Current CD4 Cell Count and the Short-Term Risk of AIDS and Death before the Availability of Effective Antiretroviral Therapy in HIV-Infected Children and Adults

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Background. Currently, there are no comparable estimates of the short-term risk of disease progression in the absence of effective antiretroviral therapy for human immunodeficiency virus (HIV)–infected adults and children.

Methods. A joint analysis of 2 large studies of children with vertically acquired HIV infection (the HIV Paediatric Prognostic Markers Collaborative Study) and adults with seroconversion (the CASCADE [Concerted Action on Sero-Conversion to AIDS and Death in Europe] collaboration) was conducted. Follow-up was censored at the end of 1995, before the introduction of combination antiretroviral therapy. The incidence rates of death and AIDS or death (AIDS/death) were estimated on the basis of age and current CD4 cell count.

Results. A total of 1260 deaths (over 20,500 person-years of follow-up) and 1894 initial AIDS events (over 17,200 person-years of follow-up) were observed among 6741 patients (3244 children [i.e., patients <15 years of age] and 3497 adults). Young children (age, <5 years) experienced high morbidity and mortality rates. After adjustment for the CD4 cell count, the effect of age on disease progression was not significant among older children, whereas the risk increased markedly in association with increasing age among adults. Death rates were similar among older children and adults aged ~20 years, as were the rates of progression to AIDS/death when cases of serious recurrent bacterial infection, which has a more restrictive case definition in adults, were excluded.

Conclusions. Similar CD4 cell count criteria for initiation of antiretroviral therapy can be applied to adults and children ≥5 years of age.
yses revealed the presence of age-associated effects, independent of the CD4 cell count, that need to be taken into consideration [2–4].

In the present study, we assessed data from both analyses by use of a common methodology, to gain a more complete picture of how, for a given CD4 cell count level, the risks of AIDS and death vary across the age range of the patients. In particular, we were interested in determining whether, for children, there is an age threshold at which the association between the CD4 cell count and the rate of disease progression approximates that noted in adults. This finding could help achieve consistency between treatment guidelines for children and adults, as well as inform age eligibility criteria for trials enrolling both children and adults.

METHODS

In the HPPMCS, which is a meta-analysis of individual patient data, information was pooled, in 2000, across 17 European and US cohort studies and trials involving children who had vertically acquired HIV infection and for whom data were available before the introduction of combination ART [3, 4]. The study includes both children who were followed from birth (after infection was diagnosed in the mother) and those whose HIV infection was detected later in life. Children in the latter group were excluded from the relevant analysis if they developed AIDS or died within 1 month of the first clinical presentation.

CASCADE is an international collaboration, established in 1997, that annually brings together data from 22 cohorts in Europe, Australia, and Canada [2]. All cohorts comprise HIV-infected persons for whom it was possible to estimate the time of HIV seroconversion, most commonly because a negative HIV antibody test result was noted a maximum of 3 years before the first positive test result was obtained. The present analysis is based on data pooled in 2004.

AIDS was defined using the clinical conditions in the 1993 Centers for Disease Control and Prevention (CDC) classification system for adults and adolescents and the 1994 CDC classification system for children (however, with the exclusion of lymphoid interstitial pneumonitis) [9, 10]. These systems differ in their definition of serious recurrent bacterial infection. For adults, such infection includes only salmonella (nontyphoid) septicemia or pneumonia. For children, the definition is broader: the infection is not organism specific, and it includes more organ systems. The cause of death was not recorded in the HPPMCS and was missing for approximately one-quarter of deaths that occurred in CASCADE [11]. Information on injection drug users was excluded from CASCADE data, because this exposure group experiences a disproportionately high number of non–HIV-related deaths [12]. Finally, to avoid an overlap between the 2 studies, all CD4 cell counts determined after patients were 15 years of age were excluded from the HPPMCS, as were measurements obtained for patients in CASCADE whose estimated date of infection occurred before 15 years of age.

The incidence rates of death and progression to initial AIDS diagnosis or death were calculated by accumulating person-time according to the most recent CD4 cell count and age at the time of CD4 cell count determination. Follow-up from the time that each measurement was obtained was censored at the earliest of the following points in time: (1) the date of the next measurement; (2) 12 months after the most recent measurement (to account for irregular follow-up); (3) the date of the last clinical visit (for analyses of AIDS or death [AIDS/death]) or the date the patient was last known to be alive (for analyses of death); or (4) 31 December 1995. Before 1996, combination ART was infrequently used in both studies, and our estimates should therefore approximately reflect the natural history of HIV infection. Smooth incidence estimates determined on the basis of CD4 cell counts and age were obtained by fitting separate Poisson regression fractional polynomial models for HPPMCS (limited to measurements obtained after 5 years of age) and CASCADE (Stata software, version 8.2; Stata Corporation) (see table A1 in appendix A, which appears only in the electronic edition of the Journal). Estimates of incidence rates are displayed on a logarithmic scale to show more clearly the effect of age.

