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Inequalities in HAART uptake and differential survival according to exposure category in Rio de Janeiro, Brazil

Desigualdades no acesso à HAART e diferenças de sobrevida de acordo com a categoria de exposição ao HIV no Rio de Janeiro, Brasil

Desigualdades en el consumo de la TARGA y supervivencia diferencial según la categoría de exposición en Río de Janeiro, Brasil

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Abstract

Despite substantial improvement in prognosis and quality of life among people living with HIV/AIDS (PLWHA) in Brazil, inequalities in access to treatment remain. We assessed the impact of these inequalities on survival in Rio de Janeiro over a 12-year period (2000/11). Data were merged from four databases that comprise the national AIDS monitoring system: SINAN-AIDS (Brazilian Information System for Notificable Diseases; AIDS cases), SISCEL (laboratory tests), SICLOM (electronic dispensing system), and SIM (Brazilian Mortality Information System), using probabilistic linkage. Cox regressions were fitted to assess the impact of HAART (highly active antiretroviral therapy) on AIDS-related mortality among men who have sex with men (MSM), people who inject drugs (PWID), and heterosexuals diagnosed with AIDS, between 2000 and 2011, in the city of Rio de Janeiro, RJ, Brazil. Among 15,420 cases, 60.7% were heterosexuals, 36.1% MSM and 3.2% PWID. There were 2,807 (18.2%) deaths and the median survival time was 6.29. HAART and CD4+ > 200 at baseline were associated with important protective effects. Non-whites had a 33% higher risk of dying in consequence of AIDS than whites. PWID had a 56% higher risk and MSM a 11% lower risk of dying of AIDS than heterosexuals. Non-white individuals, those with less than eight years of formal education, and PWID, were more likely to die of AIDS and less likely to receive HAART. Important inequalities persist in access to treatment, resulting in disparate impacts on mortality among exposure categories. Despite these persistent disparities, mortality decreased significantly during the period for all categories under analysis, and the overall positive impact of HAART on survival has been dramatic.

Acquired Immunodeficiency Syndrome; Survival Analysis; Differential Mortality; Social Inequity; Hight Active Antiretroviral Therapy

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Background

More than thirty years have elapsed since the first AIDS cases were reported by the Centers for Disease Control and Prevention (CDC) in major US cities. Globally, there were approximately 36.7 (95%CI: 34.0-39.8) million people living with HIV/AIDS (PLWHA) and 2.1 (95%CI: 1.8-2.4) million people becoming newly infected with HIV at the end of 2015. HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2015, 1.1 (95%CI: 940,000-1.3 million) million people died from HIV-related causes globally [1].

In 1996, Brazil became the first middle-income country to guarantee free and universal access to HIV treatment through its Brazilian Unified National Health System (SUS) [2]. Between 1980 and June 2016, 842,710 cases of AIDS were reported, and there were 487,000 PLWHA receiving highly active antiretroviral therapy (HAART) in Brazil in June 2016 [3].

In December 2013, the country implemented HIV Treatment as Prevention (TasP), allowing for treatment to be initiated immediately after confirmation of an HIV diagnosis, an approach intended to improve the quality of life for PLWHA and reduce the likelihood of HIV transmission [4,5]. This initiative lead to a remarkable increase in PLWHA starting HAART in Brazil, from 48,696 to 81,177 in 2012 and 2015, respectively. Since 2015, 90% of patients receiving HAART in the country had been virally suppressed [6]. The efficacy of pre-exposure prophylaxis (PrEP) and its feasibility implementation in Brazil was recently demonstrated [6,7] and the strategy has been scheduled to be offered by the SUS from 2017 onwards, with some uneven outcomes due to ongoing budget restraints.

In spite of those initiatives, AIDS-related deaths have remained stable over the last decade: 5.9 deaths per 100,000 inhabitants in 2006 and 5.6 deaths per 100,000 inhabitants in 2015. HIV prevalence among the general population has remained stable as well, at approximately 0.6% since 2004, being highly concentrated in the most of the vulnerable groups [3]. A systematic review followed by a meta-analysis identified a combined HIV prevalence for female sex workers of 6.2 (95%CI: 4.4-8.3); 13.6 (95%CI: 8.2-20.2) among men who have sex with men, and 23.1 (95%CI: 16.7-30.2) among people who use drugs [8].

People who inject drugs (PWID) had a pivotal role in the Brazilian epidemic in the late 1980s, the 1990s, and the early years of the 21st century [8], but due to a complex combination of different factors [9], HIV/AIDS among PWID has declined in recent years. However, AIDS rates have been increasing among other socially disadvantaged populations [10], with notable regional disparities between HAART uptake [11] and retention of patients in treatment. PWID and other marginalized and socially-disadvantaged populations usually start HAART in the later stages of infection [12,13,14] compared to MSM who generally start HAART earlier and have better access to health services, higher adherence to treatment and longer survival times after HIV/AIDS diagnosis [15,16,17]. Among heterosexuals, patients from impoverished social strata have higher mortality rates, findings that have been linked to factors such as low education, unemployment, unstable housing, and high transportation costs. These trends have been observed in Brazil as a whole as well as in the city of Rio de Janeiro [18,19].

Three decades later, AIDS is an urban epidemic in Brazil, clustered in the metropolitan areas of large cities such as Rio de Janeiro, among others. The city is located in the Southeast region of Brazil, a region concentrating 53% of all AIDS cases reported nationwide. During the last decade, Brazil has registered around 20.7 AIDS cases per 100,000 inhabitants, while Rio de Janeiro registered 34.1 cases per 100,000 inhabitants in 2006, and 27.8 cases per 100,000 inhabitants in 2015. AIDS-related deaths are also higher in Rio de Janeiro – the city accounted for 8.7 deaths per 100,000 inhabitants in 2015, while Brazil registered 5.6 deaths per 100,000 inhabitants in the same year [20].

