Impact of highly active antiretroviral therapy (HAART) on the incidence of opportunistic infections, hospitalizations and mortality among children and adolescents living with HIV/AIDS in Belo Horizonte, Minas Gerais State, Brazil

Impacto da terapia anti-retroviral de alta potência (HAART) na incidência de infecções oportunistas, hospitalização e mortalidade associadas em crianças e adolescentes vivendo com HIV/AIDS em Belo Horizonte, Minas Gerais, Brasil

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Abstract

The impact of highly active antiretroviral therapy (HAART) can be evaluated using indicators, such as rates of opportunistic infections, hospitalizations by cause of infection, and associated death. This study aimed to estimate the impact of HAART on the incidence of these indicators, in children and adolescents with HIV/AIDS. It was a hybrid cohort study; 371 patients were followed from 1989 to 2003. In December 2003, 76% of the patients were still being followed, while 12.1% had died, 9.5% had dropped out, and 2.4% had been transferred. The overall rate of opportunistic infections was 18.32 infections/100 persons-year and 2.63 in the pre- and post-HAART periods, respectively. In the multivariate analysis, the risk of developing an opportunistic infection was 5.4 times greater and 3.3 times greater for hospitalization risk before HAART. Respiratory causes represented 65% of the hospitalizations and they were reduced by 44.6% with therapeutic intervention. The average hospital stay of 15 days was reduced to 9.There was a post-HAART decline in deaths of 38%. This study demonstrates the effectiveness of HAART in significantly reducing opportunistic infections, hospitalizations, and deaths in this Brazilian cohort.

Highly Active Antiretroviral Therapy; Oppurtunist Infections; HIV

Introduction

Opportunistic infections are important causes of morbidity and mortality in children and adults living with HIV/AIDS [1]. Immunological disfunction caused by HIV limits the ability of the host to produce defenses against opportunistic pathogens and favors the spread of the virus [2]. Hospitalizations and deaths are the principal events resulting from opportunistic infections and are important indicators of the impact of interventions carried out in this population.

The advent of highly active anti-retroviral therapy (HAART), with the introduction of protease inhibitors in 1998, has changed the natural progression of the disease caused by HIV. This therapy reduces viral replication, increases the number of CD4 lymphocytes and improves their function, re-establishing the defenses of the host and improving chances of survival [3]. A reduction in the rate of opportunistic infections and hospitalizations in adults infected with AIDS after 6-12 months of HAART intervention is well documented [4,5]. Decreases in hospitalizations and deaths result in a substantial reduction in health care costs associated with infected patients. Worldwide, there have been very few studies [6,7,8] carried out regarding the impact of HAART therapy on vertically infected children and adolescents, none of them in the Brazilian population.

The object of this study is to describe the rates of incidence of opportunistic infections, hospital-

izations per type of infection, and the death rate, in a cohort of children and adolescents followed in a reference center in Belo Horizonte, Minas Gerais State, Brazil, before and after the introduction of HAART, and to estimate, based on selected risk factors, the impact of this intervention.

Material and methods

This hybrid cohort was conducted from March 1989 to December 2003 at the Centro de Treinamento e Referência em Doenças Infecciosas e Parasitárias (CTR-DIP). It is a service of reference for the treatment of infectious and parasitic diseases in the metropolitan area of Belo Horizonte, and other cities in the State of Minas Gerais, under the responsibility of the Belo Horizonte Municipal Health Secretariat and the Universidade Federal de Minas Gerais [Federal University of Minas Gerais – UFMG] Clinic and Hospital. The children and adolescents admitted into this program were subjected to periodical clinical and laboratory evaluations, which were conducted by pediatricians specialized in immunology and infectology. The medical records were collected with standardized procedures.

Each patient was followed closely from the date of admission into the program until their last consultation in the period of the study and classified in accordance with their clinical evolution, as: (1) in sequence, when there was at least one consultation in 2003; (2) loss of sequence, when there were no consultations in 2003; (3) death certificate after the date of the event; and (4) patient transfer, when the patient was transferred to another service on a definite date. Usually the consultations were given on a monthly basis during the first six months of life and every three months afterwards, or at lesser intervals in accordance with clinical indications.

The pertinent information for this study was obtained retrospectively through a review of medical records from 1989 to 2002, and prospectively in 2003. The data collection system developed for the study collected demographic information, how HIV was acquired, quantification of viral plasma load, CD4 lymphocyte count, use of prophylactic medicines (sulphamethoxazole, trimethoprim, intravenous immunoglobulin, ganciclovir, isoniazide, sulphadiazine, and pyrimethamine). Information about the use of antiretrovirals and anthropometric data were updated at least once every six months. Information about hospitalization was obtained from medical records, and complemented by consulting the admission records of the hospitals involved. Data from death certificates were verified through the death records information service of the Minas Gerais State Health Secretariat. In an effort to minimize the pitfalls of a retrospective study, medical records were reviewed simultaneously by three pediatric infectologists, utilizing uniform criteria for defining patients' clinical conditions. The work was approved by the Ethics in Research Committee at UFMG.

