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Research Article

Survival Time of People Living With HIV: Systematic Review and Meta-Analysis

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Keywords

 HIV; Acquired Immunodeficiency Syndrome; Survival Analysis; Antiretroviral therapy

Abstract

1.1. Introduction: Infection with the human immunodeficiency virus (HIV) is still a global epidemic. More than 40 million people died of acquired immunodeficiency syndrome (AIDS) so far. Antiretroviral treatment (ART), among other health care measures, reversed this fatal outcome. The aim of this study was to analyze the survival time of people living with HIV (PLHIV) through national and international studies in a systematic review with meta-analysis.

1.2. Material and Methods: An electronic search was conducted in three databases PubMed, SciELO and ScienceDirect identify original studies about survival time of PLHIV published until 12/31/2018.

1.3. Results: A total of 2,650 entries were retrieved from which 17 studies met the inclusion criteria. The total number of PLHIV included in these studies was 75,020 people. They were performed in 11 countries, with 35.29% of them in Brazil. The overall mean survival time of PLHIV was 6.36 years (95%CI 5.58-7.14; I2=100%; p<0.001). Survival time of PLHIV was higher for those on ART than for those without treatment: an average of 2.4 years and 1,52, respectively. Survival time of PLHIV also increased with higher educational levels and younger age.

1.4. Conclusion: This systematic review with meta-analysis consolidated the scientific evidence that ART increases survival time of PLHIV.

INTRODUCTION

Infection with the human immunodeficiency virus (HIV) is a global epidemic, still considered one of the biggest public health problems worldwide. According to data from the World Health Organization, more than 40.1 million people died by AIDS since epidemic begin, with 650 thousand mil deaths only in 2021 [1]. It is estimated that there were approximately 38.4 million people living with HIV (PLHIV) at the end of 2021, of these 85% knew their serological status and 54% were girls and women and 28.7 million of them on antiretroviral therapy (ART) [1,2]. Therefore, it is possible to recognize that the combined global efforts to respond to this pandemic has been improving effective care through timely diagnosis and early treatment [2,3].

Fortunately, for the provision of care for PLHIV, particularly health education, self-care, and improved access to ART, has considerably changed the natural course of AIDS history, leading to a constant reduction in the annual death toll worldwide [4]. The favorable scenario turned HIV infection from a fatal disease into a chronic, manageable condition [5]. It is known that regular use of ART is considered essential in the control of viral replication, recovery of the immune system, and suppression of opportunistic infections, which results in better patient outcomes after the diagnosis of HIV [6, 7].

Although the scenario for mitigating HIV/AIDS was favorable, in 2020 the world faced one of the most serious and saddest health problems in its history, a fact that left the global response to AIDS under threat, since in the last two and a half years, COVID19 subjugated all continents and their peoples, which brought social, humanitarian and economic instabilities, events that once again put pressure on public policies to combat HIV/ AIDS and further exposed the vulnerabilities of communities and the risks of people contracting HIV [2].

Although several studies have been indicating that access and adherence to ART is a key factor in improving quality of life and increasing survival time of PLHIV, to the author's best knowledge, there is no systematic review with meta-analysis of these studies to date. Considering that HIV/AIDS still represents a major challenge for public health in different regions of the world, it is of great importance to systematically consolidate evidence on the impact of ART on the survival of PLHIV. Thus, the aim of the present study was to analyze the survival time

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presented by PLHIV on ART, through national and international studies in a systematic review with meta-analysis.

MATERIAL AND METHODS

Search strategy

An electronic search was conducted in three databases: PubMed, SciELO and ScienceDirect. All searches were performed on the same day, 07/20/2019, to identify original research about survival time of PLHIV published until 12/31/2018. It had been registered in the International Prospective Register of Systematic Reviews (registration number CRD42020195895).

The search strategy, which retrieved entries in English, Portuguese and Spanish, consisted of a combination of the following MeSH terms and key-words: "Survival Analysis", "Kaplan-Meier", "Survival Rate"; "AIDS", "HTLV-III", "HTLV-III-LAV", "LAV-HTLV-III", "Lymphadenopathy Associated Virus", "Human T Cell Lymphotropic Virus", "Human Immunodeficiency Virus", "Acquired Immunodeficiency", "Antiretroviral Therapy", "Highly Active"; "HAART"; "Anti-Retroviral Agents"; "Highly Active Antiretroviral Therapy".