Although in recent years epidemiological studies on AIDS have been conducted nationwide [21,22,23,24], they do not always gather information that can adequately be applied to the State or regional levels. This study evaluated the disparities in HAART uptake and its impact on survival in the city of Rio de Janeiro from 2000 to 2011 in an effort to inform evidence-based policies in HIV-care in the local level.

Methods

We studied trends in survival among PLWHA by combining data from four national information systems: Brazilian Information System for Notifiable Diseases/AIDS (SINAN/AIDS), National Database for Laboratory Tests (SISCEL), Logistics Control System of ARV Medicines (SICLOM) and Brazilian Mortality System (SIM). Data from PLWHA diagnosed between 2000 and 2011 in Rio de Janeiro city were extracted from those datasets and merged.

Only individuals whose self-reported exposure categories were PWID, men who have sex with men (MSM) or "heterosexuals" were included in the survival analysis. The following cases of AIDS belonging to other categories of exposure were excluded from the survival analysis: blood transfusion, vertical transmission (mother-to-child), accidents with biological material, and hemophiliacs. All these categories corresponded to less than 1.5% of the cases reported in the study period.

Database linkage

Probabilistic record linkage (PRL) is based on a likelihood score that measures the degree of similarity of several matching variables. Since differential information is found in each database, comprehensive analyses must use data from all of them. Following the methods proposed by Camargo Jr. & Coeli [25], as a first step, we standardized the different databases in order to have exactly the same variable names, lengths and formats throughout all of them. An identification key was created for each patient, therefore enabling his unique identification in different databases. New variables were created using the patient's first and last name (PBLOCO and UBLOCO), date of birth, and mothers' name. The method consisted of cleaning and linking the databases using five blocking steps as follows: (1) PBLOCO, UBLOCO, and sex; (2) PBLOCO and sex; (3) UBLOCO and sex; (4) PBLOCO and UBLOCO, and (5) date of birth and sex.

Pairs with high scores have higher probabilities of being true matches, and pairs with low scores have lower probabilities. Here in the following percentages were considered: patient full name (true match [98%], false match [1%]), mother's name (true match [74%], false match [4%]), patient date of birth (true match [98%], false match [2%]). A cut-off score of 9.6 was used in all steps, trying to maximize sensitivity and minimize the need to perform manual review of pairs as much as possible. Unknown pairs were manually reviewed [26].

Statistical analyses

As a first step, an exploratory analysis was carried out, considering both sociodemographic and clinical variables for each one of the exposure categories under analysis. Pearson's chi-square test was used for the assessment of independence, using 0.05 as the a priori statistical significance and taking as outcomes: AIDS death, HAART uptake after diagnosis, and CD4+ exam at baseline.

For the survival analysis, the outcome was mortality from AIDS-related causes during the follow-up period. Survival was calculated as the time elapsed from the date of AIDS diagnosis until the date of the AIDS-related death (or censoring). All deaths from other causes were considered censored data at the date of its occurrence, and individuals who remained alive were censored on December 31st 2011. The independent variables were: exposure category, year of diagnosis, sex, age, ethnicity, level of education, first CD4+ cell count (cells/mm^3), first HIV-1 RNA viral load exam ($\log_{10}$), and HAART uptake after diagnosis.

The variables CD4+ cell count and HIV-1 RNA viral load exam were categorized according to the international classification for CD4+ (cells/mm^3) and viral load levels [27]. The normality of these variables was verified by graphical methods and the Kolgomorov-Smirnov normality test. Both violated the normality assumption. Therefore, for HIV-1 RNA viral load, the $\log_{10}$ transformation was used with the following categories: "< 4.00" (from 50 to < 10,000 copies, indicating low viral load); "4.00-4.99" (> 10,000 to < 100,000 copies, which indicates intermediate viral load); and "> 5.00" (> 100,000 copies, which indicates high viral load).

We used semi-parametric modeling, with single and multiple-covariate Cox models [28,29], first with the entire population selected (N = 15,420), adjusted for each exposure category. The likelihood ratio test p-value < 0.05 was used to select variables to be entered in the multiple-covariate Cox models, adjusting for potential confounders and testing for effect modification. The crude and adjusted hazard ratios (HR) and their 95% confidence intervals (95%CI) were used to evaluate the effects obtained by single and multiple-covariate Cox models, respectively. The coefficient R^2 was used to show the explanatory capacity of final Cox models. The proportional hazards assumption was assessed by the visual inspection of Schoenfeld's residuals [30] (see Supplementary Material: http://cadernos.ensp.fiocruz.br/csp/public_site/arquivo/csp-0096-17-supplementary-material_1717.pdf). This analysis made evident the violation, even small, of the proportional hazard assumption by the variable "HAART uptake after diagnosis", and by the isolated categories "CD4+ cell count unspecified" and "HSH".

As the sample has a considerable size, it was understood that any lack of proportionality can establish a violation of risk proportionality (a basic assumption of the original Cox model), so extended Cox models were fitted instead [28]. Then, we fitted separated extended Cox models for each exposure category in order to analyze possible inequalities between them. Likewise, Schoenfeld's residuals analysis was performed for each one of the three extended models. To better illustrate the (putative and actual) violations of proportionality, a web appendix with selected plots of some of the original analysis of residuals was made available as part of the manuscript (see Supplementary Material: http://cadernos.ensp.fiocruz.br/csp/public_site/arquivo/csp-0096-17-supplementary-material_1717.pdf).

The Brazilian city of Rio de Janeiro, capital of the homonymous state, located in the Southeast region of the country, is subdivided into 33 administrative regions, which are regional divisions organized by the State to facilitate the administration and governance of a country [31]. Due to the heterogeneity of the municipality of Rio de Janeiro, we used a random effect to evaluate the potential association of survival in a given cluster of neighborhoods of residence in the city (administrative regions) by using the gamma distribution of frailty [32,33,34].