RESULTS

A total of 3244 children from the HPPMCS and 3497 adults from CASCADE were included in the analysis. Selected characteristics of the study population are presented in table 1. In the HPPMCS, a mean of 7.1 CD4 cell counts were measured per child before an event or censoring occurred, with a median interval of 12 weeks (interquartile range [IQR], 8–19 weeks) between successive evaluations; in CASCADE, the corresponding values were 11.1 CD4 cell count measurements and 14 weeks (IQR, 8–26 weeks). These measurements were performed over a wide age range, spanning from birth to ≥60 years, although comparatively few measurements were obtained during the period of adolescence.

Progression to death. A total of 595 deaths were observed over 7790 person-years of follow-up in the HPPMCS, compared with 665 deaths observed over 12,710 person-years of follow-up in CASCADE. Crude and smoothed rates of death, as classified by age and the most recent CD4 cell count, are shown in table 2 and figure 1A. For reference, rates for the general male population in England and Wales were also tabulated. Young children (age, <5 years) had a much higher mortality rate than did older children and adults. For children ≥5 years of age, a slight decrease in the mortality rate occurred in association with increasing age (1.7% decrease/year of age), after adjustment for most recent CD4 cell count; however, this effect was not significant (95% confidence interval [CI], 9.6% decrease/year of age to 6.7% increase/year of age; P = .7). By contrast, age was strongly associated with mortality among adults, with an increase of
The interpretation of these analyses is complicated by the different spectrum of AIDS-defining conditions in children and adults (figure 2). For example, Kaposi sarcoma comprised 15.1% of all initial AIDS diagnoses in CASCADE but was not reported in the HPPMCS. Conversely, serious recurrent bacterial infection was the most frequent AIDS diagnosis in the HPPMCS (in 29.7% of patients) but was rare in CASCADE (in 1.8% of patients). This condition occurred among children ≥5 years of age who had relatively high CD4 cell counts; the median value preceding a diagnosis of AIDS was 250 cells/mm³ for serious recurrent bacterial infection, 80 cells/mm³ for wasting syndrome, 54 cells/mm³ for HIV encephalopathy, and 26 cells/mm³ for opportunistic infections. Similar findings have been reported elsewhere [14, 15]. Because the marked difference in the relative frequency of serious recurrent bacterial infection between children and adults is partly methodological, we repeated the Poisson regression analysis, with the exception that the diagnosis of serious recurrent bacterial infection was treated as a censoring event. This change substantially reduced the estimated risk of disease progression for children, particularly among those with higher CD4 cell counts (figure 1C), with risk estimates for older children becoming similar to or lower than those for young adults.

**DISCUSSION**

This analysis of 2 large, prospective studies by use of a common methodology has provided valuable insights into how the association between the CD4 cell count and the rate of disease progression varies according to patient age—from birth to ≥60 years—in the absence of effective ART.

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**Table 1. Characteristics of patients in the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) and the Concerted Action on Sero-Conversion to AIDS and Death in Europe (CASCADE) collaboration.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HPPMCS (n = 3244)</th>
<th>CASCADE (n = 3497)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year of first CD4 cell count measurement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1983–1989</td>
<td>1225 (38)</td>
<td>1662 (48)</td>
</tr>
<tr>
<td>1990–1992</td>
<td>1230 (38)</td>
<td>924 (26)</td>
</tr>
<tr>
<td>1993–1995</td>
<td>789 (24)</td>
<td>911 (26)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>583 (18)</td>
<td>1655 (47)</td>
</tr>
<tr>
<td>Black</td>
<td>1048 (32)</td>
<td>56 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>764 (24)</td>
<td>43 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>849 (26)</td>
<td>1743 (50)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1577 (49)</td>
<td>2998 (86)</td>
</tr>
<tr>
<td>Female</td>
<td>1667 (51)</td>
<td>499 (14)</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical infection</td>
<td>3244 (100)</td>
<td>27 (&lt;1)</td>
</tr>
<tr>
<td>Sex between men</td>
<td>2413 (69)</td>
<td></td>
</tr>
<tr>
<td>Sex between men and women</td>
<td>702 (20)</td>
<td></td>
</tr>
<tr>
<td>Hemophilia</td>
<td>263 (8)</td>
<td></td>
</tr>
<tr>
<td>Blood and/or tissue recipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational</td>
<td></td>
<td>21 (&lt;1)</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>71 (2)</td>
</tr>
<tr>
<td><strong>Characteristic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NOTE.</strong> Data are no. (%) of patients.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.1%/year of age (95% CI, 2.4%–3.8%/year of age; P < .001) noted. Death rates for individuals with CD4 cell counts of <400 cells/mm³ were comparable in children ≥5 years of age and adults ~20 years of age, with there being some evidence of a lower risk among children with higher CD4 cell counts. Of note, no deaths were observed among children ≥5 years of age who had a CD4 cell count of >350 cells/mm³, despite 1306 person-years of follow-up (upper 95% confidence limit, 0.23 death/100 person-years), which is significantly lower than the mortality rate of 0.63 death/100 person-years for patients aged 15–25 years who had the same CD4 cell count (P = .008, by exact 2-sided Poisson test). Among older children and adults of all ages, mortality increased sharply when the CD4 cell count decreased to a level below 150–200 cells/mm³, with 71% of deaths occurring among patients with a CD4 cell count of <50 cells/mm³.

