

**Short-term risk of disease progression in HIV-1 infected children receiving no antiretroviral therapy or zidovudine monotherapy: estimates according to CD4 percent, viral load, and age**

**HIV Paediatric Prognostic Markers Collaborative Study Group**

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See appendix for details of committees and centres

Abstract: 252 words

Text: 3239 words

Tables: 4

Figures: 2

Funding: This study received no specific funding

## Summary

**Objective:** To estimate the 12-month risks of progression to AIDS and death according to age and most recent CD4 percent or HIV-1 RNA viral load measurement in HIV-1 infected children receiving no antiretroviral therapy (ART) or zidovudine monotherapy only.

**Methods:** Individual, longitudinal data were pooled on 3941 children who participated in eight cohort studies and nine randomised trials of antiretroviral or immune therapies in Europe and the US. Estimates of risk were derived from parametric survival models.

**Findings:** 997 AIDS-defining events were observed over 7297 child-years of follow-up in the analysis of CD4 percent, and 284 events over 2282 child-years in the analysis of viral load; the corresponding numbers of deaths were 568 (9087 child-years) and 129 (2816 child-years). Over two years of age, the risk of death increases sharply when CD4 is less than around 10%, or 15% for AIDS, with a low and relatively stable risk at higher CD4 percent values. At the same CD4 percent, children under two years have a worse prognosis than older children. The risk of clinical progression increases when viral load exceeds about  $10^5$  copies/mL; at lower values, only older children show variation in risk. Both markers have independent predictive value for disease progression, although CD4 percent is the stronger predictor.

**Interpretation:** This meta-analysis provides accurate estimates of the short-term risk of AIDS and death in children in the absence of effective ART. This information is important for clinicians making decisions about starting or re-starting ART in children, and in designing clinical trials related to the decisions.

## Introduction

Early cohort studies reported that 20-25% of HIV-1 infected children progressed rapidly to AIDS or died during infancy, with slower disease progression thereafter.<sup>1,2</sup> The introduction of combination antiretroviral therapy (ART) has resulted in major reductions in morbidity and mortality,<sup>3-6</sup> but there are no trials in either children or adults addressing the question of when it should be started. In the absence of data, guidelines for starting and switching ART have taken account of the CD4 cell count/percent and HIV-1 RNA viral load as predictors of progression to symptomatic disease.<sup>7-9</sup> Although there are considerable data from adult studies on the prognostic value of these markers,<sup>10-12</sup> special factors in children include a developing immune system, a much slower attainment of a virological “set point”,<sup>13,14</sup> clinical use of CD4 cell percent rather than CD4 cell count,<sup>7</sup> and the need to take age into account.<sup>15,16</sup> A number of studies in paediatric populations have been reported,<sup>15-18</sup> with risk estimates relating to a 2-7 year time horizon. However, because CD4 and viral load are regularly monitored (typically every three months), short-term risk estimates are arguably clinically more relevant.<sup>12</sup> Here, based on individual patient data on nearly 4000 HIV-1-infected children participating in cohort studies and randomised trials in Europe and the US who received no ART or zidovudine monotherapy, we have estimated the 12-month risks of progression to AIDS and death in terms of age and the most recent CD4 percent or viral load measurement.

## Methods

The HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) is a collaboration between investigators of European and US cohort studies and randomised trials of ART or immune therapies in perinatally HIV-1 infected children.<sup>1,6,19-34</sup> Participating investigators provided individual patient data, which were subsequently pooled, on a number of specified variables, including demographic characteristics, date of diagnosis of HIV infection (if known), date of death or last known to be alive, date of last clinical assessment, whether ever diagnosed with AIDS with the exception of lymphoid interstitial pneumonia (equivalent to Clinical Category C)<sup>35</sup> and, if so, date of first diagnosis and indicator disease(s), date started zidovudine, date of start of any other antiretroviral drug, CD4 and CD8 lymphocyte counts and percentages, and viral load measurements and assay method (if available). Records that matched on key demographic variables were linked to avoid duplication. This analysis is limited to measurements before the start of ART or during receipt of zidovudine monotherapy, which has at most a marginal clinical effect.<sup>32</sup> Thus, in the randomised trials of ARTs, children allocated to combination ART or non-zidovudine monotherapy were excluded.

Separate analyses were performed to determine the 12-month predictive value of CD4 percent and viral load for (a) death (all cause mortality) and (b) progression to first AIDS event or death in the absence of AIDS. Follow-up was counted from the date of first CD4 or viral load measurement except when the study inclusion criteria would have introduced bias. For example, in death analyses, follow-up of children enrolled in randomised trials was counted from the first measurement at or after randomisation since being alive at randomisation was clearly a prerequisite to trial entry. To minimise presentation bias (i.e., children whose HIV infection only came to light when they became severely symptomatic) in the non-birth cohort studies, children were excluded if they experienced an event within one month of diagnosis of HIV infection.

