OBJECTIVE

To evaluate the survival of people with HIV/AIDS.

METHOD

A retrospective study, involving a sample of 1993 reports from 2007 to 2013, at the Clementino Fraga Hospital, in João Pessoa, Brazil, for evaluation of the Kaplan Meier survival curve and associated factors.

RESULTS: the majority were men (66.7%), mean age 37.4 years and less than 8 years of schooling (54.3%). A total of 9.9% of patients died, from AIDS, with a mean survival time of 20.7 months. Of these deaths, 25% occurred within 4 months of notification and 50%, occurred within 15 months. They were associated with a reduction in survival: male gender (p = 0.002); pulmonary tuberculosis (0.003); Central Nervous System dysfunction (0.001); prolonged fever (0.016); hematological changes (<0.001) and persistent cough (0.033). Hematologic changes, pulmonary tuberculosis, CNS dysfunction and male gender increased, respectively, by 2.4, 1.6, 1.8 and 1.6 times the risk of death.

CONCLUSION: the risk of AIDS mortality is higher in the first year after notification. Descriptors: HIV; AIDS; Survival Analysis.

RESUMO

Objetivo: avaliar a sobrevida de pessoas com HIV/AIDS. Método: estudo retrospectivo, envolvendo amostra com 1993 notificações de 2007 a 2013, no Hospital Clementino Fraga, em João Pessoa (PB), Brasil, para a avaliação da curva de sobrevida de Kaplan Meier e fatores associados. Resultados: a maioria eram homens (66.7%), idade média de 37,4 anos e escolaridade inferior a 8 anos (54.3%). Faleceram, por Aids, 9,9% dos pacientes, cujo tempo médio de sobrevida foi 20,7 meses. Destes óbitos, 25% ocorreram até quatro meses da notificação e 50%, em 15 meses. Associaram-se com redução da sobrevida: sexo masculino (p=0,002); tuberculose pulmonar (0,003); disfunção do Sistema Nervoso Central (0,001); febre prolongada (0,016); alterações hematológicas (<0,001) e tosse persistente (0,033). Alterações hematológicas, tuberculose pulmonar, disfunção do SNC e sexo masculino aumentaram, respectivamente, em 2,4, 1,6, 1,8 e 1,6 vezes o risco de óbito. Conclusão: o risco de mortalidade por Aids é maior no primeiro ano após a notificação. Descriptores: HIV; AIDS; Análise de Sobrevida.

RESUMEN

Objetivo: evaluar la supervivencia de personas con VIH/SIDA. Método: estudio retrospectivo con muestra constituida por 1993 notificaciones desde 2007 hasta 2013, en el Hospital Clementino Fraga, en João Pessoa (PB), Brasil para la evaluación de la curva de supervivencia de Kaplan Meier y factores asociados. Resultados: la mayoría eran hombres (66.7%), edad media de 37,4 años, escolaridad inferior a 8 años (54.3%). Fallecieron, por SIDA, el 9,9% de las personas, cuyo tiempo medio de sobrevida fue 20,7 meses. El 25% de estas muertes ocurrieron hasta cuatro meses tras la notificación y el 50% en 15 meses. Estuvieron asociados con reducción de la supervivencia: hombres (p=0,002); tuberculosis pulmonar (0,003); disfunción del Sistema Nervioso Central (0,001); fiebre prolongada (0,016); alteraciones hematológicas (<0,001) y tos persistente (0,033). Alteraciones hematológicas, tuberculose pulmonar, disfunción del SNC y sexo masculino aumentaron, respectivamente, en 2,4, 1,6, 1,8 y 1,6 veces el riesgo de muerte. Conclusión: el riesgo de mortalidad por SIDA es mayor en el primer año tras la notificación. Descriptores: VIH; SIDA; Análise de Supervivencia.

English/Portuguese

INTRODUCTION

Acquired Human Immunodeficiency Syndrome (AIDS) is a chronic infectious disease, described in 1981, and since its inception, has shown many changes in demographic and epidemiological characteristics.  