**Progression to AIDS/death.** A total of 949 children experienced progression to AIDS/death over 5890 person-years of follow-up in the HPPMCS, compared with 945 adults over 11,310 person-years of follow-up in CASCADE. The proportion of patients who died without a reported AIDS diagnosis was similar in the 2 studies: 10.2% (n = 97) in the HPPMCS and 8.9% (n = 84) in CASCADE. The effects of age on progression to AIDS/death, after adjustment for the CD4 cell count, were broadly similar to the effects of age on mortality (table 2) (figure 1b). The incidence of progression to AIDS/death decreased rapidly over early childhood, but the change in incidence noted after 5 years of age (i.e., a 2.7% decrease/year of age [95% CI, 9.4% decrease/year of age to 4.5% increase/year of age]), was not significant (P = .4). In adults, this incidence increased by 1.9%/year of age (95% CI, 1.3%–2.5% increase/per year of age; P < .001), which is slightly weaker than the effect of age on mortality. The incidence of progression to AIDS/death among children ≥5 years of age was within the (broad) range of incidence rates for adults with CD4 cell counts of 150–300 cells/mm³. At a CD4 cell count of 150 cells/mm³, the estimated rate of progression to AIDS/death for a 5-year-old child (12.8 events/100 person-years) was similar to that for a 20-year-old adult (13.0 events/100 person-years); at a CD4 cell count of 300 cells/mm³, the estimated rate of progression to AIDS/death for a 5-year-old child (7.1 events/100 person-years) was closer to that noted for a 50-year-old adult (7.3 events/100 person-years). Compared with adults, older children had a lower incidence of AIDS/death at a CD4 cell count of <150 cells/mm³, as well as a higher incidence at a count of >300 cells/mm³.
The present study establishes that this effect is coupled with an increased susceptibility to clinical disease at the same level of immunologic suppression.

**Comparison of children and adults.** A major objective of our analysis was to assess whether there is an age threshold at which the association between the CD4 cell count and the rate of disease progression in children approximates that observed in adults. The presence of a strong effect of age across adulthood indicates that comparisons must be made with reference to specific ages. Children ≥5 years of age and adults ≥20 years of age had similar mortality rates at a CD4 cell count of <350 CD4 cells/mm³, with there being some evidence of a lower risk among children with higher CD4 cell counts. We therefore speculate that the apparent difference in mortality between older children and younger adults with high CD4 cell counts is due to non–HIV-related deaths.

An important caveat in the comparison of AIDS incidence rates is the different case definitions used for children and adults/
adolescents. In particular, serious recurrent bacterial infection is more broadly defined in the case definition of pediatric AIDS. Also, although each diagnosis should be confirmed by culture, some of the reported cases in the HPPMCS are likely to have been only presumptively diagnosed. Our findings were sensitive to whether we included or excluded cases of serious recurrent bacterial infection. If such cases were included, children showed comparatively high rates of disease progression at higher CD4 cell counts, an effect that is partly methodological but may also reflect the lack of preexisting immunity when perinatally infected children are first exposed to bacterial organisms. Conversely, if serious recurrent bacterial infection was excluded, the difference in the rates of disease progression between older children and adults at higher CD4 cell counts was no longer apparent. One justification for placing more emphasis on the latter analysis, aside from the difficulty of a making a secure diagnosis, is evidence that serious recurrent bacterial infection is a relatively weak prognostic indicator of death (HPPMCS, unpublished data).

