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HAART and Causes of Death in Perinatally HIV-1-Infected Children

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1. Introduction

Children represent a population at higher risk of Human Immunodeficiency Virus type 1 (HIV-1) infection and AIDS-related death. Approximately 2.5 million (1.6–3.4) children are infected at present, accounting for 370,000 [230,000–510,000] new infections and 260,000 [150,000–360,000] deaths (Gray et al., 2001). About 90% of children living with HIV-1 are in sub-Saharan Africa. The paediatric HIV-1 epidemic is fuelled by HIV-1 infection in women of childbearing age. In fact, mother-to-child (perinatal) HIV-1 transmission during pregnancy, birth or breastfeeding accounts for the vast majority of HIV-1 cases in children. An estimated 2.4 million infected women give birth annually. This results in the birth of approximately 1,000 HIV-1-infected babies per day, of which 80% occur in resource-limited countries where there are no effective programs for prevention of mother-to-child transmission (MTCT) of HIV-1. Almost two decades ago, the introduction of antiretroviral chemoprophylaxis to prevent MTCT of HIV-1 was an important milestone in paediatric HIV-1. The use of antiretroviral drugs and elective caesarean section have reduced the incidence of MTCT in industrialised countries to <2% since 1997 (The European Collaborative Study [ECS], 2005; Connor et al., 1994). However, such interventions to prevent MTCT of HIV-1 are still not widely accessible or available in most resource-limited countries where the rate of transmission is estimated at 12–40% (De Cock et al., 2000). Concerning the diagnosis and treatment of HIV-1, significant improvements have been made over the last few years, yet much more needs to be done. The first evidence of the efficacy of antiretroviral therapy (ART) in HIV-1-infected children was published 20 years ago (Pizzo et al., 1988). Since then, the introduction of highly active antiretroviral therapy (HAART) into medical care for HIV-1-infected children and adolescents has increased life expectancy and resulted in AIDS incidence decline in both industrialised countries and resource-limited settings (Judd et al., 2007; Patel et al., 2008; Puthanakit et al., 2007; Reddi et

al., 2007). Some studies have also described the immunovirological impact of HAART (Fraaij et al., 2005; Scherpbier et al., 2006; Walker et al., 2004). Nevertheless, in developing countries early diagnosis is a major challenge and ART is often started late. The clinical impact of early treatment has been recognised (Faye et al., 2004; Violari et al., 2007); in fact, in the absence of treatment, 50% of infants die before their second birthday (Newell et al., 2004). Moreover, lack of resources restricts drug supply. Despite the number of children receiving ART increased from about 75,000 in 2005 to 360,000 in 2009, these represent an estimated ART coverage of 28% [21-43%] of all children less than 15 years who need ART in resource-limited settings (WHO, 2010). On the contrary, in industrialised countries antiretroviral drugs are widely available. In addition, new therapeutic options have been developed for the paediatric population in recent years, such as the protease inhibitor darunavir approved for children aged ≥ 6 years and adolescents (Blanche et al., 2009), or are under evaluation in ongoing clinical trials, including the second generation non-nucleoside reverse transcriptase inhibitor etravirine (ClinicalTrials.gov 2008b, 2009a), the new protease inhibitor tipranavir (Salazar et al., 2008), and the new families of antiretrovirals, such as the CCR5 antagonists and integrase inhibitors (ClinicalTrials.gov 2007, 2008a, 2009b).

2. Impact of antiretroviral therapy

Given that HIV-1 infection has turned into a chronic condition and that exposure to antiretrovirals is likely to be life-long, continuous assessment of the impact of HAART on progression of perinatal HIV-1 infection remains an important public health issue to improve health care strategies. Here, we report the evaluation of HAART effectiveness on the incidence of AIDS and death, and the trends in the underlying causes of death at population level over almost three decades in Madrid (Spain). In Western Europe, Spain continues to be one of the countries with the highest AIDS incidence rate and prevalence. Within Spain, the *Comunidad Autónoma de Madrid* is the area most affected by the infection, with a total of 18,866 AIDS cases up to 2010 (24% of the national cases) (Centro Nacional de Epidemiología [CNE], 2010). The high HIV-1 prevalence had a direct impact on the spread of the infection within the infant population and although the risk of perinatal transmission of HIV-1 has decreased below 2% in recent years, paediatric HIV-1 cases are still being diagnosed (Palladino et al., 2008). In the *Comunidad Autónoma de Madrid*, a total of 237 cumulative AIDS cases due to vertical transmission were reported to the National AIDS Registry from 1981 to 2010 (CNE, 2010). The introduction of HAART in late 1996 and its universal and free availability (Ministerio de sanidad y Consumo, 1998) offered the opportunity to control HIV-1 disease progression in the paediatric population (2005; Resino et al., 2006b). The aim of this study was to describe the mortality and AIDS rates and changes in underlying causes of death in HIV-1-infected paediatric patients. Moreover, risk factors associated with shorter first-line HAART duration among antiretroviral-naïve patients who began HAART after 1996 were examined.

2.1 Study population and methods

The HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid* was established in 1995 as an open cohort of paediatric patients infected by HIV-1 through MTCT, for whom it was assumed that HIV-1 transmission occurred on the date of birth (de Martino et al., 2000). The cohort has included all HIV-1-infected patients identified in a multicenter network of nine referral paediatric hospitals from January 1982 (birth date of the first MTCT-infected child in Madrid). Children infected before 1995 were enrolled retrospectively, while those infected after 1995

were enrolled prospectively. Complete ascertainment of all records was carefully sought. Informed consent was obtained from mothers of all patients. The Institutional Ethics Committee approved the study. HIV-1 testing during pregnancy was offered to all women until 1998, when routine testing was introduced for all pregnant women. Patients were actively followed up every 3–6 months (Centers for Disease Control and Prevention [CDC] 1998). At the beginning of the study, the diagnosis of HIV-1 infection was based on the results of a serologic test for HIV-1 antibody, which was performed routinely for children born to seropositive women. When the result of the serologic test was positive, the infection was confirmed by paediatricians and/or through hospital summaries. Later, the diagnosis was done by positive results of HIV-1 PCR DNA and peripheral blood mononuclear cells viral culture assays on two separate samples (Resino et al., 2006a). The clinical classification and definition of AIDS-related events were based on international guidelines (CDC 1994). Children in the A or B clinical category who became older than 13 years were not categorised as having AIDS by CD4⁺ cell count criteria when they had <200 cells/ml (CDC 1992).