All patients from 0-18 years old that were diagnosed with HIV/AIDS (according to criteria established by the Brazilian Ministry of Health) [9] and accompanied by the pediatric program at the CTR-DIP during the period cited, were included in the study. The opportunistic infections studied were part of the clinical categories B and C [10]. Only the first event of each infectious disease was considered per patient, however, if a patient contracted a different opportunistic infection, its first event could also be included in the study.

The opportunistic infections included in the study were recurrent bacterial infections caused by encapsulated germs *(Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*), esophageal candidiasis, simple herpes infection and varicella-zoster, contagious molluscum, pulmonary, ganglionar, and extrapulmonary tuberculosis, hepatitis C, visceral leishmaniasis, *Pneumocystis jirovecii* pneumonia (PJP), tuberculosis, disseminated *Mycobacterium avium* complex, infection by citomegalovirus (CMV), infection by *Cryptococcus neoformans*, *Cryptosporidium parvum,* cerebral toxoplasmosis, nocardiosis, and progressive multifocal leucoencephalophy.

All infections were classified as presumptive or definitive diagnoses in accordance with the criteria of definition of cases of AIDS in children [9]. Suggestive diagnoses were only tolerated in cases of pulmonary tuberculosis or PJP, because of the inherent difficulties in diagnosis. It was considered suggestive pulmonary tuberculosis if there was prolonged fever, nocturnal sweating, cough, hemoptysis, weight loss, radiographic alterations, and response to anti-tuberculostatics, without a positive BAAR exam. For suggestive PJP the criteria used were compatible clinic and the presence of hypoxemia or radiological alterations.

Invasive bacterial infections included in the analysis were septicemia, meningitis and pneumonia. In virtue of the difficulties in definitively diagnosing bacterial pneumonia and confusing it with other diseases that may have similar symptoms, such as bronchospasm or interstitial lymphoid pneumonia (ILP), only episodes that resulted in hospitalizations were considered.

Opportunistic infections that make up clinical category C were considered for analysis of a more generalized risk development.

The hospitalizations and deaths studied were those directly related to the opportunistic infections identified. The number of hospitalizations and length of hospital stay were evaluated and the causes of infections resulting in these admissions were classified into four major groups: respiratory, digestive, neurological, and systemic. This classification system is the same one that is used by the Brazilian Unified National Health System (SUS) to effect payments for the hospitalization of HIV/AIDS infected patients.

For analytical purposes, the patients were divided into two groups, depending on whether or not they used antiretroviral drugs during the course of the opportunistic infection evaluated: (1) non-HAART group – patients not using antiretrovirals or using antiretroviral regimes with less than three drugs, (2) HAART group – antiretroviral regimen consisting of at least three drugs, being two nucleosid transcriptase reverse analogues (ITRN), combined with a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor or three IRTN.

The data bank was created using the statistical package SPSS for Windows version 8.0 (SPSS Inc., Chicago, U.S.A.) and Epi Info version 6.4 (Centers for Disease Control and Prevention, Atlanta, U.S.A.). The anthropometric analysis was realized by means of the Epinut of Epi Info version 6.4, considering for analysis the z-score of weight/height = -2.

A descriptive analysis of the population studied was done. The incidence rates through people-time were obtained by dividing the number of events observed by the sum of the years that each subject contributed to the study, censured at the time of an event, at death, at loss, or the end of the sequence. Events evaluated were: each specific opportunistic infection, the first manifestation of clinical category C, and hospitalizations. Only the first hospital admission per participating patient in the study was considered for the calculation of the hospitalization rate. The intervals of confidence for the incidence rates were calculated through Poisson distribution [11]. The incidence density ratio was evaluated [12] by estimating the relative risk for HAART and non-HAART groups.

Univariate and multivariate analyses were carried out through the Cox model to evaluate the contribution of each risk factor for the development of a category C opportunistic infection for hospitalizations and mortality, estimating the impact of HAART on these events. The value of $p < 0.05$ was defined as the limit for statistical significance, with the calculus of 95% confidence intervals.

Results

The study included 371 HIV infected children admitted to the CTR-DIP from March 1989 to December 2003. The mean age at admission was of 22.9 months (1 to 195 months), and 50.9% of the children were female. There was a mean follow-up time of 22.1 months (2 to 163 months), with an average of 23 consultations per patient. Vertical transmission was responsible for the majority of the cases, at 91.4%, transmission through hemoderivates accounted for 4.6%, and in 3.2% of the cases the method of transmission was unknown. Reports of acquisition of the virus through mother's milk and homosexual and heterosexual relations were a contributing cause in each case.

