A Descriptive Study of HIV-infected Long-term Surviving Children in Barbados
A Preliminary Report
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ABSTRACT

OBJECTIVES: To describe the clinical and immunologic characteristics of human immunodeficiency virus type-1 (HIV-1)-infected children surviving to more than eight-years of age (long-survivors) before the introduction of antiretroviral therapy.

METHODS: This report is based on all the long-term survivors from a prospective cohort of HIV-infected children born to HIV-positive women in Barbados during 1986-1995. Infants born to HIV-infected women were enrolled into this cohort at birth or at the time of diagnosis of HIV exposure in the postnatal period and followed-up at regular intervals.

RESULTS: From a cohort of 44 HIV-infected children, 17 (38.6%) children survived to the age of eight years and beyond and were classified as long-term survivors. Median age of the sixteen long-term surviving children alive at the time of this report was 12 years (age range 8 – 16.7 years). At the age of 8 years, 17.6% of these children remained asymptomatic. Nine (52.9%) children had no immunodeficiency (CD4 counts >500 cells x 10^6/L). Of the 16 long-term surviving children who were alive and had a median follow-up of 4.1 years (range 0.1 year to 8.5 years) after their eighth birthday, 37.5% had a CD4 cell count greater than 500 cells x 10^6/L and had either no symptoms or only mild symptoms of HIV infection and were therefore categorized as the long-term non-progressors.

CONCLUSIONS: In a small cohort of HIV-infected children, in the absence of antiretroviral therapy, only about one-third survived beyond eight years of age. On further follow-up of these long-term surviving children, over one-third had a slow rate of disease progression.

Estudio Descriptivo de Niños Infectados por el VIH Sobrevivientes a Largo Plazo en Barbados
Un Informe Preliminar
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RESUMEN

OBJETIVOS: Describir las características clínicas e inmunológicas de niños infectados por el VIH-1, que lograron sobrevivir hasta más de ocho años de edad (sobrevivientes a largo plazo) antes de la introducción de terapia antiretroviral.

MÉTODOS: Este informe se basa en todos los sobrevivientes a largo plazo de una cohorte prospectiva de niños infectados por el VIH nacidos de mujeres VIH positivas en Barbados, durante los años 1986-1995. Los niños nacidos de mujeres infectadas por el VIH fueron enrolados en esta cohorte al nacer o en el momento de diagnóstico de exposición al VIH en el periodo postnatal, y seguidos a intervalos regulares.

RESULTADOS: De una cohorte de 44 niños infectados por el VIH, 17 niños (38.6%) sobrevivieron hasta los ocho años de edad y más, clasificándoseles por ende como sobrevivientes a largo plazo. La
INTRODUCTION
Survival pattern among children infected with the human immunodeficiency virus (HIV) follows a bimodal distribution. Some children survive beyond eight-years of age and are known as long-term survivors (LTS) while others had a more rapid course to death during the first few years of life (1, 2). In the LTS group of children, two populations have emerged: the long-term non-progressors (LTNP) who have remained asymptomatic or only mildly symptomatic over a period of years, and those who have survived despite clinical and laboratory evidence of disease progression, long-term progressors (LTP). Long-term survivors provide a unique opportunity to investigate the immunologic, virological and genetic characteristics of HIV-infected children to determine what factors may slow progression to disease and death.

Data on the long-term survivors among children infected with HIV type-1 (HIV-1) by perinatal exposure and followed prospectively is scarce. Available reports show a high variability in mortality and morbidity indicators according to the study settings and a probable bimodal evolution of paediatric HIV disease (3-5). The authors studied a cohort of HIV-infected children born between 1986 and 1995 and who were followed-up for eight or more years, to identify the long-term survivors and to elucidate the pattern of disease progression in these children, in the absence of any antiretroviral therapy. This study describes the clinical, immunologic and virologic characteristics of vertically HIV-1-infected children (vertical transmission) older than eight-years of age before the introduction of antiretroviral therapy.

METHODS
This is a descriptive study based on the data collected from a cohort of children infected with HIV from perinatal transmission and being followed-up prospectively from birth or the time of diagnosis. This cohort includes all the children infected with HIV from perinatal transmission in Barbados and who were born between 1986 and 1995. Detection of HIV infection in pregnant women was achieved by way of voluntary counselling and testing during pregnancy. Infants known to be exposed to HIV in the perinatal period were followed-up from birth and enrolled in the cohort when they were diagnosed to be infected. Infants were also enrolled when they were detected to have been exposed to HIV in the postnatal period when either or both parents were found to be HIV-infected.

Diagnosis of HIV was established by a positive HIV serology at 18 months of age or by two positive RNA PCR tests between four and six months of age. Children diagnosed to be infected with HIV are followed-up every six months, or more frequently, if necessary. All follow-up is done at the Queen Elizabeth Hospital. At each follow-up visit, systematic enquiries and detailed examination were conducted to ascertain the disease progression. Blood samples were drawn for CD4 cell count. Clinical and immunological classification were based on the CDC’s 1994 revised classification system for HIV infection in children less than 13 years of age (6). The HIV infected children surviving beyond eight-years of age were categorized as the long-term survivors (LTS).

Proportion and 95% confidence interval (CI) were calculated using binomial distribution and results were corrected for continuity. Epi Info 6 software (Website – http://www.cdc.gov/epiinfo/about.htm) was used for the statistical analysis including chi-square test. The chi-square test was used to compare the distribution of HIV-infected children who survived longer than eight-years, and were born during 1986 to 1990, with those who were born during 1991 to 1995. Statistical significance was evaluated at a p < 0.05 level.