The linkage process was performed using the software RecLink 3.1 [35]. Survival analysis was performed with the help of R's "survival" library (http://CRAN.R-project.org/package=survival), version 3.0.2 (The R Foundation for Statistical Computing, http://www.r-project.org). The study was approved by the Ethics Committee in Research of the Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation (CEP/ENSP/Fiocruz n. 08915712.6.0000.5240/2013).

Results

Overall, considering all the 43,199 individuals identified as being AIDS cases through the linkage procedure, 45.8% had no information about laboratory exams. For 7.6% of cases, information was exclusively available at SIM, corresponding to AIDS-related deaths of individuals who were not reported as "AIDS cases" by the other three databases (i.e. they were not registered as AIDS cases, never received HAART, neither performed any laboratory exam).

From 2000 to 2011, 43,199 AIDS cases were reported in Rio de Janeiro city, most (64.3%) of them male, with a mean age of 38.6 years [standard deviation (SD) = 11.1]. Roughly similar proportions of "whites" (37.5%) and "non-whites" (38.8%). Roughly one quarter of cases (23.7%) had no information on ethnicity. The majority had less than eight years of formal education (35.1%). During the period, 10,569 deaths (24.5%) were reported, of which 84.7% were AIDS-related. Average survival time after AIDS diagnosis was 4.72 years (SD = 3.74), with a median survival of 4.41 years.

The 12 years of follow-up were further divided in three periods of four years each (2000-2003, 2004-2007, and 2008-2011); with a roughly similar number of AIDS cases in each proportion of patients who had at least one CD4+ count and HIV-1 RNA viral load exam period. Access to CD4+ and HIV-1 RNA viral load exam increased over time (from 50.2% to 53% and from 43% to 50.6%, respectively), as well as the proportion of patients receiving HAART, which also increased, from 55.8% to 59.8%.

Non-white individuals, those with less than eight years of formal education, and people who inject drugs (PWID) were more likely to die of AIDS and less likely to receive HAART. People who had at least one CD4+ and one viral load exam registered were more likely to receive HAART and,

consequently, less likely to die of AIDS, compared to those who did not have those exams registered (Table 1). Among the 43,199 AIDS cases reported, 15,420 with exposure category information were selected for the current analysis. Heterosexuals accounted for 60.7% of AIDS cases, followed by 36.1% MSM and 3.2% PWID. The mean age was 38.05 (SD = 10.65). Most of reported AIDS cases occurred in men (63%), non-whites (43%), and people with up to primary education (53.4%). HAART uptake after AIDS diagnosis increased slightly during this 12-year period (62.7% to 65.1%) and was lower among PWID, when compared to MSM and heterosexuals (Table 2).

Roughly half of the patients had CD4+ and HIV-1 RNA viral load exams registered at a public health facility, and PWID were less likely to have ever conducted those exams. Among those with available results, PWID had lower mean CD4+ count and higher HIV-1 RNA viral load counts. During this period, 2,807 deaths were reported (18.2% from total), 77.2% of those AIDS-related deaths. Mortality from all causes was 2.2 times higher among PWID when compared to MSM, while AIDS-related deaths were similar among the exposure categories under analysis (Table 2).

The overall AIDS-related survival rate was 85.9% in 12 years, with a mean of 5.92 years (SD = 3.63) and median of 6.29 years. Both AIDS-related deaths and deaths due to any non-AIDS cause significantly decreased during the period. AIDS-deaths (2,167) declined from the first to the last period (1,061; 781; 325). Deaths due to other causes (640) declined also (364; 203; 73).

The AIDS epidemic in Rio de Janeiro city is mostly composed by heterosexual cases, with a slightly decrease over the follow-up period (63.4 to 52.5%), while the magnitude of cases among PWID remains negligible and has been decreasing over time (3.7% to 2.5%). Among MSM an increasing trend can be observed over time, from 32.9% to 45% (Table 2).

As expected we found a significant interaction between the two laboratory variables (CD4+ counts and HIV-1 RNV viral load). Baseline CD4+ count (cells/mm^3) is predictive of virologic failure and AIDS-related mortality [36,37] and, due to the strong interaction between these two laboratory variables, we decided to exclude HIV-1 RNA viral load from our final model. We also identified a significant interaction between education and ethnicity, and decided to include it in our final models ethnicity instead of education level as the key socioeconomic status variable. This decision was based in previous and robust evidence of the disproportionate burden of HIV/AIDS, late entry into HIV-treatment, and higher AIDS-related mortality among non-white patients [38,39]. The variables sex and year of diagnosis were not significant in the bivariate analysis. Therefore, our final models included age, ethnicity, CD4+ counts, HAART uptake, and exposure category (Tables 3 and 4).

The results depicted in Table 4 show an increased risk of AIDS-related death among PWID, non-white individuals and those who did not have a CD4+ exam registered at baseline, while MSM presented a lower risk (in both extended Cox model and frailty model). This model presented R^2 = 0.234. As expected, higher CD4+ counts at baseline and HAART uptake after AIDS diagnosis were stronger predictors of better survival over time.

When we analyzed the risk of AIDS-related death for each exposure category, different patterns were observed among MSM, heterosexuals and PWID. Covariates found to be independently and significantly associated with a higher survival among MSM and heterosexuals included: HAART uptake after diagnosis and CD4+ level (cells/mm^3) at baseline (the higher the CD4+, the longer the survival time). Non-whites presented a higher risk of dying in consequence of AIDS for both exposure categories. Those who did not have a CD4+ exam available at baseline had an increased risk of dying of AIDS among heterosexuals. The MSM model had an R^2 = 0.219 and heterosexuals had an R^2 = 0.242 (Table 4).

For PWID, only HAART uptake and the higher CD4+ category "> 500" predicted a longer survival. The protective effect of HAART was lower for PWID (70%) when compared to other exposure categories. Non-white PWID had almost double risk of dying of AIDS among this group when compared to whites. This model had a higher R^2 (0.389), compared to all others. The variation among regions of residence was significant (as measured by the frailty effect), except for PWID (Table 4).