Follow-up was censored, even if an endpoint was observed subsequently, at the earliest of the following: (i) date of last clinical visit (for analyses of the AIDS endpoint) or date last known alive (for analyses of the death endpoint); (ii) 12 months after the last CD4 or viral load measurement; (iii) 6 months after starting any antiretroviral drug other than zidovudine monotherapy. The rationale for the 6 month extension in (iii) was to reduce any bias resulting from selective use of combination ART or other monotherapy in children with a poor prognosis.<sup>4</sup> However, the estimated risk of disease progression was only slightly lower when the analysis was repeated without this restriction. For some children in the PACTG trials, ART information was not available after the date of discontinuation of the allocated trial treatment, in which case follow-up was censored 6 months after this date or at 01/10/1991 (month when didanosine was approved by the FDA), whichever occurred later.

Viral load was measured by Nucleic Acid Sequence-based Amplification Assay [NASBA] (30% of measurements), Roche Amplicor Monitor 1.0 (17%), Chiron bDNA 3.0 (8%), Roche Amplicor Monitor 1.5 (6%), Chiron bDNA 2.0 (2%), other (3%); for the remaining 34%, the type of assay was not recorded. Although the assays give systematically different estimates of viral load concentration, the difference between the two most commonly used assays (NASBA and Roche Amplicor Monitor 1.0) is minor compared with biological variation.<sup>36,37</sup> Viral load values below the assay-specific lower limit of detection (7% of all measurements) were set equal to this limit; values above the linear dynamic range were uncommon due to the practice of titrating out high concentration samples.

### **Statistical methods**

The 12-month risk of disease progression was estimated by a previously described “person-intervals” method<sup>38</sup> with some modifications. In brief, each CD4 or viral load measurement contributed a unit of observation to a survival analysis, with time projected up to a maximum of 12 months; i.e., the time scale was re-set to zero at each new measurement, and age at each measurement and CD4 percent or viral load defined the “baseline” covariates.

Parametric survival models were used to derive 12-month survival estimates (details in Appendix). Confidence intervals were derived from 1000 non-parametric bootstrap samples (resampling individual children rather than visits) using the bias-corrected percentile method.<sup>39</sup> Because of difficulty in extending this model to include multiple covariates, we investigated the effect of study, calendar period, and demographic variables on risk estimates indirectly through Cox proportional hazard models, on an age time scale.

As the publication in 1995 of US guidelines that recommended wider use of co-trimoxazole prophylaxis is likely to have influenced the incidence of *Pneumocystis carinii* pneumonia (PCP) and some bacterial infections,<sup>40</sup> the risk of progression to AIDS could have been over-estimated in the context of current clinical practice as a lot of the data were collected before 1995. This was investigated through multiple imputation: (1) Identify each AIDS diagnosis due to PCP before 1/1/1995 with age <1 year or any prior CD4 <15%. (2) Using a random number generator, censor at the date of PCP diagnosis with probability 0.8, otherwise leave the data unchanged, i.e., assumes a co-trimoxazole prophylaxis policy results in a 80% reduction in the risk of PCP.<sup>41</sup> (3) Repeat steps 1-2 for AIDS diagnoses due to serious bacterial infections, except censor with probability 0.2. i.e., 20% risk reduction (4) Fit model to imputed dataset (5) Repeat steps 1-4 ten times and average the parameter estimates over the ten imputed data sets.

## **Results**

Data from 17 studies conducted in Europe or the USA between 1983 and 2002 are included in the analysis (Table 1). In the analysis of the predictive value of CD4 percent, 997 children progressed to AIDS (n=898) or died without an AIDS diagnosis (n=99), compared with 284 children in the analysis of viral load (Table 2); the corresponding numbers of deaths were 568 and 129. Opportunistic infections were the most common AIDS diagnoses (37%), followed by serious recurrent bacterial infections (30%) and HIV encephalopathy (20%). The relative frequency of these conditions was strongly age-related, PCP and encephalopathy becoming proportionately less common, and serious recurrent bacterial infections proportionately more common, with increasing age.

Follow-up and number of events by age and CD4 percent or viral load is shown in Figure 1. The distributions of both markers shift to lower values with increasing age, reflecting selection effects as well as evolution of the markers within individuals. Notably few deaths were observed among older children with CD4 above 10% despite extensive follow-up, although less than 1% of the total follow-up is in children over 12 years. Slightly less than half of the follow-up was observed during 1992-95; earlier years were under-represented in the viral load analyses, reflecting the later availability of testing (Table 2). Zidovudine monotherapy was received during 34-47% of the follow-up. The median number of CD4 measurements per child was 6 (inter-quartile range [IQR] 3-10); the distribution of the interval between successive tests was <3 months (58%), 3-6 months (26%), 6-12 months (10%), >12 months (6%). Viral load data were less extensive (median 3 measurements per child, IQR 2-6), although the interval between tests was similar.