Over the 15 years of the study, there were 45 (12.1%) deaths, 35 (9.5%) losses to follow up, and 9 (2.4%) transfers to other health services; 282 (76%) patients remained in follow up until December 2003. The mean survival rate of the population studied was over 160 months.

Opportunistic infections had a great impact on this group, with 520 reports of opportunistic diseases, considering each primary episode, attacking 73.6% of the children at some moment of their accompaniment over these years. At the first consultation, 39.1% of the patients already had an opportunistic infection, which was the first manifestation of immunosuppression caused by HIV.

Of the total of opportunistic infections, 74.2% occurred in the non-HAART group, 227 in patients not using antiretrovirals, and 159 were in those that were using monotherapy or dual therapy. In the HAART group there were 134 (25.8%) episodes of opportunistic infections recorded, 83.6% of whom were using the first regimen of combined therapy.

It was observed that, of the opportunistic infections diagnosed during HAART use, half occurred during the first three months of therapy, during the phase called partial immunological restoration. The infections most frequent in this phase were bacterial ones, which represented 38.9% of events, oral candidiasis at 37.3%, and infection by the varicella-roster virus at 12%.

The majority of the opportunistic infections identified in the sample studied were presumptive (73.8%), according to the criteria established by the Brazilian Ministry of Health and used in this investigation. Next were the definitive, with 23.3%, and the suspected, with 2.9% of the cases.

Table 1 shows the general incidence rates that ran throughout the study, calculated in 100 people-year, of the principal opportunistic infections belonging to categories B and C of the Cen-

ters for Disease Control and Prevention (CDC) [10], as well as their respective incidences before, and after, HAART. These rates reveal significant differences and modifications in the profile of the more incident ones with the intervention of combined antiretroviral therapy. In both periods, invasive bacterial infections were more prevalent, with bacterial pneumonia being responsible for the majority of events. Meanwhile PJP, which occupied third place in the pre-HAART era, had its position substituted by varicella-zoster viral infection in the post-HAART era. Practically all the opportunistic infections were reduced significantly with the introduction of HAART. Table 1 shows the incident density ratios referring to both periods.

Extrapulmonary tuberculosis, hepatitis C, gangliar toxiplasmosis, and visceral leshmaniosis presented, respectively, the following pre-HAART incidence rates per person-year: 1.7% (95%CI: 0.60-3.70), 1.16% (95%CI: 0.40-2.70), 0.49% (95%CI: 0.06-1.80), and 0.48% (95%CI:0.06-1.70) while neocardiosis, progressive multifocal leucoencephalopy, and tuberculoid hansen's disease each had an incidence of 0.24% (95CI%: 0.01-1.40). None of these infections were identified after the introduction of HAART.

The rate of infection for the first manifestation of a clinical category C infection of CDC studied classification [10], was 8.11/100 persons-year (95%CI: 6.60-10.06). This rate represents a more global risk quantification of opportunistic infections for the sample studied. There has been a decrease in the rates from 18.32/100 persons-year (95%CI: 14.40-23.20) in the pre-HAART period to 2.63/100 persons-year (95%CI: 1.58- 4.01) in the post-HAART.

Considering the main risk factors for the development of opportunistic infections: use of prophylactic medication, age, score Z for height/age, CD4 lymphocyte counts, quantification of viral plasmatic load, and use of HAART, univariate and multivariate analyses were carried out with the Cox model. The results presented in Table 2 indicate that the lack of HAART therapy was an important risk factor in the development of these events in the 299 cases studied.

There was only interaction between the variables, "use of HAART" and "prophylactic medication", all others were independent.

During the 15 years in which the cohort was followed, 720 hospitalizations were registered. More than half of these hospitalizations (445 events) were associated with opportunistic infections, representing an incidence rate during the total period studied of 72.1/100 persons-year (95%CI: 66.03-78.85). Respiratory causes predominated, with 289 events (65% of opportunistic infection hospitalizations, see Table 3) of which 186 occurred pre-HAART, and 103 post-HAART, showing a decrease of 44.6% in hospitalizations. The average hospital stay for respiratory causes was reduced from 15 days (range: 1 to 116 days) with the introduction of this therapy, accounting for a 40% reduction in hospital days.

Table 1

Incidence rates of opportunistic infections diagnosed in 371 HIV infected pediatric patients, overall, and in pre- and post-HAART, with their respective relative risks and confidence intervals. Belo Horizonte, Minas Gerais State, Brazil, 1989-2003.

