Clinical Outcomes Improve with Highly Active Antiretroviral Therapy in Vertically HIV Type-1–Infected Children

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Background. Use of antiretroviral therapy has resulted in a decrease in morbidity and mortality rates in human immunodeficiency virus type 1 (HIV-1)–infected children.

Methods. We performed a retrospective study involving 427 children to determine the effectiveness of different antiretroviral therapy protocols on clinical outcome. The follow-up period was divided into 5 calendar periods (CPs): CP1 (1980–1989), before antiretroviral therapy was administered; CP2 (1990–1993), when monotherapy was administered; CP3 (1994–1996), when combined therapy was administered; CP4 (1997–1998), when ⩽50% of children were receiving highly active antiretroviral therapy (HAART); and CP5 (1999–2003), when ⩾60% of children were receiving HAART.

Results. Children experienced a progressive increase in the $CD4^+$ cell count and decrease in the viral load from 1997 onwards. A lower number of AIDS cases and deaths occurred during CP5 than during the other CPs ($P < .01$), with a relative risk of an absence of AIDS of >20 and a relative risk of survival of >30. The AIDS rate was >50% in CP1; we observed a very strong decrease to 14% in CP2, to 16% in CP3, to 7% in CP4, and to 2% in CP5. The mortality rates in CP2 and CP3 were >6% and thereafter decreased to 0.5% in CP5. The relative risks for no hospital admission in CP4 and CP5 were >3.5. The total rates of hospital admission in CP1, CP2, and CP3 were >30%; we observed a decrease in CP4 and CP5. The duration of hospitalization decreased during the follow-up period, and it was higher in CP1 (~30 days) than in the other periods.

Conclusions. We observed that HAART produces a decrease in adverse clinical outcomes (i.e., hospital admission, AIDS, and death) in children with vertical HIV-1 infection in Madrid, Spain.

Since the first study of HIV-1–infected children confirmed the efficacy of antiretroviral therapy [1], a broad range of therapies have been tested. More recently, combinations of 3 and 4 drugs have proved to be highly effective in suppressing the viral load and increasing the $CD4^+$ T cell count in children [2]. Patients receiving HAART experience general clinical improvement [3–5].

The clinical course of HIV-1 infection in children is different than that in adults [6, 7], and this fact has important implications for antiretroviral therapy in children [6, 7]. The number of children receiving HAART has been increasing, because new formulations of protease inhibitors (PIs) have subsequently been made suitable for children [8, 9]; thus, there has been a substantial decrease in progression to AIDS and in the mortality rate [10–12].

The aim of this observational study was to compare the effectiveness of different therapeutic strategies over a 2-decade period by defining the impact of newer antiretroviral therapy regimens on clinical outcomes in HIV-1–infected children in Madrid, Spain.

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MATERIALS AND METHODS

Population and study design. A retrospective observational study of a cohort of 427 vertically HIV-1–infected children was performed for the period from 29 January 1980 (when the first vertically HIV-1–infected child in Madrid was born) to 2003 at 5 large pediatric referral hospitals in Madrid (Hospital General Universitario "Gregorio Marañón," 117 children; Hospital Universitario "12 de Octubre," 110 children; Hospital Universitario "La Paz," 106 children; Hospital Universitario "Carlos III," 67 children; and Hospital Universitario "Niño Jesus," 27 children). The care delivered at the 5 sites was similar. In Spain, only cases of AIDS are registered. A total of 909 children had received a diagnosis of AIDS by 7 March 2004, and 231 children (~25%) were in our cohort. Thus, we can suppose that our cohort represents 25% of HIV-1–infected children infected in Spain.

Initially, serologic tests for HIV-1 antibody were routinely performed at each visit for children who had previously been found to be HIV-1 seropositive and who had been born to seropositive mothers. Confirmation of HIV-1 infection was determined by the physicians and/or through hospital summaries. When DNA PCR and virus culture assays became available, all infants with HIV-1 infection received diagnoses on the basis of positive results of these assays [13]. Clinical classifications and definitions of AIDS-related events were based on the 1994 revised guidelines of the Centers for Disease Control and Prevention [14]. Before 1994, HIV-1–infected children with an AIDS diagnosis were again recategorized according to Centers for Disease Control and Prevention criteria. Moreover, children in clinical category A or B who turned 13 years old were not recategorized as having AIDS by T cell count criteria when they reached a $CD4^+$ T cell <200 cells/μL [15]. Death and hospitalization data were obtained from the hospital records at the participating centers or from other associated centers (when these happened outside).

This study was approved by the ethical committees at all hospitals involved. The children were observed at least every 3 months, in accordance with published guidelines [16]. There was not a uniform approach to antiretroviral therapy or to prevention of *Pneumocystis carinii* infection. Instead, each pediatrician administered the appropriate regimen and changed the drugs according to his or her interpretation of the clinical data and international guidelines [16–19].