### ***Risk of disease progression***

The estimated probabilities of AIDS and death within 12 months according to current CD4 percent or viral load at selected ages are shown in Figure 2 and Table 3. At very low values of CD4 percent, prognosis is poor at all ages. At higher values, the risk of progression to

AIDS for a given value of CD4 percent is substantially higher in younger children, approximately 8-fold higher in a one year old child and 2-fold higher in a five year old, compared with a ten year old child. Above the age of two years, 12-month risk increases sharply when CD4 falls below about 10% for death, or about 15% for AIDS, with a low and relatively stable risk at higher CD4 percent values. In infants, however, disease progression rates are substantial even at high values of CD4 percent: at age 6 months, a CD4 value in the range 25%-50% predicts a risk of AIDS within 12 months between 23% and 14% and a risk of death between 7.9% and 4.1%. The risk of disease progression increases sharply, irrespective of age, at viral load values above  $10^5$  copies/mL; at lower concentrations, viral load gives better discrimination in risk in older children than in younger children. As an independent predictor of disease progression, age was less important than in the analysis of CD4 percent, particularly for death. Additional analyses indicated that adjustment for study or calendar period did not significantly affect the shape of the curves in Figure 2 (results not shown).

A series of analyses was performed on the comparative and joint predictive value of CD4 percent and viral load, based on the 5770 visits when both variables were measured. First, considering the markers separately, CD4 percent gave a better statistical “fit” to the observed data (by 46.8 log-likelihood units, with the same number of parameters), showing it to be the stronger individual predictor. Thus, at age 2 years the estimated risk of AIDS varies from 2.6% at the 95th age-specific centile for CD4 percent (25.5%) to 40% at the 5th centile for CD4 percent (4.2%), whereas the risk variation for viral load is narrower, 4.9% at the 5th centile ( $4.9 \log_{10}$  copies/ml) to 23% at the 95th centile ( $6.2 \log_{10}$  copies/ml). Second, there was evidence that the two markers have independent predictive value: they were only weakly associated (correlation coefficients ranged between -0.33 and -0.18 within the age groups in Figure 1), and a gradient in risk across CD4 percent quartiles persisted after adjusting for viral load and age, as did a gradient across viral load quartiles after adjusting for CD4 percent and age (results not shown).

Modelling the effect of the retrospective application of guidelines on co-trimoxazole prophylaxis made little difference to the findings. For example, for a 6-month old child with 30% CD4 T-cells, the estimated risk of AIDS within 12 months was reduced from 20% to 18%. The corresponding reductions for CD4 values of 20% and 10% were from 29% to 27% and 49% to 46%, respectively. For older children, in whom PCP is less common, the reductions were even smaller. These findings were relatively insensitive to different assumptions about the efficacy of co-trimoxazole prophylaxis in preventing PCP and serious bacterial infections (results not shown).

### ***Factors influencing risk of disease progression***

Cox proportional hazards models controlling for CD4 percent as a time-varying covariate showed significant variation between the studies in terms of disease progression (Table 4), although there was no clear pattern by study type. Children who received intravenous immunoglobulin in the NICHD IVIG trial experienced a lower incidence of bacterial infections<sup>26</sup> and thus of AIDS compared with the placebo group, although mortality rates were similar. The study-specific hazard ratios for AIDS and for death were not strongly concordant across studies, e.g., in the Italian Register for HIV Infection in Children, the incidence of AIDS was slightly lower than the combined birth cohorts (hazard ratio 0.94), whereas mortality incidence was significantly higher (hazard ratio 1.46). AIDS incidence fell substantially over calendar time – an 11% decrease in 1992-95 compared with 1983-1991 and a further 39% decrease in 1996-2002. Similar reductions, 22% and 50% respectively, were observed for mortality. Neither gender nor ethnicity were associated with disease progression after adjustment for CD4 percent.

## Discussion

In developed countries, CD4 percentage and viral load are routinely measured in HIV-1 infected children to monitor clinical progression and to inform decisions on clinical management. The ability to use this information effectively has been limited by incomplete characterisation of these laboratory markers, particularly the quantification of the short-term risk of clinical progression for given levels of the markers. In this longitudinal study of nearly 4000 HIV-1 infected children we have derived estimates of the risk of AIDS and death which are applicable up to at least 10 years of age.

Several previous related studies have been reported, which although carefully analysed, have a number of limitations.<sup>15-18</sup> First, as some of the subjects had received combination ART, the results may not have reflected the “natural” association between the laboratory markers and disease progression,<sup>10</sup> which is most relevant to the question of when to initiate ART. Our analysis, in contrast, is essentially based on follow-up while children received no ART or zidovudine monotherapy only, which has only a minor, short-term effect on disease progression and laboratory markers.<sup>32</sup> Second, the risk estimates presented in previous studies related either to “instantaneous” time (the inference from Cox proportional hazards models) or to comparatively long periods of up to seven years. However, because CD4 percent and viral load are regularly re-measured (typically every three months), we present shorter-term projections (12 months) which are arguably more relevant in clinical decision-making regarding initiation of therapy. Third, we used mathematically flexible models with CD4 percent, viral load, and age as continuous variables, which give more accurate individual predictions.

