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Abstract

We present a systematic review of historical, political, and epidemiologic aspects of AIDS in Brazilian children. Over 25 years, Brazil has developed different strategies to control AIDS in children. Three revisions of criteria for defining AIDS cases in children and nine national guidelines on antiretroviral therapy administration for management of HIV infection were published. These guidelines represent important progress, including aspects of HIV/AIDS surveillance, antiretroviral treatment, opportunistic conditions, prophylaxis, and laboratory testing. Brazil has significantly expanded access to free therapy with different classes of antiretroviral drugs. Initially focusing on treatment for HIV and opportunistic conditions, the scope of treatment guidelines gradually expanded to comprehensive health care for children and adolescents. From 1996 to 2008, the number of AIDS cases and deaths in children has been reduced by 67% and 65%, respectively, as a result of different strategies to prevent mother-to-child transmission of HIV and highly active antiretroviral therapy administration to infected children. Improved morbidity, mortality, and survival of Brazilian children with AIDS demonstrate clear benefits of adopting a policy of free and universal access to antiretroviral drugs associated with comprehensive care. However, important issues remain to be resolved, mainly concerning social, operational, and regional inequalities in coverage and quality of care, and epidemiological surveillance in different regions of the country. This broad review shows that the overall situation of pediatric AIDS in Brazil represents an incomplete process of epidemiologic and demographic transition, with the coexistence of old and new clinical and epidemiologic challenges.

Introduction

Brazil has been considered a newly industrialized country with profound social, economic, demographic, and epidemiologic advances in the last decade.1 One of the greatest examples of successful public policies in the health sector is the national policy to control HIV/AIDS, which serves as a benchmark for other nations.2 Since 1996, the Brazilian AIDS control program guarantees free and universal access to highly active antiretroviral therapy (HAART). This dynamic and innovative national health policy is a consequence of health sector reforms going on since the 1980s, and inclusion of stakeholders in decision-making processes, such as the major churches, civil society, and nongovernmental organizations (NGOs).3

The main pillars of the AIDS control program are health promotion, prevention, and care considering human rights.2,4–6 This policy forms part of the Brazilian Unified Health System (Sistema Único de Saúde, SUS)1 and is based on technical and scientific evidence, both by strategic research and epidemiologic surveillance over time. As a consequence, the Brazilian AIDS epidemic has been kept at a low level through 2009: the HIV prevalence rate was 0.6% in adults 15–49 years of age, with a prevalence of less than 1% in pregnant women in urban areas, albeit with HIV prevalence greater than 5% in vulnerable populations.7–9

After approximately three decades of the Brazilian response, the magnitude and dynamic of HIV transmission has changed over time.10–12 To adapt to these new realities the national guidelines of care and surveillance were modified, reflecting new political and technical conquests. Thus, people infected with HIV now have the opportunity to be diagnosed and treated earlier, and monitored properly, with the consequence that the disease now has a chronic...
character. On the other hand, issues related to adoption of new treatments present the need to interpret new clinical and epidemiologic profiles. This situation requires new responses from the SUS, especially for children infected by mother-to-child transmission (MTCT), related to an extended life with HIV infection and exposure to antiretroviral drugs throughout growth and development.

A major challenge now and for the future is the variety of epidemiological and operational scenarios in Brazil's different regions, related or not to HIV/AIDS. Examples in this context are the need for adjustments in the case definition of AIDS in search of more sensitive criteria, within the operational capacity of health services, and tailored to specific endemic opportunistic diseases. In relation to health care for people living with HIV/AIDS, health services must be prepared to address comorbid chronic degenerative diseases not previously found in this population. This situation remains in the noncompleted technical and political agenda for children with HIV/AIDS. Children infected with HIV become vulnerable in relation to different social, economic, and physical and mental health factors that involve parents, families, and the communities in which they live, all of which can hinder their growth and development.

