ORIGINAL ARTICLE / *ARTIGO ORIGINAL*

Mortality profiles among people living with HIV/AIDS: comparison between Rio de Janeiro and other federative units between 1999 and 2015

Perfis de mortalidade em pessoas vivendo com HIV/aids: comparação entre o Rio de Janeiro e as demais unidades da federação entre 1999 e 2015

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ABSTRACT: *Introduction:* The trend toward stabilization regarding the AIDS epidemic in Brazil over the past decade hides a very complex scenario, where two-thirds of the Brazilian federative units exhibit AIDS standardized mortality rates (ASMR) significantly above the national average and/or in upward tendency. ASMR in Rio de Janeiro State remains virtually unchanged over the years; the state currently occupies the second position in the national ranking of this indicator. *Objective:* To assess temporal trends in causes of death searching for differential profiles that could be useful for understanding mortality among patients with HIV in the state. *Methodology:* Causes of death were analyzed in any field of the death certificates from the Mortality Information System between 1999 and 2015 for individuals ≥ 15 years of age. Cardiovascular diseases, non-AIDS-related cancers, external causes, diabetes mellitus, and tuberculosis were established by the mention or not of their codes according to the 10th edition of International Statistical Classification of Diseases and Related Health Problems (ICD-10) in death certificates. Generalized linear mixed-effects models were used to describe odds ratios in relation to 1999 and adjusted mean annual variations. *Results:* The results point to the emerging role of external causes and genitourinary diseases and the persistent role played by tuberculosis, differentially affecting AIDS mortality in the state, in a scenario of high mortality due to infectious diseases. *Conclusion:* These data suggest that tuberculosis remains a major cause of death among people living with HIV/AIDS (PLWHA) in Rio de Janeiro, highlighting the need for studies that identify individual-level factors impacting their survival, thus improving local HIV/AIDS control measures.

Keywords: Acquired immunodeficiency syndrome. Mortality. Tuberculosis. Time series studies.

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RESUMO: *Introdução:* A aparente estabilidade da mortalidade por aids no país na última década encobre uma gama de cenários, com dois terços dos estados apresentando taxa padronizada de mortalidade por aids (TPMA) significativamente acima da média nacional e/ou em tendência ascendente. No Rio de Janeiro, a TPMA vem mantendo-se alta e estável ao longo dos anos; atualmente o estado ocupa a segunda posição no *ranking* nacional desse indicador. *Objetivo:* Examinar tendências temporais em causas de óbito na busca de padrões diferenciais que contribuam para o entendimento da mortalidade por aids no estado. *Metodologia:* Foram analisadas causas de óbito em qualquer campo das declarações de óbito constantes do Sistema de Informação sobre Mortalidade (SIM) entre 1999 e 2015 para indivíduos ≥ 15 anos. Doenças cardiovasculares, malignidades não relacionadas à aids, causas externas, diabetes melito e tuberculose foram estabelecidas pela menção ou não de seus códigos conforme a Classificação Estatística Internacional de Doenças e Problemas Relacionados com a Saúde (CID-10) nas declarações de óbito. Modelos lineares generalizados com efeitos mistos foram usados para descrever *odds ratios* relativas a 1999 e variações anuais médias ajustadas. *Resultados:* Verificaram-se o aumento proporcional em causas externas e doenças geniturinárias e, sobretudo, o persistente papel desempenhado pela tuberculose, impactando diferencialmente a mortalidade por aids no estado, em um cenário de alta mortalidade por doenças infecciosas. *Conclusão:* Os achados reforçam a manutenção da tuberculose na mortalidade de pessoas vivendo com HIV/aids (PVHA) no Rio de Janeiro e chamam a atenção para a necessidade de avaliar determinantes individuais atuando na redução da sobrevida desses pacientes, de forma a aprimorar o programa de controle do HIV/aids no estado.

Palavras-chave: Síndrome de imunodeficiência adquirida. Mortalidade. Tuberculose. Estudos de séries temporais.

INTRODUCTION

Globally, the morbimortality profile of people living with HIV/AIDS (PLWHA) has been changing in the combination antiretroviral therapy (cART) era, as a consequence of the decreasing incidence of AIDS-associated events and increased survival of these patients[1,2].