These analyses revealed highly non-linear associations, which were modified by age, between the risk of disease progression and both CD4 percent and viral load. This mirrors findings in HIV-1 infected adults, in whom the short-term risk of developing AIDS is substantially higher at CD4 levels below approximately 200 cells/mm<sup>3</sup> (corresponding to a

median CD4 percent of approximately 14%).<sup>10-12</sup> Our data clearly show that older children (with longer time from seroconversion) have a lower short-term risk of clinical progression than younger children, for a given value of CD4 percent. In contrast, an adult seroconverter cohort found that the risk of AIDS increased with time from seroconversion for a given CD4 count.<sup>43</sup> When interpreting the prognostic significance of a viral load measurement, age is less critical than for CD4, presumably because the intrinsic effect of age is partly offset by the effect of the decline in viral load with age in the absence of ART in children.<sup>13-14</sup> However, the accuracy of our model in the first year of life, during the dynamic changes in viral load that occur after primary infection, is uncertain.

It is anticipated that most clinicians will focus on the risk estimates for AIDS rather than those for death. However, it is notable that mortality estimates were only one-quarter to one-third of those for AIDS, indicating that most of the AIDS-defining illnesses were not immediately fatal, even in the absence of ART. In line with previous studies, we found that CD4 percent and viral load have independent predictive value.<sup>15,16,18</sup> Of the two markers, CD4 percent was the stronger individual predictor, an important result for settings where viral load testing may not be available. To obtain more accurate estimates of the risk of disease progression we are developing models that incorporate both CD4 percent and viral load, and examining whether changes in the values of the markers over time provide additional information.

### ***Generalisability***

The broad study selection criteria used, with the aim of maximising information, raises questions about the applicability of our results for individual children. There was no evidence of an effect of gender or ethnicity on disease progression, despite reports that average viral load levels may be lower in girls than in boys.<sup>21</sup> However, we did observe significant differences between studies and improvements in prognosis over calendar time. Some of the differences between studies can be explained by selection effects – for example, some of the clinical trials included only asymptomatic children. However, as neither the type of study nor

the differences in CD4 percent between studies fully explained the heterogeneity, presentation of overall risk estimates is most appropriate. Further, in practice, clinicians provide care for children presenting in a variety of ways.

The rates of both morbidity and mortality declined over calendar time, particularly after 1996 coincident with the widespread use of dual then triple ART. If, as is likely, such therapy was used selectively in children at higher risk of AIDS or death, then estimates of disease progression would be biased downwards.<sup>4</sup> We extended follow-up by 6 months to reduce this bias, but as a residual effect could not be excluded we rejected the idea of “adjusting” the risk estimates for calendar time. On the other hand, our overall estimates of disease progression rates based on data from 1983 are likely to be higher than those experienced currently by untreated children. Adjustment for PCP prophylaxis had a small effect, possibly because PCP accounted for only 28% of AIDS diagnoses in infancy.

### ***Clinical implications***

Future revisions of paediatric guidelines on when to start ART<sup>7-9</sup> may be influenced by these results. In particular, it may be appropriate to increase the number of age categories and to lower CD4 thresholds for older children. For children under one year of age, US guidelines advocate treatment for all children,<sup>7</sup> whereas in Europe “consideration” of treatment is recommended.<sup>8</sup> The observation that neither CD4 percent nor viral load could identify young children at low risk of disease progression lends some support to a universal treatment policy for infants, or at least to the need for close observation to promptly detect pre-AIDS clinical signs or symptoms.

In US and Europe, the availability of interventions to reduce mother-to-child HIV-1 transmission has led to a dramatic reduction in the number of HIV-1 infected children who are identified early in life. However, in many European countries an increasing proportion of infected children are presenting at older ages (many having acquired HIV infection in high-

prevalence countries), after the initial high risk age for clinical progression. It is for the management of these children that the results of this study may be of most relevance. In addition, this analysis could inform when to re-introduce treatment following periods of interruption, a therapeutic approach attracting increasing interest due to concerns about the long-term side effects of ART . Finally, in resource limited settings, the deferred use of ART, even in very young children, may be the only practicable strategy, partly due to the non-availability of tests for the early diagnosis of HIV infection.<sup>9</sup> The applicability of our findings to such settings, where the natural history of infection may be different, requires confirmation.

## Appendix 1

### Steering Committee

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### **Contributors**

D Gibb, M Hughes, D Dunn and T Duong formulated the collaboration. TD assembled the data and conducted the statistical analyses under the supervision of DD and DG. DD, DG, and TD drafted the paper. The other members of the Steering Committee coordinated the data extraction for their respective studies, made critical suggestions on several revisions of the analysis, and through their comments improved the clarity of the paper considerably.

### **Acknowledgements**

We would like to thank the following for their help in data extraction: Jeffrey Wiener (CDC, Atlanta) for PACTS; Clara Gabiano (Department of Pediatrics, University of Turin) and Luisa Galli (Department of Pediatrics, University of Florence) for the Italian Register for HIV Infection in Children; Laura Farrelly (MRC Clinical Trials Unit, UK) for CHIPS.

## Appendix 2. Clinical centres/collaborators

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The European Collaborative Study is a concerted action of the European Commission (Biomed II PL 97 2005 and QLRT-1999-30002). The Medical Research Council (UK) provides support to the coordinating centre.