Inclusion and Exclusion Criteria

The inclusion criteria consisted of original and complete scientific articles employing a quantitative methodology for the analysis of survival in PLHIV older than 13 years and with an emphasis on the Kaplan-Meier method. It was excluded studies with a qualitative approach, review articles, case studies, theses, conference proceedings, studies with children or pregnant women and studies that exclusively analyzed the risk of death or survival of PLHIV associated with an additional disease/ condition.

Data collection process and analysis

Selected articles were analyzed by meta-analysis models to estimate overall patient survival in relation to treatment, type of exposure, and age. The information retrieved in each study was: number of patients evaluated, mean survival, standard deviation of survival (when available), 95% confidence interval of survival (when available) and classification by age group, treatment and sexual identity.

Due to the absence of specific tools to assess the quality and risk of bias in research about survival time, especially in PLHIV, the adaptation of the criteria proposed by Zhu [8], was used. The risk of bias was indicated through in three groups: yellow circle with a question mark for uncertain risk of bias in the item, blue circles with a plus sign indicated low risk, and those marked in red with a minus sign indicated high risk of bias.

The confidence intervals in the studies without a measure of variability for survival were estimated by an iteration based on data asymmetry and the number of patients in each category [9]. The method used to calculate the combined values was inverse variance for the mean of continuous quantitative variables weighted by the size of the study population. Inter-study heterogeneity was tested with the test [3]. When heterogeneity between studies was significant (p<0.05), random effects models were used, when heterogeneity was random (not significant),

fixed effects models were used. This result was used to interpret the differences between the studies and to choose the most appropriate combination of effects model. Publication bias was tested with the Egger test. All analyzes were performed in the R environment (R Core Team, 2019) with the "meta" package [10].

The results of each article were combined into a single measure using the inverse variance method to define the weight of each study. The estimate of the single measure represents a weighted average of all studies and the calculation of the confidence interval for this measure considers intra- and interstudy variability at the same time. The weight of each individual study was defined in inverse proportion to its variance, a method that offers a higher weight for studies with larger samples and a lower weight for studies with smaller ones.

RESULTS

The literature search identified 2,650 entries. After removal of duplicates, screening by titles and abstract, and evaluation of full texts, 17 studies met the inclusion criteria. A diagram detailing the review process is presented in Table 1, summarizes the studies included in this review. The studies had a similar cohort totaling 75,020 PLHIV from five continents.

The mean survival time of PLHIV observed in the studies was 6.36 years. The survival time was further evaluated in relation to treatment, sexual identity, education, and age. Most studies had a low risk of bias in the variables evaluated (Table 2). In the treatment category, the mean survival time was 2.4 years for PLHIV on ART and 1.52 years for those without pharmacological treatment. In terms of type of exposure, it was found an average of 2.70 years of survival for those who acquired HIV via heterosexual sex, 2.63 years for bi/homosexual sex, and 2.25 years for other forms (e.g., needle sharing for drug use). The education variable indicated that survival time increased with more years of formal education. With regards to age, it was found that life expectancy of PLHIV decreased with age: an average of 9.12 years for those with 15-30 years, 7.47 years of survival for those aged 31-40 years and 6.68 years for those 41 years or more (Table 3).

Most studies about PLHIV survival time were conducted in Brazil with five publications (35.29%) in national journals (Table 1). Spain published two studies, and Australia, China, Denmark, Ethiopia, Malaysia, Nepal, Netherlands, Rwanda, and Uganda had one study each.

The articles found presented evaluation periods dating from the early the 80's to 2015, spanning 35 years of research on the survival of PLHIV (Table 1). The longest survival assessment time were seen in two studies, recording 20 years [11] and 25 years [12], for 41% of the studies, the survival was observed between 11 and 19 years [13,14,15,16,17,18,19], and 47% of studies evaluated survival up to 10 years [20,21,22,23,24,25,26,27].

The articles obtained for this review consisted essentially of cohort studies, totaling 75,020 subjects (20,461 female and 48,871 male). The participants were on average between 30 and 40 years old; with only one study not reporting participants' age (Table 4).