By the end of 2012, there were, approximately 718,000 people living with HIV/AIDS in Brazil. Of this amount, about 74% of the individuals are followed up by the health services and their clinical evolution is monitored through biological markers such as CD4 lymphocyte counts and viral load (VL). In the Northeast, the HIV incidence rate AIDS is 12.6 cases per 100,000 inhabitants. The mortality rate among HIV/AIDS is 6.3 per 100,000 people and the use of antiretroviral therapy (ART) was the main modifier in the morbidity and mortality of the disease over the years.

From the introduction of HAART, considerable improvements in HIV/AIDS survival have been observed, especially in the therapeutic regimens that have become more effective, simple and better tolerated. The health benefits associated with the use of ART, are substantial for both individuals, and populations. The therapy is effective in increasing PVHA survival and is associated with a reduction of new infections. However, the increase in life expectancy, after the introduction of ART, makes individuals more susceptible to comorbidities, compromising their quality of life. Studies demonstrate small, but persistent, differences in life expectancy between HIV-positive and HIV-negative individuals.

The identification of predictive factors of mortality is of fundamental importance, as are their relationships, highlighting the time of diagnosis, the initiation of ART, adherence to treatment, quality of life, and the individual’s psychological and cognitive status.

In a case-control study, after the implementation of HAART, it was described that the abandonment or non-use of HAART, were the strongest predictors of death, followed by late diagnosis, which increases the chance of death by 3.95 times, suggesting that Brazilians continue to die of AIDS due to possible behaviors to be modified.

Other factors described in the literature, that reduce survival, were age above 35 years, the presence of candidiasis, use of illicit drugs, lack of specialized care, low educational level and CD4 lymphocyte count below 200 cells/mm.

Although much progress has been made in the knowledge and health policies directed at HIV/AIDS since the beginning of the epidemic 30 years ago, allowing a significant decline in the incidence of the disease and in the mortality of infected people throughout Brazil, the continuous monitoring, with identification of the current factors related to mortality, is always necessary, with special attention to regional characteristics. The observed changes had an impact on the increase in survival, as well as on the occurrence of more advanced age groups. In this way, the challenge is to offer a better quality of life, better control of infection and reduction of morbidity and mortality. Follow-up studies to assess the causes associated with survival reduction may contribute to clarifying the causal relationships of mortality in the post-ART era.

OBJECTIVES

- To evaluate the survival of people living with HIV/AIDS.
- To check risk factors for reducing the survival time of people living with HIV/AIDS.

METHOD

An observational, retrospective study using all the records of the HIV/AIDS case reports for the (SINAN), from the period of 2007 to 2013, from the database of the Complex of Infectious-Contagious Diseases at Clementino Fraga Hospital in João Pessoa (PB), Brazil. All 2269 notifications made during this period were identified. We excluded 266 cases, of which their period between notification and death was less than 30 days, because there was insufficient information to relate the death to previous therapy or injuries, or those whose notification was made after death (notified by death). Ten other cases were excluded: five, due to lack of record of the evolution of the case; four, because of a different death from that object of this study, and one patient who died after 82 months of follow-up and produced distortion in the survival curve. Thus, 1,993 records containing the complete information were included and analyzed and had survived the first month after reporting the case.

Sociodemographic variables were available and analyzed for gender; age; race; schooling; The date of diagnosis and date of notification; The probable modes of transmission: sexual, hemophilia, injecting drug use, transfusions or accidents with contaminated biological material; The presence of AIDS-defining diseases or symptoms attributed to HIV or indicative of cellular immunodeficiency; And
CD4 lymphocyte counts (less than 350cel / mm³ and greater than or equal to 350cel / mm³). Descriptive analysis and survival analysis, were made considering the time between the date of notification of the case and the occurrence of death due to AIDS. The cases that remained alive were censored, and the censorship time was calculated, the difference between the date of notification and the final date of follow-up established (12/31/2013). The Kaplan-Meier estimator was used to calculate the median survival time, the survival rate and for the construction of the survival curves as a function of the descriptive variables. The log-rank test was used to compare Kaplan Meier survival curves stratified by each independent variable. All significant variables in the log-rank test were included in a Cox multiple regression model for the calculation of proportional risk of death as a function of the independent variables. The analysis were performed using Statistical Package R version 3.2.5.

