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Impact of HAART on growth and hospitalization rates among HIV-infected children

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Abstract

Objectives: To evaluate HAART-associated changes in growth and hospitalization rates over time in a cohort of HIV-infected children.

Methods: Children starting HAART were assessed during the first 3 years of therapy. Clinical response was assessed every 24 weeks by Z scores of weight-for-age and height-for-age. Linear regression models were used to detect predictors of clinical response. Pertinent information on hospitalizations was obtained retrospectively through review of medical records.

Results: A total of 196 children were assessed. Mean weight Z scores increased from -1.62 (±1.32) at baseline to -1.14 (±1.12) by week 24. Mean height z score increased from -1.88 (±1.45) at baseline to -1.66 (±1.18). Better Z scores at baseline were associated with greater increase of weight Z scores over time. Lower viral load and higher height Z scores at baseline were also associated with improved height catch-up. Eighty-five children (43.3%) were hospitalized. Most hospitalizations were prompted by infectious disease, with only two due to opportunistic infections.

Conclusion: HAART was associated with significant increases in weight and height Z scores. The present study demonstrated the effectiveness of HAART in significantly reducing hospitalization, death, and incidence of opportunistic infections among HIV-infected children. Starting HAART before HIV infection can have more detrimental effects on growth and is associated with better outcomes among infected children.

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Introduction

Failure to thrive in children infected with the human immunodeficiency virus (HIV) is a multifactorial condition due to HIV infection itself, opportunistic disease, and the absence of viral and immune control.[1] Abnormalities in thyroid function, growth hormones, and lipid metabolism, as well as abnormal resting energy expenditure, can also play a role in poor growth.[2]

The literature shows that the introduction of highly active antiretroviral therapy (HAART) has produced significant increases in weight and height among HIV-infected children.[2] Changes in growth parameters after initiation of HAART can even be used as markers of treatment effectiveness. The World Health Organization (WHO) recommends that, in countries where laboratory follow-up is limited by the

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availability of resources, treatment response be assessed by serial measurement of body weight and height. Absence of improvement after initiation of HAART can thus be regarded as a poor prognostic indicator.[3]

In addition to positive effects on growth, studies in developing countries have shown that HAART is associated with decreased morbidity, mortality, and hospitalization rates.[4] Treatment increases CD4 cell counts, decreases viral replication, and restores the immune system, consequently reducing the incidence of opportunistic infection.[5]

The present study sought to assess the clinical progression of HIV-infected children receiving HAART in the city of Belo Horizonte, state of Minas Gerais, Brazil, with particular emphasis on growth parameters and hospitalization rates.

Methods

This was a retrospective cohort study of children between the ages of 0 and 12 years who started HAART in the city of Belo Horizonte between January 1998 and December 2006. Only treatment-naïve children were included, as prior treatment with antiretroviral monotherapy or dual-agent therapy can affect response to HAART.

For analysis of clinical response to therapy, weight-for-age and height-for-age values were normalized to their z scores (standard deviation, SD) using National Center for Health Statistics (NCHS) growth curves and the Epi-Info 6.04 software package. Clinical response to HAART was assessed after 24 weeks of therapy, with a window of ±8 weeks. Increases in weight and height z scores were calculated by subtracting the baseline score from that obtained at week 24. Improvements were assessed in relation to the following variables: age, gender, antiretroviral therapy (ART), CD4 cell counts, viral load, clinical category, and baseline weight-for-age z score. Catch-up growth was assessed over time in 24±8-week increments until week 144.

Data on hospitalizations were obtained through a review of hospital discharge reports. Only the first admission for a given cause was considered for each patient. Reasons for hospitalization were classified into one of four categories: AIDS-defining clinical conditions, immune reconstitution inflammatory syndrome (IRIS), infectious diseases, and noninfectious conditions. AIDS-defining clinical conditions were defined as those in category C of the clinical classification of HIV infection recommended by the U.S. Centers for Disease Control and Prevention (CDC).[6] IRIS was defined as occurrence of conditions associated with reconstitution of immune response to opportunistic antigens after the introduction of HAART. These conditions present as atypical manifestations of infectious disease after the onset of ART or as autoimmune diseases in patients with good virologic response.