Considering the frequencies of cases by Administrative Regions (AR), two clusters were observed: a larger one, comprising AR XIII (Méier), XV (Madureira), XVI (Jacarepaguá), XVII (Bangu), XVIII (Campo Grande) and Realengo (XXXIII), which together account for 34.6% of the total cases in the period; and a smaller one, involving AR IV (Botafogo) and V (Copacabana), which accounted for 11.3% of the cases in the period (Figure 1).

Table 1

Relationship between population characteristics (full data) and the outcomes: AIDS-related deaths, HAART uptake, and CD4+ exam at baseline (N = 43,199). Rio de Janeiro, Brazil, 2000-2011.

Population characteristics	Outcomes		
	n [% of outcome in each category (95%CI)]		
	Proportion of people dying of AIDS	Proportion of who ever received HAART	Proportion of people with CD4 exam at baseline
Ethnicity	p < 0.001	p < 0.001	p < 0.001
White	3,741 [23.1 (22.5-23.7)]	10,195 [63.0 (62.5-63.5)]	7,675 [47.5 (47.0-47.9)]
Non-white	5,058 [30.2 (29.8-30.6)]	9,598 [57.3 (56.8-57.8)]	9,024 [53.9 (53.4-54.4)]
Unspecified	156 [1.5 (1.4-1.6)]	5,360 [52.3 (51.8-52.8)]	5,923 [57.8 (57.3-58.3)]
Level of education (years)	p < 0.001	p < 0.001	p < 0.001
Primary (0-7)	3,413 [22.5 (22.1-22.9)]	8,823 [58.2 (57.7-58.7)]	7,304, 48.2 (47.7-48.7)
Secondary (8-11)	1,068 [14.0 (13.7-14.3)]	5,654 [74.3 (73.9-74.7)]	4,136, 54.3 (53.8-54.8)
Superior/over (12 or more)	163 [3.7 (3.5-3.9)]	4,004 [91.0 (90.7-91.3)]	1,954, 44.4 (43.9-44.9)
Unspecified	4,311 [26.9 (26.5-27.3)]	6,672 [41.6 (41.1-42.1)]	9,228, 57.6 (57.1-58.1)
Exposure category	p < 0.001	p < 0.001	p < 0.001
Heterosexual	1,435 [15.3 (15.0-15.6)]	5,760 [61.6 (61.1-62.1)]	5,096 [54.5 (54.0-55.0)]
MSM	609 [10.9 (10.6-11.2)]	3,588 [64.5 (64.0-65.0)]	2,509 [45.1 (44.6-45.6)]
PWID	123 [24.7 (24.3-25.1)]	219 [44.0 (43.5-44.5)]	201 [40.4 (39.9-40.9)]
Others	32 [13.2 (12.9-13.5)]	153 [63.0 (62.5-63.5)]	135 [55.6 (55.1-56.1)]
Unspecified	6,756 [24.5 (24.1-24.9)]	15,433 [56.0 (55.5-56.5)]	14,681 [53.3 (52.8-53.8)]
Sex	p < 0.01	p = 0.8	p < 0.001
Women	3,074 [19.9 (19.5-20.3)]	9,001 [58.3 (57.8-58.8)]	8,813 [57.1 (56.6-57.6)]
Men	5881, 21.2 (20.8-21.6)	16,152 [58.2 (57.7-58.7)]	13,809 [49.7 (49.2-50.2)]
HIV-1 RNA exam at baseline	p < 0.001	p < 0.001	p < 0.001
No	7,739 [33.5 (33.1-33.9)]	9,372 [40.5 (40.0-41.0)]	3,341 [14.4 (14.1-14.7)]
Yes	1,216, 6.1 (5.9-6.3)	1,5781 [78.6 (78.2-79.0)]	19,281 [96.1 (95.9-96.3)]
CD4+ exam at baseline	p < 0.001	p < 0.001	-
No	7,547 [36.7 (36.2-37.2)]	7,635 [37.1 (36.6-37.6)]	-
Yes	1,408 [6.2 (6.0-6.4)]	17,518 [77.4 (77.0-77.8)]	-
HAART uptake after diagnosis	p < 0.001	-	p < 0.001
Never received HAART	7,564 [41.9 (41.4-42.4)]	-	5,104 [28.3 (27.9-28.7)]
Ever received (or still under) HAART	1,391 [5.6 (5.4-5.8)]	-	17,518 [69.6 (69.2-70.0)]

97%CI: 95% confidence interval; HAART: highly active antiretroviral therapy; MSM: men who have sex with men; PWID: people who inject drugs.

Discussion

Several studies have reported substantial improvement in terms of prognosis and survival for PLWHA in the late post-HAART era, however our results documented auspicious findings vis-à-vis previous analysis. Among all cohorts under analysis, 14.1% had died in consequence of HIV/AIDS and we identified a median survival of 6.29 years. One of the first studies in the post-HAART era in Brazil [40] made evident a median survival of 5 months for cases diagnosed in 1980, of 18 months for those diagnosed in 1995 and of 58 months (4.8 years) for cases diagnosed in 1996.

A study conducted in the Northeast Region of Brazil [41] with 597 individuals diagnosed in 1997-2004, found 1-year, 2-year and 5-year survival rates of 88%, 86% and 82%, respectively, and 75% of the patients actually survived for 5.5 years. In another Brazilian study with 2,091 patients diagnosed in 1998 and 1999 [42] and carried out in the South and Southeast Regions, a survival time of 108 months (9 years) after AIDS diagnosis was documented for over 59% of patients from both regions. For both

Table 2

Clinical and sociodemographic characteristics of all individuals included in the study, for the total (N = 15,420) and according to each exposure category. Rio de Janeiro, Brazil, 2000-2011.