Clinical implications. Current treatment guidelines for adults recommend that ART be initiated when the CD4 cell count is 200–350 cells/mm³ [6]; however, pediatric treatment guidelines tend to be more conservative, recommending ART initiation at higher CD4 cell count levels [7]. A key finding from our analysis is that, although data for the period of adolescence are sparse, children ≥5 years of age have short-term risks of AIDS and death that are lower than or similar to those for adults with a CD4 cell count in the range for which treatment is usually considered. In particular, no deaths occurred among older children with a CD4 cell count of >350 cells/mm³. Therefore, it would seem logical to achieve consistency between pediatric and adult treatment guidelines, in terms of the CD4 cell count criteria for initiation of ART, although there is important variation in the immunologic and virologic response to ART by age [22]. The CD4 cell count criteria for younger children is more problematic, and there is ongoing debate on the use of the CD4 cell count or CD4 cell percentage for clinical monitoring of this age group, including the question of how discordant values of these markers should be interpreted [4]. Finally, there currently is much interest in conducting an international trial to determine the optimal CD4 cell count thresholds for initiation of ART [23]. Our results indicate that the inclusion of older children would enhance the generalizability of data from such a study, although the possibility of heterogeneous effects associated with age would need to be carefully examined [24].

STUDY ORGANIZATIONS

HPPMCS steering committee. D.T.D., D.M.G., T.D., and A.G. Babiker (Medical Research Council Clinical Trials Unit, London, United Kingdom); J. P. Aboulker (Institut National de la Santé et de la Recherche Médicale SC10, Villejuif, France); M. Bulterys (Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; Perinatal AIDS Collaborative Transmission Study); M. Cortina-Borja (Institute of Child Health, University College London, London, United Kingdom; European Collaborative Study); C. Gabiano (Department of Pediatrics, University of Turin, Turin, Italy; Italian Register for HIV Infection in Children); L. Galli (Department of Pediatrics, University of Florence, Florence, Italy; Italian Register for HIV Infection in Children); C. Giaquinto (Department of Pediatrics, University of Padova, Padua, Italy; Paediatric European Network for Treatment of AIDS); D. R. Harris (Westat, Rockville, Maryland; National Institute of Child Health and Human Development [NICHD] Intravenous Immunoglobulin Study Group); M. Hughes (Harvard School of Public Health, Boston, Massachusetts; Pediatric AIDS Clinical Trials Group)
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CASCADE coordinating centre members. K.P. (Project Leader), Krishnan Bhaskaran (Scientific Coordinator), Sarah Walker, Abdel Babiker, and Janet Darbyshire.


CASCADE location, cohort (collaborators). In Australia, the Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (John Kaldor, Tony Kelleher, Tim Ramacciotti, David Cooper, and Don Smith); in Canada, South Alberta Clinic (John Gill); in Denmark, the Danish HIV Cohort Study (Court Pedersen, Louise Bruun Jørgensen, and Claus Nielsen); in Estonia, Tartu Ülikool (Irja Lutsar); in France, the Aquitaine cohort (Geneviève Chêne, Francois Dabis, and Rodolphe Thiebaut), the French Hospital Database (Dominique Costagliola), the Lyon Primary Infection cohort (Philippe Vanhems), and the SEROCO cohort (Laurence Meyer and Faroudy Boufassa); in Germany, the German cohort (Osamah Hamouda and Claudia Kucherer); in Greece, the Greek Haemophilia cohort (Giota Touloumi, Nikos Pantazis, Angelos Hatzakis, Dimitrios Paraskevis, and Anastasia Karafoulidou); in Italy, the Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucci, Benedetta Longo, and Claudia Balotta); in The Netherlands, the Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, Liselotte van Asten, Akke van der Buij, Ronald Geskus, and Roel Coutinho); in Norway, the Oslo and Ulleval Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, Anne Eskild, and Johan N. Bruun); in Poland, the National Institute of Hygiene (Magdalena Rosinska); in Portugal, Universidade Nova de Lisboa (Ricardo Camacho); in Russia, the Pasteur Institute (Tatyana Smolskaya); in Spain, the Badalona injection drug user (IDU) hospital cohort (Roberto Muga), the Barcelona IDU cohort (Patricia Garcia de Olalla), the Madrid cohort (Julia Del Amo and Jorge del Romero), and the Valencia IDU cohort (Santiago Pérez-Hoyos and Ildefonso Hernandez Aguado); in Switzerland, the Swiss HIV Cohort (Heiner Bucher, Martin Rickenbach, and Patrick Francioli); in Ukraine, the Perinatal Prevention of AIDS Initiative (Ruslan Malysuta); and in the United Kingdom, the Edinburgh Hospital Cohort (Ray Brettte), the Health Protection Agency (Valerie Delpch, Sam Lattimore, Gary Murphy, John Parry, and Noel Gill), the Royal Free Hae-
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References