Opportunistic infection	Overall infection rate * (95%CI)	Pre-HAART infection rate * (95%CI)	Post-HAART infection rate * (95%CI)	Incidence ratio (95%CI)	P value
Invasive bacterial infection	27.17 (23.40-31.20)	46.41 (39.40-54.30)	11.89 (8.80-15.70)	3.91 (2.83-5.39)	< 0.0001
Esophageal candidiasis	13.52 (11.30-20.60)	28.23 (23.10-34.40)	4.86 (3.30-6.90)	5.80 (3.83-8.77)	< 0.0001
Pneumocystis jirovecii pneumonia (PJP)	3.32 (2.38-4.52)	8.90 (6.20-12.30)	0.71 (0.30-1.60)	12.38 (5.21-29.42)	< 0.0001
Infection by varicella-zoster virus	3.79 (2.80-5.00)	7.6 (4.90-10.50)	2.19 (1.30-3.40)	3.31 (1.86-5.91)	< 0.0001
Pulmonary tuberculosis	1.29 (0.75-2.06)	3.18 (1.70-5.40)	0.44 (0.10-1.10)	7.22 (2.36-22.15)	0.0001
Herpes simplex	1.364 (0.80-2.00)	3.07 (1.60-5.20)	0.56 (0.20-1.30)	5.51 (1.96-15.45)	< 0.0001
Cytomegalovirus (CMV)	0.97 (0.51-1.66)	1.71 (0.70-3.50)	0.64 (0.20-1.40)	2.67 (0.90-7.95)	0.06
Cerebral or ocular toxoplasmosis	0.75 (0.36-1.37)	1.46 (0.50-3.20)	0.43 (0.10-1.10)	3.40 (0.96-12.06)	0.043
Infection by *Cryptosporidium parvum*	0.75 (0.36-1.37)	1.24 (0.40-2.70)	0.53 (0.20-1.20)	2.32 (0.67-8.01)	0.17
Molluscum contagiosum	0.68 (0.31-1.30)	1.21 (0.40-2.80)	0.44 (0.10-1.00)	2.77 (0.75-10.33)	0.11
Infection by *Cryptococcus neoformans*	0.22 (0.05-0.64)	0.24 (0.01-1.40)	0.21 (0.03-0.80)	1.16 (0.11-12.78)	0.9

HAART: highly active anti-retroviral therapy.

* 100 persons/year.

Table 2

Univariate and multivariate analysis, using the Cox model, of risk factors for developing the first manifestation of clinical C category opportunistic infection in 299 patients living with HIV. Belo Horizonte, Minas Gerais State, Brazil, 1989-2003.

Variables	HZ univariate (95%CI)	HZ multivariate * (95%CI)	p value (multivariate) *
Age (months)			< 0.001
< 12 or ≥ 12	9.6 (5.8-15.9)	3.3 (1.6-6.9)	
Prophylaxis			< 0.001
No/Yes	6.2 (3.6-10.6)	3.3 (1.5-7.1)	
HAART			< 0,001
No/Yes	5.4 (3.2-8.9)	5.4 (2.7-10.8)	
CD4 lymphocyte count			< 0.001
< 15% or > 15%	0.2 (0.1-0.3)	0.3 (0.2-0.5)	
Plasmatic viremia (copies)			< 0.001
> 100,000 or < 100,000	11.5 (6.5-20.4)	4.7 (2.4-9.3)	
Score Z weight/height			0.76
≤ -2 or > -2	4.5 (2.5-8.2)	-	

HZ: hazard ratio; HAART: highty active antiretroviral therapy.

* Final model of multivariate Cox regression analysis.

The incidence of those hospital admissions caused by opportunistic infections showed a decline from 113.73/100 persons-year (95%CI: 102.24-126.46) in those patients not using HAART to 41.30/100 persons-year (95%CI: 35.52-47.99) in those using this therapy. In multivariate analysis HAART was shown to be the main risk factor determining hospitalizations in the population studied, as can be seen in Table 4. Evaluations comprised 229 patients in the final multivariate model and no interactions between the variables were found.

The opportunistic infection episodes were important causes of death in the sample studied, representing 94.1% of deaths of a known cause (34 deaths), the most frequent infection being invasive bacteria in 39% of the cases. The number of deaths was also influenced by HAART. There were 31 deaths recorded in people who had not used combined antiretroviral therapy, and 14 in those who had used this therapy. Before HAART all the deaths were caused by opportunistic infections, after the introduction of these therapies the percentage fell to 85%, of HIV (15%), totaling a reduction of 38% in post-HAART deaths. Univariate analysis revealed that the non-use of HAART was statistically significant for an increase in mortality (p = 0.001), but this was not confirmed in the multivariate analysis, which evaluated 318 cases, probably because of the influence of the high plasmatic viral loads, attributed to be the main predictor of death in this cohort (hazard ratio – HZ = 10.21; 95%CI: 3.20-33.25). Other significant factors were, to be less than 12 months old (HZ = 6.4; 95%CI: 1.60-25.90) and to have had an opportunistic infection of clinical category C (HZ = 5.4; 95%CI: 1.90-15.10). The variables did not present interaction between each other, being, therefore, independent.