The research was carried out after the informed consent of the study site through the Institution's Statement of Consent and approval by the Research Ethics Committee, as foreseen in Resolution 466/12 of the National Council of Ethics in Research under the Certificate of Presentation for Ethical Appreciation Number 36661314.6.0000.5188.9. The researchers declare no conflicts of interest with the search results.

RESULTS

Table 1. Distribution of prevalence of signs and symptoms among the 1993 PLH/A in the clinical presentation for notification. João Pessoa (PB), Brazil.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence(%)</th>
<th>% Ignored data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counting of CD4 &lt; 350 cel/mm³</td>
<td>68.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Cachexia</td>
<td>56.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Persistent Fever</td>
<td>49.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>49.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Hematologic changes *</td>
<td>36.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Cough</td>
<td>30.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>17.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>14.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Pulmonary Tuberculosis</td>
<td>8.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Herpes</td>
<td>5.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Neurotoxoplasmosis</td>
<td>5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Dysfunction of the central nervous system **</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Disseminated tuberculosis</td>
<td>2.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>2.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>2.1</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Source: Data base.

*Anemia and/or lymphopenia and / or thrombocytopenia.

** According to the Rio de Janeiro / Caracas Criteria.

The probability of survival at one year was 95.4% and 86.3% at five years. It should be noted that this figure refers to the PLH/A who survived the first month after notification, who were excluded for the better correlation with exposure factors. When analyzing the 198 patients who died, we observed that the median survival time, between these cases...
was 15.5 months. This distribution of deaths as a function of time was not homogeneous, since 25% of cases occurred before the fourth month after notification, which can be verified by the risk function, which shows that the risk of death is higher in the first year after they are followed by a period of stabilization of the death rate and a subsequent fall in risk.

Figure 1 shows the survival curves in the total sample and in the group that evolved to death, and the risk-of-mortality function over time. The calculated AIDS case fatality rate, according to the definition of the population of this study, was 9.9% of the registered cases. Considering all AIDS deaths, and all those exposed that contained the available evolution information, including those occurring within 30 days after notification, the case fatality rate is 20.6%.

![Figure 1](image_url)

**Figure 1.** Survival curves in the total sample in A (n = 1993); in B survival curve in the group that presented the death outcome (n = 198), and in C the risk of death function over time. João Pessoa (PB), Brazil.

Survival curves were made for each descriptive variable of the sample, comparing the categories of each variable using the log-rank test and adopting a significance level of 95%. The variables that were significantly associated with decreased PLH/A survival were: male sex and the presence of co-morbidities: pulmonary tuberculosis; central nervous system (CNS) dysfunction, prolonged fever, hematological changes and persistent cough. All survival curves as a function of these variables are shown in figure 2.
Figure 2. Gender-dependent survival curves, in A (p=0.002*), pulmonary tuberculosis in B (p=0.003*), central nervous system dysfunction in C (p=0.001*), hematological alterations in D (p=0.000*), persistent cough and or pneumonia in E (p=0.007*) and prolonged fever in F (p=0.036*) between 1993 PLH/A in João Pessoa-PB, between 2007 and 2013. João Pessoa (PB), Brazil. *p-value in the Test Log-Rank.

