AIDS Morbidity and Mortality in Brazilian Children Before and After Highly Active Antiretroviral Treatment Implementation

An Assessment of Regional Trends

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Original Studies

Background: The objective of this study was to analyze regional trends over time of acquired immunodeficiency syndrome (AIDS) cases and deaths in Brazilian children, before and after implementation of free access to highly active antiretroviral treatment (HAART).

Methods: We performed a nation-wide study with an ecologic design and a time-series analysis of AIDS incidence and mortality rates in children (0–12 years of age), using polynomial regression models. Data were obtained from official national databases on age group, residence region, and year of AIDS diagnosis and death (1984–2008).

Results: Between 1984 and 2008, 14,314 (2.7%) AIDS cases and 5041 deaths (2.3% of all AIDS-related deaths) were reported in Brazilian children. Incidence after 1996 was reduced by 23%, as compared with the pre-HAART era. The mortality rate observed in the HAART era was reduced by 63.6%. There was a significant reduction in the incidence in the Southeast and Central-West regions (P < 0.001), but the less industrialized North region showed an increase in the pre-HAART era (P < 0.001), and the Northeast region showed a stabilization trend (P < 0.001). In the South region, the incidence of AIDS increased in the 0 to 4 years subgroup. A reduction of AIDS mortality in the Southeast (P < 0.001), South, and Central-West regions (P < 0.001) was seen, but the Northeast and North regions maintained an increasing mortality trend (P < 0.001).

Conclusions: Despite the overall reduction in AIDS-related cases and deaths among children in Brazil since HAART, marked regional differences continue to exist. These reflect structural factors, different transmission dynamics, and operational issues. There is a need for improving the health service network with special emphasis on the less developed regions.

Key Words: AIDS, children, HAART, inequality, Brazil

Infection of human immunodeficiency virus (HIV) in children has become a chronic condition, with declines in mortality and increased quality of life.1–4 This is a result of systematic adoption of effective control measures, such as the use of highly active antiretroviral treatment (HAART), prenatal HIV testing, cesarean delivery, and noneuse of breast-feeding.5–8 In 2008, approximately 16.5% of the estimated 2 million people deaths from acquired immunodeficiency syndrome (AIDS)-related events worldwide were children,9 with a disproportionately higher burden on underprivileged populations.5,10 Despite the great inequalities that still exist around the world and the difficulties of implementing control measures,2 positive epidemiologic and operational results have been observed in some low- and middle-income countries, such as Brazil.11–14

Brazil provides universal and free access to HAART since 1996, a benchmark among low- and middle-income countries worldwide,15,16 and has developed a national plan for reducing mother-to-child transmission (MTCT) of HIV17,18 As a consequence, studies have shown a marked reduction in hospitalizations related to AIDS and increased survival of people with AIDS.19–23 MTCT rates were estimated at 8.6% in 2000 and 7.1% in 2001.22 The probability of survival in children to 60 months after AIDS diagnosis increased from 58.3% among those diagnosed in 1995 and 1996, to 86.3% among those diagnosed between 1999 and 2002.21–23

Considering the absence of systematic epidemiologic studies targeting the pediatric AIDS population, the huge size of the country, and its major social and economic inequalities,24 there is a clear need for further study of this population. To fill this gap, we present trends of AIDS mortality and incidence over time in Brazilian children, stratified by the country’s major regions.

Materials and Methods

Study Population and Design

Between January 1984 and December 2008, we performed an ecological time-series study, based on official data from the Brazilian Ministry of Health. The study included children 0 to 12 years of age diagnosed with AIDS, and those who died with AIDS as an underlying cause of death on their death certificates.

Brazil (population about 191 million) is composed of 26 states, 1 Federal District (the capital city Brasilia), and 565 municipalities. For political and operational purposes, the states and the Federal District are divided into 5 regions with distinct geographical, economic, and cultural characteristics. In 2009, 42.3% of the population was living in the Southeast (SE) region, 28% in the Northeast (NE), 14.5% in the South, 8% in the North, and 7.3% in the Central-West (CW). Of the total population, 22.2% were children ≤12 years of age.