In terms of treatment of PLHIV, 64.71% of studies included this analysis, while 35.29% did not state whether PLHIV

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Table 1: Articles on PLHIV survival time published until December 31, 2018 indexed in Pubmed, ScIELO, and/or ScienceDirect databases.										
Study number	First author and year of publication	Journal	Span of time evaluated	Country	Results/outcomes					
1	SOCAS, et al., 2000	Medicina Clínica	1985-1999	Spain	95% of people who started HAART treatment were alive until the end of the study.					
2	DORE, et al., 2002	Journal of Acquired Immune Deficiency Syndromes	1993-2000	Australia	Improving survival time in the HAART era and its impacting in the natural history of the HIV/AIDS.					
3	GUERRIERO, et al., 2002	Rev Saúde Pública	1986-1998	Brazil	ART had a significant impact on the survival time of patients with HIV/AIDS.					
4	SIGNORINI, et al., 2005	Revista Brazileira de Epidemiologia	1995-2002	Brazil	The survival time was influenced by the use of triple therapy, clearly modifying the course of HIV infection, thus reducing mortality.					
5	RIUS, et al., 2006	Medicina Clínica	1981-2001	Spain	Increased survival time in AIDS cases is influenced by the introduction of ART.					
6	PETERS, et al,. 2007	AIDS	1988-2003	Rwanda	The average survival time of HIV-infected women in Rwanda was similar to the survival time observed in high-income countries.					
7	LOHSE, et al., 2007	Annals of internal medicine	1995-2005	Denmark	Median survival time was estimated to be over 35 years at the end of the ART era. The survival projections were dependent on continuous treatment with HAART.					
8	VAN DER PALL, et al., 2007	AIDS	1990-2003	Uganda	Survival time and eligibility for ART treatment in PLHIV with LT-CD4+ <200 cells/mm3 was greater than 2 years, superior to another study in Uganda which obtained a median of 9 months.					
9	MELO, et al., 2008	Brazilian Journal of Infectious Diseases	1997-2004	Brazil	Although HAART has been shown to be effective and with good survival, it is extremely important that the treatment being initiated in a timely manner.					
10	BOER-VAN DER KOLK, et al., 2010	Clinical Infectious Diseases	1998-2000	Holland	Health-related quality of life predicts the survival of PLHIV on HAART.					
11	SHAH, et al., 2012	Journal of Experimental & Clinical Medicine	1997-2008	Malasia	Morbimortality becomes high in PLHIV who are not being treated with HAART.					
12	TANCREDI, et al., 2014	BMC infectious diseases	1998-2003	Brazil	Increased survival rates and benefits with early introduction of HAART. For the maximum follow-up period 108 months - More than 50% of patients were alive at the end of follow-up.					
13	LI, et al., 2015	AIDS research and human retroviruses	2001-2011	China	The median survival time of treatment-naive patients was 14 months, and those who underwent treatment, 6.4 years.					
14	TACHBLE, et al., 2016	Epidemiology and health	2010-2015	Etiópia	Overall patient survival on HAART was 64.00 at 72 months of follow-up.					
15	LIMA, et al., 2018	Cadernos de saúde pública	2000-2011	Brazil	Despite persistent disparities, mortality declined significantly over the period for all categories under review, and the overall positive impact of HAART on survival.					
16	MOTA, et al., 2018	Revista Brazileira de Epidemiologia	1980-2005	Brazil	Access to combined ART in reference services in the city possibly reduced the influence of this laboratory indicator as a predictor of death.					
17	BHATTA, et al., 2019	BMJ global health	2004-2015	Nepal	Long-term survival is related to early initiation of ART for those with higher LT-CD4+ counts, thus providing increased life expectancy and reduced mortality.					

Table 2: Quality analysis of the studies included in this systematic review.																
a. 1		Critoria												Risk		
study	of publication	crite	Criteria											High	Unknown	
number	of publication	1	2	3	4	5	6	7	8	9	10	11	+	-	?	
1	SOCAS, et al., 2000	+	+	+	-	+	+	?	?	+	-	?	54,55%	18,18%	27,27%	
2	DORE, et al., 2002	+	+	+	+	+	+	+	?	+	-	+	81,82%	9,09%	9,09%	
3	GUERRIERO, et al., 2002	+	+	+	+	+	+	+	-	+		+	81,82%	9,09%	9,09%	