This new agenda should be confronted with new strategies. A review of historical processes of development of the national response is useful to understand these different epidemiologic and operational scenarios and to help find better ways to control the HIV/AIDS epidemic in Brazil. Special consideration should be given to the surveillance and therapeutic historical perspective, including trends in patterns of morbidity, mortality, and survival in children. The aim of this article is to describe epidemiologic surveillance and care for Brazilian children with AIDS. We focus on the history of AIDS case definitions in children in the last two decades, epidemiologic data on morbidity and mortality, and therapeutic options offered. Our hope is that a historical review of the Brazilian experience will provide lessons that will be useful to Brazil and other countries in the future as they deal with HIV/AIDS and other epidemics that require evolving responses due to changing patterns and treatments over time.

Methods

This study is divided into two main parts: an historical overview of epidemiologic surveillance and antiretroviral therapy for children (indication for and availability of antiretroviral drugs) in Brazil; and a brief description of epidemiologic data relating to AIDS cases and AIDS deaths in children, from 1984 to 2008, rate of MTCT of HIV and survival data.

We carried out an extensive review of official documents and publications related to: national HIV/AIDS policy, AIDS case definitions, and guidelines for antiretroviral therapy in Brazilian children infected with HIV since the 1980s. Documents, technical manuals, epidemiologic bulletins, therapeutic guidelines, and other publications of Brazilian Ministry of Health were analyzed.

We contextualized Brazilian case definitions with European and U.S.-American definitions. Brazilian guidelines of therapy for HIV-infected children were reviewed, focusing on criteria for starting therapy. These criteria were compared to case definition for epidemiologic surveillance purposes. Results of national survival studies in children were analyzed.

Data on AIDS cases in children stratified by age group (0–12 years, 0–4 years, and 5–12 years), and calendar year were obtained from official databases. The consolidated database of AIDS cases at the national level is systematically processed by the Epidemiology Unit of National Department of STD, AIDS and Viral Hepatitis (Secretariat of Health Surveillance, Ministry of Health), using probabilistic database linkage to eliminate duplications and optimize completeness of records.

This process uses the database of the national Information System for Reportable Diseases of AIDS Cases (Sistema de Informação de Agravos de Notificação, SINAN-AIDS) as reference and includes other databases:

- System for Control of Laboratory Examinations (Sistema de Controle de Exames Laboratoriais, SISCEL),
- System for Logistic Control of Drugs (Sistema de Controle Logístico de Medicamentos, SICLOM), and
- Mortality Information System (Sistema de Informações de Mortalidade, SIM).

The SINAN-AIDS database represents the reference data set of epidemiologic surveillance of AIDS cases in Brazil (based on compulsory reporting of AIDS cases), maintained by routine health services of all Brazilian municipalities. This system presents AIDS cases meeting the specific criteria for case definitions established in 2004 for children and adults. In addition to epidemiologic information specific to the transmission of HIV and clinical characterization of opportunistic diseases, the data set includes sociodemographic information (age, gender, race/ skin color, education level, and municipality of residence).

SISCCEL represents a data system developed to monitor specific laboratory tests for HIV infection, such as CD4 count and plasma viral load (HIV-RNA quantification).

SICLOM has been developed for logistics control of providing antiretroviral drugs in the country and is interlinked with SISCCEL database.

SIM records nationwide all deaths and their standardized causes. We included all deaths with AIDS as an underlying cause: until 1995 via the International Classification of Diseases (ICD), 9th revision (ICD-9), with code 279.1 and after 1996 via ICD its 10th revision (ICD-10) through codes B20 to B24.

Raw data from SINAN, SISCCEL, SICLOM, and SIM are available from the official AIDS website of the Brazilian Ministry of Health. The population estimates for children (0–12, 0–4, and 5–12 years of age) in Brazil from 1984 to 2008 were obtained from the database of the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE).

The longitudinal patterns of cases and deaths were analyzed by graphic description of rates from 1984 to 2008. Incidence and mortality rates were defined by dividing the number of AIDS cases and deaths in each calendar year by the reference population (0–12, 0–4, and 5–12 years of age) and presented per 100,000 inhabitants (children).