Discussion

The cohort under analysis, conducted at the pediatric AIDS ambulatory clinic of UFMG School of Medicine, is representative of epidemiological behavior exhibited by children infected by HIV in Brazil. Vertical transmission totalized 91.4% of the cases, according to data from the Brazilian Ministry of Health that showed proportions that varied from 79.2% to 85.8% [13]. The criteria defined by the study were met by 370 children, and, during a long period of accompaniment, there was only a 9.5% loss to follow-up. There was a 12.1% mortality rate among the children who survived for 160 months. This proportion is low when compared to an Argentinian cohort [14] of children followed during pre- and post-HAART, with a 23.1% mortality rate, and with that of an African child cohort [15], with 39%, where the use of antiretrovirals was not yet a reality.

In Brazil, the antiretrovirals are supplied to all the infected population through the SUS and, since 1991, zidovudine was already available for

Table 3

Distribution of hospitalization causes of opportunistic infections in 371 children followed in a cohort study. Belo Horizonte, Minas Gerais State, Brazil, 1989-2003.

Causes of hospitalizations	Pre-HAART	Post-HAART	Total	
			n	%
Respiratory causes				
Pneumonia	152	86	238	53.5
Cytomegalovirus (CMV)	0	4	4	0.9
Nocardiosis	1	0	1	0.2
Pulmonary tuberculosis	5	1	6	1.3
Pneumocystis jirovecii pneumonia (PJP)	28	12	40	9.1
Total	186	103	289	65.0
Systemic causes				
Calazar (visceral leshmianiasis)	2	0	2	0.4
Cytomegalovirus (CMV)	2	2	4	0.9
Infection by *Cryptcoccus*	1	2	3	0.7
Sepsis	25	17	42	9.4
Infection by varicella-zoster	14	12	26	5.9
Simple herpes	5	3	8	1.8
Total	49	36	85	19.1
Neurological causes				
Cerebral toxoplasmosis	4	3	7	1.6
Progressive multifocal leukoencephalopathy	1	0	1	0.2
Herpetic encephalitis	1	0	1	0.2
Meningitis	3	0	3	0.7
Cerebral cytomegalovirus (CMV)	0	1	1	0.2
Total	9	4	13	2.9
Digestive tract causes				
Diarrhea from *Cryptosporidium*	4	1	5	1.1
Esophageal candidiasis	34	13	47	10.6
Herpetic esophagitis	1	0	1	0.2
Total	39	14	53	11.9
Others	4	1	5	1.1
Total	287	158	445	100.0

HAART: highly active anti-retroviral therapy.

use. In a national study carried out with adult Brazilian HIV patients published by Marins et al. [16], in 2003, the survival rate increase in these patients was shown. Those diagnosed in 1996 had an average survival rate three times greater than those diagnosed in 1995. This improvement was associated with the ample distribution of antiretroviral medication in the country, principally protease inhibitors, beginning in 1996.

Summing these initiatives and others, such as the implementation of chemo-prophylaxis protocols, greater access to early diagnosis, and clinical-laboratorial and multidisciplinary accompaniment, the reality of the HIV-infected people in Brazil has approached the reality of the HIV-infected people living in developed countries, as documented by an increase in survival rates and reductions in the incidence of opportunistic diseases [17]. However, the socioeconomic conditions in Brazil reflect the difficulties typically encountered in developing countries, such as the bad nutritional state of those infected and the low educational level of family members, which may be decisive in the clinical response, and adherence to, antiretroviral treatment. Thus, our findings reveal the peculiarities of the Brazilian reality.

In the present study, the introduction of HAART is associated with a dramatic effect in the overall reduction of incidence rates of opportunistic infections, of the number and duration of hospital stays associated with infectious events, and of the mortality of this group of Brazilian children and adolescents living with HIV/AIDS. These findings are in agreement with various

Table 4

Univariate and multivariate analyses, using the Cox model, of risk factors for hospitalization caused by infections in 299 patients living with HIV. Belo Horizonte, Minas Gerais State, Brazil, 1989-2003.

Variables	HZ univariate (95%CI)	HZ multivariate * (95%CI)	p value (multivariate) *
Age (months)			0.002
< 12 or ≥ 12	3.3 (2.4-4.5)	1.9 (1.3-2.8)	
Prophylaxis			0.06
No/Yes	60.5 (0.4-0.6)	-	
HAART			< 0.001
No/Yes	4.0 (2.7-5.9)	3.3 (2.1-5.1)	
CD4 lymphocyte count			0,001
< 15% or > 15%	2.0 (1.5-2.7)	1.9 (1.3-2.7)	
Plasmatic viremia (copies)			0.008
> 100,000 or < 100,000	2.8 (2.0-3.9)	1.7 (1.1-2.4)	
Score Z weight/height			0.74
≤ -2 or > -2	1.6 (1.1-2.5)	-	

HZ: hazard ratio; HAART: highly active anti-retroviral therapy.