Deaths were reported by paediatricians. The underlying cause of death (the disease/injury which initiated the morbid event leading to death) was confirmed by reviewing medical histories or autopsy certificates and interviewing paediatricians. Patients were cross-checked with the National Death Index to validate their causes of death classified as: “AIDS-defining” when attributable to a disease in the C clinical category (CDC 1992, 1994); “HIV-related” when attributable to a category A or B disease (CDC 1992, 1994) or to ARV adverse events; “non-HIV-related”: all other causes. To report the underlying cause of death, when multiple concurrent causes contributed to death, patients were included as many times as the number of illnesses diagnosed. The study period comprised a pre-HAART era (1982–1996) and a post-HAART era (1997–2009), and was divided into six calendar periods (CP) on the basis of the changing HIV-1 therapy management. CP1 (1982–1989): it was chosen as the reference period, when ART was not routinely available; CP2 (1990–1993): the standard of care was zidovudine monotherapy; CP3 (1994–1996): children were receiving dual-nucleoside regimen; CP4 (1997–1998): when HAART, a combination of three or more drugs, was introduced; CP5 (1999–2004): early-HAART period; CP6 (2005–2009): late-HAART period. Information on socio-demographic characteristics, mother’s transmission category, clinical and immunovirological data and the antiretroviral therapy were recorded. Any change in two or more antiretroviral drugs that lasted ≥ 14 days, excluding dosage changes, in the presence of detectable HIV-1 RNA, was considered to indicate the start of a new regimen.

2.1.1 Statistical analysis

AIDS and mortality rates were calculated as the number of new AIDS and death cases per hundred person-years (p-y) of follow-up. Individuals were followed from the date of enrolment (i.e., date of HIV-1 diagnosis or first blood test) until the date of development of the event of interest (AIDS or death) or December 31, 2009 (administrative censoring date), whichever occurred first. The risk of progression to AIDS and death over time was estimated by survival analyses using Kaplan-Meier curves and Cox proportional hazards models. Time was calculated from the birth date so that comparisons across different calendar periods were based on individuals who were infected for the same length of time. All models were stratified by hospital and adjusted for potential confounders (gender, mother’s transmission category and immunological category). Fisher exact test, χ^2 or Mann-Whitney U test were used to derive *P*-values. Poisson regression was used to compare mortality and infection rates between our cohort and the age-similar general population

living in the *Comunidad Autónoma de Madrid*. The median duration of initial HAART regimen was determined by Kaplan-Meier analysis. Univariate proportional hazards regressions were used to identify factors associated with a shorter initial regimen. The variables examined included demographics, socio-economic characteristics, baseline laboratory values (CD4⁺ cell count, HIV-1 RNA, haemoglobin), clinical status and adherence to initial HAART regimen. Then, multivariate regression analysis was performed including all factors for which the results of univariate analysis were statistically significant ($P < 0.05$, 2-sided). Analyses were performed with SPSS 16 and Epidat 3.1.

3. Results

Overall, 484 children who acquired HIV-1 from their mothers between 1982 and 2009 were enrolled and followed for 5298.2 person-years (11.6 years; interquartile range (IQR): 5.2-16.7). HIV-1 infection occurred mainly in 1992 [IQR: 1988-1995]; 270 (56%) patients were girls and 299 (62%) had a mother who acquired the virus through injection drug use. Table 1 provides the characteristics of the children at the end of each calendar period (CP). The cohort had the highest number of enrolled children between 1994 and 1996; in the last period (2005-2009) there were 279 children included, of whom 13 were born in this period. The sex ratio remained stable over time (CP1: 1.0; CP6: 1.4), while the median age (CP1: 2.6 [1.0-4.4]; CP6: 14.8 [11.6-17.5]; $P < 0.001$) and the proportion of immigrants (CP1: 3.1; CP6: 15.5; $P < 0.0001$) increased. An increase of the median CD4⁺ cell percentage at the end of each calendar period was observed (CP2: 22.5 [11.9-32.1]; CP4: 26.5 [18.2-33.7]; CP6: 33.4 [28.0-39.7]) and a concomitant decrease of HIV-1 RNA since 1997 (median log₁₀ copies/ml CP4: 4.31 [3.80-4.91]; CP6: 2.60 [1.70-3.55]). The proportion of children with < 400 copies/ml was 9% (13/151) in CP3, 20% (39/196) in CP4, 60% (150/248) in CP5, and 80% (160/199) in CP6. Two adolescents died in CP2 achieving undetectable HIV-1 RNA at death. The CD8⁺ cell percentage remained stable (CP2: 42.0 [29.0-52.0]; CP4: 43.7 [35.6-52.5]; CP6: 38.9 [31.7-45.7]). The changes over time in antiretroviral therapy management are described in Fig. 1. Monotherapy was used in the early 1990s and dual-nucleoside therapy in mid-1990s. An increasing proportion of children receiving HAART from 1997 onward was observed; by 2005, up to 80% of the children were on HAART.

3.1 Time to AIDS or death

Information on 471 children, of whom 285 (61%) developed an AIDS-defining disease, was available for the progression to AIDS analyses. The AIDS incidence rate increased over time until 1989 (32.6 per 100 p-y), it arose again during the first half of the 1990s (13.2 in 1991; 18.8 in 1995) and waned off thereafter (3.2 in 1999; 0.0 in 2009) (Fig. 2). The cumulative incidence curves showed a reduction in the proportion of patients developing AIDS after 1997 compared to the period 1982-1989 (Fig. 3A). Multivariate Cox analysis showed a more pronounced decline in the last period (CP6) (AHR: 0.07; 95%CI: 0.04-0.16) than in the CP5 (AHR: 0.23; 95%CI: 0.15-0.37) (Table 2). A total of 159/484 (33%) deaths occurred. The death incidence rate was 7.4 per 100 p-y at risk in 1986, it peaked in 1995 (10.1 per 100 p-y) and declined thereafter (0.7 in 1999; 0.0 in 2009) (Fig. 2). The incidence of death decreased since 1997 compared to the period 1982-1989 (Fig. 3B, Table 2). Multivariate analysis showed more marked improvements in survival in the CP6 (AHR: 0.16; 95%CI: 0.05-0.50) than in the CP5 (AHR: 0.25; 95%CI: 0.11-0.56).