Results

Milestones in epidemiologic AIDS surveillance

In 1981, epidemiologic surveillance of AIDS started through the initiative of the U.S.-American Centers for Dis-

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ease Control and Prevention (CDC), after occurrence of the first reported cases of *Pneumocystis carinii* (now *Pneumocystis jiroveci*) pneumonia, Kaposi’s sarcoma, and other opportunistic infections. In September 1982, the CDC established a first AIDS case definition, based on presence of opportunistic diseases diagnosed by noninvasive methods with high specificity. That same year, the first AIDS cases were reported in children. This first case definition was revised in 1985, however, it remained a unique classification for both adults and children. Given the high specificity of U.S. criteria based on definitive diagnosis of indicative diseases, the applicability in developing countries was very difficult.

The new CDC definition was endorsed by the World Health Organization (WHO) that established the possibility of using a temporary AIDS clinical case definition, to be applied in countries with limited diagnostic resources (so-called Bangui criteria). For both adults and children, this clinical definition was based on major and minor signs in the absence of other immunodeficiency causes. The evaluation of applicability of this criterion showed a low sensitivity and specificity, especially in children. Thus, there was an urgent need for more simplified criteria that would not rely on complex and sophisticated laboratory procedures.

Considering the great variability of HIV infection, in 1986 a staging system of infection in adults was established, based on data comprising clinical categories to be used for epidemiologic surveillance. Finally, in 1987 a specific staging system of HIV infection in children younger than 13 years of age was established, based on clinical data (more limited than those for adults).

**Epidemiologic AIDS surveillance in Brazil: the first years**

In Brazil, a meeting promoted by the Ministry of Health in 1986 resulted in a first document officially defining AIDS cases. In addition, public legislation was launched defining AIDS as a disease of compulsory reporting. Since then, epidemiologic surveillance of the HIV/AIDS epidemic has been performed in Brazil taking as a reference the universal and compulsory reporting of AIDS cases. Cases reported before 1986 were obtained retrospectively from the Brazilian states that had consolidated data in a nonstandardized manner.

The first steps toward the creation of Brazilian National AIDS Program were established around 1986, with composition of national HIV/AIDS policies. As a result, the program was officially established in 1987 based on successful experiences in some states, particularly Rio de Janeiro and São Paulo. The first AIDS case definition in Brazilian adults for surveillance purposes used as a reference the CDC case definition of 1985 for individuals with 15 years of age or older. The Brazilian AIDS definition criteria, modified from the original CDC criteria, were based on laboratory evidence of HIV infection and/or presence of indicative diseases of immunodeficiency, using basically methods for definitive diagnosis with high specificity.

The classification system for HIV infection established by the CDC in 1986 was potentially applicable for more sophisticated clinical and epidemiologic records (scientific research or in the assessment of demand from patients to health services), not resulting in changes in AIDS case definition adopted for surveillance purposes. Given the high specificity of this criterion (based on definitive diagnosis of indicative diseases) its applicability in the Brazilian reality was very difficult in that moment.

**Context of AIDS case definitions in Brazilian children**

The first AIDS case definition for children in Brazil dates back to 1988. It focused on those aged younger than 15 years, based on clinical case definition and classification systems for HIV infection in children, both established by CDC. In 1994, there was a revision of the classification system for HIV infection for AIDS cases among U.S. children, now under 13 years of age, which reflected the disease stage in HIV-infected children. This permitted a balance between simplicity and accuracy of medical evaluation for classification process.

In 1995 the AIDS case definition in children was revised for epidemiologic surveillance in Europe, based on review of case definitions from the CDC in 1987, incorporating also the revision of the classification system for HIV infection instituted by CDC. Starting from the European experience and focusing on the population of adolescents and adults, the proposal was to increase the sensitivity of the surveillance system in detection of AIDS cases.

The WHO proposed in 1994 a modification of the Bangui criteria that were now comprised of two case definitions: one referring to the WHO AIDS case definition and another to the WHO expanded case definition, both for adults and adolescents. The discussion about the need for criteria adapted to operational reality of network of health services was raised by other authors.

In April 1994, a revised definition of AIDS cases in children was published which aimed at maintaining high specificity of the criterion, but with increased sensitivity as well as incorporating national experience. There was a restriction to cases in children under 13 years who had laboratory evidence of HIV infection in addition to two fundamental criteria (A and B criteria), the “Modified CDC criteria” (B criteria, adapted from the CDC definition of 1994) and the “Criteria by Confirmation Signs” (A criteria, adapted from the WHO temporary definition, 1986).