* Final model of multivariate Cox regression analysis

studies that have linked the of use of HAART therapy to a decline in opportunistic infections in adult HIV-infected patients [7,18,19,20,21]. In an investigation realized by Schmidt-Westhausen et al. [21] in 2000, the prevalence of oral opportunistic infections associated with HIV was analyzed before and after beginning HAART. A statistically significant reduction in oral candidiasis was observed, with a pre-HAART incidence rate of 66%, contrasting with one of 5.8% after this therapy was introduced. Other infections, such as molluscum contagiosum, and herpes simplex were observed in 4.9% and 2.9% of the cases, respectively, before the use of antiretroviral treatment, and not observed at all after the implementation of HAART. Brodt et al. [7], in 1997, also found this association. Infections like PJP also fell: from 17.8/100 persons-year in 1992 to 6.4/100 persons-year in 1996; disseminated CMV fell from 14.7/100 persons per year to 3.6/100 persons per year.

This cohort covered different periods in terms of definition of AIDS cases and of opportunistic infections. As most of the information was collected retrospectively, care was necessary to minimize this effect. Each case was evaluated by three different pediatric infectologists, who reviewed the medical records to standardize the classification of children using CDC criteria [10], permitting a reliable inclusion of these data.

Nevertheless, the majority of these diagnoses of opportunistic infections were presumptive (70%), which may have over-estimated the incidence rates, even if only the first episode of each opportunistic infection is considered in order to reduce the influence of recurring infections. Only 27.7% of the diagnoses actually found the infectious agent, with 2.4% of presumptive diagnoses. This data reflects the difficulty of diagnosing opportunistic infections in pediatric patients, because the diagnostic techniques are many times invasive and require the patients' cooperation. In pediatrics, presumptive diagnoses are more tolerated, and the type of diagnosis given reflects the quality of the doctors' service given, in terms of diagnostic resources available, and the weight given to a definitive diagnosis. A definitive diagnosis is the gold standard, but at least a presumptive one is essential for the management of an HIV-infected patient, as it determines the present as well as the future prognosis of these patients, be it related to the therapy instituted when diagnosis is made, in the avoidance of empirical therapies, or be it in long-term or permanent secondary chemoprophylaxis for opportunistic agents.

Various factors are associated with a decline in the rates of opportunistic infections: age, CD4 lymphocyte count, plasmatic viral load, hemoglobin rate, use of chemoprophylaxis against principal opportunistic infections, nutritional aspects [22], and a previous opportunistic event [23]. Among the variables analyzed in this study using the multivariate model, the non-utilization

of HAART was found to be the key predictor of opportunistic infections of the clinical category C, with a risk of 5.4% (95%CI: 2.70-10.80). High viral loads were also associated with high opportunistic infection risk, showing itself as a predictor, independent of CD4 count, for the development of diseases related to AIDS (opportunistic infections in the majority of instances) [24,25]. In multivariate models, the viral load appears as a predictor of opportunistic infections. In these studies in patients that had a basal viral load of > 90,000 copies/ml the risk of developing PJP was eleven times greater in comparison to those with a viral load of < 30,000 copies/ml. In the multivariate model fitted for this study, there was no interaction between the variables "non-utilization of HAART" and "viral load", suggesting they are independent predictors for developing opportunistic infections of clinical category C.

The CD4 lymphocyte count is considered an independent predictor for the disease progression of HIV infection [26]. In the present study, a CD4 count less than 15% did not represent a risk for the development of an opportunistic infection. This fact can be interpreted as a necessity of immunological reconstruction for the development of certain infections. In this analysis, 50% of the opportunistic infections that occurred while under HAART treatment were identified during the first three months of this therapy, a phase known as partial restoration, constituting quite a paradoxical observation [27].

In this investigation a reduction by more than half of hospital stays resulting from infection was observed, which occurred 3.3 times more frequently in the pre-HAART period (95%CI: 2.10-5.10).The non-use of HAART again was found to be a relevant factor, this time as an independent predictor of hospitalization risk, among this cohort of children and adolescents living with HIV/AIDS in a study carried out over 15 years. The ample use of HAART seems not only to reduce the frequency of hospitalizations of these patients, but also to reduce the length of hospital stays by almost one half, when hospitalization became necessary, if compared with those observed before HAART. Another study showed a decrease in hospital stays, time of stays, and in the use of antibiotics, as observed in Italian children infected with HIV using protease inhibitors [6]. In Madrid, Spain, after the institution of HAART, hospital stays diminished by a factor of three in relation to children presenting the same clinical picture [28]. Viani et al. [29] evaluated 129 children during the period from 1994 to 2001 and observed that almost a third (32.8%) of these patients had hospital admissions in 1994, while only 5.9% were hospitalized in 2001, after the introduction of HAART. Similarly, the average hospital stay decreased from 8.2 to 2.8 days. A decline of 26% in hospital stays in the post-HAART era was reported in a study published in 2004 by the group EuroSIDA [30], with a reduction of 58% in the length of the average hospital stay (from 12 days in 1995 to 2 days in 2002).