Patients were followed during the first 3 years of treatment. Onset of HAART was defined as the moment in which three or more antiretroviral drugs (ARVs) of at least two therapeutic classes were prescribed. Children were assessed for at least 24 weeks, and were excluded from the sample when ART was switched or discontinued or when poor treatment adherence was detected. Adherence was assessed subjectively on the basis of information gleaned by the attending physician during patient encounters.

On average, patients were assessed every 3 months. Assessments consisted of an interview, physical examination, sample collection for laboratory tests, and classification into clinical and immunologic categories of HIV infection according to CDC criteria.[6,7] Laboratory tests, such as absolute and percentage CD4 cell counts and quantitation of plasma viremia, were performed at the Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG) reference laboratory. Quantitation of viral RNA (viral load) was performed with the HIV-1 RNA 3.0 Assay (bDNA 3.0), with a detection limit of 50 copies/mL. CD4 cells were counted by flow cytometry. Opportunistic infections were defined as those associated with *Pneumocystis jirovecii*, *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, cytomegalovirus, *Cryptococcus neoformans*, and *Toxoplasma gondii*. Diagnosis was based on clinical, radiological, and laboratory findings obtained during hospitalization. Identification of the causative pathogen through cultures was not always achievable. Admissions not associated with infectious conditions were due to hematologic, surgical, allergic, and neurologic diseases, as well as conditions of unknown origin. Patients admitted due to adverse drug reactions or interactions were included in the latter group.

Z scores obtained during treatment were compared to baseline using the paired samples *t* test. The Student *t* test and analysis of variance (ANOVA) were used to assess increases in weight-for-age and height-for-age z scores at week 24. Factors predicting increase in weight-for-age and height-for-age z scores were assessed with univariate and multivariate linear regression analysis. Variables with a p-value < 0.25 were included in multivariate analysis. The significance level was set at 5% ($p < 0.05$) for final analysis.

This study was approved by the UFMG Research Ethics Committee and by the municipal government of Belo Horizonte.

Results

Population profile

A total of 436 children with HIV were seen at the Infectious Diseases Clinic of Universidade Federal de Minas Gerais/Prefeitura de Belo Horizonte (UFMG/PBH) between 1998 and 2006. Of these, 22 (5.0%) were on antiretroviral monotherapy for treatment; 140 (32.1%) were on dual

ARV therapy and were thus excluded from analysis; 74 (16.9%) had no indications for treatment and thus did not receive ART during the study period; e and four received ART including only one class of antiretrovirals. Therefore, 196 (45%) treatment-naïve patients started HAART between the years 1998 and 2006. During the study period, sample size declined due to loss to follow-up (9 patients), treatment discontinuation (7), medication switching (34) and deaths (9). Furthermore, four patients were excluded from analysis due to poor compliance. Thirty-eight patients completed the study after at least 144 weeks of follow-up.

Patient age at the onset of treatment ranged from 0 to 12 years (mean, 3.4±3.0 years). Just over half of patients (101, 51.5%) were male. Most were classified in clinical category C of HIV infection (47.2%) and had moderate immunosuppression (42.6%) (Table 1).

A total of 134 patients (68.4%) started treatment with protease inhibitors (PIs), and 62 (31.6%), with non-nucleotide analog reverse transcriptase inhibitors (NNRTIs). Nelfinavir was the most common PI (prescribed to 92 patients), followed by lopinavir/ritonavir (34).

Assessment of clinical response

Growth

HAART was associated with significant increases in weight and height z scores during the first 96 weeks of treatment, with scores remaining stable thereafter. Mean weight-for-age z scores were -1.62 (±1.32) at baseline and -1.14 (±1.12) at week 24. Mean height-for-age z scores were -1.88 (±1.45) before treatment and -1.66 (±1.18) at week 24. Changes in growth parameters were seen from week 24 onward (Table 2).

According to univariate analysis, HAART with a PI and younger age at treatment onset were predictors of greater weight and height gain. Patients starting treatment at more advanced clinical categories of infection also experienced greater weight catch-up (Table 3). On multivariate analysis, patients in more advanced clinical categories of HIV were found to achieve greater weight and height gains ($p < 0.001$ and 0.046 respectively). Administration of HAART including an agent of the PI class was also associated with greater weight gain ($p < 0.001$), whereas younger age was associated with height gain ($p = 0.020$).