Analysis of the CD4 variable showed that this variable presented a loss of 3.6% (71 patients did not have this record) and 70.8% of the 1,923 individuals who were evaluated presented CD4 <350 cells/mm$^3$. This fact corroborates, once again, with the notification being made in advanced stages of the disease and prejudged the evaluation of the correlation with the cases of death in this population, since it was expected that a greater proportion of cases with CD4 ≥ 350 cells/mm$^3$ and with consequently lower number of deaths in this group. This justifies the absence of CD4 <350 cells/mm$^3$ as a risk variable for death in this population when the Cox, multiple regression model was performed, although it is known that low levels of CD4 are associated with severe opportunistic infections and higher risk of evolution to death, in this population, the distribution of the cases regarding the CD4 value produced a bias of confounding and its correlation with the cases of death was not demonstrated.

The variables associated with decreased survival were included in a Cox multiple regression model in order to estimate the independent risk associated with each factor. The presence of hematological alterations, pulmonary tuberculosis, CNS dysfunction and male patients remained in the model. Table 4 presents the results of the Cox model, with the associated risks, the p-value and the confidence interval, with the agreement of 66.5%. These results indicate that the presence of these variables increases the risk of death by 2.4, when PLH/A has hematological abnormalities (anemia and/or lymphopenia and/or thrombocytopenia), 1.6 times, when presenting tuberculosis, 1.8 times, when it has CNS dysfunction and 1.6 times when it is male.
DISCUSSION

There were 2,269 reports of PLH/A in the period 2007 to 2013 and, among those who survived the first month after notification, the evolution to death predominated from the second to the fourth month after notification, when 25% of deaths, were recorded; And 50% occurred by the 15th month of follow-up. This suggested that the reports were in advanced stages of the disease, even though 266 cases that died within the first month after notification were excluded. The late diagnosis of infection reflects negatively on the prognosis of the disease, especially in underdeveloped countries where one in four individuals presents a significant decline in their immune status, with CD4 lymphocyte counts below 100 cells/mm³.\(^\text{10}\) In a 15-year cohort, with 1187 PLH/A in Cameroon, with a reality different from ours, the probability of survival in the first year was 77% and 47% after five years.\(^\text{11}\) In our country, in a reference service in Rio de Janeiro, with a probability of survival of 89.6% in five years,\(^\text{12}\) approaching the probability found in the present study of 86.3% in five years.

The studied population had a socio-demographic profile similar to that of other studies: male predominance; young adult age, and low schooling.\(^\text{6}\) Even so, it is important to highlight, in recent years, the increase in cases of infected women, difference in the proportion of cases between men and women and contributing to the increase in the incidence of cases coming from heterosexual transmission. Also, we observed in this study, another recent phenomenon that is the social inequality of the occurrence of the disease, affecting more frequently, people with less schooling.\(^\text{13}\)

Regarding gender, it is known that, in general, male patients have a lower adherence to treatment, which may contribute to the higher risk of death among these individuals. In PLH/A, some studies did not show an association due to methodological difficulties,\(^\text{9}\) but, in 2001, a higher survival rate in female PLH/A was reported.\(^\text{14}\) The present study demonstrated a superior survival time associated with the female gender, which seems to corroborate other studies that analyzed this variable. A study carried out in a cohort of 2091 people living with AIDS in Southern and Southeastern Brazil, also showed an increase in survival among women.\(^\text{15}\) In the same study, the authors also found an association with greater survival for individuals with no history of tuberculosis.

The observed AIDS case-fatality rate was 9.9%, disregarding the deaths of the first month after the notification. However, considering all cases, it increased to 20.6%, a value similar to that described in a study developed in Blumenau, Santa Catarina (SC), Brazil, where a rate of 24.2% of deaths was observed. This study analyzed the period from 1997 to 2004 and presented in its sample, 20.4% of PLH/A, due to injecting drug use, a group with lower survival.\(^\text{13}\) Considering these unfavorable characteristics of the Blumenau study, data from up to 16 years earlier to the present study and a more vulnerable population, the data found in Paraiba demonstrates a greater severity than expected, especially, with the improvement of the attention directed to PLH/A. In a recent meta-analysis, involving 57 cohort studies, involving more than 290,000 PLH/A, the probability of death among those receiving HAART was 87%, 86%, 78%, 78% and 61%, respectively, two, four, six, eight and ten years. But without treatment, most of them died after the first two years of AIDS, but, with considerable heterogeneity between the studies and moderate to high risk of bias.\(^\text{17}\)