Characteristics	Period					
	CP1 (80-89)	CP2 (90-93)	CP3 (94-96)	CP4 (97-98)	CP5 (99-04)	CP6 (05-09)
N. of HIV-1-infected patients	168	280	317	282	315	279
Age, years (median, IQR)	2.6 (1.0 - 4.4)	4.0 (1.8 - 6.6)	5.0 (2.6 - 8.0)	6.7 (3.8 - 9.6)	11.1 (7.8 - 14.0)	14.8 (11.6-17.5)
Date of birth, n. of patients						
1980-1989	168	144	115	85	79	47
1990-1993	-	136	115	93	90	85
1994-1996	-	-	87	73	68	63
1997-1998	-	-	-	31	29	27
1999-2004	-	-	-	-	49	44
2005-2009	-	-	-	-	-	13
Sex ratio, n. of girls	1.00	1.19	1.23	1.27	1.32	1.41
Geographic origin, n. (%)						
Spain	156 (92.9)	264 (94.3)	298 (94.0)	256 (90.8)	271 (86.0)	235 (84.0)
Central America	0 (0)	3 (1.1)	4 (1.3)	8 (2.8)	10 (3.2)	9 (3.2)
South America	3 (1.8)	4 (1.4)	6 (1.9)	6 (2.1)	8 (2.5)	8 (2.9)
North Africa	0 (0)	0 (0)	1 (0.3)	1 (0.4)	1 (0.3)	2 (0.7)
Sub-Sahara Africa	0 (0)	3 (1.1)	5 (1.6)	8 (2.8)	19 (6.0)	20 (7.2)
Other	2 (1.2)	2 (0.7)	2 (0.6)	3 (1.1)	5 (1.6)	4 (1.4)
Unknown/Unavailable	7 (4.2)	4 (1.4)	1 (0.3)	-	1 (0.3)	1 (0.4)
Maternal transmission, n. (%)						
Injecting drug use	119 (70.8)	189 (67.5)	196 (61.8)	168 (59.6)	185 (58.7)	154 (55.2)
Heterosexual	29 (17.3)	56 (20.0)	69 (21.8)	69 (24.5)	78 (24.8)	74 (26.5)
IDU / Heterosexual	13 (7.7)	23 (8.2)	29 (9.1)	24 (8.5)	23 (7.3)	19 (6.8)
Transfusion	3 (1.8)	3 (1.1)	7 (2.2)	6 (2.1)	6 (1.9)	6 (2.2)
Unknown/Unavailable	4 (2.4)	9 (3.2)	16 (5.0)	15 (5.3)	23 (7.3)	26 (9.3)
Clinical category C, n. (%)	69 (41.3)	106 (38.3)	137 (44.1)	102 (37.4)	124 (40.8)	102 (37.5)
Death, n. (%)	21 (12.5)	49 (17.5)	63 (19.9)	12 (4.3)	10 (3.2)	4 (1.4)

Table 1. Demographic and clinical characteristics of the HIV-1-infected patients enrolled in the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid* at the end of each calendar period (CP). IQR: interquartile range; clinical classification was based on the 1994 revised CDC guidelines. IDU: injecting drug use.

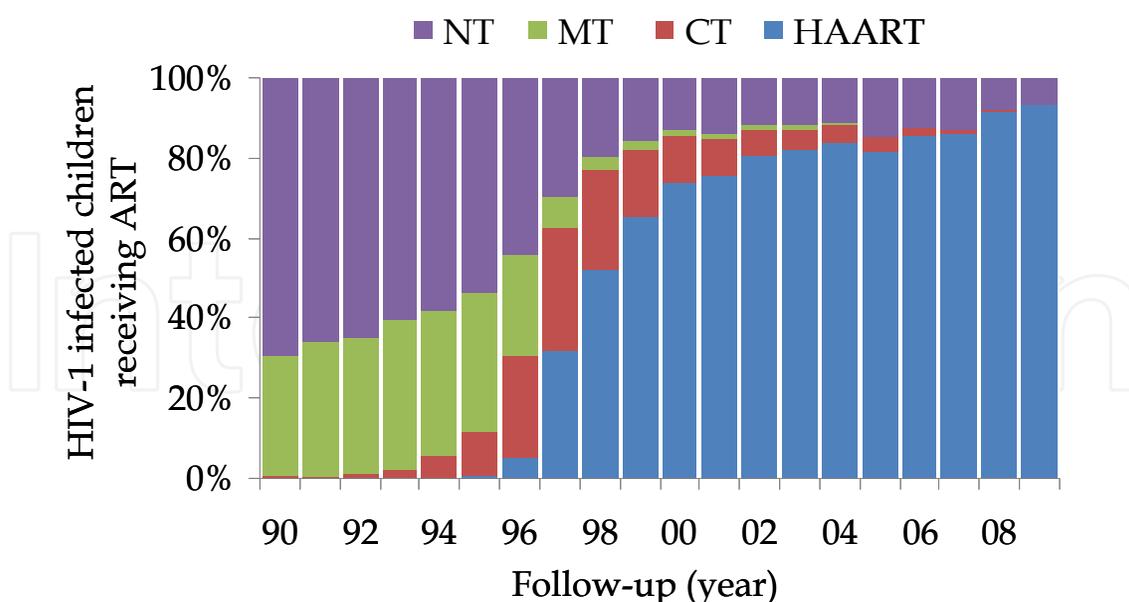
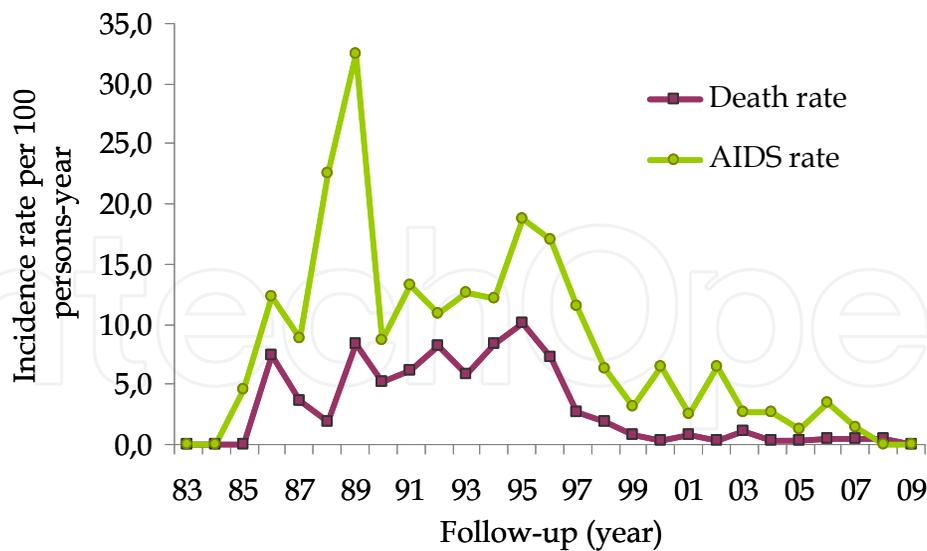


Fig. 1. Use of antiretroviral therapy among HIV-1 vertically infected children enrolled in the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid*. NT: not treated; MT: monotherapy; combined/dual-nucleoside therapy; HAART: highly active antiretroviral therapy.