Table 1 - Baseline data for HIV-infected children receiving ART between 1998 and 2006

Variable	Value
Number of patients	196
Mean age in years (SD)	3.4 (3)
Gender	
Male (%)	101 (51.5)
Female (%)	95 (48.5)
Clinical category of HIV infection (CDC) (%)	
N	7 (3.6)
A	40 (20.4)
B	56 (28.7)
C	92 (47.2)
Immunologic category of HIV (CDC) (%)	
Mild immunosuppression	58 (37.4)
Moderate immunosuppression	66 (42.6)
Severe immunosuppression	31 (20.0)
Mean weight-for-age z score (SD)	-1,62 (1.32)
Mean height-for-age z score (SD)	-188 (1.45)
Antiretroviral therapy	
NRTI+PI (%)	134 (68.4)
NRTI+NNRTI (%)	62 (31.6)
Mean baseline CD4 percentage (SD)	18.56% (10.78)
Median baseline CD4 cell count (range)	605 cells/mm^3 (12-4,308)
Median baseline viral load (range)	188,237 copies/mL (0-11,000,000)
Median log baseline viral load (SD)	5.11 log (1.1)

CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; log = logarithmic transformation; NNRTI = non-nucleoside analog reverse transcriptase inhibitor; NRTI = nucleoside analog reverse transcriptase inhibitor; PI = protease inhibitor; SD = standard deviation.

Table 2 - Timeline of mean weight-for-age and height-for-age z scores in HIV-infected children 0 to 12 years of age during antiretroviral therapy

		Weight-for-age z score		Height-for-age z score	
Week	**n***	**Mean (SD)**	**p†**	**Mean (SD)**	**p†**
0	196	-1.62 (1.32)		-1.88 (1.45)	
24	163	-1.14 (1.12)	< 0.001	-1.66 (1.18)	< 0.001
48	146	-0.92 (1.14)	< 0.001	-1.43 (1.18)	< 0.001
72	132	-0.86 (1.14)	< 0.001	-1.15 (1.11)	< 0.001
96	119	-0.75 (1.11)	< 0.001	-0.99 (1.08)	< 0.001
120	108	-0.73 (1.17)	< 0.001	-0.99 (1.09)	< 0.001
144	90	-0.72 (1.18)	< 0.001	-1.01 (1.06)	< 0.001

HIV = human immunodeficiency virus; SD = standard deviation.
* Number of children for whom weight and height information was available during the study period.
† Comparison of means from each treatment week vs. week 0 (baseline).

Major weight and height gains were observed in patients who did not achieve undetectable viral loads during treatment and whose CD4 percentage remained > 25%. During the study period, no differences were detected between this group and patients in whom virologic success was achieved (p > 0.005). When associated with immune recovery, sustained viral replication during treatment was no obstacle to clinical improvement.

Hospitalizations and deaths

During the study period, 85 of 196 (43.3%) children were hospitalized 132 times, for an overall hospitalization rate of 34.4 admissions per 100 patients per year. The mean number of admissions per patient was 1.6 (1-8). Hospitalization rates for each 24-week treatment period declined from 28% in the first 24 weeks of treatment to 7.6% for the last observation period (Table 4).

Throughout the study period, 73.5% of the hospital admissions of the 85 children assessed were associated with infectious conditions. The most common infectious causes of hospitalization were pneumonia (39), varicella (14), sepsis (11) and diarrhea (10). Among opportunistic infections, only two cases of *Pneumocystis jirovecii* pneumonia were detected. Infections with other opportunistic agents only occurred prior to starting therapy.

Eight admissions (5.3%) were associated with an AIDS-defining condition, such as non-Hodgkin lymphoma (2), HIV encephalopathy (3), and wasting syndrome (2). All hospitalizations due to AIDS-defining conditions occurred in the first 2 years of treatment. IRIS occurred in 18 hospitalized patients (13.6%). Infectious causes included varicella zoster virus (VZV) (4) and herpes simplex virus (HSV) infection (4). Other infections reported were pneumocystis pneumonia and partial bowel obstruction due to *Ascaris lumbricoides* infestation. Noninfectious causes of IRIS included non-Hodgkin lymphoma (2) and lymphocytic interstitial pneumonia (1).

Nine deaths occurred during the study period, which corresponds to an overall mortality rate of 2.3 deaths per 100 patients per year. Seventy-seven percent of deaths occurred in the first 24 weeks of treatment. Most cases were associated with infectious conditions, such as sepsis (6), pneumonia (1), and *Pneumocystis jirovecii* infection (2).