To establish serologic evidence of HIV infection the reference cutoff of 24 months was established. The B criterion was based on reviewing the CDC list of opportunistic diseases. The A criterion, nonexclusive with respect to B criterion, was based on presence of signs, symptoms, and diseases. The “signs” of the latter criterion were classified at a meeting of experts coordinated by the Brazilian Program for Control of STD/AIDS in October 1993.

In 1999, the Brazilian AIDS case definition in children was revised, keeping all above-mentioned criteria, and extending criteria for laboratory diagnosis of HIV infection and updating the “Modified CDC criteria,” taking reference to the review conducted by CDC. In addition, to include changes made by the CDC in 1994, it was decided to exclude coccidioidomycosis and tuberculosis as diseases considered indicative of AIDS. In this revision another main criterion was included—the “CD4 count” based on laboratory evidence of immunosuppression by CD4 lymphocyte count measured in absolute and proportional manner, according to child age and two exceptional criteria: “Exceptional HIV + Death” and “Exceptional Death.” Constituted in this modification, the “Exceptional HIV + Death Criteria” covered those situations
in which children, known to be infected with HIV, presented signs or symptoms related to AIDS and who died due to non-external causes. The “Exceptional Death Criterion” tested and confirmed as a useful criterion in the AIDS case definition in individuals with 13 years of age or older, was also established in children to account for situations in which the death certificates mentioned AIDS in any field, and epidemiologic investigation was inconclusive. Similar to adults, this criterion reflected failure of the surveillance system to detect the case during life, compromising, often, the quality of information obtained post mortem. Another modification of the AIDS case definition came into force in January 2004 (the current definition), which was based on accumulated experience of 16 years of AIDS surveillance in Brazil. It aimed at simplifying the existing criteria, without reducing accuracy of diagnosis.

Regarding laboratory evidence of HIV infection in children by detection of antibodies for epidemiologic surveillance purposes, the reference age was changed from 24 months of age to 18 months. This change led to adjusting the age limit set by the national guidelines for Antiretroviral Therapy in Children published in 2001. Even for children exposed to HIV through MTCT, aged younger than 18 months, the presence of detectable viral DNA or RNA above 1000 copies per milliliter in two samples—plasma viral load—obtained in different moments, defines this condition. For children younger than 18 months exposed to HIV through MTCT, or those of any age whose exposure to HIV has been another form of transmission, it follows the same criteria as for individuals with 13 years or older.

In late 2008, the CDC changed U.S. criteria for AIDS case definition for adults and children (between 18 months and 13 years old), considering wide availability of HIV testing. It defined the requirement for laboratory confirmation for conclusive evidence of infection. For children younger than 18 months, only the category “presumptively uninfected” was changed. Considering the Brazilian reality this new definition of criteria for HIV is not applicable. In Brazil, beyond the laboratory evidence of HIV infection for AIDS case definition, there is a need for evidence of clinical and/or laboratory immunodeficiency.

Based on results of evaluation of the criteria for AIDS cases so far established, the “CDC Modified” and “CD4” criteria were reviewed and began to compose a single criterion: the “CDC Adapted Criteria.” In addition, the “Criteria for Confirmation Signs” were excluded, and incorporated into the CDC Adapted Criteria. This change generated the need for adjustments in the criteria for clinical and complementary diagnosis in certain clinical conditions established in the previous criteria definition.

Taking as a reference the original CDC criteria, the Brazilian definition included the following conditions: hepatitis, leiomyosarcoma, nephropathy, nocardiosis, and disseminated varicella. These new criteria represent a Brazilian adaptation of the clinical categories of mild, moderate, or severe character, respectively, A, B, and C, that define immunodeficiency according to the CDC classification, ensuring international comparability. Case definition now requires, in addition to the laboratory evidence of HIV infection, two clinical situations considered mild or one situation of moderate or severe character.

Regarding the laboratory definition of immunodeficiency, the CD4 count by age remained the reference established by the review of AIDS cases in adults in 1998, with a view to its relevance in detecting cases.