AIDS			
Calendar period	N.	N. of cases	Adjusted HR (95% CI)
1982 - 1989	167	69	1.00
1990 - 1993	232	61	0.49 (0.33 - 0.69)
1994 - 1996	255	81	0.64 (0.44 - 0.91)
1997 - 1998	199	28	0.39 (0.25 - 0.63)
1999 - 2004	216	37	0.23 (0.15 - 0.37)
2005 - 2009	178	9	0.07 (0.04 - 0.16)

Death			
Calendar period	N.	N. of cases	Adjusted HR (95% CI)
1982 - 1989	168	21	1.00
1990 - 1993	280	49	1.33 (0.77 - 2.28)
1994 - 1996	317	63	1.71 (1.00 - 2.94)
1997 - 1998	282	12	0.54 (0.25 - 1.14)
1999 - 2004	315	10	0.25 (0.11 - 0.56)
2005 - 2009	279	4	0.16 (0.05 - 0.50)

Table 2. Effect of calendar period on the risk of AIDS and death. Note: Adjusted hazard ratios were derived from a standard Cox proportional hazard model that included calendar period (external time-dependent covariate), gender, mother's transmission category, immunological category and it is stratified by hospital.



Years	AIDS			Death		
	p-y	N.	Rate	p-y	N.	Rate
1982	2	0	0,0	2	0	0,0
1983	10	0	0,0	10	0	0,0
1984	24	0	0,0	24	0	0,0
1985	44	2	4,6	45	0	0,0
1986	65	8	12,4	68	5	7,4
1987	79	7	8,9	84	3	3,6
1988	89	20	22,6	105	2	1,9
1989	98	32	32,6	133	11	8,3
1990	103	9	8,7	154	8	5,2
1991	121	16	13,2	177	11	6,2
1992	147	16	10,9	206	17	8,3
1993	158	20	12,7	221	13	5,9
1994	173	21	12,2	239	20	8,4
1995	170	32	18,8	248	25	10,1
1996	164	28	17,1	248	18	7,3
1997	156	18	11,5	256	7	2,7
1998	158	10	6,3	263	5	1,9
1999	155	5	3,2	269	2	0,7
2000	155	10	6,5	275	1	0,4
2001	155	4	2,6	278	2	0,7
2002	155	10	6,5	283	1	0,4
2003	152	4	2,6	276	3	1,1
2004	151	4	2,6	271	1	0,4
2005	150	2	1,3	263	1	0,4
2006	142	5	3,5	244	1	0,4
2007	136	2	1,5	233	1	0,4
2008	132	0	0,0	217	1	0,5
2009	128	0	0,0	209	0	0,0

Fig. 2. Annual AIDS and mortality incidence rates per 100 person-years (p-y) in the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid*.

In the population aged 0-19 years of the *Comunidad Autónoma de Madrid*, the mortality decreased from 4.2 deaths per 10,000 inhabitants in 1996 to 3.5 in 2007. In spite of the mortality decline in our cohort, it still was 10.4-fold (95%CI: 5.8-18.8; $P<0.001$) higher than in age-similar general population after 1999. Since 1999, the HIV-1-infected infants had a higher mortality rate than children/adolescents (IRR: 6.9; 95%CI: 2.3-20.3; $P<0.001$), as in the general population (IRR: 18.9; 95%CI: 17.9-19.9; $P<0.001$). A lower decrease of mortality among HIV-1-infected infants (IRR: 2.6; 95%CI: 0.9-7.4; $P=0.069$) between pre-HAART and post-HAART era than among older patients (IRR: 12.5; 95%CI: 7.6-20.4; $P<0.001$) was observed. On the contrary, mortality decreased equally in infants (IRR: 1.8; 95%CI: 1.8-1.9; $P<0.001$) and children/adolescents (IRR: 1.5; 95%CI: 1.5-1.6; $P<0.001$) in the general population.

3.2 Causes of death

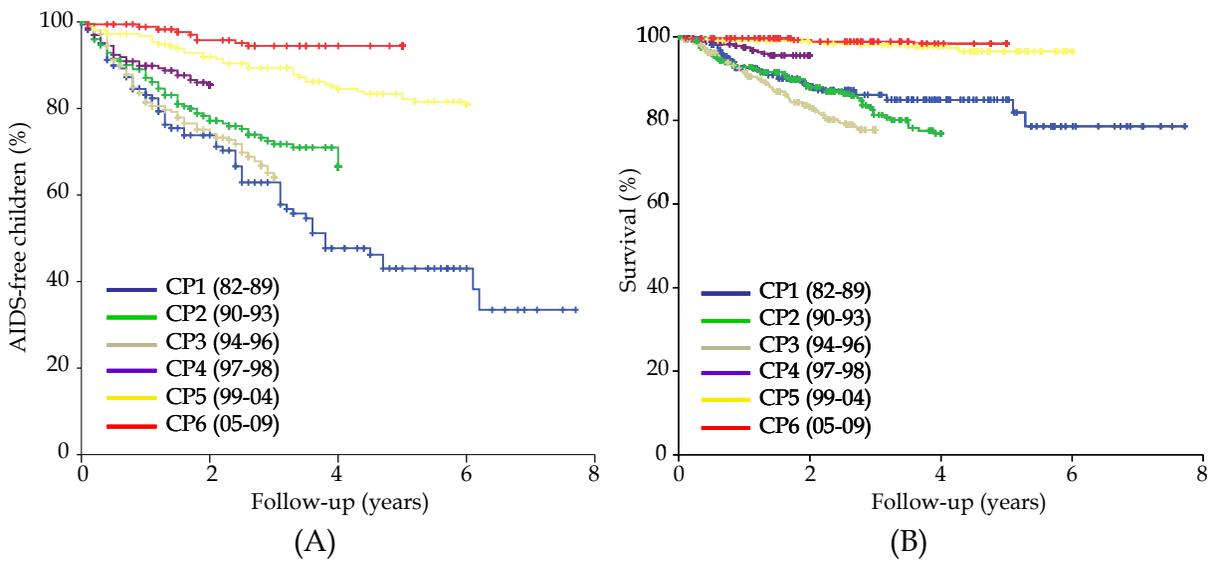
Overall, 169 causes of death were documented for 151/159 (95%) patients (Table 3). The 81% (137/169) were AIDS-defining, 12% (20/169) HIV-related and 7% (12/169) non-HIV-related. Multiple causes of death were reported in 16/151 (11%) patients, 3.2 (0.6–6.3) years old at death, of which 7 were infants: 13/129 (10%) died in pre-HAART era and 3/22 (14%) in post-HAART era. Concomitant pathologies were diagnosed in 101/151 (67%) patients (Table 4). The majority (83%) of the subjects died in the post-HAART era had a low/medium socio-economic status. From 1999 to 2007, the risk of death from infections was 115.9 times (95% CI: 42.0–265.8; $P<0.001$) higher in our cohort than in the *Comunidad Autónoma de Madrid*. It was not possible to evaluate the risk of death from other causes than infections due to the low number of events.

