Abstract: We performed a retrospective study using a cross-sectional design for each year from 1997 to 2008 to evaluate the trend in pneumonia rates among HIV-infected children in the highly active antiretroviral therapy (HAART) era in Spain. We found that rate of pneumonia decreased among HIV-Infected children in the highly active antiretroviral therapy era but still remained higher than in the general population. Non–AIDS-defining pneumonia remains a significant health problem for HIV-infected children.

Key Words: HIV, pneumonia, highly active antiretroviral therapy, incidence

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Highly active antiretroviral therapy (HAART) has proved highly effective in suppressing viral load and increasing CD4+ T cell (CD4+) counts in HIV-infected children decreasing HIV-related opportunistic illness, morbidity, hospitalizations and death. Besides, opportunistic infections have also diminished with the use of HAART, and preventive chemotherrapy has contributed to the decreased incidence of opportunistic infection complications.

Pneumonia is among the leading causes of morbidity and mortality among HIV-infected patients in the HAART era, mainly in children with persistently low CD4+ counts. AID-defining pneumonia (ADP), occurring in advanced stages of immunosuppression and, non-ADP or community-acquired pneumonia, are major causes of death and hospitalization in HIV-infected children.

The aim of our study was to evaluate the trend in pneumonia rates among HIV-infected children in the HAART era through the use of comprehensive records of the Minimum Basic Data Set (MBDS) in Spain.

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MATERIALS AND METHODS
We performed a retrospective study using a cross-sectional design for each year of study from 1997 to 2008 among all HIV-infected children under 17 years of age with a hospital admission in Spain (see Fig., Supplemental Digital Content 1, http://links.lww.com/INF/B126). In addition, we selected a control group composed of 4 HIV-uninfected children for each HIV-infected child studied. The control group was randomly selected from all HIV-uninfected children under 17 years of age with hospital admissions, and matched by gender and age to avoid these confounding factors and achieving a control group as close as possible to the study group (HIV-infected children).

Data were obtained from the records of the MBDS of hospitals in Spain, as we previously described. The MBDS is a database that captures 97.7% of all public hospital admissions and 25% of all private hospital admissions in Spain. All patients having International Classification of Diseases, 9th ed, Clinical Modification codes of 042 and V08, corresponding to HIV infection, in any diagnosis (whether primary or secondary), were selected. In this study, the children who were readmitted with pneumonia in the same hospital in the same calendar year were counted as new episodes of pneumonia diagnosis. However, the probability of a child having a second hospital admission for the same pneumonia is low because treatment is usually completed on an outpatient basis.

In this study, we divided the follow-up period from 1997 to 2008 into 3 subperiods or calendar periods, according to the widespread use of HAART in children as previously described: (a) from 1997 to 1999 (1997–1999) for early-period HAART; (b) from 2000 to 2002 (2000–2002) for midperiod HAART; and (c) from 2003 to 2008 (2003–2008) for late-period HAART. The index episode was defined as the occurrence of a hospital discharge with pneumonia diagnosis via International Classification of Diseases, 9th ed, Clinical Modification codes (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B127).

We calculated the incidence rate, or the number of events per 1000 children-years, for overall and specific pneumonia diagnosis, according to each calendar period. The numerator was the number of diagnoses of pneumonia among HIV-infected children within each period (whole follow-up or calendar period). The denominator was different according to the type of rate calculated. When we calculated the events per 1000 children with hospital admission-year, we used the estimated number of HIV-infected children with a hospital discharge in Spain within whole follow-up period. When we calculated the events per 1000 HIV-infected children-years, we used the estimated number of all HIV-infected children in Spain within each year that fell into each calendar period, as previously described.

Pneumonia rates were compared using Poisson regression. Statistical analysis was performed using the R statistical package (GNU General Public License; http://www.r-project.org/). All tests were 2-tailed with P < 0.05 considered significant.
RESULTS

Pneumonia Diagnoses Among Children in Spain

In this study, we included 1307 HIV-infected children with at least 1 hospitalization episode. The median age was 8 years (interquartile range = 7) from 1997 to 2008, increasing from 6 years (interquartile range = 7) between 1997 and 1999 to 10 years (interquartile range = 10) between 2003 and 2008. Of these, 168 children had 180 pneumonia diagnoses, including 137 non-ADP and 43 ADP diagnoses (see Fig., Supplemental Digital Content 1, http://links.lww.com/INF/B126). Moreover, we also included a control group of 5228 HIV-uninfected children of which 180 children had non-ADP and 6 children had ADP (tuberculosis).

HIV-infected children had a higher overall rate of pneumonia (events per 1000 children with hospital admission/year) than HIV-uninfected children (Table 1; \( P < 0.001 \)). HIV-infected children also had higher non-ADP and ADP rates than did HIV-uninfected children (Table 1; non-ADP: \( P < 0.001 \) and ADP: \( P < 0.001 \)). Moreover, HIV-infected children had higher rate of non-ADP than ADP (Table 1, \( P < 0.001 \)).

| Description                      | HIV-uninfected children | HIV-infected children |
|----------------------------------|-------------------------|-----------------------|
|                                  | No.  | Rate (95% CI)      | No.  | Rate (95% CI)      |
| Non-ADP                          | 180  | 34.43 (29.40–39.45) | 137  | 104.82 (87.26–122.37) |
| ADP                              | 6    | 1.14 (0.22–2.06)   | 43   | 32.90 (23.06–42.73) |
| All pneumonia (Non-ADP plus ADP) | 186  | 35.57 (30.46–40.69) | 180  | 137.72 (117.60–157.84) |

*events per 1,000 children with hospital admission/year*

†Significant differences between Non-ADP and ADP categories within a study group (\( P < 0.001 \)).
‡Significant differences between groups of study within a pneumonia diagnosis category (\( P < 0.001 \)).