For “exceptional criteria” to AIDS case definition in children, the “HIV + Death Exceptional Criteria” were excluded and the “Death Exceptional Criteria” were revised, which remained outstanding as the unique criterion, similar to adults. The previous definition was expanded to incorporate, in addition to AIDS or the related terms, HIV infection or related terms, since there was still the record of associated diseases with HIV infection, in case the epidemiological investigation proves inconclusive.

Table 1 depicts the history of criteria used for AIDS case definitions in children for purposes of epidemiological surveillance.

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Table 1. History of AIDS Case Definitions in Brazilian Children

<table>
<thead>
<tr>
<th>Year</th>
<th>Age of reference</th>
<th>Definition criteria—AIDS case definition</th>
<th>Benchmark</th>
<th>Excluded criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>&lt;15 years</td>
<td>Modified CDC definition</td>
<td>CDC, 1987</td>
<td>—</td>
</tr>
<tr>
<td>1994</td>
<td>&lt;13 years</td>
<td>Modified CDC definition</td>
<td>CDC, 1994</td>
<td>—</td>
</tr>
<tr>
<td>2000</td>
<td>&lt;13 years</td>
<td>Modified CDC definition (clinical immunodeficiency)</td>
<td>WHO, 1986</td>
<td>—</td>
</tr>
<tr>
<td>2004</td>
<td>&lt;13 years</td>
<td>Adapted CDC Definition</td>
<td>CDC, 1994</td>
<td>Confirmation by signs</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.
Antiretroviral therapy for Brazilian children

In 1988, after more than 20 years of military dictatorship, the reform of the Brazilian health system (with establishment of the SUS) and a new constitution facilitated control measures against the AIDS epidemic. The Ministry of Health started providing drugs for treatment of major opportunistic complications to public health services. Since 1991, the Ministry of Health had also delivered antiretroviral therapy but not yet in a systematized form. The number of patients and of drugs distributed has been increasing steadily (Table 2). A series of political and economic initiatives made possible the construction of a solid and sustainable strategy for recommended treatment in public and private health sectors. Much of this achievement is due to a strong relationship among government, civil society groups and NGOs, with active participation. As the main reference, in 1996, law number 9313 was passed guarantying free and universal distribution of medicines, including HAART.

In this year, the first “National Guidelines on Antiretroviral Therapy in Brazil” were established. This strategy brought new opportunities and challenges for AIDS control and epidemiologic surveillance. Therapeutic options at that time were restricted to zidovudine, didanosine, lamivudine, and zalcitabine (with limited use in children).

In relation to children, since 1994 the National Department of STD and AIDS Control published technical guidelines for antiretroviral treatment, under the title until 2006 of “Guide to Clinical Treatment of HIV Infection in Children,” containing important information about the progress made in the guidelines for treatment and monitoring of children exposed to HIV infection in Brazil.

Table 2 details the inclusion of antiretrovirals (ARVs) in Brazilian recommendations for therapy of HIV infection in children. In general, the Brazilian guidelines include more ARVs in comparison to other low and middle income countries. The criteria to introduce a new drug in the consensus reflect the combination of clinical and social factors.

The criteria for starting antiretroviral therapy are based on HIV infection classification as defined by Brazilian therapeutic guidelines in children. It is noteworthy that since 2006 there was a change in Brazilian criteria used for this definition, which no longer used exclusively the criteria of HIV infection classification of the CDC. The new approach integrated, according to the child’s age, the clinical criteria of the CDC classification, immunologic parameters of the WHO classification of HIV-associated immunodeficiency in infants and children, and virologic parameters based on plasma viral load of HIV.

From a qualitative point of view, the “Brazilian Guide to Clinical Treatment of HIV Infection in Children” has shown over the years important progress incorporating other aspects beyond specific antiretroviral treatment and the use of drugs for prophylaxis of opportunistic conditions or laboratory testing. In addition to more clinical issues, socio-cultural aspects are also included (Table 3).