AIDS-defining causes were 82% (118/144) in pre-HAART and 76% (19/25) in post-HAART era. The most frequent contributing events were opportunistic infections (58%, 79/137) (Table 4), wasting syndrome (19%, 26/137) and lymphoid interstitial pneumonia (12%, 16/137). The largest components of opportunistic infections were bacterial (20%, 28/137), fungal (mainly *Pneumocystis jirovecii*; 15%, 20/137), and mycobacterial infections (mainly *Mycobacterium tuberculosis*; 10%, 14/137). These three etiologic pathogens were associated with the only cases of death occurred in 2005-2007. No statistically significant changes over time were observed in the proportions of the causes of death. HIV-related causes were 11% (16/144) in pre-HAART and 16% (4/25) in post-HAART era. Overall, the leading causes of death were infections (75%, 15/20), mainly bacterial (65%, 13/20), and bleeding (15%, 3/20). The causes of death reported in post-HAART era were: bacterial infection, pulmonary bleeding caused by thrombocytopenia, pulmonary arterial hypertension and lactic acidosis (1 case each). Non-HIV-related causes were 7% (10/144) in pre-HAART and 8% (2/25) in post-HAART era. Infections were the main cause of death (75%, 9/12), mainly viral infections (67%, 8/12), followed by cancer (17%, 2/12) and hepatic pathology (8%, 1/12). The only causes of death reported in post-HAART era were cancer and hepatic failure (1 case each).

3.3 Duration of HAART regimen

Of 484 patients included in the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid*, 105 (22%) were naïve to antiretrovirals when HAART began as of January 1997. It was possible to analyse the duration of the first HAART regimen in 82 of them. Half of the patients were girls (42; 51%) and had a median age at HAART initiation of 3.6 years (0.6-7.3).

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Fig. 3. Kaplan-Meier curves for HIV-1-infected children enrolled in the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid* without AIDS (A) and for survival (B) in different calendar periods.

Cause of death	Pre-HAART (1982-1996)	Post-HAART (1997-2009)
	N=144 (85.2%)	N=25 (14.8%)
Cancer	6 (4.2)	3 (12.0)
NHL	5 (3.5)	2 (8.0)
HL	1 (0.7)	--
Others	--	1 (4.0)
Infections	90 (62.5)	13 (52.0)
Bacterial infections	34 (23.6)	7 (28.0)
Pneumonia	20 (13.9)	3 (12.0)
Sepsis	14 (9.7)	3 (12.0)
Meningitis	--	1 (4.0)
Fungal infections	17 (11.8)	3 (12.0)
Pneumonia	13 (9.0)	3 (12.0)
Esophageal	4 (2.8)	--
Mycobacterial infections	13 (9.0)	3 (12.0)
Nontuberculous	8 (5.6)	2 (8.0)
Tuberculosis	5 (3.5)	1 (4.0)
Viral infections	15 (10.4)	--
Pneumonia	5 (3.5)	
Sepsis	6 (4.2)	
AGE	3 (2.1)	
PML	1 (0.7)	
Parasitic infections	11 (7.6)	--
Cryptosporidiasis	9 (6.3)	
Toxoplasmosis	1 (0.7)	
Leishmaniasis	1 (0.7)	
Other causes	48 (33.3)	9 (36.0)
Wasting	22 (15.3)	4 (16.0)
Pulmonary	15 (10.4)	2 (8.0)
Encephalopathy	9 (6.3)	--
Hepatic	--	1 (4.0)
Bleeding	2 (1.4)	1 (4.0)
Lactic acidosis	--	1 (4.0)

Table 3. All causes of death for HIV-1-infected children enrolled in the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid* stratified by pre-HAART era and post-HAART era. Pulmonary cause of death includes lymphoid interstitial pneumonia cases and 1 case of pulmonary hypertension. AGE: acute gastroenteritis; HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma; PML: progressive multifocal leukoencephalopathy (JC virus). Percentage may not total 100 because of rounding.

	Pre-HAART (1982-1996)	Post-HAART (1997-2009)
Opportunistic infection	N=67/129 (51.9%)	N=12/22 (54.5%)
Recurrent bacterial infection	22 (32.8)	6 (50.0)
<i>Pneumocystis jiroveci</i>	13 (19.4)	3 (25.0)
Cryptosporidiosis	9 (13.4)	0
Nontuberculous mycobacteria	6 (9.0)	2 (16.7)
<i>Mycobacterium tuberculosis</i>	5 (7.5)	1 (8.3)
Candidiasis	4 (6.0)	0
Cytomegalovirus	6 (9.0)	0
Toxoplasmosis	1 (1.5)	0
JC virus	1 (1.5)	0
Comorbidity*	N= 87/129 (64.9%)	N=14/22 (60.9%)
Wasting	52 (38.8)	11 (47.8)
Encephalopathy	50 (37.3)	7 (30.4)
Hepatic	17 (12.7)	2 (8.7)
Miocardopathy	20 (14.9)	2 (8.7)
Hematologic alterations	15 (11.2)	3 (13.0)
Candidiasis	10 (7.5)	--
Hypertension	3 (2.2)	--
Nephropathology	3 (2.2)	--
Giardiasis	1 (0.7)	--
HSV	1 (0.7)	--

Table 4. Prevalence of opportunistic infections and comorbidity in the deceased patients of the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid*, stratified by pre-HAART and post-HAART era. HSV: Herpes simplex virus. *Note: Patients can be counted more than once.