CD4 lymphocyte count, viral load, and onset of symptoms are commonly used to monitor the clinical evolution of PLHA. Although the criteria used in Brazil for the diagnosis of AIDS are similar to international standards, the cutoff point for the CD4 count (<350 cells / mm³) that defines as the most serious condition is a classification that notably presents significant limitations due, in part, to the relatively arbitrary choice of this value, measurement errors and the common occurrence of classification errors.\(^\text{6}\) In the
present study, the data found about the relationship between CD4 levels and patient survival are not consistent with the expected in clinical practice and previous studies.\(^4\) The justification for such an outcome was a probable classification bias, since the data were already categorized in the database and there was no access to the data with absolute values for each notified individual, thus impairing stratification of the CD4 values associated with higher mortality. Other studies also found that other criteria for defining AIDS, other than “CD4 <350”, were associated with a higher probability of death.\(^7\)

In the sample studied, people who had dysfunction of the central nervous system lived less than those who did not. According to this criterion, dysfunction of the central nervous system is defined as mental confusion, dementia, decreased level of consciousness, seizures, encephalitis, meningitis of any known etiology (except for Cryptococcus neoformans) or unknown, myelitis and/or tests Cerebellar abnormalities, excluding dysfunctions caused by external causes. It is worth noting that in the evaluation of neurological diseases specified and evaluated in this study, there was no association with higher mortality for neurotoxoplasmosis, leuкоencephalopathy and cerebral lymphoma. However, it is known that, low CD4 levels present as a predictive variable in the neurological status of PLH/A and possibly contribute to the relation with the higher mortality described. Although AIDS mortality is declining since the introduction of HAART, the frequency of neurological disorders associated with HIV, is still a clinical challenge. Although the survival time of patients with dementia associated with HIV infection has increased with therapy, recent studies have shown that dementia and opportunistic infections are associated with increased mortality rates.\(^18\) The risk of death associated with CNS dysfunction was described in a study in Southeastern Brazil, in which PLH/A presented a 1.57 times higher risk of death.\(^12\)

Tuberculosis (TB) is the second most common opportunistic infection in Europe and the most common in the world.\(^19\) Biological evidence suggests that TB can accelerate the progression of HIV infection. Although the highest mortality after TB is reported, the epidemiological evidence seems to be less clear. Thus, it is difficult to distinguish whether TB is a cause of the disease’s rapid progression or a marker for it. Lower survival after pulmonary TB is expected, even when the analysis are adjusted for other indicators, and constitute a functional marker of independent immunosuppression.\(^20\) These reports corroborate the results found, which describes a lower survival rate among patients presenting with Pulmonary TB, with a 1.5-fold higher risk of death in the presence of TB.\(^7\)

Patients with TB who delay the use of ART for more than 30 days from the diagnosis of opportunistic infection present twice the risk of clinical progression of the disease or death when compared to those who started ART immediately.\(^19\)

The presence of fever (defined as temperature ≥ 38° for a time equal to or greater than one month), presence of hematological changes (defined as anemia and/or lymphopenia and/or thrombocytopenia) and persistent cough or any pneumonia (excluding TB as the cause), these are signs and symptoms that may be related to various clinical situations and underlying diseases, and in fact corroborate the severity and chronicity of the cases. Thus, patients in these situations possibly tend to evolve with worse prognosis, as found in the survival curves. It is important to note that the collection of this data was based only on the data as indicated in the notification form, which uses the description of these signs and symptoms according to the Rio de Janeiro/Caracas Criteria for the diagnosis of AIDS.

When assessing early mortality, it is necessary to reflect on the issue of early diagnosis in the less advanced phase of immunodeficiency, especially the serological detection of the virus, without AIDS manifestations per se. Many people are still discouraged from taking the test voluntarily and find it difficult to perform it adequately in health services.\(^21\) Even during prenatal care, for example, pregnant women are not properly advised about the test. These authors conducted 1,298 interviews in 2003 involving sexually active people and found that only 29.7% had been tested at least once in their lifetime and only 31.9% of them had undergone the test in the last six months.