Characteristics	Exposure category n (% among those with known category)		
	MSM	PWID	Heterosexual
Subjects	5,564 (36.1)	498 (3.2)	9,358 (60.7)
Sex			
Male	5,564 (100.0)	364 (73.1)	3,795 (40.6)
Female	-	134 (26.9)	5,561 (59.4)
Ethnicity			
White	2,792 (50.2)	171 (34.3)	3,367 (36.0)
Non-white	1,902 (34.2)	213 (42.8)	4,514 (48.2)
Unspecified	870 (15.6)	114 (22.9)	1,477 (15.8)
Level of education (years)			
Primary (0-7)	2,299 (41.3)	295 (59.2)	5,649 (60.4)
Secondary (8-11)	1,615 (29.0)	86 (17.3)	1,960 (20.9)
Superior/over (12 or more)	1,121 (20.2)	26 (5.2)	719 (7.7)
Unspecified	529 (9.5)	91 (18.3)	1,030 (11.0)
HAART uptake after diagnosis			
Never received HAART	1,976 (35.5)	279 (56.1)	3,598 (38.4)
Ever received (or still under) HAART	3,588 (64.5)	219 (44.0)	5,760 (61.6)
CD4+ exam at baseline			
No	3,055 (54.9)	297 (59.6)	4,262 (45.5)
Yes	2,509 (45.1)	201 (40.4)	5,096 (54.5)
CD4+ lymphocytes (cells/mm^3) *			
Mean (± SD)	331.0 (±242.59)	298.94 (±217.22)	306.79 (±236.64)
Range	1-2,221	1-984	1-2,867
Median (interquartile range)	292 (319)	258 (300)	269 (298.75)
HIV-1 RNA Viral Load exam at baseline			
No	3,286 (59.1)	326 (65.5)	4,846 (51.8)
Yes	2,278 (40.9)	172 (34.5)	4,512 (48.2)
HIV-1 RNA in plasma, $\log_{10}$ copies/ml (first exam available)			
Mean (± SD)	3.60 (±1.43)	3.67 (±1.48)	3.60 (±1.40)
Range	1.70-6,82	1.70-6.04	1.70-6.76
Median (interquartile range)	3.95 (3.14)	4.11 (3.31)	3.87 (3.05)
Deaths for every causes			
No	4,762 (85.6)	338 (67.9)	7,513 (80.3)
Yes	802 (14.4)	160 (32.1)	1,845 (19.7)
AIDS-related deaths **			
No	193 (24.0)	37 (23.1)	410 (22.2)
Yes	609 (76.0)	123 (76.9)	1,435 (77.8)
New AIDS cases through periods			
2000-2003	2,055 (32.9)	234 (3.7)	3,958 (63.4)
2004-2007	1,745 (33.3)	164 (3.1)	3,340 (63.6)
2008-2011	1,764 (45.0)	100 (2.5)	2,060 (52.5)

HAART: highly active antiretroviral therapy; MSM: men who have sex with men; PWID: people who inject drugs; SD: standard deviation.

* New AIDS cases through periods (n);

** n and % from every death causes.

Table 3

Hazard ratios of AIDS-related deaths according to clinical and sociodemographic variables, for all individuals included in the study (N = 15,420). Rio de Janeiro, Brazil, 2000-2011.

Predictor	Unadjusted HR (95%CI)	Adjusted – Cox model HR (95%CI)	Adjusted – frailty model HR (95%CI)
Exposure category			
Heterosexual	1.00	1.00	1.00
MSM	0.77 (0.70-0.85) *	0.85 (0.77-0.93) *	0.89 (0.81-0.98) **
PWID	1.56 (1.30-1.88) *	1.54 (1.28-1.85) *	1.56 (1.30-1.88) *
Age (per year of increase)	1.01 (1.00-1.01) *	1.00 (1.00-1.00)	1.00 (1.00-1.01)
Ethnicity			
White	1.00	1.00	1.00
Non-white	1.45 (1.33-1.58) *	1.41 (1.29-1.54) *	1.33 (1.21-1.45) *
Unspecified	0.04 (0.03-0.06) *	0.02 (0.01-0.03) *	0.02 (0.01-0.03) *
HAART uptake after diagnosis			
Never received HAART	1.00	1.00	1.00
Ever received (or still under) HAART	0.20 (0.18-0.22) *	0.19 (0.17-0.21) *	0.19 (0.17-0.21) *
CD4+ cells count (cells/mm^3) [first exam available]			
< 200	1.00	1.00	1.00
200-349	0.49 (0.40-0.60) *	0.51 (0.42-0.63) *	0.51 (0.42-0.63) *
350-499	0.38 (0.29-0.48) *	0.36 (0.29-0.47) *	0.37 (0.29-0.47) *
> 500	0.23 (0.17-0.31) *	0.23 (0.17-0.31) *	0.23 (0.17-0.32) *
Unspecified	1.83 (1.62-2.07) *	1.16 (1.01-1.32) ***	1.24(1.09-1.43) ***
HIV-1 RNA (log_{10} copies/mL) [first exam]			
< 4.00	1.00	Not included in the model	Not included in the model
4.00-4.99	1.86 (1.52-2.27) *		
> 5.00	2.20 (1.77-2.73) *		
Unspecified	4.05 (3.51-4.67) *		
Education (years)			
Primary (0-7)	1.00	Not included in the model	Not included in the model
Secondary (8-11)	0.59 (0.52-0.66) *		
Superior/over (12 or more)	0.23 (0.17-0.30) *		
Unspecified	1.77 (1.57-1.99) *		
Estimated frailty variance	-	-	0.11 *

95%CI: 95% confidence interval; HAART: highly active antiretroviral therapy; HR: hazard ratio; MSM: men who have sex with men; PWID: people who inject drugs.

* p-value < 0.001;

** p-value < 0.05;

*** p-value < 0.01.

regions, survival was significantly longer for patients under HAART and for those with higher levels of education.

A nationwide Brazilian study conducted with 28,426 patients diagnosed with AIDS between 2000-2006 compared survival between MSM and PWID [12] and identified a median survival of 2.45 years and a chance of survival of 76.2% in 7 years of follow-up. A 2.4-fold higher mortality among PWID than MSM was observed. Our results corroborate those findings, identifying almost 2-fold higher mortality among PWID, when compared to MSM.