Discussion

Vertical transmission of HIV has been one of the major public health challenges of recent times. In Brazil, although interventions meant to prevent vertical transmission are made available to all pregnant women with HIV, factors such as difficulties in obtaining laboratory diagnoses through the Unified Health System, the low percentage of women tested during prenatal care, and the subpar quality of prenatal care have hampered reduction of vertical transmission rates. The present study assessed a large number of children infected with HIV between 1998 and 2006 as a consequence of failures in implementation of preventive actions. Furthermore,

Table 3 - Analysis of predictors of greater increase in do weight-for-age and height-for-age z scores at week 24 (univariate analysis)

Variable	Mean increase in weight-for-age z score (SD)	p	Mean increase in height-for-age z score (SD)	p
Age				
0-11 months	0.46 (0.90)	0.023	0.28 (0.90)	< 0.010
12-35 months	0.71 (0.86)		0.46 (0.71)	
36-59 months	0.40 (0.66)		0.08 (0.42)	
> 59 months	0.19 (0.46)		-0.08 (0.21)	
Gender				
Male	0.40 (0.71)	0.430	0.13 (0.58)	0.219
Female	0.50 (0.82)		0.26 (0.72)	
Baseline clinical category				
N	-0.35 (0.64)	< 0.001	0.27 (0.49)	0.059
A	0.22 (0.50)		-0.31 (0.47)	
B	0.27 (0.65)		0.16 (0.56)	
C	0.77 (0.84)		0.34 (0.78)	
Baseline CD4%				
< 15%	0.43 (0.68)	0.854	0.21 (0.59)	0.637
15-24%	0.36 (0.70)		0.10 (0.56)	
≥ 25%	0.44 (0.53)		0.16 (0.66)	
HAART				
NRTI+NNRTI	0.21 (0.46)	< 0.001	0.02 (0.39)	< 0.001
NRTI+PI	0.58 (0.86)		0.30 (0.74)	
Baseline viral load (log_{10})		0.140		0.780

HAART = highly active antiretroviral therapy; log = logarithm; NNRTI = non-nucleoside analog reverse transcriptase inhibitor; NRTI = nucleoside analog reverse transcriptase inhibitor; PI = protease inhibitor; SD = standard deviation.

Table 4 - Hospitalizations and deaths among HIV-infected children 0 to 12 years of age during antiretroviral therapy

Treatment week	Patients at risk	Hospital admissions	Hospitalization rate for treatment period (%)	Deaths	Mortality rate for treatment period (%)	Reasons for hospitalization			
						Infection	IRIS	AIDS-defining conditions	Other non-infectious diseases
0-24	196	55	28.06	7	3.6	41	10	4	15
25-48	163	37	22.69	0	0	26	2	1	11
49-72	143	12	8.39	2	1.4	7	3	2	3
73-96	130	19	14.61	0	0	10	3	0	5
97-120	120	10	8.33	0	0	6	0	0	6
121-144	105	8	7.61	0	0	7	0	0	1

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; IRIS = immune reconstitution inflammatory syndrome.

the mean age of onset of ART in our sample (3.4 years) is indicative of delayed diagnosis of HIV infection in these children, which jeopardizes treatment outcomes.

Children with HIV gain less weight and height than non-infected children. No changes in birth weight and height have been described, but a distinct difference in the speed of growth is detectable as early as the first months of life.[8]

Failure to thrive and poor nutritional status appear to be some of the most sensitive indicators of the clinical progression of HIV infection.[9] The use of NCHS growth curves

in the present study allowed comparison of our sample with those of other studies, which found mean baseline weight-for-age and height-for-age z scores of -0.16 and -0.57 in the U.S., -1.90 and -1.30 in Thailand, and -2.30 and -2.54 in African nations.[10-14] Nutritional deficiencies in the African population are believed to have an indirect influence on growth control.[10,15,16]

HIV infection has been responsible for increasing rates of early compromise of anthropometric indicators.[8] However, data on inadequate food provision and intake were not assessed in the present study. Due to the absence of this information, the role of malnutrition due to inadequate dietary intake cannot be ruled out as an additional determinant of growth failure. Early detection of failure to thrive in these children should therefore also be regarded as a red flag, signaling the need for reassessment of nutritional interventions to be implemented in this group.