The majority originated from Spain (58; 71%) and 19 (23%) were adopted or lived in institutions. The socio-economic status was medium-high for 28 (56%) out of 50 patients and low for 22 (44%). At baseline, the median CD4⁺ cell count was 707 (19%) cells/ml (212-1,443) and HIV-1 RNA was 100,000 (5.0 log₁₀) copies/ml. The median duration of the first HAART regimen was 40.5 months (20.9-80.2). Fifty (61%) subjects were still on the same regimen at the end of the follow-up (Fig. 4, circle chart), being the median HAART duration in this group of 64.5 months (28.6-95.1). The rest of the study group (32/82; 39%) switched to a second regimen after 25.9 months (12.4-39.2) of first regimen. The median first-line HAART duration was significantly different between the two groups ($P<0.0001$). Among the 32 patients who experienced first-line HAART discontinuation, up to 6 switches to successive regimens were observed and had a median duration of 25.9 months (20.7-29.2) (Fig. 4, bar chart). The cumulative incidence curves for time to initial HAART regimen discontinuation showed a longer median HAART duration for the 65/82 (79%) children who started the

therapy after 6 months of age compared with the 17 (21%) infants who started at or before 6 months ($P=0.033$) (Fig 5A). In addition, this analysis showed a longer median HAART duration for the 31 (60%) out of 52 subjects with good/perfect adherence compared with the 21 (40%) subjects with poor/intermediate adherence ($P<0.0001$) (Fig. 5B). Initial HAART regimen discontinuation remained associated to younger ages (AHR: 4.56; 95%CI: 1.76–11.86; $P=0.002$) and poor adherence (AHR: 5.02; 95%CI: 2.02–12.47; $P=0.001$) in the multivariate analysis performed for 52 patients (Table 5). The most frequently prescribed first-line regimen was based on protease inhibitors, while one-quarter of the patients received therapy based on non-nucleoside reverse-transcriptase inhibitors (Fig. 6). Two nucleosides backbone therapy remains the cornerstone for all patients but one who had 3 nucleosides. For patients who discontinued the first-regimen, there was a difference, approaching statistical significance, between the duration of the PI-based therapy (30.0 months [13.1–40.5]) and the NNRTI-based therapy (15.2 [5.5–23.2]; $P=0.054$).

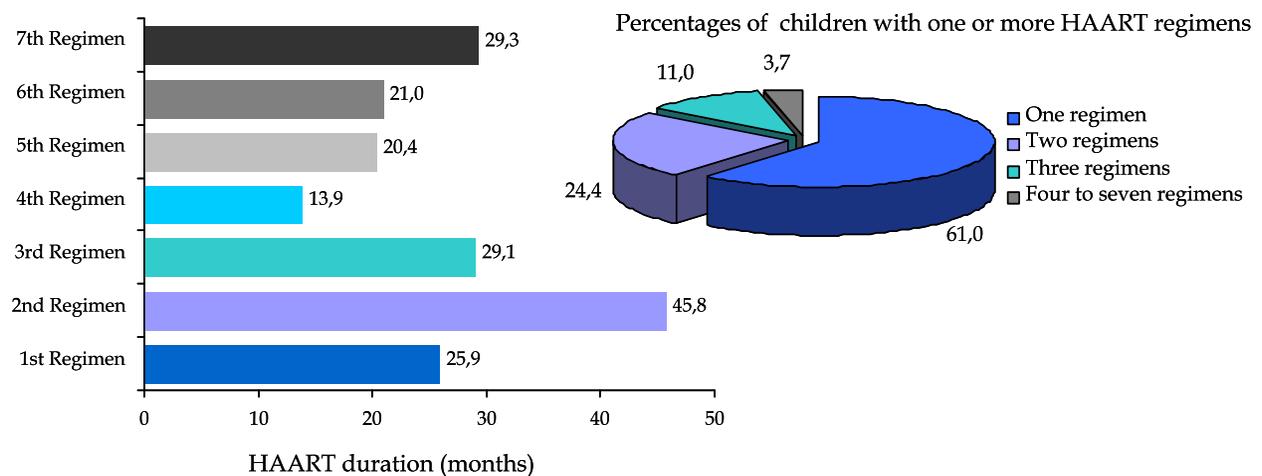


Fig. 4. Relative proportion of patients according to the number of HAART regimens among the 82 antiretroviral-naïve patients who start HAART since 1997 (circle chart); months of HAART regimen duration among the 32 patients with regimen switch (bat chart).

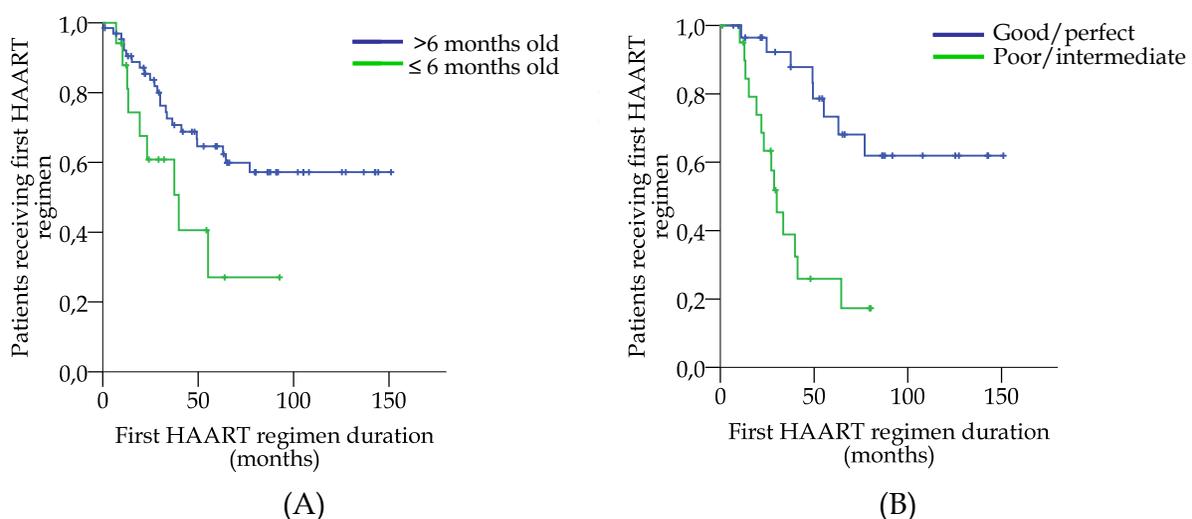


Fig. 5. Kaplan-Meier curves for time to discontinuation of first HAART regimen according to the age of HAART initiation (A) and to adherence to first HAART regimen (B).

	First HAART regimen discontinuation		
	N.	N. of cases (%)	Adjusted HR (95% CI)
Age at HAART initiation			
> 6 months	40	14 (35.0)	1.00
≤ 6 months	12	8 (66.7)	4.56 (1.76 - 11.86)
Adherence to first HAART regimen			
Good/perfect	31	8 (25.8)	1.00
Poor/intermediate	21	14 (66.7)	5.02 (2.02 - 12.47)

Table 5. Effect of age at HAART initiation and adherence on the risk of first HAART regimen discontinuation. Note: Adjusted hazard ratios were derived from a standard Cox proportional hazard model.