The latest guidelines (2009) represent a milestone in these advances. Due to the increasing complexity of clinical management of children, the title changed to “Recommendations for Antiretroviral Therapy in Children and Adolescents Infected with HIV,” incorporating the perspective of a longitudinal approach to children in a separate chapter. Comprehensive care, diagnosis disclosing, adherence to treatment, and a specific chapter on adolescents are the innovations incorporated. Actions on mental health and HIV infection, pain management, palliative care and willingness to talk about death were also included (Table 3).

From the standpoint of more specific clinical management, it became important to perform genotyping in all children before the start of antiretroviral therapy, allowing a more accurate indication of therapy. The use of rapid tests for diagnosis was a great achievement that has enhanced the
definitive diagnosis of HIV infection, with high sensitivity and reliability.51 Even though costs of care of children living with HIV/AIDS are strongly defined by use of antiretroviral drugs, the impact of this policy is unquestionable for SUS, especially when considering classification of ambulatory care and prevention of infection progression.4,5,52

Morbidity and mortality in children with AIDS in Brazil

Despite the increase in the proportion of heterosexual women and men, the history of AIDS in Brazil maintains as a concentrated epidemic and is expected to remain at this level in future years, if no significant social or political changes will occur.53,54 However, even with the “fertility boom” observed among women living with HIV/AIDS in Brazil in recent years, the number of infected exposed children has systematically been reduced.9,55 This improved control of MTCT takes place in the context of a pronounced decline of the overall fertility rates in the country, from 2.5 per 1000 live births per woman in 1996 to 1.8 in 2006.56

The cumulative number of reported AIDS cases from 1980 to June 2009 was 544,846. Of this total, 18,128 (3.3%) were children 12 years of age or less: 13,036 (71.9%) aged younger than 5 years, and 5092 (28.1%) aged 5–12 years. Since 1996, more than 90% of reported cases in children were reported as MTCT, reaching almost 93% in 2008.

Figure 1A shows the trend in incidence rates of AIDS among children in Brazil. There is a reduction, especially since 2002; from 1996 to 2008 (HAART era) there was a significant reduction of the incidence rate by 22.6% (children 0–12 years of age) and by 46.0% (children 0–4 years of age). This reduction in children is largely a reflection of actions implemented to reduce MTCT of HIV and use of HAART in HIV-infected children throughout the country, despite different patterns observed in other studies related to performance among regions for operational services, as well as social and economic factors.8,11,57

Between 1984 and 2008 (preliminary data from 2008), the number of deaths from AIDS in children was 5,041. Since 1996 there was a downward mortality trend in this population (Fig. 1B): the reduction was 39.3% in adults, 63.6% in children (0–12 years of age), and 71.2% in children 0–4 years of age.9 This trend can largely be explained by improved access to HAART as guaranteed by the national policy on antiretroviral therapy in Brazil, and by improved clinical monitoring of patients, including the control of MTCT.55

MTCT of HIV in Brazil

In the first years of the epidemic, the MTCT rate was estimated at 16% (95% confidence interval [CI]: 13.0–20.9) between January 1988 and April 199358. Another national study included 2924 children from 63 health services in 20 states, with estimated transmission rates of 8.6% (95% CI: 7.2–10.2) in 2000, and 7.1% (95% CI: 5.8–8.6) in 2001.59

A surveillance study among pregnant women carried out in 2000 demonstrated an HIV infection rate of 0.47% in pregnant Brazilian women. Considering this situation and the birth rate, an estimated 16,600 HIV-infected women were reached. In a 2004 sentinel study, in a representative sample of pregnant women between 15 and 49 years of age from all regions of the country, the HIV infection rate was 0.42% at moment of birth, which corresponded to an estimated num-
ber of 12,600 pregnant women infected (in each year, approximately 3 million women give live birth in Brazil).\textsuperscript{9,10,60}

Considering these two studies, there was an estimated reduction of HIV infections by MTCT of more than 50% in Brazil.\textsuperscript{9,10,60}