In the past, children treated with monotherapy or dual agent therapy experienced temporary improvement in growth parameters.[17,18] HAART now enables sustained, lasting weight and height gain in children with HIV. Despite this gain, growth parameters have yet to reach normal levels as found in the non-infected population.[18]

Clinically advanced disease at baseline has been correlated with greater weight and height catch-up after starting HAART. Advanced infection is no impediment to satisfactory catch-up growth after institution of antiretroviral therapy; therefore, the benefits of therapy are more readily observed in these patients.[1,2]

Younger children may also experience greater height catch-up after starting HAART.[1] Nachman et al.[11] reported that, in their sample, children under the age of 2 exhibited higher height-for-age z scores during therapy. More pronounced weight gain in younger patients has also been described.[10,15]

HAART including an agent of the PI class has been associated with improved clinical and laboratory response.[19,20] However, most studies stress that the choice of ART regimen should not be based on the efficacy of the scheme alone, but also on factors such as the safety profiles of individual ARVs, cost, and quality of life.[20]

In the literature, HAART has been described as a major variable associated with declining hospitalization and mortality rates.[21,22] In a Brazilian population, Candiani et al.[21] reported hospitalization rates of 113.73 admissions per 100 patients per year prior to HAART and 41.3 per 100 patients per year after introduction of highly active therapy. This investigation corroborates the findings of prior studies that have reported high hospitalization rates during the first weeks of treatment, followed by a steep decline in admissions after the first year of therapy.[4]

In this sample, hospital admissions were mostly due to infectious diseases (73.5% of cases). In most studies, pneumonia is the foremost cause of hospitalization, followed by acute diarrhea.[21,23,24] In Africa, pulmonary tuberculosis has also been reported as a highly prevalent cause of hospitalization, in addition to pneumonias and diarrhea.[8,13] The literature shows that the incidence of opportunistic infections has declined with the advent of HAART.[4,21] Candiani et al.[21] found that no opportunistic infections occurred in their sample after the introduction of HAART.

Varicella zoster virus infection played a prominent role in our sample, as the second most frequent infectious disease in hospitalized HIV-infected children.[21] The varicella vaccine is available through the Unified Health System for at-risk patients, such as people living with HIV; however, the indications for immunization of these patients depend on clinical and immune status. Furthermore, hospitalization for intravenous therapy immediately after diagnosis is indicated in most children with HIV/VZV coinfection.

The onset of illness due to restoration of the immune response after introduction of HAART has come to be known as IRIS. The clinical manifestations of this condition are quite diverse and depend on the involvement of infectious agents or lack thereof. Few studies have assessed the incidence of IRS in children on HAART.[25] The incidence found in the present is consistent with the data available in the literature, with rates of 7.6 to 32% in pediatric populations.[25] The spectrum of IRS was similar to that of most studies, which reveal an overall predominance of VZV and HSV-associated infections. *Mycobacterium tuberculosis* and *Mycobacterium avium* complex infections have also been frequently described in the literature, and are implicated in up to 43.7% of IRS episodes.[25-27]

In a study conducted in the U.S. state of California, use of HAART in children was described as a protective factor against conditions classified in clinical category C of HIV infection.[28] In Spain, Sánches et al.[5] found a 43% reduction in risk of developing AIDS after 5 years of HAART. Another Brazilian study showed that children not on HAART were at a 5.4% greater risk of developing category C infections.[21]

Lower mortality rates have also been observed after the introduction of HAART.[4,21] Reductions in mortality of up to 38% have been reported; however, most deaths are still associated with infectious diseases.[21] High mortality rates in the first 24 weeks of treatment have been described in other developing countries as well as Brazil, which shows that many patients are still diagnosed at advanced stages of infection.[4]

Poor treatment adherence was documented in only four patients throughout the study period. High rates of adherence to HAART were likely due to the subjective manner in which this condition was assessed.

The inherent limitations of large retrospective cohort studies include the absence of information on all patients during follow-up. However, despite data loss over the course

of the study, a substantial number of patients remained in the sample at the end of the study period. Weight and height data were available throughout the study for most children, which allowed significant results to be obtained over the 3-year observation period. New studies assessing the progression of anthropometric parameters in HIV-infected children and comparing these measurements to those of non-infected controls can provide new information on the real benefits of ART toward achieving weight and height values considered normal for this population.

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