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4	SIGNORINI, et al., 2005	+	+	+	+	+	+	+	+	+	+	+	100%	0%	0%
5	RIUS, et al., 2006	+	+	+	+	?	+	+	+	+	+	+	90,01%	0%	9,09%
6	PETERS, et al,. 2007	+	+	+	+	+	?	+	-	+	+	+	81,82%	9,09%	9,09%
7	LOHSE, et al., 2007	+	+	+	+	+	?	+	-	+	+	?	72,73%	9,09%	18,18%
8	VAN DER PALL, et al., 2007	+	+	+	+	+	?	+	-	+	+	?	81,82%	9,09%	9,09%
9	MELO, et al., 2008	+	+	+	-	+	+	+	-	+	+	?	72,73%	18,18%	9,09%
10	BOER-VAN DER KOLK, et al., 2010	+	+	+	?	?	?	+	-	+	+	?	54,55%	9,09%	36,36%
11	SHAH, et al., 2012	+	+	+	+	+	+	+	+	+	-	?	81,82%	9,09%	9,09%
12	TANCREDI, et al., 2014	+	+	+	+	+	+	+	+	+	-	+	90,01%	9,09%	0,00%
13	LI, et al., 2015	+	+	+	+	+	+	+	+	+	+	?	90,01%	0%	9,09%
14	TACHBLE, et al., 2016	+	+	+	+	+	+	+	+	+	+	?	90,01%	0%	9,09%
15	LIMA, et al., 2018	+	+	+	+	+	+	+	+	+	+	?	90,01%	0%	9,09%
16	MOTA, et al., 2018	+	+	+	+	+	+	+	+	+	+	+	100%	0%	0%
17	BHATTA, et al., 2019	+	+	+	+	+	+	+	+	+	+	+	100%	0%	0%

Criterion 01: Presents survival time analyses. The number of types of survival analyses.

Criterion 02: Reports survival endpoint (such as overall survival, disease-free survival, local control survival, etc., if survival endpoints were defined).

Criterion 03: Reports average survival time, the survival rate of different years and the survival time range.

Criterion 04: The RR value was reported, the meaning of statistical significance, and it was explained through text or graphics.

Criterion 05: Reports follow-up information (i.e. follow-up end time, follow-up mode, median follow-up time, average follow-up time, follow-up time interval, follow-up rate, and handling of missing data).

Criterion 06: Whether the sample size and sample size calculation method were reported.

Criterion 07: Whether censorship events were clearly reported.

Criterion 08: Whether the inclusion and exclusion criteria for the sample were reported.

Criterion 09: Whether survival curves were drawn.

Criterion 10: Reports statistical software usage.

Criterion 11: Whether statisticians and epidemiologists were included as authors.

Table 3: Survival analysis by variable.										
	N*	Average survival time	IC 95%	I ² ; p-value heterogeneity	p-value bias test					
General	269	6,36	5,58 - 7,14	I ² =100%; p<0,001	0,4864					
Treatment (ART)	31	2,4	1,57 - 3,23	I ² =100%; p<0,001	0.0(02					
No treatment	8	1,52	0,65 - 2,40	I ² =100%; p<0,001	0,9693					
Heterossexual sex	2	2,7	1,43 - 3,96	I ² =100%; p<0,001						
Homo/bissexual sex	3	2,63	1,38 - 3,88	I ² =100%; p<0,001	0,3289					
Other types of exposure/behavior	5	2,25	1,64 - 2,85	I ² =100%; p<0,001						
15-30 years old	57	9,12	7,52 - 10,72	I ² =100%; p<0,001						
31-40 years old	17	7,47	5,54 - 9,41	I ² =100%; p<0,001	0,3467					
41 anos ou mais	69	6,68	5,90 - 7,47	I ² =100%; p<0,001						
Source: authors	·		•							

* Number of observations found in the studies for the variables listed.

