Improving Survival Among Brazilian Children With Perinatally-Acquired AIDS

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Brazil was the first developing country to provide free, universal access to antiretroviral treatment for AIDS patients. The Brazilian experience thus provides the first evidence regarding the impact of such treatment on the survival of perinatally acquired AIDS cases in the developing world. Material and Methods: This retrospective cohort study used medical record reviews to examine characteristics and trends in the survival of a representative sample of 914 perinatally acquired AIDS cases in 10 Brazilian cities diagnosed between 1983 and 1998. Results: Survival time increased steadily and substantially. Whereas half of the children died within 20 months of diagnosis at the beginning of the epidemic, 75% of children diagnosed in 1997 and 1998 were still alive after four years of follow-up. Conclusions: Advances in management and treatment have made a great difference in the survival of Brazilian children with AIDS. These results argue strongly for making such treatment available to children in the entire developing world.
Key Words: Acquired immunodeficiency syndrome, Brazil, human immunodeficiency virus, pediatric, perinatal transmission, survival.

Monitoring trends in survival for AIDS patients is important for several reasons. In addition to providing prognostic information and a basis for health services planning, survival time is a key indicator of the impact of medical care. Enhanced overall survival is the litmus test of effectiveness for new treatment approaches.

Many recent studies have demonstrated substantial improvement in survival among both adult and pediatric patients with HIV infection in developed countries, where antiretroviral treatment is generally available [1-3]. However survival time has remained poor in developing countries that do not provide such treatment. Brazil was the first developing country to provide free, universal access to antiretroviral treatment (ART) through its national health care system. *Pneumocystis carinii* prophylaxis became available in 1992 and monotherapy with AZT began in 1994. This was followed by double antiretroviral treatment in 1997 and triple therapy, including protease inhibitors, in 1998. Since then, new treatments and laboratory tests for HIV infection have become available in Brazil at about the same time as in developed countries.

While some have questioned whether ART can be effective in a developing country that lacks the health infrastructure of richer countries [4], survival time has increased substantially among adult Brazilian AIDS patients [5]. No previous study has examined the impact of universal access to ART on survival among pediatric AIDS patients in Brazil or any other developing country. We conducted a study of perinatally-acquired AIDS cases in 10 Brazilian cities to examine trends in survival.

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Materials and Methods

We examined AIDS cases in persons less than 13 years old listed in the Brazilian national AIDS registry as of December 31, 2000, with reported dates of diagnosis between 1983 (the year that the first case was diagnosed) and December 31, 1998. The first stage of sampling involved the purposive selection of 10 Brazilian cities: São Paulo, Rio de Janeiro, Porto Alegre, Ribeirão Preto, Recife, Santos, Campinas, Brasília, Belém, and São José do Rio Preto. The sample included the two largest cities in both population and number of pediatric AIDS cases, São Paulo and Rio de Janeiro, both in the southeastern region of the country. It also included the city with the largest number of reported cases from each of Brazil's other four macroregions (Belém, Recife, Brasilia, and Porto Alegre) plus three medium-sized cities with high rates of AIDS (Santos, Campinas, and Riberao Preto). Overall, these 10 cities accounted for approximately 60% of all reported pediatric AIDS cases in Brazil during the period of study.

Of the 3,031 reported cases in these cities, we excluded 206 attributed to transfusion, 136 in hemophiliacs, and 9 attributed to sexual transmission or injected drug use. The remaining 2,680 had been reported as perinatal transmission or as unknown transmission. Based on sample size estimates for adequate statistical power, we randomly selected 1,268 of the 2,680 for medical record reviews. Of these, 1,065 records were located and contained sufficient information for review. Additional exclusions included 60 cases that on review did not meet the official Brazilian pediatric AIDS diagnostic criteria in effect at the time [6-8] or did not do so until after December 31, 1998, 26 duplicate cases, and 20 with uncertain dates. Of 121 cases originally reported as "unknown," 76 were reclassified as perinatal transmission based on review and were included in the study; the remaining 45 were excluded. This left 914 cases for analysis.

Medical records were reviewed by abstracters who received standardized training in study procedures. Record reviews took place between May 2000 and January 2002. Date of diagnosis was reassessed based on the AIDS diagnostic criteria in effect at the time of diagnosis. Date of death was established by medical record review and/or by local mortality data, when available. For patients not known to have died, the date of censor was their last recorded clinic visit. Data were entered using Excel 97 [9] and analyzed using STATA version 7.0 [10]. Curves of survival from date of AIDS diagnosis based on all-cause mortality were produced using the Kaplan-Meier method. Comparisons of survival time used the log-rank test. This study received clearance from the ethical review board of the Sao Paulo State STD/AIDS Program following standards of the National Committee on Research Ethics.

Results

Slightly over half of the 914 cases were female (Table 1). The number of cases diagnosed each year was fairly steady after 1988, with only 16 cases diagnosed in 1987 or earlier. The most common diagnoses were bacterial infections and *Pneumocystis carinii* pneumonia. About 75% received some form of ART. This proportion was higher among the recent cases, with almost all diagnosed in 1997 and 1998 receiving combination therapy.

Survival increased progressively among the more recently diagnosed cases ($p < 0.001$, Figure 1). Median survival for cases diagnosed before 1988 was 20 months. This increased to 24 months for cases diagnosed between 1988 and 1992 and to 50 months for cases diagnosed from 1993 to 1994. Median survival could not be calculated for the more recently diagnosed cases, because more than half were still living by the end of follow-up, but continuing improvement in survival has been evident. Over 75% of cases were still alive four years after diagnosis among cases diagnosed in 1997 and 1998, the most recent group studied.