Brazil was the first developing country to provide universal and free cART, offering first-line antiretroviral drugs to all eligible PLWHA since 1996[3]. Given its magnitude, it was expected that the initiative would provide the country with benefits comparable to those found in developed regions[4].

Despite the success initially achieved, the Brazilian initiative has shown increasing signs of exhaustion, especially in the context of inequality in the implementation of HIV-response as a whole[5]. As a result, AIDS mortality in the country has tended to stabilize, as evidenced by virtually unchanged AIDS standardized mortality rates (ASMR) since 2007[6]. Additionally, this scenario of national stability conceals a complex epidemiological situation, in which all of the country's macro-regions present an increase in ASMR, except the Southeast[7,8].

At present, two-thirds of the federative units display ASMR above the national average or at upward trend, despite the national expansion of antiretroviral coverage[6]. These regional

and even local distinctions pose additional challenges to control policies regarding the homogeneity of the reduction in AIDS mortality among the different federative units[9].

Changes in mortality profile among PLWHA in Brazil were first reported by our group, characterized by the emergence of diabetes mellitus and cardiovascular disease as causes of death in this subpopulation in contrast to the general population[10]. More recently, we restated and expanded these results by highlighting the proportional increase in cancers not related to HIV/AIDS and external causes, as well as the persistence of tuberculosis in PLWHA mortality in the country[11].

Rio de Janeiro, consonant with the entire country, has been showing a reduction in the proportion of deaths related to HIV/AIDS and a consequent increase in the participation of chronic conditions and external causes in mortality among PLWHA[12]. However, ASMR in the state remains considerably above the averages calculated for the country and the Southeast Region since 2004[13]. In 2015, ASMR in the state was 8.7/100 thousand inhabitants, largely outnumbering the national average, estimated at 5.6/100 thousand inhabitants, occupying the second place in the national ranking, together with Amazonas State[8].

Examining the temporal trends in the proportions of causes of death related and not related to HIV/AIDS among PLWHA in Rio de Janeiro and comparing these findings with those found for other federative units may reveal differential patterns that contribute to the understanding of maintaining high rates of AIDS mortality in the state.

The present work aimed to analyze the death profile among PLWHA in Rio de Janeiro in contrast to those verified for the other federative units in the context of their ASMR between 1999 and 2015.

METHODOLOGY

DATA SOURCES AND INCLUSION CRITERIA

Data were obtained from the Mortality Information System (*Sistema de Informações sobre Mortalidade* – SIM). All death certificates (DC) issued between 1999 and 2015 to individuals ³ 15 years old were included, as previously proposed[14].

DATA TABULATION

Files were obtained in DBC format and later converted to CSV format using TabWin. Codes for causes of death according to the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) were extracted from DC with the aid of a Python algorithm. Tabulated variables included the number of DC, sociodemographic characteristics (date of birth, ethnic group, gender, education, place of birth,

and marital status), information on death (date, federative unit [*Unidade Federada* – UF] of death registration and ICD-10 codes).

OUTCOMES OF INTEREST

Outcomes of interest were defined according to whether or not their corresponding ICD-10 codes were mentioned in any field of DC: cardiovascular diseases (CVD), non-HIV/ AIDS-related cancers (CA), external causes (EC), diabetes mellitus (DM), genitourinary diseases (GEN), and tuberculosis (TB) (Figure 1).

STATISTICAL ANALYSES

Crude and standardized mortality rates were calculated by UF and by region. Deaths were defined as the mention of the conditions of interest in any field of DC. Age standardization was performed using the reference population of the World Health Organization (WHO).

UFs were categorized according to their AIDS standardized mortality rates (ASMR) trends, calculated as the average annual variation obtained by Poisson models and generalized additive models. Such grouping was adopted given the great intra-regional heterogeneity of AIDS mortality[7,8] and the low number of cases presented by some states.

Outcome/Group	ICD–10 Code	Comments
HIV/AIDS group	B20–B24, Z21	Certain codes (e.g., Z11.4) are outside the scope of the analysis.
Non-HIV/AIDS Cancers (CA)	C00 – C96 (except C46 and C81 – C96)	Kaposi's sarcoma, primary brain lymphoma, and immunoblastic lymphoma excluded.
External causes (EC)	S00 – Y98	Included deaths from violence, poisoning, and drug abuse.
Cardiovascular Diseases (CVD)	I00 – I99 (except I46)	Cardiac arrest excluded.
Diabetes mellitus (DM)	E10 – E14	-
Tuberculosis (TB)	A15 – A19, B20.0	-
Genitourinary diseases (GEN)	N00 – N99	-

HIV: human immunodeficiency virus.