Table 4: Analysis of variables by number of participants, gender, age, education, and treatment.										
Study number	Number of participants	Female participants	Male participants	Average age	Average education (years)	No ART (%)	Some sort of ART (%)			
1	807	653	154	-	-	17	83			
2	4351	235	4116	38 years	-	-	-			

3	362	49	313	<30 years (38,55%)*	Low level (n=264)**	25,52	74,48
4	1420	470	950	36,4 years	≥ 8 anos (n=736)	39	61
5	13485	2531	10954	25-34 years (51,67%)*	-	-	-
6	548	548	-	27 years	Literate (n=401)***	47,7	52,29
7	3990	1197	2793	37,2 years	-	-	-
8	240	121	119	28,7 years	-	-	-
9	119	29	90	37,9 years	< 8 years (n=72)	8,4	91,6
10	560	56	509	40,5 years	-	-	100
11	1479	208	509	38,2 years	≥ 8 years (n=329)	40	60
12	6594	1526	5068	30-39 years (62,01%)*	≥ 8 years (n=3316)	43,9	56,1
13	19020	4727	14293	38 years	< 8 years (n=12.224)	-	-
14	350	207	143	30 years	< 8 years (n=286)	-	100
15	15420	5697	9723	38,5 years	< 8 years (n=3413)	38	62
16	3084	1002	2532	30-49 years (60,90%)*	< 8 years (n=1129)	-	-
17	3191	1205	1986	35-39 years (24,15%)*	-	-	100

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were undergoing treatment. Among those which reported the treatment variable, 66.54% of PLHIV in these studies used some regimen with ARTs (ART/HAART, combined/dual therapy, monotherapy) during the follow-up periods, when verified the use only of ART/HAART, which is configured as the most effective and recent treatment in the history of HIV/AIDS, the rate declines by 56.40% (Table 4).

The education level of PLHIV was assessed in 58.82% of the studies (Table 4), of these 06 studies had an average educational level of less than 8 years for PLHIV in their cohorts, with 04 articles from Brazil, one from China and one from Ethiopia. Populations with an average of schooling above 8 years of study were only verified in two studies conducted in Brazil and Malaysia.

The epidemiological data from these studies revealed that HIV infection risk has been related to the same vulnerabilities over time. Although there were regional differences, it was possible to observe that the risk for HIV infection continued to be linked to male gender, heterosexuality, age between 30 and 40 years, low educational level (less than 8 years), and exposure through sexual contact.

DISCUSSION

This is the first systematic review with meta-analysis about PLHIV survival time. Data from several original studies related to treatment, type of exposure, education, and age were evaluated. All studies analyzed were unanimous in emphasizing that there has been a substantial improvement in survival of PLHIV, especially when they are on ART. However, despite several years since the introduction of ART, the general data indicated a low average survival rate related to PLHIV. It is important to mention that there was great methodological heterogeneity between the studies, especially in regards the variables used to measure the survival of the cohorts, which contributed to the great variability of inter-study results. The meta-analysis process was based on the number of occurrences (mentions) related to PLHIV survival, described in each study. This factor directly influenced the analysis, as the uniformity of the variables was not constant, being closely related to the choices made by their respective authors. Thus, it was decided to group the occurrences into categories, for which it was possible to find an average denominator.

The mean survival time was assessed in 269 occurrences found in the studies. The meta-analysis estimated a general survival time of 6.36 years (95%CI 5.58-7.14; I2=100%; p<0.001). There were great discrepancies with some studies reporting very low survival time, some of them less than 1 year [11,13,16,17,18,24,25]; while two studies mentioned much higher survival rates, surpassing two decades [15,26]. The lower life expectancy observed may be directly related to late diagnosis, a factor that is aggravated by the association of multimorbidity, which are more present in adults and older adults. A study with 331 PLHIV with a mean age of 40 years, found that 53.13% of participants had another disease [28].

The studies in this review also highlighted the importance of timely access to ART and its contribution to the drastic reduction in morbidity and mortality due to the great recovery of the LT-CD4+ lymphocyte count and viral suppression [12,13,14,15,24,25], leading to improved quality of live [20] and increased life expectancy [15]. However, the studies in this review that evaluated this showed an incredibly low average survival time for PLHIV either with or without treatment. It is worth mentioning that during the evaluation period of these studies, numerous changes regarding the clinical practices were introduced.

This category included nine studies that addressed the treatment approach, three of which started their research in the early and mid-80s until the 2000s [11,18]. Another four based

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their analyzes within the period from 1993 to 2008 [13,23,24,25]. It is noteworthy that the 90's of the last century were marked by the introduction of highly effective ART, which brought numerous benefits to PLHIV through triple therapy. And, finally, only two studies had more current scenarios, with research carried out between 2001 and 2015 [22,27].