### Italian Register for HIV Infection in Children

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### Appendix 3. Statistical analysis and calculation of disease progression probabilities

The hazard rate of disease progression,  $\lambda$ , was expressed as  $\lambda = a + b \cdot \exp(-k \cdot x)$  where  $x = \text{CD4}$  percent or  $7 - \log_{10}(\text{viral load})$ . The parameters  $a$ ,  $b$ , and  $k$  were allowed to depend on age:  $\log_e(a) = a_1 + a_2 \cdot \text{age}$ ,  $\log_e(b) = b_1 + b_2 \cdot \text{age}$ ,  $\log_e(k) = k_1 + k_2 \cdot \text{age}$ . Models were estimated using the **ml** command in Stata 7.0.<sup>44</sup> Goodness of fit, as assessed by log-likelihood, was improved by applying the following transformations:  $\log_e(\text{age} + 0.3)$  with age recorded in years,  $\sqrt{(\text{CD4}\% + 10)}$  for death endpoint,  $\sqrt{(\text{CD4}\% + 4)}$  for AIDS endpoint. The inclusion of the  $b_2$  parameter did not significantly improve the fit of any model, nor did the  $k_2$  parameter in models involving viral load, which were therefore set to zero. The maximum likelihood estimates are shown in the following table.

Transformed variable	Endpoint	Parameter estimate				
		$a_1$	$a_2$	$b_1$	$k_1$	$k_2$
$\sqrt{(\text{CD4}\% + 4)}$	AIDS	-2.3608	-0.9428	2.3746	-0.1915	0.2074
$\sqrt{(\text{CD4}\% + 10)}$	Death	-3.5380	-1.2683	4.7643	0.3203	0.1420
$7 - \log_{10}(\text{viral load})$	AIDS	-2.4231	-0.8246	-0.3937	0.3487	--
$7 - \log_{10}(\text{viral load})$	Death	-4.0474	-1.1982	-1.0972	0.3637	--

**Example:** Estimated 12-month probability of AIDS for a 2.0 year old child with 40% CD4 cells.

1.  $\log_e(a) = -2.3608 + (-0.9428 \times \log_e(2.0 + 0.3)) = -3.1461$
2.  $a = \exp(-3.1461) = 0.04302$
3.  $b = \exp(2.3746) = 10.7467$
4.  $\log_e(k) = -0.1915 + (0.2074 \times \log_e(2.0 + 0.3)) = -0.01875$
5.  $k = \exp(-0.01875) = 0.9814$
6.  $\lambda = 0.04302 + 10.7467 \times \exp(-0.9814 \times \sqrt{(40+4)}) = 0.05902$
7. 12-month probability of AIDS =  $1 - \exp(-0.05902) = 0.05731$  or 5.7%

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**Table 1. Summary of participating studies**

Study	Reference	Calendar period	No. children in CD4 percent analysis	No. children in viral load analysis	Interval between first and last measurement (median [months])
<b>Prospective birth cohorts</b>					
Perinatal AIDS Collaborative Transmission Study	19	1986-2000	342	241	16.6
Pediatric Pulmonary and Cardiovascular Complications of HIV Infection Study, Group 2A <sup>1</sup>	20	1990-1995	265	185	17.5
Women and Infants Transmission Study	13	1990-2001	142	116	12.1
European Collaborative Study <sup>2</sup>	21	1985-2000	99	41	47.0
PACTG 076 (infected children)	22	1991-1995	47	41	15.6
<b>General cohorts</b>					
Italian Register for HIV Infection in Children <sup>3</sup>	1	1983-2000	927	164	35.0
Collaborative HIV Paediatric Study (CHIPS) of UK & Ireland <sup>3</sup>	6,23	1986-2002	486	393	16.2
Swiss Mother and Child HIV Cohort Study <sup>3</sup>	24,25	1985-2001	100	60	18.4
<b>Randomised trials (interventions)</b>					
NICHD IVIG Clinical Trial (IVIG vs albumin placebo)	26	1988-1991	335	225	18.4
PACTG 128 (high vs low dose of ZDV)	27	1989-1994	339	0	37.1
PACTG 152 (ZDV vs ddl vs ZDV+ddl) <sup>4</sup>	28	1991-1995	232	160	24.6

PACTG 051 (IVIG vs placebo)	29	1988-1994	252	0	25.8
PACTG 240 (ZDV vs d4T) <sup>4</sup>	30	1994-1996	94	76	13.8
PACTG 190 (ZDV vs ZDV+ddC) <sup>4</sup>	31	1992-1994	90	0	17.0
PENTA 1 (immediate vs deferred ZDV)	32	1992-2000	164	78	37.7
PENTA 3 (ddC+ZDV vs ZDV) <sup>4</sup>	33	1994-1996	11	7	11.1
PENTA 4 (adding 3TC or placebo to current therapy) <sup>4</sup>	34	1995-1998	16	11	51.0
<b>Total</b>			<b>3941</b>	<b>1798</b>	<b>23.5</b>