Opportunistic infections represented an important cause of death among HIV infected children. In a cohort followed by Chakraborty [4] in the period from 1995 to 2001 there was a reduction of 39% in the mortality rate. In the data presented in the present investigation there can be seen a 38% reduction in the number of deaths in the post-HAART period, but 85% of the causes of death in the post-HAART period are still persistently opportunistic infections. Due to the high viral loads present in the patients in this cohort that ended up dying, a factor that is a known predictor for this event, HAART was not found to have significance in the multivariate analysis as a protector against the mortality of this population. However, once HAART had reduced the plasmatic viral load of these patients, it became an indirect factor in the reduction of death risk.

It is important to emphasize that control of viral replication is not attained in all patients. The group that requires the greatest care in relation to opportunistic infections risk is represented by the patients that are not using antiretrovirals, through non adherence to medication, failure of therapeutic scheme because of viral resistance, or late diagnosis of AIDS [31]. Thus, a deterioration of the immune system can occur, and the risk of developing opportunistic diseases will persist.

Our findings confirm the effectiveness of HAART as the best intervention for the prevention of opportunistic infections, and, consequently, hospitalizations and deaths in children and adolescents living with HIV/AIDS in Brazil. Therefore, the initial force for the ample distribution of this therapy has been responsible for the reduction of expensive hospitalizations, as well as an improvement in the quality of life and survival rate of this population.

Resumo

O impacto da terapia anti-retroviral de alta potência ativa (HAART) pode ser avaliado utilizando-se indicadores, como taxas de incidências de infecções oportunistas, hospitalizações por causas infecciosas e mortalidade associada. O objetivo deste trabalho foi estimar o impacto da HAART na incidência desses indicadores em crianças e adolescentes com HIV/AIDS. Trata-se de uma coorte híbrida, na qual foram acompanhados 371 pacientes no período de 1989-2003. Em dezembro de 2003, 76% dos pacientes permaneciam em acompanhamento, 12,1% faleceram, 9,5% foram perda de seguimento e 2,4% transferidos. A taxa de incidência global de infecções oportunistas foi de 18,32 infecções/100 pessoas-ano e 2,63 nos períodos pré e pós-HAART, respectivamente. Na análise multivariada, risco relativo de desenvolvimento de infecção oportunista foi 5,4 vezes maior e 3,3 vezes maior para hospitalizações, antes da HAART. Causas respiratórias representaram 65% das hospitalizações, sendo reduzidas em 44,6% com a intervenção terapêutica. A mediana de duração das hospitalizações apresentou queda: 15 para 9 dias. Houve 38% de declínio nos óbitos pós-HAART. Este estudo demonstrou a efetividade da HAART, associando-a com significativa redução na incidência das infecções oportunistas, hospitalizações e mortalidade nesta coorte brasileira.

Terapia Anti-Retroviral de Alta Atividade; Infecções Oportunistas; HIV

Contributors

T. M. S. Candiani participated in the data collection, analysis, writing, and editing of the article. C. A. A. Cardoso collaborated in data collection, preparation, and analysis the of data bank. I. R. Carvalho contributed to data collection A. C. M. Dias worked on data collection and preparation of the data bank. M. Carneiro carried out statistical analysis. E. A. Goulart participated in statistical analysis, writing, and editing of the article. J. Pinto was responsible for the cohort of HIV infected children, and contributed to the design, analysis, and final editing of the article.

References

1. Dankner WM, Lindsey JC, Levin MJ. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. Pediatr Infect Dis J 2001; 20:40-8.
2. Powderly WG, Landay A, Lederman MM. Recovery of the immune system with antiretroviral therapy: the end of opportunism? JAMA 1998; 280:72-7.
3. Lederman MM, Valdez H. Immune restoration with antiretroviral therapies: implications for clinical management. JAMA 2000; 284:223-8.
4. Chakraborty R. Infections and other causes of death in HIV-infected children in Africa. Paediatr Respir Rev 2004; 5:132-9.
5. Dufour V, Cadranel J, Wislez M, Lavole A, Bergot E, Parrot A, et al. Changes in the pattern of respiratory diseases necessitating hospitalization of HIV-infected patients since the advent of highly active antiretroviral therapy. Lung 2004; 182:331-41.
6. Canani RB, Spagnuolo MI, Cirillo P, Guarino A. Decreased needs for hospital care and antibiotics in children with advanced HIV-1 disease after protease inhibitor-containing combination therapy. AIDS 1999; 13:1005-6.
7. Brodt HR, Kamps BS, Gute P, Knupp B, Staszewski S, Helm EB. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS 1997; 11:1731-8.
8. Sterling TR, Chaisson RE, Keruly J, Moore RD. Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. J Infect Dis 2003; 188:1659-65.
9. Ministério da Saúde. Critérios de definição de casos de AIDS em adultos e crianças. Brasília: Ministério da Saúde; 2004.