Figure 1. Definition of outcomes and study groups with respective codes of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)

Trends for a selected group of death causes were assessed for individuals who had B20-B24 codes mentioned in the DC (HIV group; Figure 1). On the other hand, the non-HIV group was composed of individuals whose DC did not mention such codes. The age ranges adopted were 15–29, 30–39, 40–49, 50–59, ≥ 60 years old and unknown, according to the cutoff presented in the WHO reference population. The covariates of interest were HIV/AIDS status, calendar year and region. Age and gender were used to control confounding.

Generalized linear mixed models (GLMM) were adjusted as previously described[10,11]. Briefly, the year of death was treated either as a continuous or a categorical variable. In the first case, linear trends were described as the average per year variation, while in the second, odds ratios (OR) were used to compare the annual variation in relation to 1999.

The difference between the slopes of the lines for the HIV and non-HIV groups was represented by Δ; its statistical significance, which indicates differential accelerations or decelerations, was assessed by means of an interaction term between the HIV/AIDS and calendar year variables. To assess whether Δ presented distinctions between regions, an interaction term was inserted between the HIV/AIDS status, calendar year and region variables.

All analyses were performed in the R software environment for Windows version 3.3.1, by means of the packages *lme4* for estimation of mixed models and *epiTools* for standardized mortality rates calculation. The project was approved by the Research Ethics Committee of the *Escola Nacional de Saúde Pública Sérgio Arouca* under number 1.172.797.

RESULTS

ASMR remained virtually unchanged between 1999 and 2015 in both the country and Rio de Janeiro, with adjusted average annual variations of -0.7 and -0.9%, respectively. Similar trends were observed for Santa Catarina, Mato Grosso do Sul, Distrito Federal, Mato Grosso, Minas Gerais, Acre, and Roraima (stable region – STB). Rondônia, Amazonas, Pará, Amapá, Tocantins, Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraiba, Pernambuco, Alagoas, Bahia, Sergipe, Espírito Santo, Paraná, Rio Grande do Sul, and Goiás presented an upward trend in AIDS mortality (ascending region – ASC), while only São Paulo showed a clearly decreasing trend in AIDS mortality.

Mean adjusted annual variations of ASMR did not differ when the analyses included proportional redistribution of deaths with ill-defined causes (codes R00-R99) considering all causes of death.

The temporal evolution of EC among PLWHA in Rio de Janeiro has been occurring indistinctly to the process verified for STB and São Paulo; on the other hand, the trend observed for the state differed significantly from that observed for the region with ascending ASMR (p <0.001; Table 1 and Figure 2). Similarly, the trend of GEN mortality among PLWHA in Rio de Janeiro differed from the trend observed for the set of upward ASMR states, which

presented a significantly higher differential adjusted mean annual variation when compared to Rio de Janeiro (3 against 1%, respectively, p <0.05; Table 1).

Table 1. Mean adjusted annual variations for mentioning different outcomes in death certificates categorized by region between 1999 and 2015.

		OR		p*	Δ	p**
		HIV	non-HIV	year:HIV		year:HIV:region
EC	RJ	1.08	1.01	< 0.001	0.07	
	SP	1.08	0.99	< 0.001	0.09	> 0.05
	ASC	1.02	1.04	> 0.05	-0.02	< 0.001
	STB	1.08	1.02	< 0.001	0.06	> 0.05
GEN	RJ	1.06	1.05	> 0.05	0.01	
	SP	1.05	1.03	< 0.05	0.02	> 0.05
	ASC	1.07	1.04	< 0.001	0.03	< 0.05
	STB	1.06	1.03	< 0.001	0.03	> 0.05
CVD	RJ	1.03	1.01	< 0.01	0.02	
	SP	1.03	1.01	< 0.01	0.02	> 0.05
	ASC	1.02	1.01	< 0.01	0.01	> 0.05
	STB	1.02	1.00	< 0.001	0.02	> 0.05
CA	RJ	1.03	1.01	> 0.05	0.02	
	SP	1.06	1.02	< 0.001	0.04	> 0.05
	ASC	1.04	1.02	< 0.001	0.02	> 0.05
	STB	1.05	1.01	< 0.001	0.04	> 0.05
DM	RJ	1.03	1.01	> 0.05	0.02	
	SP	1.01	1.01	> 0.05	0.00	> 0.05
	ASC	1.03	1.03	> 0.05	0.00	> 0.05
	STB	1.03	1.02	> 0.05	0.01	> 0.05
TB	RJ	1.03	0.99	< 0.001	0.04	
	SP	0.96	0.96	> 0.05	0.00	< 0.001
	ASC	1.01	0.97	< 0.001	0.04	> 0.05
	STB	1.01	0.96	< 0.001	0.05	> 0.05