In an Italian study with 9,662 PLWHA, carried out in 1999-2005 [43], 1, 2 and 5-year survival corresponded to proportions of 80.6%, 75.2%, and 66.4%, respectively. A study with 910 patients receiving HAART in Haiti [44] in 2003-2008 found an 89% survival at 6 months, 87% at 12 months and 78% at 60

Table 4

Hazard ratios of AIDS-related deaths for different transmission categories: MSM (n = 5,564), PWID (n = 498) and heterosexual (n = 9,358). Rio de Janeiro, Brazil, 2000-2011

Predictor	Exposure category and model					
	MSM		PWID		Heterosexual	
	Cox model HR (95%CI)	Frailty model HR (95%CI)	Cox model HR (95%CI)	Frailty model HR (95%CI)	Cox model HR (95%CI)	Frailty model HR (95%CI)
Age (per year of increase)	0.99 (0.98-1.00)	1.00 (0.99-1.00)	0.99 (0.97-1.01)	0.99 (0.97-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Ethnicity						
White	1.00	1.00	1.00	1.00	1.00	1.00
Non-white	1.54 (1.31-1.81) *	1.42 (1.20-1.67) *	1.84 (1.26-2.69) **	1.97(1.33-2.93) *	1.31 (1.18-1.47) *	1.27 (1.13-1.42) *
Unspecified	0.02 (0.01-0.03) *	0.02 (0.01-0.04) *	***	***	0.02 (0.01-0.03) *	0.02 (0.01-0.03) *
HAART uptake after diagnosis						
Never received	1.00	1.00	1.00	1.00	1.00	1.00
Ever received (or still under)	0.17 (0.14-0.20) *	0.17 (0.14-0.21) *	0.29 (0.17-0.49) *	0.30(0.17-0.50) *	0.20 (0.17-0.23) *	0.20 (0.17-0.22) *
CD4+ cells count (cells/mm^3)						
< 200	1.00	1.00	1.00	1.00	1.00	1.00
200-349	0.47 (0.31-0.71) **	0.46 (0.31-0.70) **	0.68 (0.31-1.50)	0.66 (0.30-1.46)	0.52 (0.41-0.66) *	0.52 (0.41-0.66) *
350-499	0.46 (0.30-0.71) *	0.46 (0.30-0.72) *	0.83 (0.34-2.02)	0.71 (0.27-1.85)	0.31 (0.22-0.42) *	0.31 (0.23-0.43) *
> 500	0.18 (0.10-0.34) **	0.19 (0.10-0.35) *	0.12 (0.02-0.90) #	0.13 (0.02-0.98) #	0.26 (0.18-0.36) *	0.26 (0.18-0.36) *
Unspecified	1.08 (0.83-1.40)	1.17 (0.89-1.52)	1.26 (0.68-2.33)	1.42 (0.75-2.68)	1.22 (1.03-1.43) #	1.28 (1.08-1.50) **
Estimated frailty variance	-	0.12 *	-	0.12	-	0.05 *

95%CI: 95% confidence interval; HAART: highly active antiretroviral therapy; HR: hazard ratio; MSM: men who have sex with men; PWID: people who inject drugs.

* p-value < 0.001;

** p-value < 0.01;

*** Not included since there was no frequency of AIDS-related deaths for unspecified ethnicity (PWID model);

p-value < 0.05 .

months (5 years). An Iranian cohort study [45], with 585 patients diagnosed from 1997 to 2011, found a 1-year and a 5-year survival of 76% and 46%, respectively. Our findings documented a better scenario, with survival above 80% during the entire follow-up.

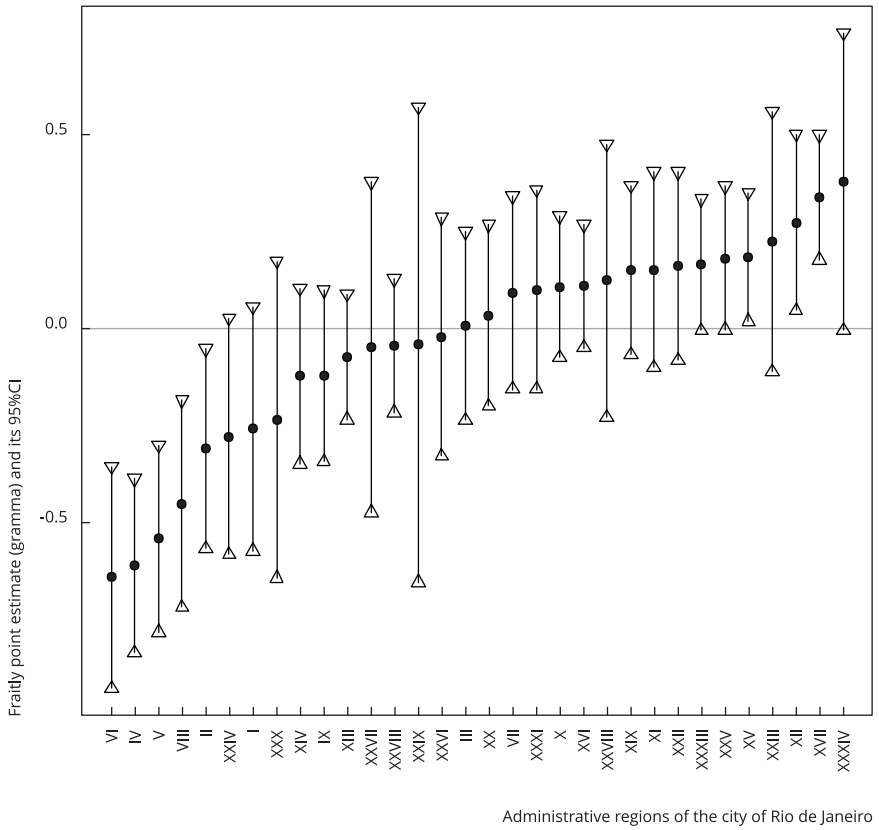
These promising trends may be explained by the substantial improvement of HAART intake in Brazil and, specifically, in Rio de Janeiro during the study period. Our analysis identified that 62% of the population analyzed had received HAART or was under treatment, compared to 28.3% of the population evaluated in a nationwide study conducted in Brazil between 2000-2006 [12]. AIDS-related mortality decreased among heterosexuals from both genders and among MSM, with modest improvements among PWID.