More recently a study carried out in São Paulo State has shown that the MTCT rate was 2.7% (95% CI: 1.86–3.94) in 2006, decreasing by 83.1% in relation to 1988–1993 (L.H. Matida, N.J.S. Santos, A.N. Ramos Jr et al., unpublished data). The main factors in this study associated with an increased MTCT were: no or insufficient prenatal care; no performance of antiretroviral prophylaxis during labor; incomplete antiretroviral therapy of neonates (less than 6 weeks); and maternal breastfeeding. The state of São Paulo has the major burden, with 38.3% of the total number of reported AIDS cases from MTCT in Brazil from 1980–2009, and with 36.5% of the total of AIDS cases among children in Brazil.\textsuperscript{9}

Survival in Brazilian children

In Brazil, few studies have been conducted to define the survival of children with AIDS.\textsuperscript{11,61–63} The first national study of AIDS survival in children (AIDS diagnosis from 1983 to 1998) obtained evidence regarding the impact of access to HAART on survival probability in children infected by MTCT. The survival probability to 60 months was 0.528 (95% CI: 0.419–0.608) in 914 reported AIDS cases (MTCT of HIV) in the period from 1983 to 1998 and with follow-up until June 30, 2002.\textsuperscript{62}

In the second national study, data were obtained from a retrospective cohort conducted in a random sample of all 27 states. The study population consisted of children (under 13 years old) diagnosed with AIDS at SINAN in Brazil between 1999 and 2002 ($n = 945$), outpatients followed until 2007 and exposed to HIV by MTCT (97.5% of the children investigated). The survival probability of more than 60 months was 0.863 (95% CI [0.841–0.885]). In the first national study this probability was 0.528 (95% CI [0.419–0.608]), reflecting a significant improvement over the period.\textsuperscript{63,64}

Further analysis of the second national study reinforces the results: comparing cases diagnosed before 1988 with those diagnosed from 2001–2002 it increased 3.5-fold (from 25% to 86.3%). Additionally, this study shows that use of ART, initial clinical classification, and final classification were significant predictors of survival. However, 65.4% of the 920 children included in this analysis presented with the diagnosis of AIDS with clinical classification B (31.3%) or C (34.4%), suggesting late diagnosis.\textsuperscript{53}

Discussion

This is the first systematic review of historical, operational, and epidemiologic aspects of AIDS in Brazilian children. The data show that Brazil has been implementing a successful national HIV/AIDS control program also for children, but new challenges are ahead and historical needs persist. Despite the remaining gaps in terms of technical and scientific knowledge related to HIV infection and AIDS among children, Brazil has undergone important changes in terms of policies since 1984.

Changes in strategies for epidemiological surveillance through reporting of AIDS cases in children have made possible the adoption of criteria for defining cases more suitable to health care settings and to ensure international comparability. These changes always adapted to the Brazilian reality and ensured the sensitivity of the criteria, without compromising specificity. An example of this initiative was the introduction of surveillance to pregnant women infected with HIV and their exposed children in 2000. With more than 90% of children reported with AIDS exposed to HIV through MTCT, this means that Brazil since then would have the technical foundations for early HIV surveillance in children.

The efforts developed by the Brazilian Ministry of Health to improve the quality and accuracy of the official AIDS database, using probabilistic linkage of different sources of information, are considered strategic. This linkage method has great advantages\textsuperscript{15,65} but also some limitations, such as a lower specificity compared to hierarchical deterministic linkage.\textsuperscript{66} The Brazilian data show clearly the improved diagnosis of HIV-infected children over the years, especially with the introduction of free and universal access to HAART, but also because of epidemiological monitoring and quality clinical care. These approaches include issues such as greater access to early diagnosis and management of HIV infection and opportunistic diseases. Epidemiologic data suggest a downward trend in number of AIDS cases in children (mostly by MTCT) and in mortality related to AIDS, mainly from the late 1990s. These trends reflect the national policy to ensure free antiretroviral therapy, prophylaxis, and treatment for opportunistic conditions. Over the years, Brazil has been updating its recommendations with potential antiretroviral regimens and also by expanding the scope of care, incorporating dimensions that must necessarily be conducted by a multidisciplinary and interdisciplinary team, linking the different levels of technological complexity in the health system. These recommendations include, for example, different strategies of vaccinations in persons with HIV/AIDS.\textsuperscript{51,67}

Despite the unequivocal results concerning survival time in Brazilian children with AIDS, the issues previously raised about quality of health care deserve special attention. HIV infection and AIDS need to be considered as chronic conditions that require reactive social responses, as well as continuous and integrated health care. Additionally, the occurrence of late diagnosis in children still presents a major challenge to overcome. Other issues not addressed by this study include adherence to ART, the expression patterns of subtypes of HIV, and HIV resistance to antiretroviral drugs extend the challenges for the country.