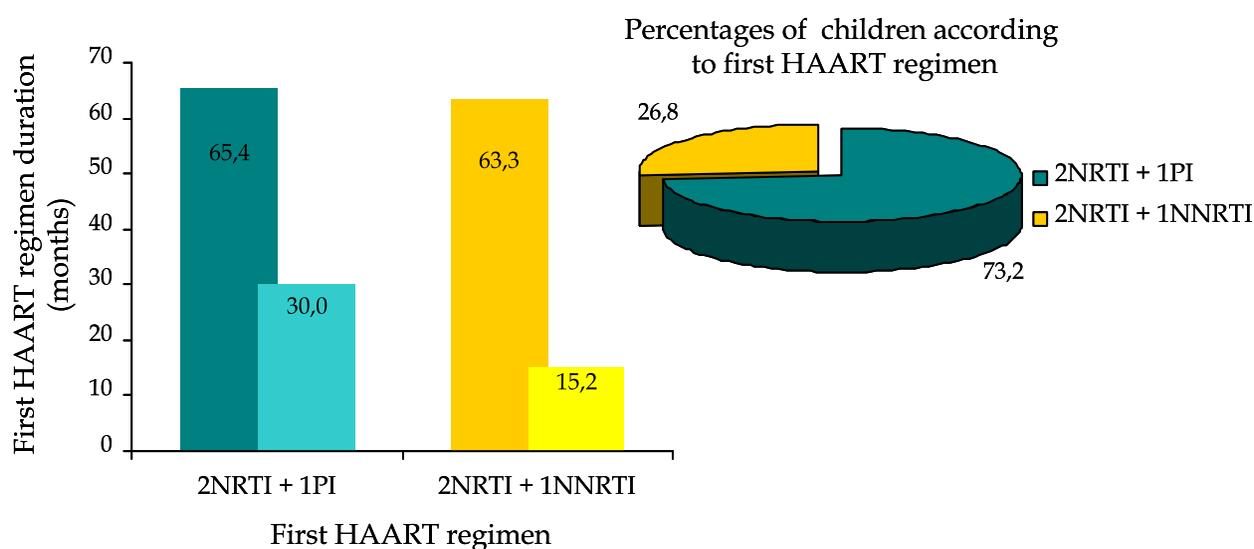


Fig. 6. Relative proportion of initial HAART regimen types among the 82 antiretroviral-naïve patients who started HAART since 1997 (circle chart); months of HAART regimen duration in patients who did not suspended the first HAART regimen (dark coloured bars) and who suspended the first regimen (light coloured bars). NRTI: nucleoside reverse-transcriptase inhibitor; NNRTI: non-nucleoside reverse-transcriptase inhibitor; PI: protease inhibitor.

4. Discussion

The results of this multicenter study on 484 patients infected by HIV-1 through perinatal transmission from the region of Madrid, show that the immunovirological response observed after the introduction of HAART has improved steadily since 1997. Also, an increase in clinical outcome with calendar period was observed. The marked reduction in progression to AIDS and death (by 93% and 84%, respectively) in recent years compared to 1982-1989 suggests a relationship between clinical outcome and HAART, which became widely available from 1997 onward. However, in the latter period, a low but stable mortality rate was recorded, in accordance with those recently reported by others (Brady et al., 2010; Judd et al., 2007).

Remarkably, mortality continued to be more than ten-fold higher in our cohort than in age-similar general population after 1996 and mainly affected patients of low/medium socioeconomic status (Palladino et al., 2008). In addition, HIV-1-infected infants were still at higher risk for death compared with older paediatric patients, being this pattern mirrored in the general paediatric population and maybe attributable to the immature of the immune system (Gortmaker et al., 2001). Finally, the mortality trend had a strikingly lower decrease among infants than among children aged ≥ 1 year in our cohort, where it decreased equally in both groups in the general population. These findings highlight the HIV-1-infected infants as a major target for healthcare policy. We observed very high AIDS and mortality incidence rates during the first years of follow-up. These data on mortality are consistent with historical European series (ECS, (1994). and with data on HIV-1 progression in children living in setting where they do not receive medical care (Brahmbhatt et al., 2006; Marinda et al., 2007). In fact, zidovudine monotherapy administration to paediatric patients started only in 1988 (Pizzo et al., 1988) and in our cohort the majority of the children were still untreated in this year. Moreover, the high HIV-1 prevalence among the female population fuelled by the so called “epidemic of heroin” had a direct impact on the spread of the infection in infants.

Our study shows that monotherapy exerted some benefit in the management of symptomatic children (Butler et al., 1991; McKinney et al., 1991; Resino et al., 2006b). Nevertheless, it had a time-limited effect due to ongoing viral replication that inevitably leads to the emergence of resistant HIV-1 quasispecies, which was also promoted by the lack of drug dosage adjustments for children at that time. The dual-nucleoside therapy proved to be more effective than monotherapy (Englund et al., 1997; Resino et al., 2006b). However, in our setting its effect on mortality or AIDS prevention between 1994- 1996 was similar to that exerted by monotherapy. This finding might be partially attributable to the regimen switch to dual-drug therapy (mainly zidovudine plus didanosine) after several years of zidovudine treatment in many children, when zidovudine was not more completely active. Thus, even with perfect adherence, dual-drug therapy was only partially suppressive being administered as functional monotherapy and due to cross-resistance within the nucleoside analogue class. In addition, during this period more than 40% of the children were still untreated and more than 35% were on monotherapy. Previous studies reported the effectiveness of HAART on the risk of death in the setting of large paediatric cohorts, but these had limited follow-up and lacked assessment of the progression to AIDS (de Martino et al., 2000; Gortmaker et al., 2001). In 2000, the Italian Register for HIV Infection in Children (de Martino et al., 2000) observed a reduction in the mortality rate of 71% in individuals undergoing triple-combination therapy compared with untreated patients, while Gortmaker and colleagues found a 67% reduction comparing HAART with other therapy (Gortmaker et al., 2001). Important reductions of 76% have also been reported recently by a 10-year follow-up survey (Patel et al., 2008). Our analyses found a stronger reduction (84%), but it is not directly comparable with previous published data due to the longer follow-up and to the difference in the performed analyses. In fact, we dealt with the trend of the risk of death in different calendar periods considered as an external time-dependent covariate. The high prevalence of comorbidities, along with multiple causes of death, resulted in increasing complexity of the management of patients with HIV/AIDS.