Exposure variables. Children were divided into 5 groups on the basis of the antiretroviral therapy protocols that had been preferentially used (figure 1*A*) during the follow-up calendar period (CP) [20–22]. CP1 was the period from 29 January 1980 to 31 December 1989 and included HIV-1–infected, untreated children. CP2 was the period from 1 January 1990 to 31 December 1993 and included children who were receiving monotherapy with 1 nucleoside analogue reverse-transcriptase inhibitor (NRTI); in this group, >60% of the children were not receiving antiretroviral therapy, and >25% were receiving monotherapy. CP3 was the period from 1 January 1994 to 31 December 1996 and included children who were receiving combined therapy with 2 NRTIs; >40% of the children were not receiving antiretroviral therapy, and >35% were receiving monotherapy. CP4 was the period from 1 January 1997 to 31 December 1998 and included children who were receiving HAART with ⩾3 drugs (NRTIs, PIs, and/or nonnucleoside reverse-transcriptase inhibitors [NNRTIs]); <50% of the children were receiving HAART. CP5 was the period from 1 January 1999 to 31 December 2003; in this period, >60% of the children were receiving HAART, and <10% remained untreated. When a child included in a CP switched his or her antiretroviral therapy protocols or antiretroviral drugs (PIs or NNRTIs), we counted him or her as many times as he or she changed treatments.

Outcomes. The outcome variables were hospital admission, AIDS, and death. Additional variables were a $CD4^+$ cell percentage of >25% and a viral load of <400 copies/mL.

Statistical analysis. We calculated the mean $CD4^+$ T cell count and $\log_{10}$ viral load per year, which were considered to be representative measurements from each patient per year and per CP. The $CD4^+$ cell percentage and viral load were calculated only for groups that included >6 children. We calculated the percentage of children with a $CD4^+$ cell percentage >25% and the percentage of children with a viral load <400 copies/mL per year and per CP. These $CD4^+$ T cell counts and viral loads were used to measure the changes during each calendar year and were plotted.

For the purpose of this study, the moment of infection was assumed to be the date of birth [11]. The children entered the risk set at the date of birth, the date of entry into the cohort group, or the date at the beginning of each CP [11]. We divided the times into 5 periods, and the specific treatment that a child received was not considered, such that, for each CP, the times from birth to hospital admission, AIDS, or death were subdivided into several periods. For example, in CP5, for an individual child, if the child was included in the study period at the age of 1 year, he or she was evaluated at the age of 1, 2, 3, 4, or 5 years, corresponding to each year of the study period. The patients were censored at 18 years of age; thus, 3 children were censored in CP4 and 31 were censored in CP5 among the children born before 1990, because they were >18 years old at the start of the CP.

We determined the occurrence of hospital admission, AIDS, and death using the Greenwood method with use of Kaplan-Meier curves on SPSS software, version 12 (SPSS). CP groups were compared using the Mantel-Haenszel log-rank test. We estimated the relative risk (RR) of absence of hospital admission, AIDS, and death by proportional hazard Cox regression, according to the effect of CP. The American Society of Anesthesiologist Physical Status Classification Scale (PSCS) was used