1. Includes 175 children enrolled retrospectively
2. European Collaborative Study omitted children reported from its Italian and PENTA centres because of overlap
3. Proportion followed from birth in general cohorts: 39% Italian, 12% CHIPS, 36% Swiss
4. Children randomised to an antiretroviral drug other than zidovudine are excluded

IVIG=intravenous immunoglobulin, ZDV = zidovudine, ddI=didanosine, d4T=stavudine, ddC=zalcitabine, 3TC=lamivudine  
Children who appear in more than one study have been allocated to the study which provided the earliest information

**Table 2. Follow-up and number of events**

<b>Endpoint</b>	<b>AIDS (or death)</b>		<b>Death</b>		
	<b>Laboratory Marker</b>	<b>CD4 percent</b>	<b>Viral load</b>	<b>CD4 percent</b>	<b>Viral load</b>
No. children		3371	1527	3908	1789
Total no. events		997	284	568	129
Total follow-up (years)		7297	2282	9087	2816
Follow-up during ziduvudine monotherapy		3238 (44%)	771 (34%)	4312 (47%)	1040 (37%)
Follow-up during:	1983-1991	2035 (28%)	314 (14%)	2745 (30%)	424 (15%)
	1992-1995	3586 (49%)	1011 (44%)	4426 (49%)	1275 (45%)
	1996-2002	1676 (23%)	957 (42%)	1917 (21%)	1117 (40%)

**Table 3. Estimated risk of AIDS and death within 12 months at selected values of age and CD4 percent or viral load. 95% confidence interval shown in parenthesis.**

Age years	Endpoint	CD4 percent				Viral load (copies/ml)		
		10%	20%	30%	40%	10 <sup>4</sup>	10 <sup>5</sup>	10 <sup>6</sup>
0.5	AIDS	49 (43-55)	29 (26-32)	20 (18-22)	16 (14-18)	11.0 (6.7-16.2)	13.6 (10.5-16.2)	24 (16-27)
	Death	29 (24-33)	11.0 (9.3-13.1)	6.2 (5.3-7.2)	4.7 (3.9-5.6)	2.7 (0.9-4.1)	4.1 (2.9-5.4)	9.7 (8.1-12.0)
1	AIDS	38 (34-43)	20 (18-22)	13 (12-14)	10.1 (9.0-11.4)	7.8 (4.4-12.1)	10.5 (8.5-12.2)	21 (12-24)
	Death	19 (17-22)	6.5 (5.6-7.6)	3.4 (2.9-4.0)	2.5 (2.1-3.1)	1.7 (0.8-2.8)	3.1 (2.4-4.0)	8.8 (7.2-11.0)
2	AIDS	27 (26-30)	12 (11-14)	7.5 (6.7-8.4)	5.7 (4.9-6.8)	5.3 (3.2-8.5)	8.1 (6.5-9.3)	19 (8-22)
	Death	12 (10-13)	3.4 (2.9-3.9)	1.6 (1.3-2.0)	1.2 (0.9-1.6)	1.1 (0.6-1.8)	2.5 (1.8-3.1)	8.2 (6.4-10.4)
5	AIDS	14 (13-16)	5.3 (4.6-6.2)	3.1 (2.6-3.8)	2.4 (1.8-3.1)	3.2 (2.1-4.9)	6.0 (4.5-8.0)	17 (5-21)
	Death	5.0 (4.1-5.8)	1.2 (0.9-1.4)	0.5 (0.4-0.7)	0.4 (0.3-0.6)	0.7 (0.4-1.0)	2.1 (1.4-2.9)	7.8 (5.9-10.2)
10	AIDS	7.9 (6.1-9.8)	2.5 (2.0-3.1)	1.5 (1.1-2.0)	1.2 (0.7-1.7)	2.2 (1.4-3.2)	5.1 (3.0-7.7)	16 (3-20)
	Death	2.3 (1.7-3.0)	0.5 (0.3-0.6)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.6 (0.3-0.9)	2.0 (1.2-2.9)	7.7 (5.7-10.0)

**Table 4. Results of Cox proportional hazards models**

Factor		Adjusted hazard ratio (95% CI) <sup>1</sup>			
		AIDS		Death	
Study	Prospective birth cohorts combined*	1.00	P<0.001	1.00	P<0.001
	Italian Register	0.93 (0.78-1.12)		1.44 (1.15-1.81)	
	CHIPS UK & Ireland	0.96 (0.72-1.27)		2.41 (1.27-4.59)	
	Swiss	1.14 (0.72-1.80)		0.75 (0.36-1.55)	
	IVIG – placebo arm	2.10 (0.47-3.01)		1.33 (0.86-2.06)	
	– intervention arm	1.61 (1.07-2.43)		1.81 (1.13-2.91)	
	PACTG trials combined	1.20 (0.98-1.47)		0.81 (0.61-1.07)	
	PENTA trials combined	0.64 (0.43-0.96)		0.39 (0.19-0.80)	
Calendar year <sup>2</sup>	1983-1991*	1.00	P<0.001	1.00	P<0.001
	1992-1995	0.89 (0.76-1.04)		0.78 (0.64-0.97)	
	1996-2002	0.54 (0.41-0.70)		0.39 (0.24-0.62)	
Sex	Female*	1.00	P=0.8	1.00	P=0.4
	Male	0.98 (0.87-1.12)		0.93 (0.79-1.10)	
Ethnicity	White*	1.00	P=0.8	1.00	P=0.9
	Black	0.92 (0.73-1.13)		1.11 (0.80-1.53)	
	Hispanic	0.92 (0.71-1.20)		1.10 (0.74-1.65)	
	Other	0.83 (0.55-1.25)		0.90 (0.78-1.68)	