EC: external causes; GEN: genitourinary diseases; CVD: cardiovascular diseases; CA: cancers not associated with human immunodeficiency virus (HIV)/AIDS; DM: diabetes mellitus; TB: tuberculosis; ASC: federative units with ascending AIDS standardized mortality rate; STB: federative units with stable AIDS standardized mortality rate; *p-value compared to Rio de Janeiro; **p-value for the difference between Δ.
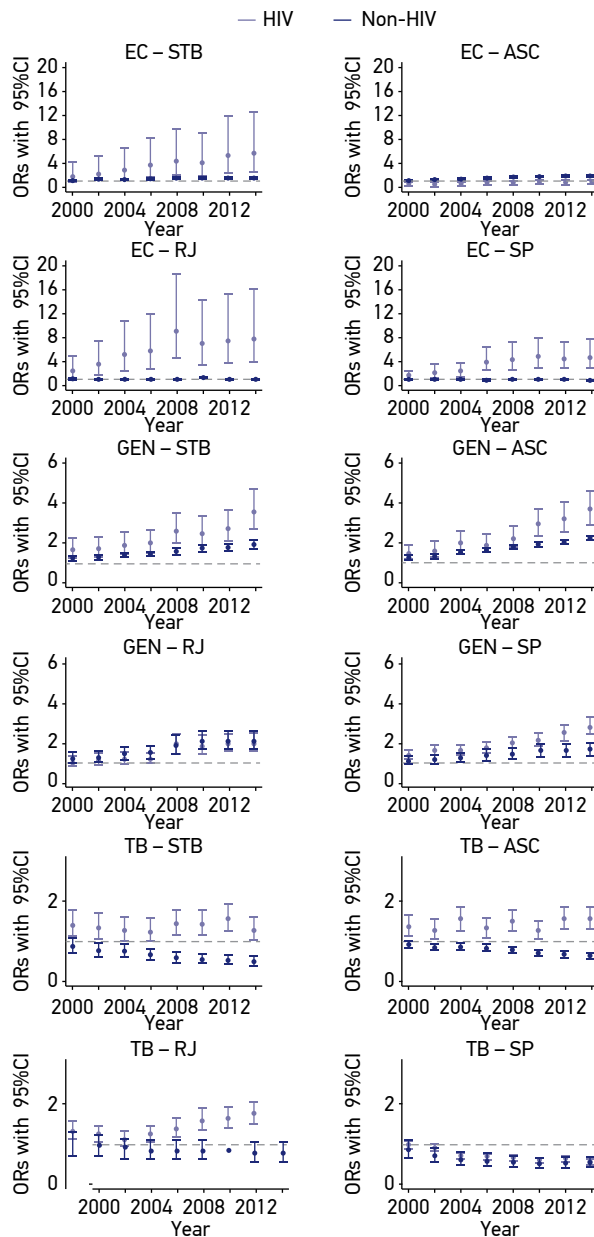
EC: external causes; GEN: genitourinary diseases; CVD: cardiovascular diseases; DM: diabetes mellitus;
TB: tuberculosis; ASC: federative units with ascending AIDS standardized mortality rate;
STB: federative units with stable AIDS standardized mortality rate.

Figure 2. Odds ratios (OR) and 95% confidence intervals (95%CI) comparing the chance of mentioning external causes, genitourinary diseases, and tuberculosis in death certificates over the years among different regions. Year as categorical variable; 1999 used as a reference.