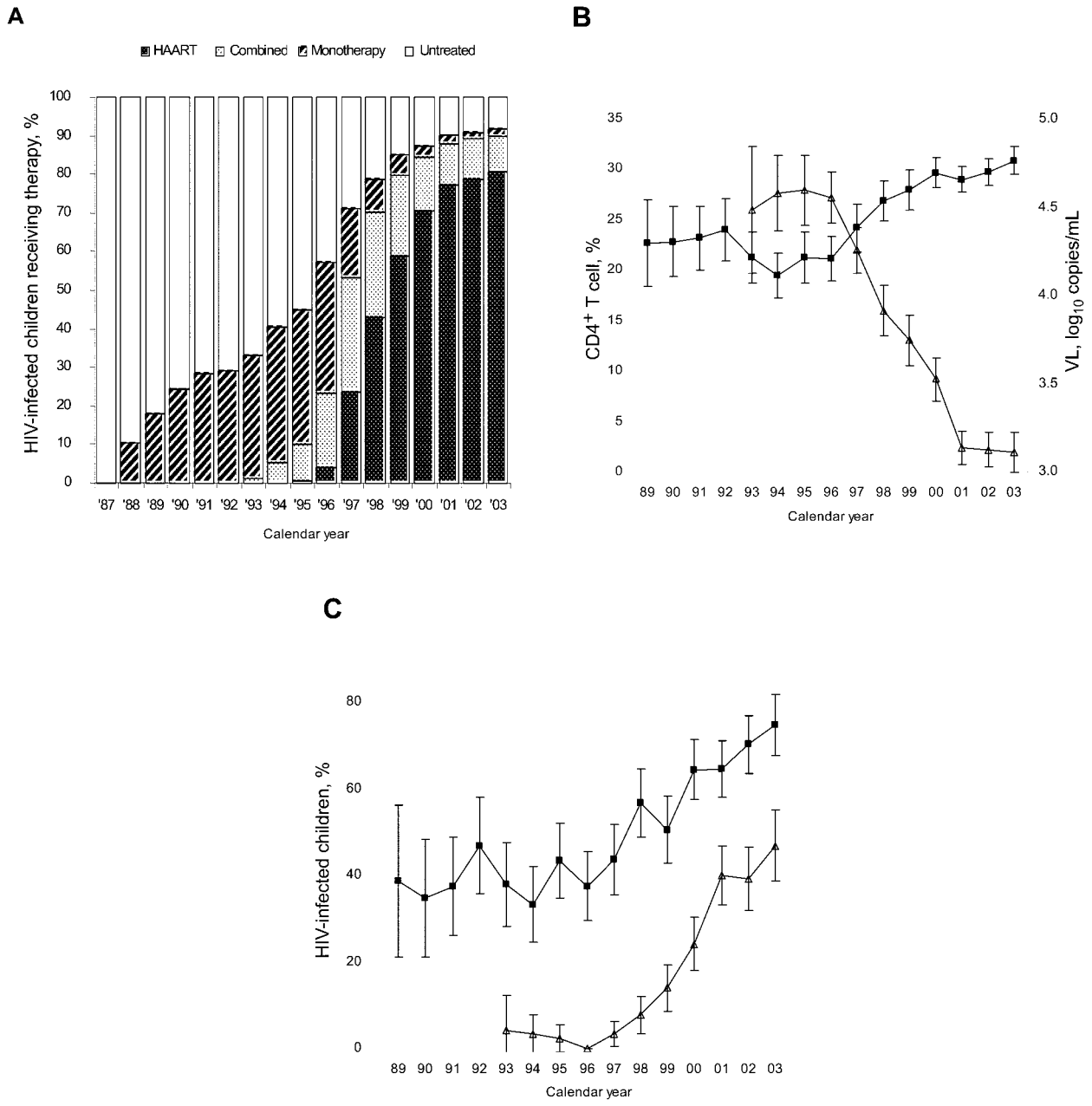


Figure 1. Antiretroviral therapy, CD4+ T cell percentage, and viral load (VL) among HIV-1–infected children, by calendar year. *A,* Use of antiretroviral therapy among vertically HIV-1–infected children, according to calendar year, 1987–2003. *B,* Mean CD4+ T cell percentage (■) and plasma $\log_{10}$ VL (△). *C,* Percentage of HIV-1–infected children with a CD4+ T cell percentage >25% (■) and a VL <400 copies/mL (△).

to asses the physical status of children at hospital admission [23, 24]. We divided the PSCSs of the children into 2 groups (<4 and ⩾4) on the basis of clinical severity at each hospital admission. The CP was introduced in the model as a time-dependent variable.

A Poisson model was used for calculating the event rate in each CP, as follows: the event rate percentage equalled the number of events/(100 × the number of person-years at risk). We also calculated significant statistical differences by Poisson regression analysis. Poisson regression analysis was used because it is particularly good for hospitalization in which the majority of the population has undergone ⩽1 hospitalization (i.e., it adjusts for the overdispersion of data). Moreover, we calculated the length of stay in each period as follows: the length of stay equalled the duration of hospitalization (in days)/the number of children who had a hospital admission.

We used the first hospital admission in Kaplan-Meier and Cox regression analyses, but we used all hospital admissions to

calculate the event rate and length of stay, because one period could include several hospital admissions, and because subjects could have had different grades of severity and lengths of stay.

RESULTS

Characteristics of children. The mean age of children increased during the follow-up period, and the percentage of children with a prior diagnosis of AIDS was high in the last period (CP5; 1999–2003), because there were few deaths. Also, the number of new vertically HIV-1–infected children decreased after 1996 (table 1). Unfortunately, we have only the date of diagnosis of HIV-1 infection for ~50% of children. According to these data, 28% of children in CP1 (1980–1989), 11% of those in CP2 (1990–1993), 7.8% of those in CP3 (1994–1996), and 0% of those in the HAART era (CP4; 1997–1998) received a diagnosis of HIV-1 infection when they were >5 years of age.

The patients observed at these 5 hospitals had similar demographic and clinical characteristics. Moreover, the rates of AIDS, death, and hospitalization were similar across the sites. The treatments administered were also comparable across the 5 centers during each period.

Figure 1*A* shows the antiretroviral therapy protocols that were used. Some children received only NRTIs during all follow-up periods, but the percentage decreased as HAART was incorporated. No children began to receive antiretroviral therapy regimens that included only NRTIs during CP4 and CP5, but the children who continued to receive only NRTIs (because they started treatment during a previous CP) had $CD4^+$ cell percentages >25% and viral loads <10,000 copies/mL. Moreover, children experienced a progressive increase in the $CD4^+$ T cell count and decrease in the viral load from 1997 onwards (figure 1*B* and 1*C*).

Clinical progression of children. We found that HAART use had a considerable impact on outcome. During CP5, there were fewer AIDS cases among children, compared with other CPs ($P < .01$), and the RR for absence of AIDS was >20 in CP5 (figure 2*A* and 2*C*). Moreover, the lowest number of deaths among children occurred during CP5, and the RR for survival was >30 (figure 2*C*).