In terms of specific causes of death, AIDS-defining events were the most represented, with proportions higher than that recently observed in adults (Martinez et al., 2007; Palella et al., 2006). This finding might be directly linked to a late HIV-1 diagnosis at the beginning of the epidemic and to the persistence of opportunistic infections, that were the leading AIDS-defining causes of death (Brady et al., 2010; Selik & Lindegren 2003), although less represented since HAART advent (Currier et al., 1998; Kaplan et al., 2001). As in previous studies, bacterial infections were the largest component of opportunistic infections (Gona et al., 2006; Langston et al., 2001). Although specific information for their aetiology was mainly unavailable, we supposed that pneumococcus (*Streptococcus pneumoniae*) might have been the prominent microbial on the basis of recent reports (Cotton et al., 2008; Gortmaker et al., 2001; Kapogiannis et al., 2008). In addition, the pneumococcal conjugate vaccine available since 2000 (Black et al., 2000) and recommended for all HIV-infected children, has a lower efficacy in these patients than in HIV-uninfected children (Bliss et al., 2008). Some bacterial infections occurred with normal CD4⁺ cell percentage ($\geq 25\%$), consistently with previous report (Gona et al., 2006), maybe because the HIV-1 infection does not allow the correct development of primary immune function leading to the production of polyclonal, non-specific immunoglobulin increasing the risk of infections with encapsulated bacteria (Brady et al., 2010; Cotton et al., 2008; Gortmaker et al., 2001; Kapogiannis et al., 2008). The population-based analysis yielded consistent results with studies of HIV-infected patients (Kapogiannis et al., 2008; Martinez et al., 2007), highlighting a higher incidence of infections in our cohort than in the general population of similar age from the same region. Along with host immune factors (Janoff et al., 1992), antimicrobial resistance (Cotton et al., 2008; Jaspan et al., 2008), comorbidity and co-infections might have contributed to the high risk of death from opportunistic infections. The introduction of both *Pneumocystis* pneumonia prophylaxis (CDC 1995; Simonds et al., 1995) and HAART in our cohort has been accompanied by substantial reductions in mortality caused by *Pneumocystis* pneumonia (Gona et al., 2006; Kaplan et al., 2000), which have continued to occur in post-HAART era only in infants born to women with late HIV-1 diagnosis or unmonitored pregnancy, causing failure to implement *Pneumocystis* pneumonia prophylaxis (Gibb et al., 2003; Simpson et al., 2000). The cases of *M. avium* complex infection in our cohort have decreased over time (Gona et al., 2006). The cases reported in CP2 were diagnosed in children 6-11 years old, probably as a complication of advanced immunologic deterioration and the difficulty to realize a complete adherence to HAART and *M. avium* complex chemoprophylaxis. On the other hand, our data have shown an increase in the median age at death over time that might reflect improved management and prolongation in the time to development of a first bacteremia (Kapogiannis et al., 2008). More prolonged survival might allow chronic underlying comorbid conditions to become more clinically relevant in the next future. The proportion of HIV-related causes of deaths (12%) increased over time even if not statistically significant. Interestingly, the case of lactic acidosis was related to HAART regimen (stavudine + didanosine + efavirenz) that caused mitochondrial toxicity, whose rate is known to be increased by stavudine + didanosine co-administration (Blanco et al., 2003; Cote et al., 2002). Among non-HIV-related causes of death, the 7% of all the underlying causes, the fulminant hepatic failure occurred in 2008 was HCV-associated. We did not observe the increase of conditions, including diabetes mellitus, cancer, cardiovascular, liver and renal diseases that have become frequent in HIV-1-infected adults (Crum et al., 2006;

Lewden et al., 2008; Novoa et al., 2008; Palella et al., 2006; Sackoff et al., 2006; Smit et al., 2006). The lack of increase of non-HIV-related causes of death might be due to the long duration pathogenesis of these diseases as well as to their rarity, which might have limited power to identify such evolution.

The duration of initial HAART regimens for antiretroviral-naïve children has not been reported. On the contrary, several studies have assessed this public health issue in HIV-1-infected adults (Chen et al., 2003; Miller et al., 1999; Palella Jr et al., 2002; Phillips et al., 2001). The median duration of the first regimen observed in our study population was more than 3 years, the double of the duration described by Cheng and colleagues (2003) in a group of 405 antiretroviral-naïve adults and longer than that observed by Palella et al. (2002) who enrolled patients with previous antiretroviral experience. Notably, our study had a longer follow-up which could in part explain this difference. Among the therapy-naïve paediatric patients enrolled in the HIV Paediatric Cohort of the *Comunidad Autónoma de Madrid*, poor adherence has been identified as primary risk factor for initial HAART regimens discontinuation and short duration. This result is in agreement with the association between adherence and response to antiretroviral therapy reported for paediatric patients, being incomplete adherence the primary cause of treatment failure (Chiappini et al., 2006; Gray et al., 2001; Hainaut et al., 2003; Resino et al., 2003). In addition, the age at HAART initiation was found to be another independent risk factor for first HAART regimen discontinuation. The impact of HAART on the morbidity and mortality in Spanish HIV-1 vertically infected children has been discussed elsewhere (Resino et al., 2006b; Sanchez et al., 2003). However, an assessment of underlying causes of mortality and a population effectiveness analysis have never been performed in the context of an observational paediatric cohort in Spain. A number of limitations of this study should be noted. First, temporal changes in the spectrum of causes of deaths were not statistically significant; whether this result has been due to the limited number of deaths occurred after 1996 should be cautiously taken into account. Second, a survivor bias due to the partially retrospective enrolment might have caused mortality underestimation in infants at the beginning of the epidemic. Nevertheless our cohort remains more than representative of the HIV-1 epidemic in one of the Spanish regions most affected by the disease over almost three decades.

5. Conclusion

Despite the population effectiveness of HAART in reducing HIV-1-associated mortality, new challenges could arise for national surveillance systems as prolonged survival and long-term antiretroviral exposure might contribute to additional and different causes of death in perinatally infected patients in the future.

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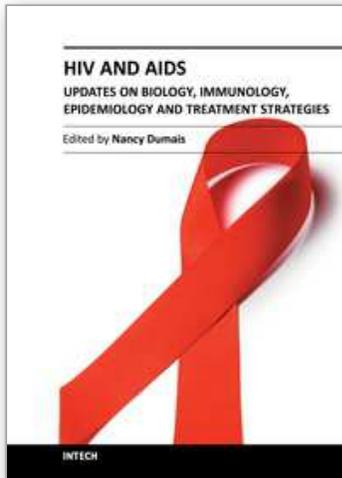
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