RESULTS
During 1986 to 1995, 44 HIV-infected children comprising 25 (58.6%) males and 19 (43.2%) females were enrolled in the Barbados cohort of perinatally HIV-infected children (Table 1). Twenty-nine (65.9%) children were born to women known to be HIV-infected at the time of delivery and were diagnosed to be HIV-infected during their routine postnatal follow-up. Fifteen (44.1%) children were born to women who were not known to be HIV-infected at the time of delivery but were diagnosed to be HIV-infected during the postpartum period when either one of their parents or siblings
became known to be HIV-infected. None of the HIV-exposed infants born to women known to be HIV-infected in pregnancy had had any perinatal antiretroviral prophylaxis. None of the infected children received any antiretroviral therapy before 2002. Co-trimoxazole prophylaxis for Pneumocystis jirovecii pneumonia was prescribed for all HIV-infected children under one year of age and to all others as needed based on their CD4 cell count.

From a cohort of 44 HIV-infected children, 17 (38.6%, 95% Confidence Interval [CI]: 24.7%, 54.5%) survived to the age of eight years and beyond and were classified as long-term survivors (LTS). Sixteen children were alive at the time of this report (June 2003). Median age of the long-term surviving children alive at the time of this report was 12 years (age range 8 – 16.7 years). Of the HIV-infected children born during 1986 to 1990, 42% (95% CI: 21.1%, 66.0%) survived to the age of eight years or more and were LTS while children born during the 1991 to 1995, 36% (95% CI: 18.7%, 57.4%) were LTS and all were alive at the time of this report. There was no significant difference in the proportion of children born during 1986 to 1990 who survived to the age of eight years or more as compared with those born between 1991 to 1995 (p = 0.9).

The pattern of disease status of the long-term surviving HIV-infected children is shown in Table 2. At the age of eight-years, 17.6% (95% CI: 4.7%, 44.2%) presented no HIV-1-associated signs (CDC class N) and 17.6% (95% CI: 4.7%, 44.2%) had severe clinical manifestations (CDC class C symptomatic conditions). Nine (52.9%, 95% CI: 28.5%, 76.1%) children had no immunodeficiency (CD4 counts >500 cells x 10^6/L) whereas three (17.6%, 95% CI: 4.7%, 44.2%) had severe immunodeficiency (CD4 cell counts < 200 cells x 10^6/L).

The follow-up of the 17 children from eight years of age (median follow-up period 4.1 years, range 0.1 year to 8.5 years) showed that one (5.9%, 95% CI: 0.3%, 30.8%) child died at the age of nine years and 16 (94.1%, 95% CI: 69.2%, 99.7%) were alive at the time of this report. Clinical and immunological characteristics of the 16 LTS children at their last follow-up are shown in Table 3. Of the 16 LTS children alive at the time of this report, 6 (37.5%, 95% CI: 16.3%, 64.1%) had a CD4 cell count greater than 500 cells x 10^6/L and had either no symptoms (CDC Class N) or only mild symptoms (CDC Class A) and had either no symptoms (CDC Class N) or only mild symptoms (CDC Class A) of HIV infection and were therefore categorized as the long-term non-progressors (LTNP). Whereas 62.6% (95% CI: 35.9%, 83.7%) were categorized as the long-term progressors (LTP) and had CD4 cell counts less than 500 cells x 10^6/L and/or were symptomatic with CDC class B or C sign and symptoms (Fig. 1).

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### DISCUSSION

This is the first report describing the clinical and immunologic characteristics of long-term surviving HIV-infected children of Afro-Caribbean descent from a prospective cohort infected perinatally. From a cohort of 44 children with HIV infection acquired from perinatal transmission and followed-up from birth or early infancy, 45.5% survived to the age of five years or more and 38% survived to the age of eight years or older and qualified for the category of long-term survivors.
In the absence of any antiretroviral treatment, a smaller proportion of the HIV-infected children in Barbados survived to the age of eight years or more compared to those from developed countries in Europe and the Americas with reported survival of 68% to 75% at five years of age (2, 7–11). However, many of the children reported in the studies from the developed countries had some antiretroviral therapy with or without protease inhibitors. Studies from the developing countries in Africa have reported a similar pattern with survival at five years of age in the range of 38% to 49% (11–13). We did not find any long-term prospective cohort studies which followed HIV-infected children without any antiretroviral medication exposure for eight or more years so as to make suitable comparison. This study adds to our knowledge of the natural course of the HIV infection among children of African descent.

At eight years of age, just under two-thirds of the LTS children were either asymptomatic (CDC Class N) or had only mild (CDC Class A) symptoms. These findings are similar to those reported by Salvini et al from Italy (14). They observed that at the age of eight years, only 16.6% had severe clinical manifestations (AIDS) and 23.3% of children presented no HIV-1-associated signs or only mild ones. The disease progression after the age of eight years among these 17 LTS children was also similar to those reported by Salvini et al (14). It is of note that children described by Salvini et al received some antiretroviral therapy, although protease inhibitors were not used. Over a third of LTS children alive at the time of this report remained asymptomatic or had only mild non-specific symptoms with no immunodeficiency and was therefore defined as long-survivors non-progressors (LSNP). Only four (25%) children had AIDS defining features. Less than one-third of the LTS children had a CD4 cell count less than 200/cubic mm. In a report from the Italian Register, 41% of HIV-infected children eight years or older who were infected perinatally had a CD4 cell count less than 200/mm (9).

In another study from the USA, Nielsen et al found that 50% of vertically infected children had an AIDS-defining condition by eight years or older at their last contact date (15). We conclude that the overall disease progression in LTS HIV-infected children in the present study in the absence of any antiretroviral therapy was at a slower pace when compared with some other reports (9, 15).

REFERENCES