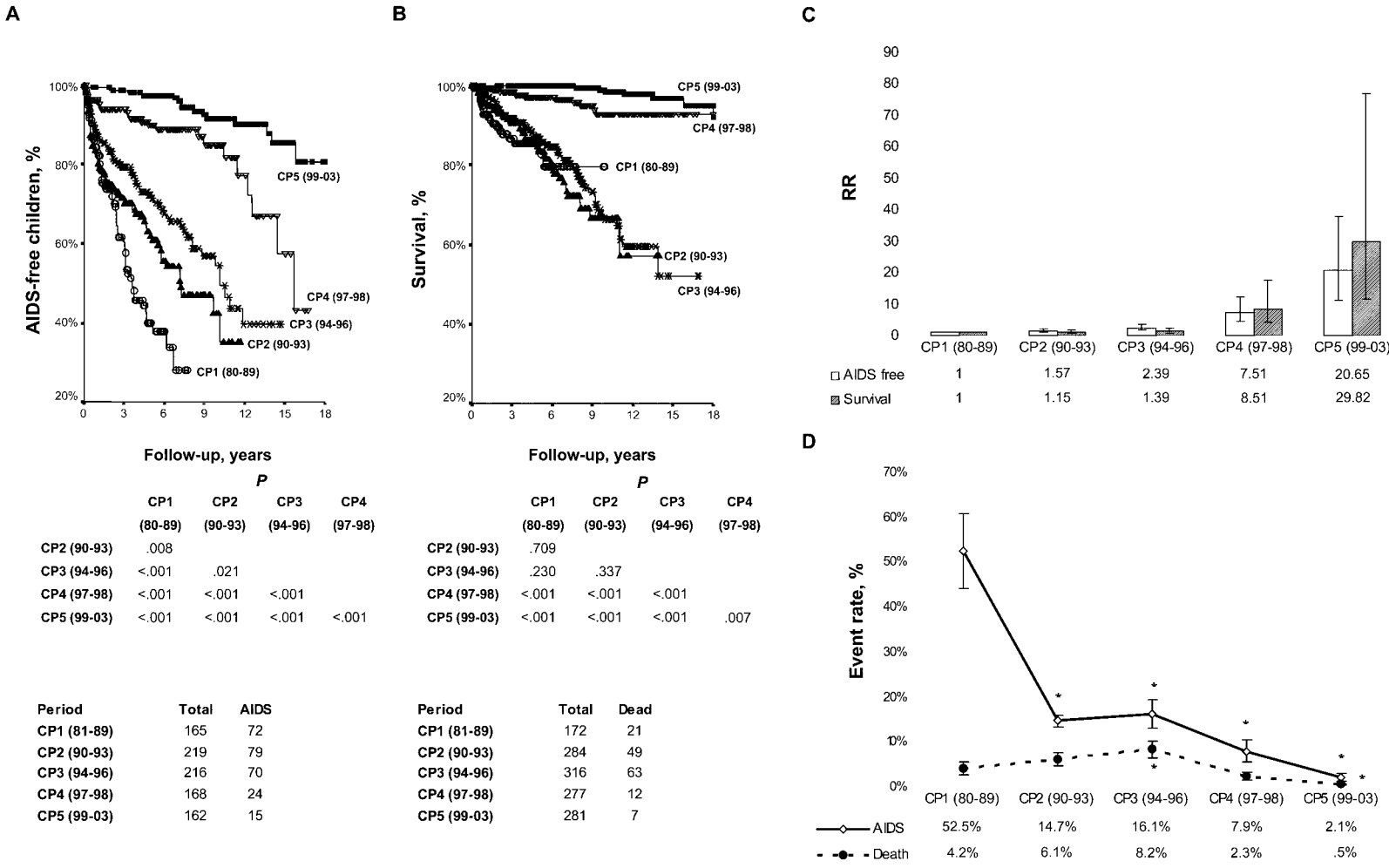
The AIDS rate was >50% in CP1, but it slowly decreased in CP2 and CP3. We observed a very strong decrease in CP4 and CP5, when the rate reached 7% and 2%, respectively (figure 2*D*). The death rate in CP1 was lower than in CP3, and the rate decreased thereafter, until it reached 0.5% in CP5.

Moreover, we found that the cumulative incidences of AIDS, encephalopathy, and death for each birth period decreased during the follow-up CPs (figure 3), although during the HAART period (1997–2003), the cumulative incidences were very low for all birth periods. Figure 3*C* does not include the cumulative incidences of encephalopathy during CP1 and birth period 1

Table 1. Demographic, clinical, immunological, and virological characteristics of HIV-1–infected children at the start of each calendar period (CP).

Characteristic	Period			
	CP2	CP3	CP4	CP5
No. of HIV-1–infected children	284	316	277	281
Age, mean years ± SEM	3.6 ± 0.6	4.6 ± 0.6	6.1 ± 0.6	7.7 ± 0.6
No. of male children	131	141	122	122
Date of birth, no. (%) of children				
Before 1990	151 (53.2)	121 (38.3)	92 (33.2)	87 (31.0)
1990–1993	133 (46.8)	115 (36.4)	92 (33.2)	90 (32.0)
1994–1996	…	80 (25.3)	69 (24.9)	64 (22.8)
1997–1998	…	…	24 (8.7)	22 (7.8)
1999–2003	…	…	…	18 (6.4)
CDC clinical stage of HIV-1 infection, % of children				
A	39	34	31	32
B	22	29	20	18
C	39	37	49	50
Immunological characteristic, mean % ± SEM				
$CD4^+$ T cell percentage	22.8 ± 1.7	19.5 ± 1.1	24.2 ± 1.2	28.2 ± 1.0
$CD8^+$ T cell percentage	42.5 ± 2.5	41.3 ± 1.5	42.8 ± 1.3	39.8 ± 1.1
Viral load, mean $\log_{10}$ copies/mL ± SD	…	4.58 ± 0.11	4.26 ± 0.06	3.75 ± 0.07
No. (%) of children with a viral load <400 copies/mL	…	2 (3.3)	5 (3.4)	23 (14.1)

NOTE. The dates of the CPs are as follows: CP1, 1980–1989 (not shown); CP2, 1990–1993; CP3, 1994–1996; CP4, 1997–1998; and CP5, 1999–2003. The data for CP1 are not included. CDC, Center for Disease Control.