ART has been shown to be highly effective in transforming HIV infection from a fatal condition into a controllable and chronic one, in addition to providing improved quality of life for people living with HIV, with a substantial increase in survival, especially when therapy is started early, regardless of the stage of infection. The timely and rapid initiation of ART is a critical indicator of viral suppression in the process of care for PLHIV.

Regarding the type of exposure to HIV infection (heterosexual, homosexual, or bisexual sex and other forms of exposures (needle sharing for injecting drugs, blood transfusions or not specified), only three studies analyzed this variable relating it to survival time [16,23,24]. In all scenarios, the survival time remained relatively low, between 2.25 to 2.70 years.

It has long been recognized that HIV infection disproportionally affects men. However, there were few reflections on what it really represents for different groups of men, i.e. heterosexual, homosexual, bisexual or even according to the social positions in society [28,29]. To try to understand the complexity involved in HIV infection prevention strategies for males, it is necessary to recognize that there is a plurality of masculinity expressions which are connected but hierarchically structured. In this scenario, demonstrations of masculinity though socially valued can be troublesome, particularly healthwise, as men tend to express dominant behavior and suppress demonstration of fear exposing themselves to risky situations [30]. Additionally, men are much more frequently exposed to sexually transmitted infections (STIs), including HIV, due to the social imposition of multiple sexual partners, an apparent sense of resilience to diseases, and heterosexuality self-assertion [29].

Regarding the influence of age on the survival of PLHIV, this was the category that revealed the highest survival rate among the surveys in this review, although analyzed by only 6 of the 17 articles. It was observed that the younger age group prevailed as a protective factor for survival, while PLHIV aged 41 years or older were those with the lowest survival time. This is in line with studies reporting that mortality tends to increase significantly up to 49 years, with a peak in the age group between 40 and 44 years, and with fluctuations in survival times for older ages, culminating in the lowest survival among 75 and 79 years old [30]. It has also been shown that children between 5- and 14-years old living with HIV survive longer than adolescents and adults [28,31-33].

Most participants were adults in the studies included in this review. This shows that studies evaluating survival time of PLHIV not necessarily reflect the age group of increased risk for HIV infection. It has been found that adolescents and young adults (i.e. those aged between 13 and 24 years) are more vulnerable to the risk of contamination currently [34,35]. Age stratification is of great importance for public health, as it allows surveillance services to establish strategies to minimize the impacts that the disease can cause on different population segments. It is worth considering that the period of adolescence and the transition to adulthood is at high risk from the perspective of HIV, as this moment is often marked by physical and cognitive changes; for instant gratification; greater peer influence in decision making; and where previously imposed rules and limits are now being reexamined; events that can culminate in the vulnerability of young people when relating without the use of safer methods [35]. Thus, young people are characterized as a significant challenge to control the epidemic, as they are the ones where the worst results in the cascade of care for PLHIV (diagnosis, retention, attachment, treatment and viral suppression) are seen when compared to adults [36].

Regarding education, it was shown that this variable is still considered a major factor in the risk of HIV infection, as it was observed in 13 studies (in this review) the assessment of educational level among its participants, 7 of them with results that point to the low education level and another 6 studies for 8 years of education or more. This is in line with findings of other studies that have shown that people with a higher level of education have easier access to information relevant to HIV prevention, as well as a better understanding of their health, treatment and coping with AIDS [37].

CONCLUSION

This meta-analysis verified survival in people living with HIV and, according to the results, most of them obtained significant benefits from the use of ART in all scenarios. Future research with the objective of studying survival in PLHIV would need to build a pattern of variables of general interest that permeate the biomedical model, which are applicable to different population segments, and the analyzes relying on measures of statistical variation.

Study limitations

This study had some limitations, such as the absence of measures of survival time variability (standard error, standard deviation, or confidence interval); the lack of clear information about the use of ART in some studies; constant changes in clinical practice in the period evaluated; variation of demographic data which changed over time. Additionally, observational retrospective studies may present heterogeneities, missing data, biases, and a large number of different variables applied to survival analysis (absence of a clear pattern), and these are configured as factors that can blur and limit the analysis.

To minimize the impacts of these limitations, the variables presented in each of the articles were categorized with the maximum possible standardization to bring greater uniformity to the analyses.

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