Our findings corroborate previous Brazilian studies that also identified a higher risk of AIDS-related death among non-whites patients [23,46,47] and those with lower education levels [48].

The important prognostic value of high levels of CD4+ at baseline has been documented by several studies. A multicenter cohort study conducted with 24,037 patients treated between 2001-2010 in 4 HIV-clinics from Sub-Saharan Africa [49] reported better survival among people with CD4+ levels higher than 500 cells/μL at baseline. A study with 20,730 patients from 10 HIV-clinics in Uganda [50] also demonstrated that higher baseline CD4+ cell count at HAART initiation increases the likelihood of survival over time.

Figure 1

Frailty point estimate and its 95% confidence interval per Administrative Regions of the city of Rio de Janeiro, for the general model: heterosexual, MSM and PWID.



95%CI: 95% confidence intervals; MSM: men who have sex with men; PWID: people who inject drugs.
Note: I: Portuária; II: Centro; III: Rio Comprido; IV: Botafogo; V: Copacabana; VI: Lagoa; VII: São Cristóvão; VIII: Tijuca; IX: Vila Isabel; X: Ramos; XI: Penha; XII: Inhaúma; XIII: Méier; XIV: Irajá; XV: Madureira; XVI: Jacarepaguá; XVII: Bangu; XVIII: Campo Grande; XIX: Santa Cruz; XX: Ilha do Governador; XXI: Paquetá; XXII: Anchieta; XXIII: Santa Teresa; XXIV: Barra da Tijuca; XXV: Pavuna; XXVI: Guaratiba; XXVII: Rocinha; XXVIII: Jacarezinho; XXIX: Complexo do Alemão; XXX: Complexo da Maré; XXXI: Vigário Geral; XXXII: Realengo; XXXIII: Cidade de Deus.

In Brazil, late entry into HIV treatment has also been consistently associated with increased mortality risk [48,51]. Corroborating those studies, our results identified HAART uptake and CD4+ > 500 at baseline as key predictors for improved survival, with protective effects of 81% and 77%, respectively.

Although the variance of the frailty effect was similar for both MSM and PWID (0.12), it was not significant among the latter, probably because of the small size of this group. PWID tend to live in underserved areas and many of them have unstable residence or are homeless. Mobility and lack of a stable residence usually precluded/compromised affiliation to local health programs and services, which have an essential role in the Brazilian public health system [52].

Despite the relevance of our study and its findings, comprising a large number of AIDS cases from Rio de Janeiro city over a 12-year follow-up period, including clinical, laboratory and epidemiological data, this study has important limitations that need to be acknowledged. Those limitations are mostly related to the data sources used. A key problem might be the possibility that, due to AIDS-cases underreporting, SINAN failed to include a proportion of HIV-infected individuals. In an attempt to

minimize the limitations resulting from underreporting, we used several datasets, which allowed us to retrieve a variety of clinical, laboratory and socio-demographic information.

Different kinds of information is collected by each dataset. For instance, upper- and middle-class patients may have had their exams reimbursed by private health insurance and prefer to have their exams performed in private laboratories (and therefore their data might not be available on SISCEL dataset), whereas the most marginalized and stigmatized segments might never access HIV-related treatment and care, being identified as "AIDS-case" only after AIDS-related death (and therefore identified only on the mortality dataset, SIM). Regardless of where medical care is received, all PLWHA receive their antiretroviral drugs through SUS, the single accredited source of ART in Brazil (which are not sold in pharmacies or drugstores); hence, all patients under HAART should be registered in the SICLOM database. Linkage is nowadays a key procedure in the analysis of Brazil's AIDS databases, a strategy that allows a better and more efficient utilization of available data.

If new AIDS cases were exclusively tracked with the help of SINAN-AIDS (AIDS cases database), this would generate spurious conclusions, pointing to a putative drastic reduction in the number of AIDS cases in recent years. What is happening, in fact, is a gradual increase in reports which are exclusively available at other databases, whose primary purpose is not epidemiological surveillance, but rather the ongoing assessment of laboratory exams and the delivery of medicine. Information about day-to-day logistics of medicines procurement, prescription and delivery of medicines, as well as the routine of laboratory exams, do not exist in most countries as nationwide databases. From this point of view, the Brazilian effort is commendable. On the other hand, such databases should not replace surveillance systems, as has been occurring in Brazil, with adverse consequences for both surveillance itself and the monitoring of routine procedures.

In order to evaluate a possible effect of selection bias, we analyzed the characteristics of 27,779 patients who didn't have information about their exposure category and were not included in our survival analysis. These patients had similar characteristics to the 15,420 patients herein analyzed in terms of sex, age, ethnicity, and education levels (data not shown).

It is important to highlight that the criteria for antiretroviral therapy prescription underwent changes throughout the study period, and the initial criteria differed from the current ones. Therefore, it is possible that some of the patients living with HIV did not receive HAART because they did not meet the valid criteria for initiation of therapy at the time of their diagnosis. However, over time, not only were these criteria progressively updated, but several patients progressed to compatible clinical conditions with these successive criteria. This is a universal limitation, considering that is not possible to explore these complex interactions unless we have a database that could record the successive "status" of each individual and the successive changes of criteria, as well as the advent of new drugs and new therapeutic regimens.

