hiv/epidemiology/files/NSHPC_Oct_2005.ppt
- ⁶ Cook PA, Downing J, Hargreaves SC, Madden H, Syed Q, Bellis MA. HIV and AIDS in the North West of England 2005. Liverpool John Moores University, Centre for Public Health; 2006.
- ⁷ Gortmaker SL, Hughes M, Cervia J, Brady M, Johnson GM, Seage GR 3rd, Song LY, Dankner WM, Oleske JM; Pediatric AIDS Clinical Trials Group Protocol 219 Team. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *The New England Journal of Medicine* 2001; 345:1522-1528.
- ⁸ Eley B, Nuttall J, Davies MA, Smith L, Cowburn C, Buys H, Hussey G. Initial experience of a public sector antiretroviral treatment programme for HIV-infected children and their infected parents. *South African Medical Journal* 2004;94:643-646.
- ⁹ Gibb DM, Duong T, Tookey PA, Sharland M, Tudor-Williams G, Novelli V, Butler K, Riordan A, Farrelly L, Masters J, Peckham CS, Dunn DT, for the National Study of HIV in Pregnancy and Childhood (NSHPC), and for the Collaborative HIV Paediatric Study (CHIPS). Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *British Medical Journal* 2003;327:1019-1023.
- ¹⁰ Sharland M, Blanche S, Castelli G, Ramos J, Gibb DM on behalf of the PENTA Steering Committee. PENTA guidelines for the use of antiretroviral therapy, 2004. *HIV Medicine* 2004; 5(Suppl 2), 61-86.
- ¹¹ Menson EN, Walker AS, Sharland M, Wells C, Tudor-Williams G, Riordan FAI, Lyall EGH, Gibb DM. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *British Medical Journal* 2006; 332(7551):1183-1186.
- ¹² King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population - A review . 2002. *Clinical Pharmacokinetics*; 41(14):1115-1133.
- ¹³ Bitnun A, Sochett E, Babyn P, Holowka S, Stephens D, Read S, King SM. Serum lipids, glucose homeostasis and abdominal adipose tissue distribution in protease inhibitor-treated and naive HIV-infected children. 2003. *AIDS*;17(9):1319-1327.
- ¹⁴ Rhoads MP, Smith CJ, Tudor-Williams G, Kyd P, Walters S, Sabin CA, Lyall EGH. Effects of highly active antiretroviral therapy on paediatric metabolite levels. *HIV Medicine* 2006; 7(1): 16-24.
- ¹⁵ McCullagh J, Syed Q, Bellis MA. HIV and AIDS in the North West of England 1996. University of Liverpool, Department of Public Health; 1997.
- ¹⁶ Cook PA. HIV/AIDS in children and adults in the North West of England. Oral presentation to the North West Paediatric HIV Network's 2nd Annual Workshop, Whiston, Merseyside, 18 May 2006.
- ¹⁷ Dunn DT, Gibb DM, Duong T, Babiker AG, Aboulker JP, Bulterys M et al. Predictive value of absolute CD4 cell count for disease progression in untreated HIV-1-infected children. 2006. *AIDS*; 20(9):1289-1294.
- ¹⁸ Shearer WT, Quinn TC, LaRussa P, Lew JF, Mofenson L et al. for the Women and Infants Transmission Study Group. Viral Load and Disease Progression in Infants Infected with Human Immunodeficiency Virus Type 1. *New England Journal of Medicine* 1997; 336(19):1337-1342.
- ¹⁹ Bellis MA, McVeigh J, Thomson R, Syed Q. The national lottery. *Health Service Journal*; 17 June 1999: 22-3.