\* reference category

1. Effects adjusted for all other factors plus most recent CD4 measurement, modelled as a restricted cubic spline with age interaction<sup>42</sup>

2. Fitted as time varying covariates

## Legends to Figures

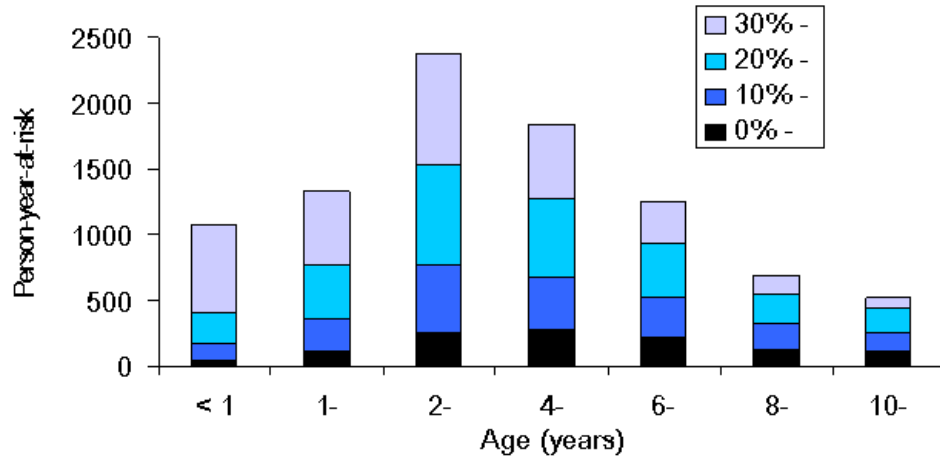
### Figure 1

Distribution of follow-up within age groups: (A) CD4%, death (B) CD4%, AIDS (C) Viral load, death (D) Viral load, AIDS. Follow-up was accumulated between successive measurements up to a maximum of 12 months. Number of events shown below each graph.

### Figure 2

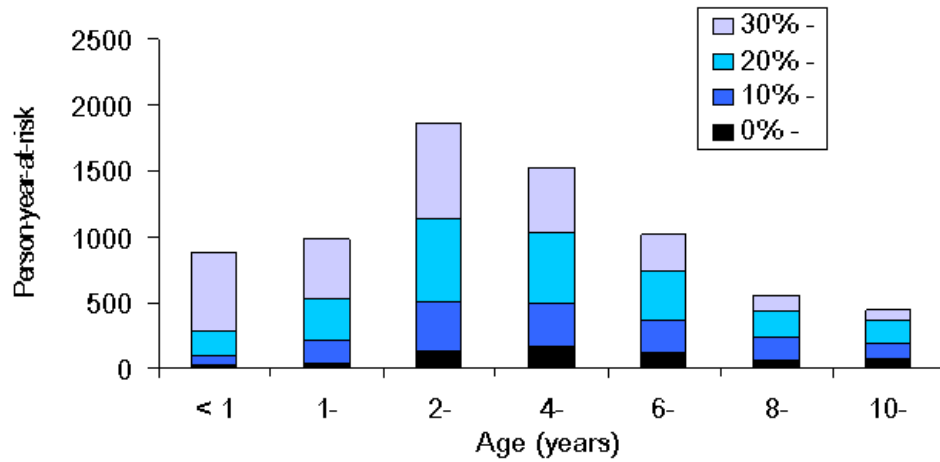
Estimated probability of an event within 12 months at selected ages: (A) death related to CD4%, (B) AIDS related to CD4% (C) death related to viral load (D) AIDS related to viral load. Note the different scale on the vertical axes.

(A) CD4% and death



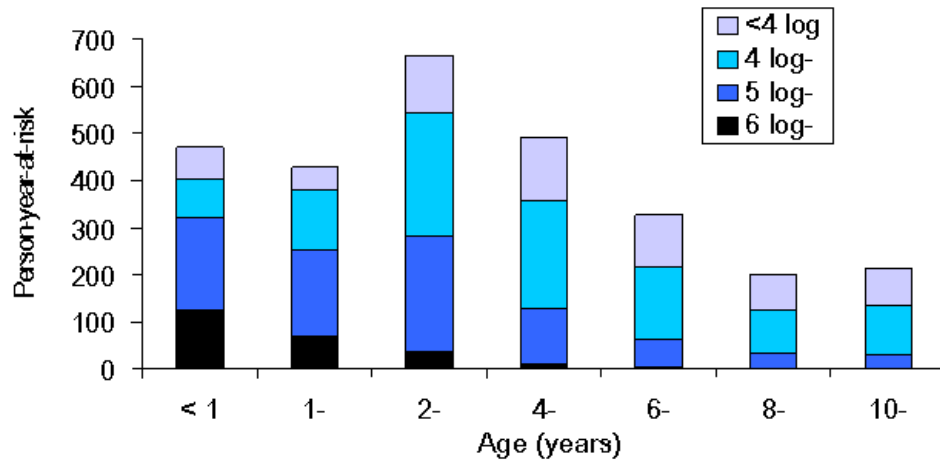
30% -	59	14	11	2	2	0	0
20% -	43	21	8	3	0	0	0
10% -	31	26	31	5	4	3	3
0% -	24	53	90	50	44	26	15