Data Sources

For analysis of AIDS mortality, data of children who died and were reported in the Brazilian Mortality Information System (Sistema de Informações sobre Mortalidade—SIM) between 1984 and 2008 were included. SIM records nationwide all deaths and their causes, based on standardized death certificates. All deaths with AIDS as an underlying cause were included in analysis, defined as ICD 9 code 279.1 (until 1995), and ICD 10 codes B20

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Incidence and mortality rates were calculated for each year dividing the number of pediatric AIDS cases and child AIDS deaths in each calendar year by the corresponding reference population, and presented per 100,000 children. Data were stratified by geographical regions of the country and periods 1984 to 1995 and 1996 to 2008, representing the pre-HAART and HAART eras, respectively (1995/1996 as the cut point with introduction of universal and free HAART).

As a first step, we calculated the relative differences of incidence and mortality rates in pre-HAART and HAART eras, stratified by age group and region. In a second step, we calculated the incidence and mortality rate ratios among pre-HAART and HAART eras.

Then, trend analysis was performed by polynomial regression models for time series data. The dependent variables were defined as the incidence and the mortality rates from AIDS, and the independent variable the years of AIDS diagnosis. We used $\alpha = 0.05$ to identify significant trends in the regression model. To prevent collinearity among the terms of the regression equation, we centralized “year of AIDS case diagnosis” or “year of death,” based on transformation from the midpoint of the temporal series (central year). For the period between 1984 and 1995, the midpoint was 1989.5 and for the period between 1996 and 2008, it was 2002. To reduce the chance of oscillation of points from small numbers of AIDS cases or deaths in some strata (white noise), we softened the time series by calculating the centered moving average of 3 terms. We constructed and analyzed scatter diagrams to ascertain the function that would best explain potential trends and selected the order of the polynomial for the analysis. We started the model with the lowest order ($Y = \beta_0 + \beta_1X$), then proceeded to more complex models, such as second-order ($Y = \beta_0 + \beta_1X + \beta_2X^2$) and the third-order ($Y = \beta_0 + \beta_1X + \beta_2X^2 + \beta_3X^3$), and finally, the exponential model ($Y = \beta_0 + \beta_1X + \beta_2X^2 + \beta_3X^3$). These steps were initially generated for each age group (including all children) and region.

Selection of the final model was based on the following factors: (1) the analysis of the dispersion diagram of AIDS incidence or mortality rates observed over time; (2) the $P$ values of the $F$-statistical analysis of variance; (3) the adjusted coefficient of determination ($R^2$); and (4) residual analysis to provide independence and constant variance of the errors (true homoscedasticity assumption). When the trend was not statistically significant, the model was chosen according to the coefficient of determination. On the basis of these assumptions, preference was given to the explanatory models of lower order, i.e., greater simplicity.

Statistical analysis was done with the STATA 11.0 software package (Stata Corporation, College Station, TX).

RESULTS

Between January 1984 and December 2008, a total of 530,209 AIDS cases and 261,314 AIDS-related deaths were reported in Brazil. Children less than 12 years of age accounted for 14,314 (2.7%) of AIDS cases and 5041 (2.3%) of AIDS-related deaths. Within this age group, 75.6% (10,821) of the AIDS cases and 74.5% (3757) of the AIDS-related deaths were in children less than 4 years of age.

There were marked regional differences in AIDS-related cases and deaths in children. The majority of cases occurred in the SE region (56.9%), followed by the South (24.6%), NE (10.1%), CW (5.0%), and North (3.4%) regions. A similar pattern was noted for the subgroup of children less than 4 years of age, with 57.4% cases in the SE, 24.6% in the South, 9.6% in the NE, 5.2% in the CW, and 3.2% in the North region. Deaths also occurred mostly in the SE (63.0%), followed by the South (20.1%), NE (8.5%), CW (4.8%), and North (3.6%) region.

In the early years of the epidemic, the proportion of children aged 0 to 4 years with AIDS in relation to the total number of children increased rapidly, reaching 80% in the 1990s and subsequently demonstrated a consistent and sustained decline to 57% in 2008 (57.5% in North, 64.5% in NE, 54.8% in SE, 55.2% in South, and 50% in CW).

Before introduction of HAART in 1995, deaths and cases in children (0–12 years) occurred almost exclusively in the SE and South regions, with its major cosmopolitan cities of São Paulo and Rio de Janeiro. After 1995, the epidemic dispersed more and more throughout the country, reaching smaller municipalities (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A839, illustrating Brazilian municipalities with at least one AIDS case and death in children aged 0 to 12 years before and after HAART introduction in the 5 regions, 1984–2008).