Late diagnosis appears to be one of the main determinants of mortality and, in this context, a study in the Southeast of Brazil, involving 520 PLH/A, revealed that, at diagnosis, 53.7% had CD4 <350 cells/mm\(^3\), and 37.1% had advanced disease and CD4 <200 cells/mm\(^3\). Among these, 75% already had a viral load> 10,000 copies / ml.22 This data, reflects that there is still resistance in seeking health services for early diagnosis. In our study, the unavailability of absolute CD4 values in the database made it impossible to

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better characterize this issue during the notification of the case.

The lack of knowledge in the service itself, the difficulty of perceiving itself as vulnerable to infection, the justifications for not belonging to the so-called “risk groups”, the fear of embarrassment and of precarious care as important limitations of access to the centers of testing and counseling. These authors identified a paradox between the participatory aspect in overcoming vulnerability and the search for pragmatic solutions to risk exclusion.21

The issue of access to HIV serostatus, in the context of an expanded context involving the understanding of related diseases and conditioning factors, revealed that in 16 months rapid tests were extrapolated from the initial target of two years, when there was the incentive of the “I Want to Do” Program, with the commitment of nongovernmental and governmental institutions.24 It is important to emphasize that health services and teams must be prepared to face the global fears associated with the positive outcome and the economic, social and personal effects,24 so that individuals become more confident and motivated to perform the serological test. A group that should not be forgotten are people 50 years of age or older, a group that, initially did not have a great representation in the incidence of AIDS but which, as a result of the chronic presentation of the clinical presentation, became a susceptible and often, neglected group to perform the early diagnosis.25 PLH/A aged 50 years or more has been elevated in several regions, and 20% have been described in a reference center in Rio de Janeiro.26

Treatment outcomes, often, depend on patient adherence to the drug, social and family factors that determine the patient’s attitude towards their pathology. CD4 count is an important prognostic parameter in the evolution of patients, since it correlates with the presentation of opportunistic diseases, which are the main causes of death among these patients.

In a review article, a positive correlation was described between adherence to treatment and quality of life.5 People with higher quality of life present a greater tendency towards adherence to treatment. Quality of life and adherence to treatment are associated with viral load, disease stage and symptoms. Therefore, non-adherence to treatment is associated with a higher viral load, and this increase in viral load is associated with lower quality of life scores and shorter survival time. In turn, having the diagnosis of AIDS and presenting symptoms associated with the disease also imply a lower quality of life and a greater adherence to the treatment.

**CONCLUSION**

The survival analysis of 1993 cases of PLH/A registries reported in a reference hospital in João Pessoa-PB, Brazil, who survived the first month after notification, demonstrated that the probability of survival at one year was 95.4% and 86.3% in five years. There were 198 deaths during the period, among which the median survival time was 15.5 months. The non-homogeneous distribution of mortality as a function of time is highlighted, since 25% of the deaths happened until the fourth month after the notification, which suggests records made in aggravated situations of the disease.

They were associated with a decrease in patient survival: being male, presenting pulmonary tuberculosis, central nervous system dysfunction, prolonged fever, hematological alterations and persistent cough. Hematologic changes, represented by anemia and/or lymphopenia and/or thrombocytopenia, Pulmonary tuberculosis, CNS dysfunction and male gender increased, respectively, by 2.4, 1.6, 1.8 and 1.6 times the risk of death.

It is recommended that the early diagnosis of the disease be stimulated by the health services, through educational measures to stimulate the routine performance of the serological test for HIV, which could contribute to the diagnosis at a lesser stage of the disease and reduction of mortality. Special clinical care should also be given to patients presenting the comorbidities associated with the increased mortality risk identified in this study, in addition to the markers already adopted and the timely institution of ART.

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