P

	CP1 (80-89)	CP2 (90-93)	CP3 (94-96)	CP4 (97-98)
CP2 (90-93)	.008			
CP3 (94-96)	<.001	.021		
CP4 (97-98)	<.001	<.001	<.001	
CP5 (99-03)	<.001	<.001	<.001	<.001

Period	Total	AIDS
CP1 (81-89)	165	72
CP2 (90-93)	219	79
CP3 (94-96)	216	70
CP4 (97-98)	168	24
CP5 (99-03)	162	15

P

	CP1 (80-89)	CP2 (90-93)	CP3 (94-96)	CP4 (97-98)
CP2 (90-93)	.709			
CP3 (94-96)	.230	.337		
CP4 (97-98)	<.001	<.001	<.001	
CP5 (99-03)	<.001	<.001	<.001	.007

Period	Total	Dead
CP1 (81-89)	172	21
CP2 (90-93)	284	49
CP3 (94-96)	316	63
CP4 (97-98)	277	12
CP5 (99-03)	281	7

Figure 2. Kaplan-Meier curves for vertically HIV-1–infected children without AIDS *(A)* and for survival *(B),* according to calendar period (CP). Also, we evaluated the relative risk (RR) of absence of AIDS and survival *(C)* and rates of AIDS and death in each period *(D).* Statistically significant differences were defined as $P < .05$ and were calculated in comparison with CP1 (1980–1989).

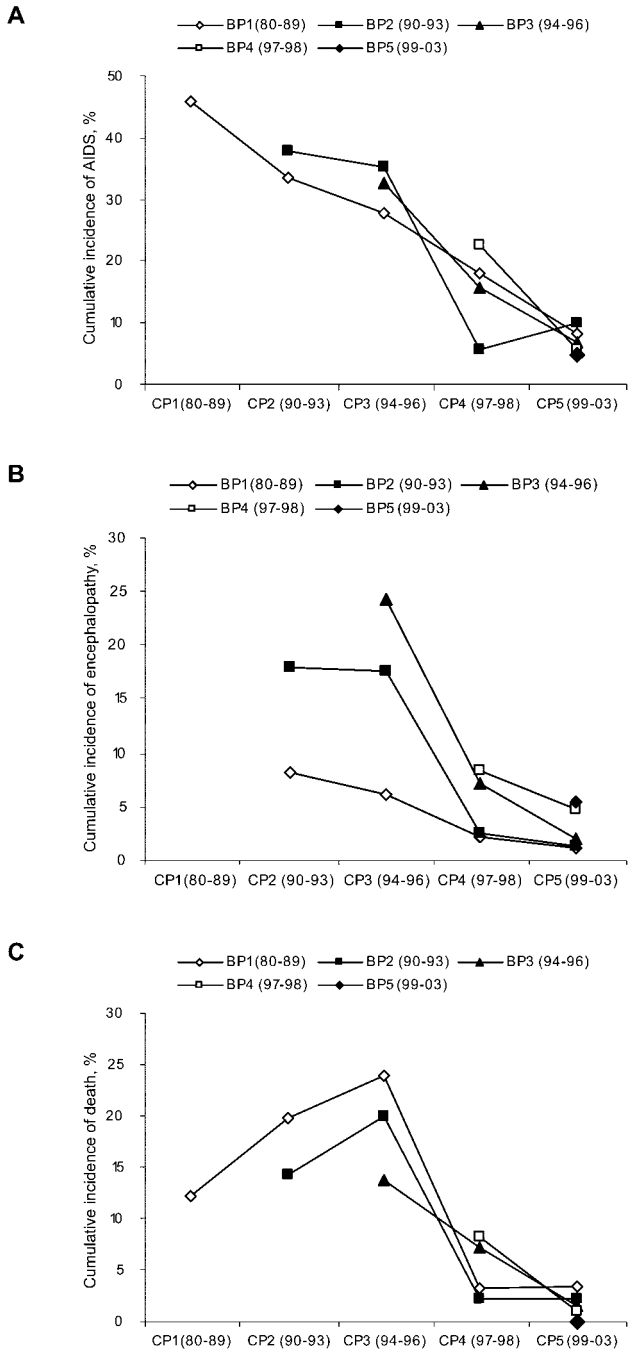


Figure 3. Cumulative incidence of new cases of AIDS *(A),* encephalopathy *(B),* and death *(C)* among children, according to birth period (BP) and calendar period (CP).

(1980–1989), because we did not have trustworthy data. It is possible that the incidences were elevated and that children had died before encephalopathy was diagnosed.

Hospital admission. Despite introduction of antiretroviral therapy in CP2, there was not an evident benefit to therapy with regard to hospital admission. However, CP3 showed significant differences from the previous CPs (figure 4*A*). From 1997 onwards, the number of children who did not have any hospital admissions was high, and we did not find any differences in this number between CP4 and CP5. The RRs for no hospital admissions in CP4 and CP5 were >3.5 (figure 4*C*). The total rates of hospital admission for CP1, CP2, and CP3 were >30%; however, we observed a decrease in these rates for CP4 and CP5 (figure 4*D*).