There were distinct regional patterns in the relative differences in mean mortality and incidence rates of the pre-HAART years as compared with the HAART years. All regions showed an increase, but in the North and NE this effect was more pronounced than in the other regions (Table 1).

In general, the increase was higher in 0- to 4-year-olds (Table 1). Consequently, incidence rate ratios were also higher in the 0- to 4-year-olds, mainly in the North (12.4) and NE regions (6.9), as compared with the 0- to 12-year-olds (8.4 and 5.1, respectively; Fig. 1). The SE region had lower incidence ratios in both age strata (2.0 and 1.8), followed by the CW (3.2 and 2.6) and the South (3.5 and 3.3). The mortality rate ratios among regions showed a similar pattern to that observed in incidence (Fig. 1). However, in the CW region, mortality ratios (2.2 and 2.6) were higher than in the South (2.0 and 2.4).

In polynomial regression analysis, there was a clear general pattern of AIDS incidence over time (children, 0–12 years) with an increasing trend in the first period from 1984 to 1995 ($P < 0.001$) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A840, illustrating polynomial regression models of AIDS incidence and mortality rates by Brazilian regions, and by age strata in the pre-HAART and HAART eras, 1984–2008). This statistically significant positive trend was observed in all regions, mainly in the SE and South. Similarly, in the pre-HAART era there was a
TABLE 1. AIDS Incidence and Mortality Ratio (per 100,000 Children) and Percent Trend in Pre-HAART and HAART Eras, by Region and Age Group

<table>
<thead>
<tr>
<th>Brazilian Region</th>
<th>Age Group</th>
<th>Indicator</th>
<th>Rate (per 100,000 Children)</th>
<th>% Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-HAART Era</td>
<td>HAART Era</td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>0–4 yr</td>
<td>Incidence</td>
<td>0.12</td>
<td>1.47 +1125.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.05</td>
<td>0.58 +1090.0</td>
</tr>
<tr>
<td></td>
<td>0–12 yr</td>
<td>Incidence</td>
<td>0.10</td>
<td>0.81 +710.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.05</td>
<td>0.29 +480.0</td>
</tr>
<tr>
<td>Northeast</td>
<td>0–4 yr</td>
<td>Incidence</td>
<td>0.20</td>
<td>1.35 +575.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.08</td>
<td>0.37 +362.5</td>
</tr>
<tr>
<td></td>
<td>0–12 yr</td>
<td>Incidence</td>
<td>0.14</td>
<td>0.69 +392.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.05</td>
<td>0.19 +280.0</td>
</tr>
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<td>Southeast</td>
<td>0–4 yr</td>
<td>Incidence</td>
<td>2.60</td>
<td>5.17 +98.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>1.36</td>
<td>1.57 +15.4</td>
</tr>
<tr>
<td></td>
<td>0–12 yr</td>
<td>Incidence</td>
<td>1.47</td>
<td>2.62 +78.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.83</td>
<td>0.84 +1.2</td>
</tr>
<tr>
<td>South</td>
<td>0–4 yr</td>
<td>Incidence</td>
<td>2.01</td>
<td>7.14 +255.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.94</td>
<td>2.02 +140.5</td>
</tr>
<tr>
<td></td>
<td>0–12 yr</td>
<td>Incidence</td>
<td>1.11</td>
<td>3.64 +227.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.46</td>
<td>0.94 +104.4</td>
</tr>
<tr>
<td>Central-West</td>
<td>0–4 yr</td>
<td>Incidence</td>
<td>0.91</td>
<td>2.87 +215.4</td>
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<td></td>
<td></td>
<td>Mortality</td>
<td>0.32</td>
<td>0.82 +156.3</td>
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<tr>
<td></td>
<td>0–12 yr</td>
<td>Incidence</td>
<td>0.54</td>
<td>1.41 +161.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.21</td>
<td>0.46 +119.1</td>
</tr>
<tr>
<td>Brazil</td>
<td>0–4 yr</td>
<td>Incidence</td>
<td>1.40</td>
<td>3.72 +165.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.68</td>
<td>1.11 +63.2</td>
</tr>
<tr>
<td></td>
<td>0–12 yr</td>
<td>Incidence</td>
<td>0.81</td>
<td>1.90 +134.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>0.42</td>
<td>0.57 +35.7</td>
</tr>
</tbody>
</table>

AIDS indicates acquired immunodeficiency syndrome; HAART, highly active anti-retroviral treatment.