Despite the aforementioned limitations, our results add to existing evidence and could guide better local strategies targeting PLWHA in Rio de Janeiro. It should also be highlighted here the importance of the Brazilian HIV/AIDS response and the broad availability of national and local dataset that provides clinical, laboratory and socio-demographic information of all patients under treatment and care at public health care facilities.

Conclusions

Some important inequalities persist in access to treatment, resulting in disparate impacts on mortality among exposure categories. PWID, non-whites and people without at least the first CD4+ exam registered at baseline had higher AIDS-related mortality. HAART early intake presented a key protective effect and allowed us to highlight the urgent need to address the issue of late entry into HIV care in the local and national levels.

Despite these persistent disparities, mortality decreased significantly during the period for all categories under analysis, and the overall positive impact of HAART on survival has been dramatic.

Contributors

T. A. Lima participated in the definition of the methodological design, literature review, probabilistic linkage, data processing and analysis, discussion of the results, elaboration of the article, and final version. C. Beyrer contributed to the discussion of the results and revision of the final version. J. E. Golub contributed to the discussion of the results and revision of the final version. J. C. Mota participated in the probabilistic linkage, data processing, discussion of the results and revision of the final version. M. S. Malta contributed to the discussion of the results, the revision of the final version, and is the project coordinator. C. M. F. P. Silva contributed to the discussion of the results and revision of the final version. F. I. Bastos participated in the definition of the methodological design, discussion of the results, and revision of the final version.

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Resumo

Apesar de uma melhora substancial no prognóstico e na qualidade de vida de pessoas vivendo com HIV/aids (PVHA) no Brasil, permanecem desigualdades no acesso ao tratamento. Avaliamos o impacto dessas desigualdades na sobrevida na cidade do Rio de Janeiro ao longo de 12 anos (2000/11). Os dados foram consolidados a partir de quatro bases que constituem o sistema nacional de monitoramento da aids: SINAN-aids (Sistema de Informação de Agravos de Notificação; casos de aids), SISCEL (exames laboratoriais), SICLOM (controle logístico de medicamentos) e SIM (Sistema de Informações sobre Mortalidade), usando relacionamento probabilístico. As regressões de Cox foram ajustadas para avaliar o impacto da HAART (terapia antirretroviral altivamente ativa) na mortalidade relacionada à aids entre homens que fazem sexo com homens (HSH), usuários de drogas injetáveis (UDI) e heterossexuais diagnosticados com aids entre 2000 e 2011 na cidade do Rio de Janeiro. Dos 15.420 casos, 60,7% eram heterossexuais, 36,1% HSH e 3,2% UDI. Houve 2.807 óbitos (18,2%) e a sobrevida mediana foi 6,29 anos. Houve associação significativa entre HAART e contagem de CD4+ > 200 na linha de base e importantes efeitos protetores. Comparados aos brancos, os não-brancos tiveram um risco 33% maior de morrer de aids. Os UDI tiveram um risco 56% maior, enquanto HSH tiveram um risco 11% menor de morrer de aids, comparados aos heterossexuais. Os indivíduos não-brancos, aqueles com menos de oito anos de escolaridade e UDI mostraram probabilidade mais alta de não receber HAART e de morrer de aids. No Rio de Janeiro, persistem desigualdades importantes no acesso ao tratamento, que resultam em impactos diferenciados na mortalidade de acordo com as categorias de exposição. Apesar da persistência dessas disparidades, a mortalidade diminuiu significativamente ao longo do período em todas as categorias analisadas, e o acesso à HAART teve impacto dramático no tempo de sobrevida.

Síndrome de Imunideficiência Adquirida; Análisis de Sobrevida; Mortalidade Diferencial; Iniquidade Social; Terapia Antirretoviral de Alta Atividade

Resumen

Pese a la mejora sustancial en el pronóstico y calidad de vida entre las personas que viven con VIH/SIDA (PLWHA) en Brasil, persisten las desigualdades en el acceso al tratamiento. Evaluamos el impacto de estas desigualdades en la supervivencia en Río de Janeiro, durante un período de 12 años (2000/11). Los datos fueron recabados de cuatros bases de datos que comprenden el sistema nacional de monitoreo del SIDA: SINAN-SIDA (Sistema de Información de Agravios de Notificación; casos de SIDA), SISCEL (pruebas de laboratorio), SICLOM (sistema dispensador electrónico), y SIM (Sistema de Información sobre la Mortalidad), usando una vinculación probabilística. Las regresiones de Cox fueron usadas para evaluar el impacto de la TARGA (terapia antirretroviral de gran actividad) en la mortalidad relacionada con el SIDA, entre hombres que tienen sexo con hombres (HSH), individuos que se inyectan drogas por vía intravenosa (PWID por sus siglas en inglés), y heterosexuales diagnosticados con SIDA, entre 2000 y 2011, en la ciudad de Río de Janeiro, RJ, Brasil. Entre 15.420 casos, un 60,7% eran heterosexuales, un 36,1% HSH y un 3,2% PWID. Hubo 2.807 (18.2%) muertes y el tiempo medio de supervivencia fue 6,29. TARGA y CD4+ > 200 en la base de referencia estuvieron asociados con efectos importantes de protección. Los no-blancos tuvieron un riesgo un 33% mayor de morir a consecuencia de SIDA que los blancos. Los PWID tuvieron un riesgo un 56% mayor, y los HSH un riesgo un 11% menor, de morir de SIDA que los heterosexuales. Los no-blancos, con menos de ocho años de educación formal, y los PWID, eran más propensos a morir de SIDA y menos a recibir TARGA. Existen importantes inequidades en el acceso al tratamiento, resultando en efectos dispares en la mortalidad entre las diferentes categorías exposición. A pesar de estas persistentes disparidades, la mortalidad decreció significativamente durante el periodo para todas las categorías bajo análisis, y el impacto general positivo del TARGA en la supervivencia había sido importantísimo.

Síndrome de Inmunodeficiência Adquirida; Análisis de Supervivencia; Mortalidad Diferencial; Iniquidad Social; Terapia Antirretroviral Altamente Activa

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