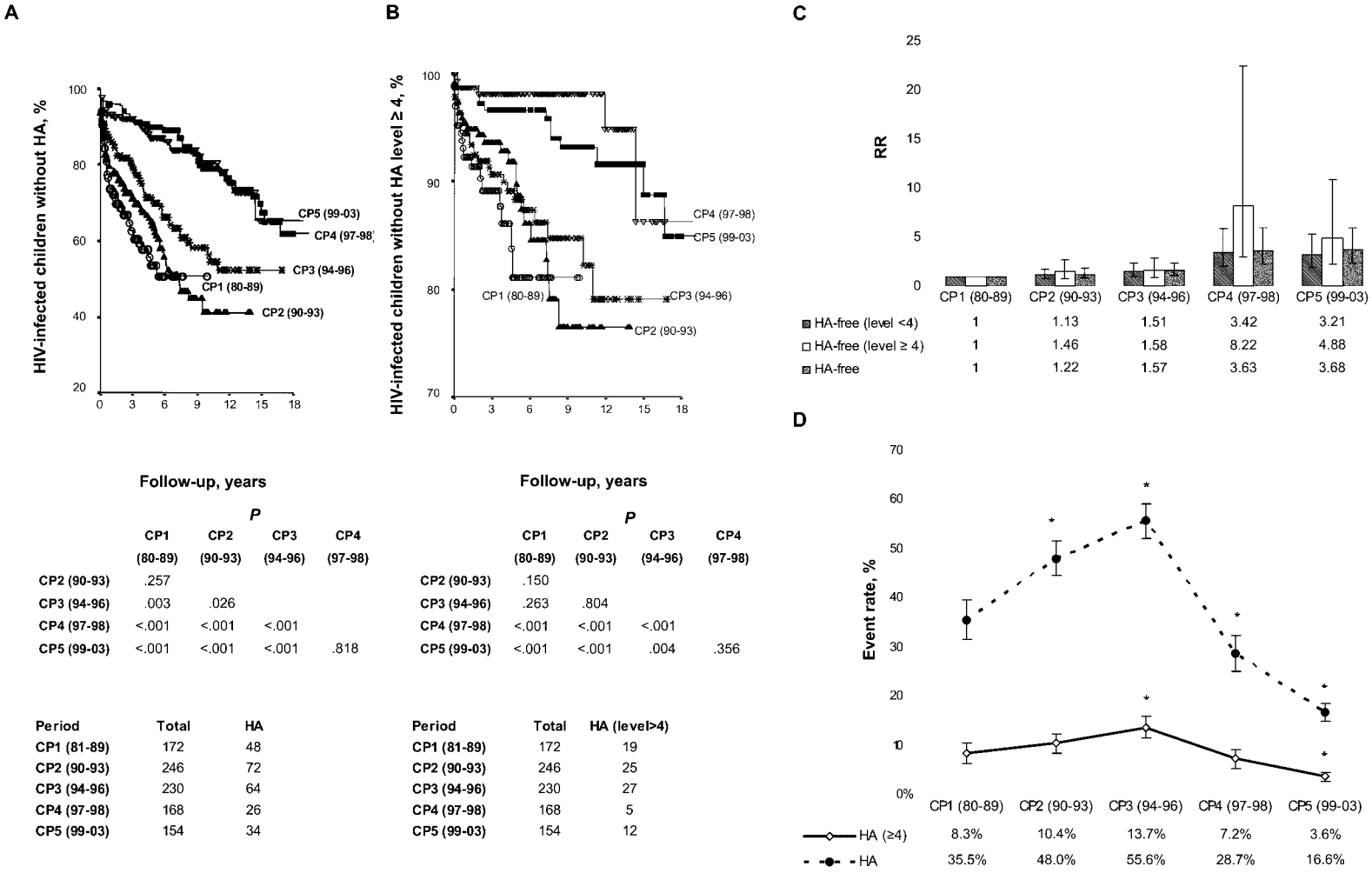
Figure 4*B* shows the percentages of children without hospital admissions and of those with hospital admission PSCSs of 4 or 5. In this analysis, the impact of antiretroviral therapy appears later. Only CP4 and CP5 were shown to have had significant differences from the previous CPs. The RRs for nonsevere/very severe physical status (PSCS, 4 or 5) in CP4 and CP5 were >3 (figure 4*C*). Also, the hospital admission rates for children with a severe/very severe physical status (PSCS, 4 or 5) in CP1, CP2, CP3, and CP4 (>7%) were higher than the rate for CP5 (3.6%) (figure 4*D*).

Additionally, the mean length of hospitalization for children who were admitted to the hospital was higher in CP1 (~30 days) than in other CPs, and the length decreased over the follow-up period (figure 5*A*). Furthermore, figure 5*B* shows the changes in the length of hospital stay across the different periods. Again, despite the introduction antiretroviral therapy in CP2 and CP3, there was not an evident benefit with regard to hospital admission. From 1997 onwards, the number of hospital admissions with long lengths of stay per admission was lower, but we did not find differences in that number between CP4 and CP5.