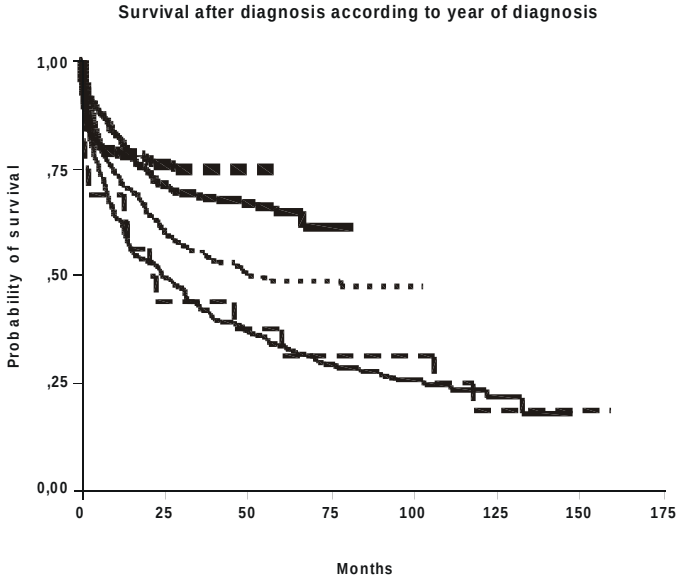
We examined trends in age at AIDS diagnosis. Median age gradually increased from 14 months for cases diagnosed before 1988 to 19 months for cases diagnosed in 1997-1998.

Table 1. Characteristics of 914 cases of perinatally transmitted AIDS in Brazil

Sex	
Female	461
Male	453
Year of diagnosis	
1983 – 1987	16
1988 – 1992	265
1993 – 1994	196
1995 – 1996	221
1997 – 1998	216
Most common presenting diagnoses*	
Multiple bacterial infections	519
Pneumocystis carinii pneumonia	193
Bacterial meningitis or sepsis	143
Interstitial lymphocytic pneumonia	107
Received antiretroviral treatment	
Yes	682
No	207
Unknown	25

*Multiple presenting diagnoses possible.

Figure 1. Survival after AIDS diagnosis among 914 cases of perinatally transmitted HIV in Brazil by year of AIDS diagnosis.



Discussion

There was substantial improvement in survival among Brazilian children with perinatally transmitted AIDS. Other studies have shown similar increases in survival, but the degree of improvement and recent levels of survival achieved are difficult to compare. Most reports of survival time among perinatally-acquired AIDS cases are based on cohorts of HIV-infected children who were identified at birth or soon thereafter. Survival time is usually calculated from birth or date of HIV diagnosis rather than from date of meeting AIDS diagnostic criteria, leading to longer reported survival. For example, survival to age five of Canadian children infected perinatally increased from 72% for those born in 1992-1995 to 92% for those born in 1996 [11]. In the United States, survival to age five increased from 72% to 83% when comparing children born before and after 1994 [12].

Our study was based on national AIDS reporting data and thus has the advantage of being representative of the general Brazilian population. But because cases were not reported until after AIDS was diagnosed, we are only able to provide unbiased estimates of survival starting from this point. Although adding median age of AIDS diagnosis to median survival after diagnosis gives a rough estimate of median survival from birth, this remains biased to the extent that infected children who have gone undiagnosed or who have not yet met AIDS diagnostic criteria are not included in the denominator. This may change in the future because screening to prevent and detect perinatal transmission of HIV has now become the norm, and Brazil is implementing a registry of all HIV-infected children. Comparable national data on survival from date of AIDS diagnosis in perinatally acquired cases have been reported from the United States. Among cases diagnosed in 1998, survival to 36 months was 87% [13]. Our data indicate survival approaching similar levels in the most recently diagnosed group of Brazilian children.

Our study has many potential limitations. While the 10 cities selected for this study are geographically representative and account for the majority of reported pediatric AIDS cases in Brazil, it is possible that underreporting of cases may be higher and that both absolute survival and the recent improvement in survival may be lower outside of these major epicenters. Underreporting of AIDS cases is estimated to be relatively low in Brazil [14], but unreported cases may have shorter survival, as might the 16% of cases in our original sample for which we were unable to obtain information. While these factors could cause an overestimate of survival, they would not explain the secular increase in survival that was observed, unless the magnitude of any such bias increased substantially over time.

One factor that might affect observed survival time is earlier diagnosis if patients were diagnosed earlier rather than living longer. The case definition for AIDS in Brazil was changed in 1994 to become more sensitive, and CD_4 testing became generally available in 1997. On the other hand, improved early treatment and prophylaxis for mother and child would be expected to delay progression to AIDS. Our data indicate that the net effect of these changes has been a slight increase in average age at diagnosis of AIDS. This would not have caused the longer survival after AIDS diagnosis that we observed; on the contrary, it indicates that improvement in survival from birth has been even greater.

The Brazilian experience is encouraging in many ways. It demonstrates that it is possible for a developing country to establish an effective system for providing free, universal access to ART. It also demonstrates that such care, even in a country that lacks an ideal health infrastructure, can make a substantial difference in survival. Since the years covered by this study, Brazil has made great progress in reducing perinatal transmission of HIV, and the number of new cases of perinatally-acquired AIDS is falling [15]. There is good reason to believe that remaining cases will experience further improvements in survival. We also hope that children elsewhere in the developing world will gain access to the benefits of life-sustaining treatment.

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