Rate indicates events per 1000 children with hospital admission/year; 95% CI, 95% confidence interval.

FIGURE 1. Summary of the epidemiologic trend of pneumonia (events per 1000 HIV-infected children/year) among HIV-infected children in Spain from 1997 to 2008.
Pneumonia Rates Among HIV-infected Children Over Time in Spain

The overall rate of pneumonia (events per 1000 HIV-infected children/yr) in the whole follow-up period (from 1997 to 2008) was 13.77 (95% confidence interval: 11.75–15.78). The non-ADP rate was 10.48 (95% confidence interval: 8.72–2.23) and the ADP rate was 3.28 (95% confidence interval: 2.30–4.27).

The pneumonia rate decreased from 1997–1999 to 2003–2008 and from 2000–2002 to 2003–2008 (Fig. 1; P < 0.001). When we compared within each category of pneumonia, the non-ADP rate decreased from 1997–1999 to 2003–2008 (Fig. 1; P < 0.001), and the ADP rate had the same tendency from 1997–1999 to 2003–2008 (Fig. 1; P < 0.001). Furthermore, the non-ADP diagnoses decreased from 1997–1999 to 2000–2002, although it did not reach statistical significance (Fig. 1; P = 0.081). Finally, when we compared the 2 categories of pneumonia diagnoses, the non-ADP rates were higher than ADP rates throughout the whole follow-up and within each calendar period (Fig. 1; P < 0.001).

DISCUSSION

In our study, HIV-infected children had an overall rate of pneumonia (ADP and non-ADP) about 4-fold higher than that in HIV-uninfected children, but the pneumonia rate among HIV-infected children fell sharply throughout the HAART era (about 3-fold lower in 2003–2008 than in 1997–1999). Despite this, the incidence of pneumonia in the last calendar period (2003–2008) still remains higher in HIV-infected children than in the general population. ADP is an important cause of morbidity and mortality in HIV-infected children. In our study, HIV-infected children were at increased risk of developing ADP compared with the general population, even in the HAART era, although the ADP rate decreased during the last calendar period (about 4-fold lower in 2003–2008). This may be due to an increasing use of HAART and improved immunosurveillance over time. Moreover, the burden of bacterial and viral infections is substantially higher in HIV-infected compared with HIV-uninfected children. In our study, the rate of non-ADP diagnoses was 3-fold higher in HIV-infected children than in HIV-uninfected children, but the rate of ADP in HIV-infected children declined with the widespread use of HAART (about 3.5-fold lower in 2003–2008). HAART-derived immune reconstitution may be a more important protective factor against pneumonia. However, it is also important to note that the non-ADP were over 50% of all pneumonia diagnoses among HIV-infected children in Spain, and the incidence of non-ADP in the last calendar period still remains higher in HIV-infected children than in the general population (about 2-fold higher in HIV-infected children). These values might be due to the lack of complete immune reconstitution and persistent CD4+ lymphopenia due to failure of therapy. The capacity of CD4+ recovery during long-term HAART in HIV-infected children with CD4+ below 5% is lower than in children with CD4+ from 5% to 15%, and restoration of the CD4+ cell percentage to a normal level is not necessarily achieved during long-term HAART.

This study had several limitations that may impact our findings. This work was a retrospective study, and we had no access to patient clinical data (antiretroviral treatment regimen, duration of HAART, CD4+ count, HIV viral load, Centers for Disease Control and Prevention stage) that might affect our results. MBDS data are anonymous, and it is impossible to identify when the same patient is hospitalized at different hospitals within the same calendar year. This may have caused a slight overestimation of our results because we may have calculated disease exacerbations or remissions as new participants. We cannot know the total number of HIV-infected children in Spain at present, because there is no national coverage data of HIV infection in children in Spain. We used an estimation of the number of HIV-infected children in Spain, which was calculated from 2 reliable databases (Spanish National AIDS Register and Madrid Cohort HIV Children). Finally, our results show an “aging cohort” phenomenon in Spanish HIV-infected children. Given this and the fact that pneumonia is less common in older than in younger children, the overall fall of pneumonia rate in our study over time should be interpreted carefully.

In conclusion, the rate of pneumonia decreased among HIV-infected children in the HAART era although the pneumonia rate still remains higher than in the general population. Non-ADP remains a significant health problem for HIV-Infected children in Spain.

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Authors’ Contributions: DM, JJ and SR contributed to the study concept and design; AA-M contributed to the acquisition of data; AD, AA-M and SR were responsible for statistical analysis and interpretation of the data; DM, JJ and SR contributed to the drafting of the manuscript; DM, AD and SR critically revised the manuscript for important intellectual content; and SR supervised the study.

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