Trend of pneumonia incidence among children infected with HIV in the era of highly active antiretroviral therapy

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Pediatr Infect Dis J. 2012 Jun;31(6):599-601.

https://doi.org/10.1097/INF.0b013e3182501cd4

Brief Report

Title: Trend of pneumonia incidence among children infected with HIV in the era of highly active antiretroviral therapy

Abbreviated title: Decrease in pneumonia in HIV-infected children

Running head: Pneumonia trend in HIV-infected children

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Financial support: This work has been supported by a grant from "Instituto de Salud Carlos III" (Ref. PI08/0738) to SR.

Disclosures: The authors have no conflicts of interest or funding to disclose

Key Words: HIV; pneumonia; HAART; infection; pediatric; epidemiology

ABSTRACT

We carried out 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 HAART era but still remained higher than in the general population. Non- AIDS defining pneumonia remains a significant health problem for HIV-infected children.

INTRODUCTION

Highly active antiretroviral therapy (HAART) has proved highly effective in suppressing viral load and increasing CD4+ T-cell (CD4+) counts in human immunodeficiency virus (HIV) infected children (1); decreasing HIV related opportunistic illness, morbidity, hospitalizations and death (2, 3). Besides, opportunistic infections (OIs) have also diminished with the use of HAART (2, 4), and preventive chemotherapy has contributed to decreased the incidence of OIs complications (5, 6).

Pneumonia is among the leading causes of morbidity and mortality among HIV-infected patients in HAART era (7), mainly in children with persistently low CD4+ counts (4). AIDS defining pneumonia (ADP), occurring in advanced stages of immune-suppression (8) and, non-AIDS defining pneumonia (non-ADP), or community-acquired pneumonia, are major causes of death and hospitalization in HIV-infected children (8).

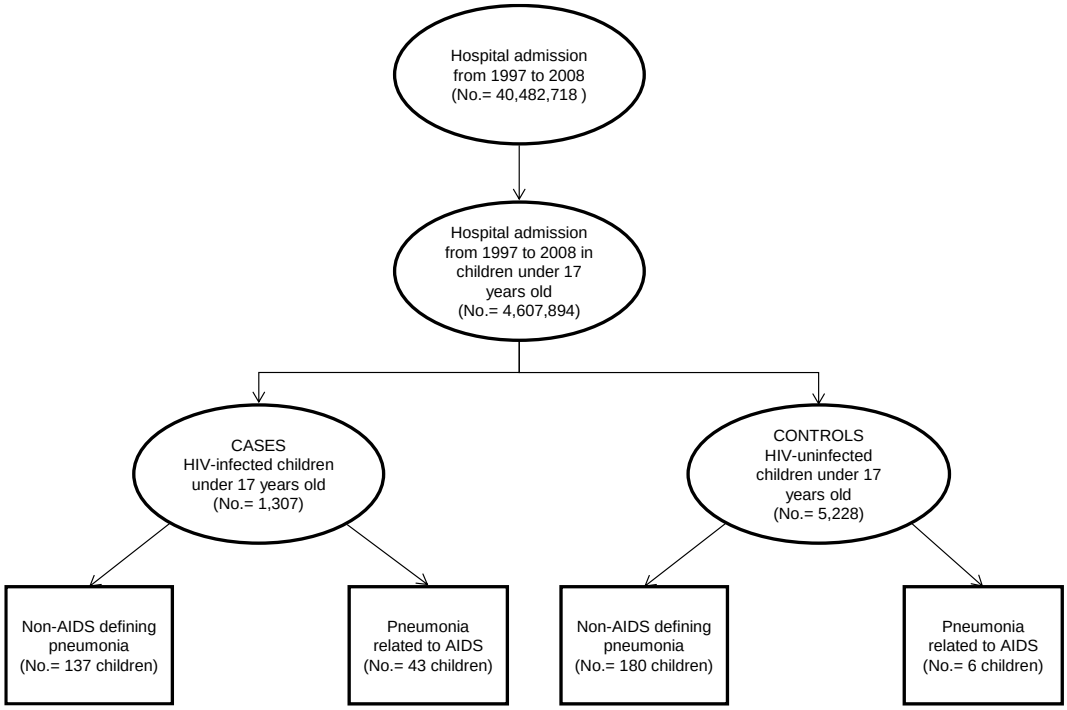
The aim of our study was to evaluate the trend in pneumonia rates among HIV-infected children in the HAART era through the use of comprehensive records of the Minimum Basic Data Set (MBDS) in Spain.