The AIDS epidemic shows different regional characteristics, with a more pronounced importance of injection-drug users for transmission dynamics in the South region.31 Additionally, the AIDS epidemic profile of Brazil is notable for HIV-1 subtype variations across geographical regions. This may be especially important for pediatric AIDS, as the subtype C, which is more common in the South,31,32 may be more likely to cause MTCT and progression of HIV infection.33

The more pronounced mortality decline in the SE, South, and CW regions, in all age groups, probably indicates different regional patterns of adoption of the implementation of HAART and the control of MTCT. The sustained upward trend in the less industrialized North and NE may reflect HIV transmission dynamics in these areas; HIV transmission by heterosexual exposure is more and more common, and the epidemic has been expanding to poorer regions later than in the SE. The trend in the NE already points to a possible stabilization/reduction of mortality in the coming years as a result of the broad and systematic introduction of HAART.

In 1996, free and universal distribution of medications was guaranteed by Brazilian Federal Law.17 By 2008, the estimated number of Brazilian children receiving antiretroviral therapy was 8000, with a coverage ranging from 65% to >95%.9,50 The reduced number of children with AIDS in some regions can also be mainly attributed to the implementation of effective actions reducing MTCT.2,20,26,34

Interventions to prevent MTCT of HIV are available for the entire population of HIV-infected pregnant women and their children since the late 1990s, but the implementation of a structured network of primary health services in providing comprehensive care is still a major obstacle in the country.35,36 Especially in the most vulnerable populations, quality of prenatal and obstetric care is still below targets.12 One of the problems of less developed regions is the concentration of skilled care in the few major cities. In more developed regions of the country, the support network has been organized since the late 1990s, which brings a greater possibility of ensuring access for the population.35 The higher transmission rates in the North and NE reflect weaker maternal healthcare services.15,28,29 A national HIV-sentinel study among childbearing women in 2006 estimated a coverage of HIV testing during pregnancy at 62.3%. These results ranged from 40.6% in the NE to 85.8% in the South region; significant differences were observed by race, educational level, and municipality size.38 A study conducted in Porto Alegre, a capital city in South Brazil, not only revealed urban poverty as a strong determinant of MTCT...
transmission of HIV, but also showed that surveillance coordinated with primary care may reverse this trend.35

Brazilian studies of survival in people with AIDS indicate that the general decline in mortality due to AIDS and opportunistic infections was largely attributable to increased use of HAART in children.21–23,39 Poorer regions account for a low proportion of cases and deaths nationally; therefore, national averages do not reflect these regions. The greatest burden of deaths throughout the study period was in the SE and South. From this perspective, one of the possibilities raised by this study is the “inverse equity hypothesis.”40 This hypothesis states that inequalities in health may deteriorate to the extent that new, effective public health interventions, such as HAART, become available first in the higher socioeconomic status population, and only then for the poor. Health inequalities diminish only after the wealthiest achieve minimum levels of morbidity and mortality and the poorest also gain access to health interventions.40 Increased decentralization of health care for people living with HIV/AIDS may contribute not only to greater access, but also to quality of care.29,36,41

Our study is subject to limitations. Due to the regional scope, we did not perform an analysis on the municipality level, which may have revealed precise priority areas for intervention. Data quality may also have affected the trend analysis, especially in North and NE regions, that are known for some problems with the quality of death reporting. The SIM underreports about 25% of all deaths in the North region and 29% in the NE.28 Another potential limitation is the possible underreporting of AIDS cases in the SINAN database, with regional differences. On the other hand, results are likely to be representative and valid, given the linkage of multiple databases (SIM, SINAN, Sistema de Controle de Exames Laboratoriais).25 Moreover, epidemiological surveillance in Brazil is based on compulsory reporting of AIDS cases in adults and children, as well as HIV-infected pregnant women and exposed children.

We conclude that there is a need for improving the health service network in the country, with special emphasis on the less developed regions. Priority areas include the following: (1) providing quality prenatal care, including diagnosis of infection in mothers
(including HIV subtyping), and measures to eliminate MTCT of HIV; (2) early diagnosis of HIV infection in children; (3) early treatment with HAART; (4) prophylaxis and appropriate management of opportunistic conditions; and (5) adoption of measures for long-term comprehensive care of HIV-infected children.

REFERENCES