DISCUSSION

Previously published studies have documented the effectiveness of HAART in reducing the number of cases of AIDS and the number of deaths among HIV-1–infected children [10–12, 20]. However, the follow-up periods of those studies were somewhat short. In this study, we divided the study period of 1997–2003 into 2 subperiods on the basis of the percentage of children who were receiving HAART [20, 25]: CP4 (1997–1998) and CP5 (1999–2003). There were important limitations to therapy during the earliest years of HAART, because there were few approved pediatric formulations of PIs, as well as administration difficulties and low adherence rates. The introduction of new drugs and formulations after 1999 [8, 9] extended the use of HAART to a larger number of children [20]. Children who remained antiretroviral therapy naive toward the end of our study period are likely to be a self-selected group at low risk of disease progression.

Our study shows that monotherapy regimens exert some benefit in the management of symptomatic children, as supported by previous reports [26, 27]. However, the beneficial effect of monotherapy is transitory and disappears with time as a result of the development of antiretroviral drug resistance.



P

	CP1 (80-89)	CP2 (90-93)	CP3 (94-96)	CP4 (97-98)
CP2 (90-93)	.257			
CP3 (94-96)	.003	.026		
CP4 (97-98)	<.001	<.001	<.001	
CP5 (99-03)	<.001	<.001	<.001	.818

Period	Total	HA
CP1 (81-89)	172	48
CP2 (90-93)	246	72
CP3 (94-96)	230	64
CP4 (97-98)	168	26
CP5 (99-03)	154	34

P

	CP1 (80-89)	CP2 (90-93)	CP3 (94-96)	CP4 (97-98)
CP2 (90-93)	.150			
CP3 (94-96)	.263	.804		
CP4 (97-98)	<.001	<.001	<.001	
CP5 (99-03)	<.001	<.001	.004	.356

Period	Total	HA (level>4)
CP1 (81-89)	172	19
CP2 (90-93)	246	25
CP3 (94-96)	230	27
CP4 (97-98)	168	5
CP5 (99-03)	154	12

Figure 4. Kaplan-Meier curves for vertically HIV-1–infected children without hospital admission (HA; *A*) and without HA and American Society of Anesthesiologist Physical Status Classification Scale of 4 or 5 *(B)*, according to calendar period (CP). We also calculated the relative risk (RR) of HA and HA with American Society of Anesthesiologist Physical Status Classification Scale of <4 or ⩾4. Also, we show the hospitalization admission rates in each period *(D)*. Statistically significant differences were defined as $P < .05$ and were calculated in comparison with CP1 (1980–1989).

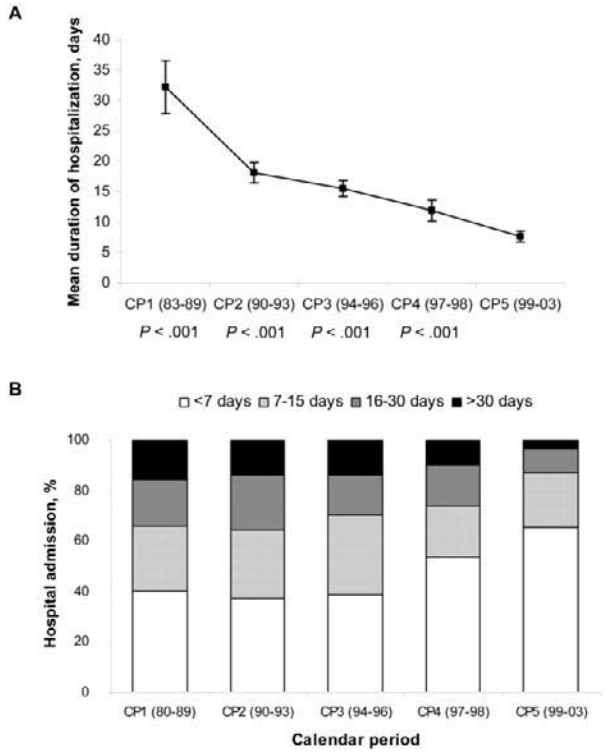


Figure 5. Hospital admission among HIV-1–infected children, according to calendar period (CP). *A,* Mean duration of hospitalization (calculated as the duration of hospitalization (in days)/the number of children who were admitted to the hospital). *B,* Percentage of HIV-1–infected children with a duration of hospitalization of <7, 7–15, 16–30, or >30 days.

The introduction of combined therapy proved to be more effective than the introduction of monotherapy [28]. Thus, we observed that therapy during CP3 (1994–96) was more effective than therapy during CP2 (1990–1993) with regard to hospital admission rate, progression to AIDS, and death. Interestingly, from 1997 onward, we observed a strong decrease in the rates of hospital admission, AIDS, encephalopathy, and death. This fact suggests a relationship between HAART and clinical outcome, and it would explain the increase in survival observed in our cohort of children.

In our study, a high percentage of children achieved viral loads less than detectable limits (<400 copies/mL) and $CD4^+$ cell percentages of >25% during the HAART era throughout CP5. This is in agreement with the findings of previous reports, which showed that the use of HAART results in a lower incidence of AIDS and death [11, 20, 22]. In this regard, our study shows that the generalized use of HAART results in clinical benefit, with a parallel decrease in viral load and an increase in $CD4^+$ cell percentage. This control of HIV-1 infection and the subsequent increase in $CD4^+$ T cell count and $CD4^+$ T cell function above the critical threshold [29] leads to a decrease in the number of opportunistic infections [30]. From 1997 onward, there was a marked reduction in the hospital admission rate [31, 32]. The rate of hospital admission during CP4 (when HAART had been implemented for <50% of children) were not different than that for CP5 (when HAART was generally used). This could be because the first children to have received HAART were at an advanced stage of HIV-related illness.