MATERIALS AND METHODS

We carried out 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 old with a hospital admission in Spain (see figure, **supplemental digital content (SDC) 1**) (9). 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 and 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).

Supplemental digital content 1. Flow-chart for the selection of HIV-infected children (cases) and HIV-uninfected children (controls) under 17 years old and pneumonia in Spain from 1997 to 2008.



Data were obtained from the records of the MBDS of hospitals in Spain, as we previously described (9). The MBDS is a database which 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* (ICD-9-CM) 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 three subperiods or calendar periods, according to the widespread use of HAART in children as previously described (9): a) From 1997 to 1999 (1997-1999) for early-period HAART; b) from 2000 to 2002 (2000-2002) for mid-period HAART; 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 ICD-9-CM codes (see table, **SDC 2).**

Supplemental digital content 2. Summary of ICD-9-CM codes to define the occurrence of a hospital discharge with pneumonia diagnosis.

Diagnosis of ADP:	**Diagnosis of non-ADP**
011 (Pulmonary tuberculosis)	480.XX (Viral pneumonia)
031.0 (Pulmonary diseases due to other mycobacteria)	481.XX (Pneumococcal pneumonia)
136.3 (Pneumocystosis)	482.XX (Other bacterial pneumonia)
112.4 (Candidiasis of lung)	483.XX (Pneumonia due to other specified organism)
114.0 (Primary coccidioidomycosis (pulmonary))	485.XX (Bronchopneumonia organism unspecified)
114.4 (Chronic pulmonary coccidioidomycosis)	486.XX (Pneumonia organism unspecified)

114.5 (Chronic pulmonary coccidioidomycosis)
117.5 (Cryptococcus neoformans)
115.15 (Histoplasma duboisii pneumonia)
115.05 (Histoplasma capsulatum pneumonia)
115.95 (Histoplasmosis pneumonia unspecified)
130.4 (Pneumonitis due to toxoplasmosis)
484.6 (Pneumonia in aspergillosis)
117.3 (Aspergillosis).
487.0 (Influenza).

We calculated the incidence rate, or the number of events per 1,000 children-years (children-yr), 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 1,000 children with hospital admission-yr, 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 1,000 HIV-infected children-yr, we used the estimated number of all HIV-infected children in Spain within each year that fell into each calendar period, as previously described (9).

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 two-tailed with p-values <0.05 considered significant.

RESULTS

Pneumonia diagnoses among children in Spain

In this study, we included 1307 HIV-infected children with at least one hospitalization episode. The median age was 8 years (interquartile range (IQR)= 7) from 1997-2008, increasing from 6 years (IQR= 7) in 1997-1999 to 10 years (IQR= 10) in 2003-2008. Of all these, 168 children had 180 pneumonia diagnoses, including 137 non-ADP and 43 ADP diagnoses (see figure, **SDC 1**). Moreover, we also included a control group of 5228 HIV-uninfected children. Of them, 180 children had non-ADP and 6 children ADP (tuberculosis).

HIV-infected children had a higher overall rate of pneumonia (events per 1,000 children with hospital admission/yr) 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).

Table 1. Summary of the number and rates of pneumonia diagnoses (events per 1,000 children with hospital admission/year) in HIV-infected children and HIV-uninfected children in Spain from 1997 to 2008.