(B) CD4% and AIDS



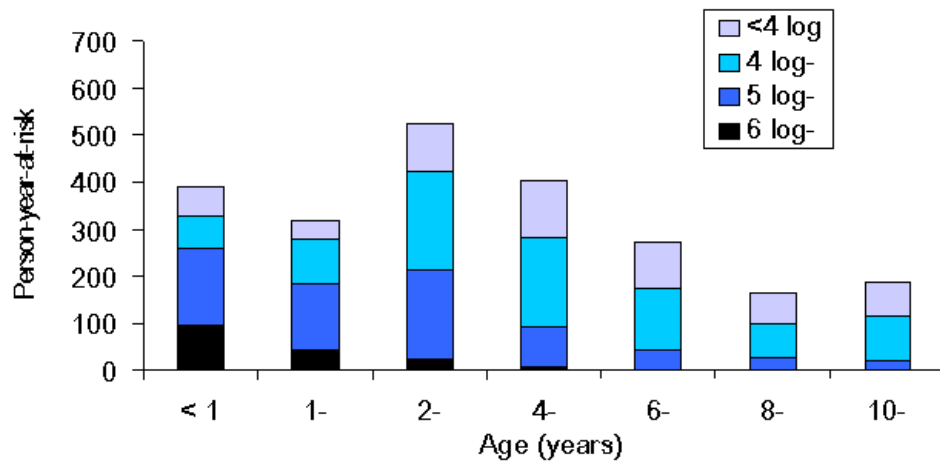
30% -	170	47	29	15	10	1	2
20% -	90	48	41	29	7	5	3
10% -	51	42	67	28	22	8	9
0% -	26	36	55	64	48	25	19

(C) Viral load and death



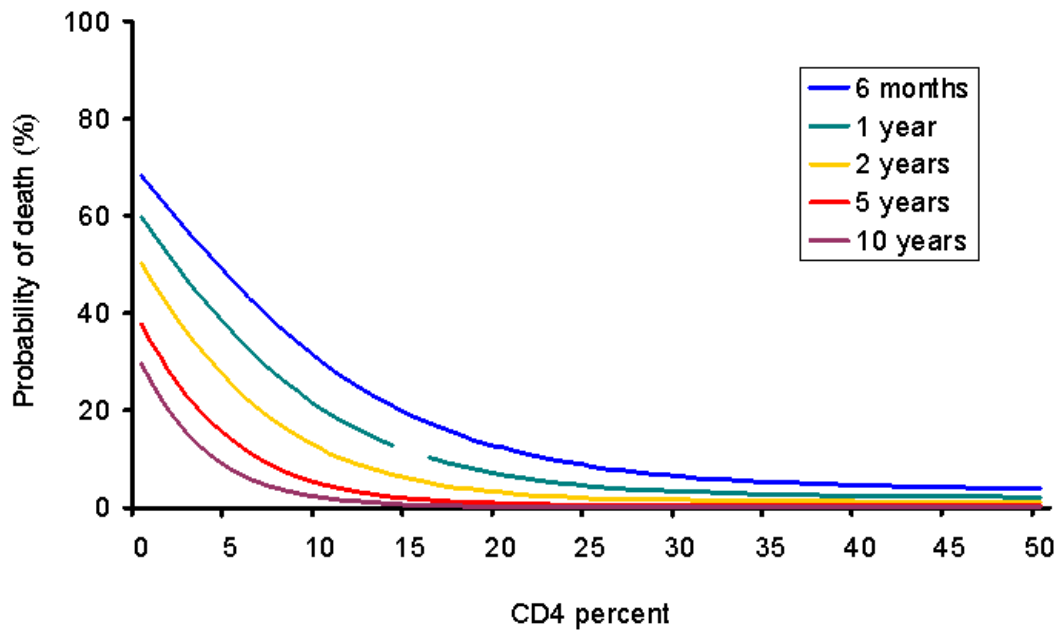
<4 log	2	1	2	0	0	0	1
4 log -	7	1	9	1	4	1	1
5 log -	21	9	7	4	1	2	1
6 log -	22	17	12	1	0	2	0

(D) Viral load and AIDS



<4 log	14	6	6	4	1	1	2
4 log -	16	8	8	13	4	2	2
5 log -	42	23	24	9	7	3	3
6 log -	53	15	14	1	1	2	0

Probability of death within 12 months



Probability of AIDS within 12 months