This line of approach is evident from the last therapeutic guidelines in 2009 that address issues of great complexity to the health service network. These issues represent “current” challenges for health professionals and families. They include dimensions such as living and growing up with HIV infection or AIDS (both from the standpoint of the individual and family or community), diagnostic disclosure, sexuality, reproductive health, mental health, oral health, adherence, social assistance, infection by different subtypes of HIV, antiretroviral drug resistance, adverse effects associated with therapy (such as chronic degenerative conditions in children), and dealing with bereavement/orphans.

All these challenges imply the need for new practices in health services that go beyond exclusive monitoring of clinical status, CD4$^{+}$ T cells, opportunistic conditions, antiretroviral therapy and prophylaxis for opportunistic conditions. This same perspective also should be directed at prenatal care, considering all dimensions involved. Unfortunately, despite efforts made by the Brazilian health system, the quality of prenatal care has been below the desirable level.\textsuperscript{68} An HIV-sentinel study among childbearing women carried out in Brazil during 2006 estimated a coverage of HIV testing during pregnancy of 62.3%. There were considerable regional differences, with coverage ranging from 40.6% in the Northeast to 85.8% in the South; significant differences were observed according to race, educational level, and municipality size.\textsuperscript{69}

Brazil is a federal republic with 27 states and 5 major geographical regions, with approximately 190 million inhabitants. It is currently among the 10 largest economies in the world, the largest Latin American economy and one of the five major emerging economies along with China, India, Mexico, and South Africa.\textsuperscript{70} Although this scenario indicates a great potential for economic and social growth for all, Brazil still represents one of the countries with the greatest social and economic inequalities worldwide,\textsuperscript{70} including unequal per-
formances of health services,71 with the regions in the south (southeast and south) more developed. The northeast, north, and central–west regions are, in decreasing order, less developed regions. However, this study does not include subnational analysis that could indicate different patterns of implementing these recommendations over the years by different issues. Considering the magnitude of the epidemic in Brazil, the data presented here largely reflect a pattern observed in more developed regions of the country, requiring more specific regional approaches in the face of wide differences on demographic, social, economic, cultural, epidemiologic, and operational factors.

Regardless of these considerations, the historical reconstruction of technical guidelines and policies for the pediatric population with AIDS in the country, particularly the management of HIV infection and epidemiologic surveillance, has an important role. This not only because this analysis allows us to understand more clearly the patterns of the epidemic and control options, but mainly because it will define guidelines and policies in the future, from epidemiologic patterns observed during the development of these actions. Likewise, it allows accurate identification of changes in trends associated with different interventions, increasing their cost effectiveness.

The events depicted in a time sequence relate to each other and allow access to the contexts that enabled Brazil to have over 25 years of international prominence in their public policies to combat HIV/AIDS. This analysis allows increasing the possibility of advances in controlling HIV/AIDS in other developing countries and supporting the specificity of the historical process in the Brazilian experience. Despite the national results that in many respects are comparable to those observed in developed countries, this incomplete transition shows that there are still important issues to overcome the many regional differences found in the country. With this, the universality of benefit in the country would indeed be guaranteed.

In conclusion, the historical reconstruction of the technical–political scenario undertaken in Brazil presents, in detail the ways adopted by country to control HIV/AIDS in the pediatric population. It also provides important background on the dynamics of HIV transmission as well as the patterns of morbidity, mortality and survival in children with AIDS in the country throughout the period considered in this analysis. We hope this will contribute to improvement of public policies adopted by the country in future planning efforts, especially regarding monitoring and impact evaluation of these policies.

Author Disclosure Statement

No competing financial interests exist.

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