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

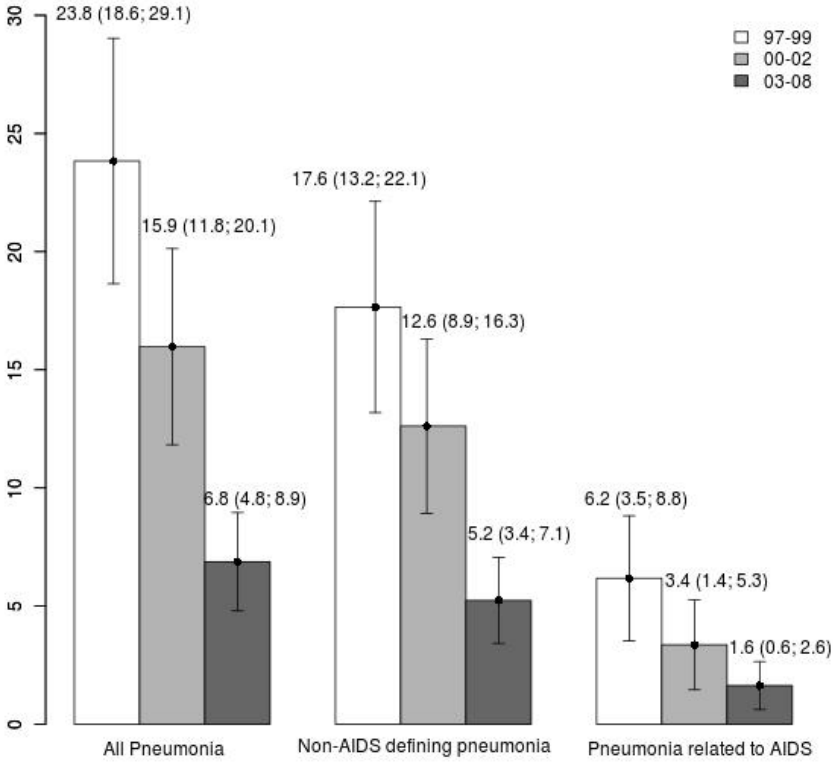
Abbreviations: Rate, events per 1,000 children with hospital admission/year; 95%CI, 95% of confidence interval. (†): Significant differences between groups of study within a pneumonia diagnosis category (p<0.001). (*): Significant differences between Non-ADP and ADP categories within a study group (p<0.001).

Pneumonia rates among HIV-infected children over time in Spain

The overall rate of pneumonia (events per 1,000 HIV-infected children/yr) in the whole follow-up period (from 1997 to 2008) was 13.77 (95% of confidence interval (95%CI): 11.75; 15.78). The non-ADP rate was 10.48 (95%CI: 8.72; 12.23) and ADP rate was 3.28 (95%CI: 2.30; 4.27).

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

Figure 1. Summary of the epidemiologic trend of pneumonia (events per 1,000 HIV-infected children/year) among HIV-infected children in Spain from 1997 to 2008.



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 (6, 10).

ADP is an important cause of morbidity and mortality in HIV infected children (7). In our study, HIV-infected children were at increased risk of developing ADP compared to 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 (4, 7, 11). Moreover, the burden of bacterial and viral infections is substantially higher in HIV-infected compared to HIV-uninfected children (8). 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 (12). 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 general population (about 2-fold higher in HIV infected children) (10). These values might be due to the lack of complete immune reconstitution and

persistent CD4+ lymphopenia due to failure of therapy (1). 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 5–15%, and restoration of the CD4+ cell percentage to a normal level is not necessarily achieved during long-term HAART (1).

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, CDC stage) that might affect our results. MBDS data are anonymous and it is impossible to identify when the same patient is hospitalized has been 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 two 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 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.

AUTHORS' CONTRIBUTIONS

Study concept and design: Dariela Micheloud, Julia Jensen, Salvador Resino.

Acquisition of data: Alejandro Álvaro-Meca.

Statistical analysis and interpretation of data: Alejandro Álvaro-Meca, Asunción Díaz, Salvador Resino.

Drafting of the manuscript: Dariela Micheloud, Julia Jensen, Salvador Resino.

Critical revision of the manuscript for important intellectual content: Dariela Micheloud, Asunción Díaz, Salvador Resino.

Administrative, technical, or material support: Alejandro Álvaro-Meca, Salvador Resino.

Study supervision: Salvador Resino.

ACKNOWLEDGEMENTS

Additional Contributions: We wish to thank: a) The Madrid HIV Paediatric Infection Collaborative Study Group (Santiago Jiménez de Ory, Dr. Jose Tomas Ramos, Dra. Mª Ángeles Muñoz-Fernandez) for records of HIV-infected children in Madrid cohort; b) Spanish National AIDS Register (National Centre for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain) for number of HIV-infected children with an AIDS diagnosis; c) Spanish Ministry of Health and Social Policy for records of the Minimum Basic Data Set (MBDS).

Financial Disclosures: None reported.

Financial support: This work has been supported by grants from Instituto de Salud Carlos III (Ref. PI08/0738 and PI11/00245) to SR.

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