Although the total hospital admission rate decreased to ~0% during the HAART periods, that level emphasizes the need for continued inpatient services, because the continued and prolonged use of HAART has resulted in the development of complications [5], including changes in body fat distribution and metabolic disturbances, such as insulin resistance and atherogenic dyslipidemia [33]. We also found a marked reduction in length of hospital stay in the last CPs. The hospital admissions were less serious during CP4 and CP5, compared with the earlier periods (data not shown). Furthermore, the duration of hospitalization decreased after CP2, and it further decreased during CP4 after the introduction of HAART. This decrease during CP2 and CP3 could have resulted from the use of NRTIs, improvements in earlier diagnosis of HIV-1 infection, improvements in the treatment of opportunistic infections, improvements in the immunological status of children and in the care delivered, and improved knowledge about the illness. Our study is one of the first to have reported a reduction in the hospital admission rate and in the duration of hospitalization among children, as well as a reduction in the rates of mortality and progression to AIDS [12, 34].

We observed an increase in the rates of hospital admission, AIDS, and death in CP3. These data could reflect the effect of the age in the era prior to HAART. Children born before 1994 were more likely to develop AIDS. Moreover, they were older when they received antiretroviral therapy, and they had poor response to antiretroviral therapy and incomplete immune reconstitution. Furthermore, in CP3, there was a high number of patients with AIDS who had a high risk of death. Thus, when we analyzed these outcomes on the basis of birth period and CP, we found a high cumulative incidence of AIDS and death among children born before 1989 and a very low incidence among children born after 1997. Furthermore, diagnosis of HIV-1 infection at the age of >5 years did not occur during CP4 and CP5, and these children were less likely to develop AIDS or to die.

Early versus deferred initiation of HAART is an important issue. In another article [35], we reported that commencement of HAART after severe immunosuppression is detrimental for recovery of the $CD4^+$ T cell count after a long-term period of HAART. We found that the age of children at the initiation of antiretroviral treatment during CP2 and CP3 was higher than that during CP4 and CP5 (data not shown). Also, we found that rates of AIDS and death were lower among children born during the HAART periods. Thus, early administration of an-

tiretroviral therapy improves the outcome for HIV-1–infected children [3].

During the HAART period (1997–2003), children presented with few AIDS cases, and there were few deaths. As expected, the children in CP5 had a higher mean age than did children in the other CPs. The direct relationship between survival and age in children may be the result of natural selection occurring in the study population. We began the study in 1980, when antiretroviral therapy was still not available. Later, monotherapy and combined therapy were introduced, but a high percentage of the children in this period were already in an advanced phase of illness, and many of them died before 1997. Also, the rate of vertical transmission of HIV-1 during the years of 1980–1997 was still high [36, 37]. Many of these children died during their first years of life, contributing to the lowering in the survival curve. After these first years of life, many of the children who survived had a longer life thereafter [38, 39]. After a few years, the children adapted better to HIV-1 infection, survived for a longer time, and were accumulated with newly recruited children who were receiving HAART, accounting for the overall increase in the survival rates and mean age observed in CP5. Another variable for which data were not provided was the implementation of prophylaxis for opportunistic infections—in particular, *P. carinii* infection. In advanced disease, opportunistic infections may be a common cause of death; thus, prophylaxis should be implemented, but the suitable time for commencement of treatment varies.

Our study has several limitations. First, the lack of information about antiretroviral therapy on an individual basis and the lack of assessments of adherence may have had a significant, unaccounted effect on the interpretation of our results. However, the data presented here derive from routine clinical practice. Second, prophylaxis for infection due to *P. carinii* or *Mycobacterium avium* may have had a substantial impact on outcomes and may have been differentially applied across the CPs. Thus, the administration of prophylaxis may have led to an underestimation of the rates of hospital admission, AIDS, and death among children with low $CD4^+$ T cell counts during the first CPs. Third, the lack of follow-up since birth for all children may have had a potential impact on our results. HIV-1–infected children received diagnoses late during the firsts CPs, and they could have had symptoms of AIDS before HIV-1 infection was diagnosed. It is possible that AIDS, encephalopathy, and hospital admission were underestimated in the first CPs; this could have introduced bias regarding the estimation of clinical and biological outcomes. Fourth, earlier CPs could have been overrepresented by younger children with higher inherent risks, and the later CPs could have been overrepresented by long-term survivors. This may have biased the analyses, precluding the ability to rigorously assign outcomes in each CP to evolutions in antiretroviral therapy use. Finally, perinatal prevention measures and maternal treatment evolved dramatically over the time periods and may have impacted pediatric health.

In conclusion, we observed that HAART produced a decrease in adverse clinical outcomes (hospital admission, AIDS, and death) in HIV-1–infected children in Madrid, Spain. Although there was a marked improvement in HIV-1 infection among Spanish children, we would need a longer follow-up period to asses whether rates of hospital admission, AIDS, and mortality will remain stable or whether they will again increase.

SPANISH GROUP OF PEDIATRIC HIV INFECTION

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