10. Centers for Disease Control and Prevention. Revised classification system of human immunodeficiency virus infection in children less than 13 years of age. MMWR Morb Mortal Wkly Rep 1994; 43:1-10.
11. Szklo M, Niel F. Epidemilogy: beyond the basies. Frederick: Aspen Publishers; 2000.
12. Bernard P, Lapoint C. Mesures statistiques en épidémiologie. Québec: Université du Québec; 1987.
13. Coordenação Nacional de DST/AIDS. Boletim Epidemiológico AIDS 2003; Ano XVI, nº. 1.
14. Fallo AA, Dobrzanski-Nisiewicz W, Sordelli N, Cattaneo MA, Scott G, Lopez EL. Clinical and epidemiologic aspects of human immunodeficiency virus-1-infected children in Buenos Aires, Argentina. Int J Infect Dis 2002; 6:9-16.
15. Spira R, Lepage P, Msellati P, Van De Perre P, Leroy V, Simonon A, et al. Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. Pediatrics 1999;104:e56.
16. Marins JR, Jamal LF, Chen SY, Barros MB, Hudes ES, Barbosa AA, et al. Dramatic improvement in survival among adult Brazilian AIDS patients. AIDS 2003; 17:1675-82.
17. Matida LH, Marcopito LF. O aumento do tempo de sobrevida das crianças com AIDS – Brasil. Boletim Epidemiológico AIDS 2002; Ano XV, nº. 1. p. 49-55.
18. Detels R, Tarwater P, Phair JP, Margolick J, Riddler SA, Munoz A. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. AIDS 2001; 15:347-55.
19. Dromer F, Mathoulin-Pelissier S, Fontanet A, Ronin O, Dupont B, Lortholary O. Epidemiology of HIV-associated cryptococcosis in France (1985-2001): comparison of the pre- and post-HAART eras. AIDS 2004; 18:555-62.
20. Nachman S, Gona P, Dankner W, Weinberg A, Yogev R, Gershon A, et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. Pediatrics 2005; 115:e488-94.
21. Schmidt-Westhausen AM, Priepke F, Bergmann FJ, Reichart PA. Decline in the rate of oral opportunistic infections following introduction of highly active antiretroviral therapy. J Oral Pathol Med 2000; 29:336-41.
22. Chantry C. Growth, survival and viral load in symptomatic childhood human immunodeficiency virus infection. Pediatric Infect Dis J 2003; 22:1033-8.
23. Finkelstein DM, Williams PL, Molenberghs G, Feinberg J, Powderly WG, Kahn J, et al. Patterns of opportunistic infections in patients with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol 1996; 12:38-45.
24. Chaisson RE, Gallant JE, Keruly JC, Moore RD. Impact of opportunistic disease on survival in patients with HIV infection. AIDS 1998; 12:29-33.
25. Holmes CB, Losina E, Walensky RP, Yazdanpanah Y, Freedberg KA. Review of human immunodeficiency virus type 1-related opportunistic infections in sub-Saharan Africa. Clin Infect Dis 2003; 36:652-62.
26. Powderly WG. The interaction of opportunistic infections and HIV replication. AIDS 1999; 13:1603-6.
27. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA 1999; 282:2220-6.
28. Granados JMS, Amador JTR, Miguel SF, Tome MIG, Conejo PR, Vivas PF, et al. Impact of highly active antiretroviral therapy on the morbility and mortality in Spanish human immunodeficiency virus-infected children. Pediatr Infect Dis J 2003; 22:863-7.
29. Viani RM, Araneta MR, Deville JG, Spector SA. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. Clin Infect Dis 2004; 39:725-31.
30. Mocroft A, Monforte A, Kirk O, Johnson MA, Friis-Moller N, Banhegyi D, et al. Changes in hospital admissions across Europe: 1995-2003. Results from the EuroSIDA study. HIV Med 2004; 5:437-47.
31. Cohen J, West AB, Bini EJ. Infectious diarrhea in human immunodeficiency virus. Gastroenterol Clin North Am 2001; 30:637-64.

Submitted on 15/May/2006
Final version resubmitted on 01/Nov/2006
Approved on 29/Nov/2006