As for CVD, CA and DM, Δ did not show significant differences among regions, indicating the occurrence of similar temporal profiles for these conditions (Table 1).

The HIV group in Rio de Janeiro presented the highest adjusted annual mean variation for the mention of TB among those analyzed (3% compared to -4, 1, and 1% for São Paulo, ASC and STB, respectively). On the other hand, TB in the non-HIV group in Rio de Janeiro presented the lowest annual reduction (-1%) compared to -4, -3, and -4%, respectively for São Paulo, ASC and STB. The Δ reached statistical significance only when Rio de Janeiro was contrasted with São Paulo (p <0.001; Table 1).

Lastly, the analysis of mortality rates according to the ICD-10 clusters revealed that HIV/AIDS-related diseases still constitute the leading cause of death among PLWHA in all regions considered (Figure 3).

Mortality in PLWHA by ICD-10 Blocks
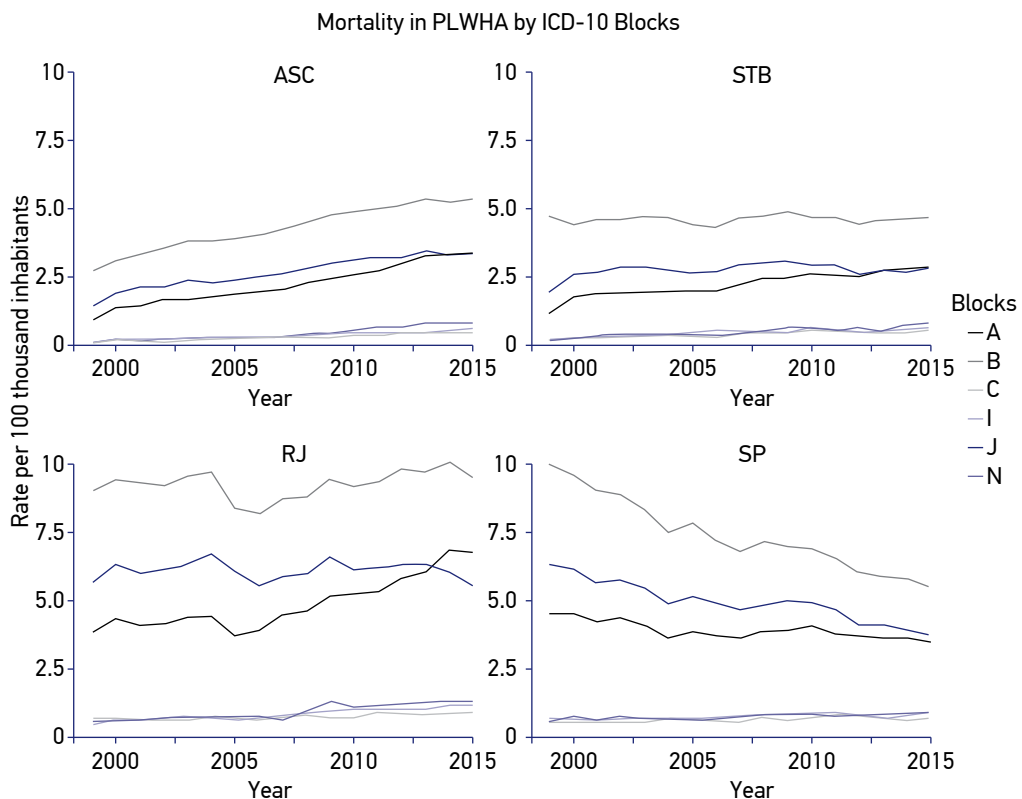
ICD-10 Blocks: A: infectious parasitic diseases I (A00 – A99); B: infectious parasitic diseases II (B00 – B99); C: Cancers (C00 – C97); I: circulatory system diseases (I00 – I98); J: respiratory system diseases (J00 – J99); N: genitourinary system diseases (N00 – N99); ASC: federative units with ascending AIDS standardized mortality rate; STB: federative units with stable AIDS standardized mortality rate.

Figure 3. Mortality rates of people living with HIV/AIDS (PLWHA) per groups of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) between 1999 and 2015.

DISCUSSION

Results show the proportional increase of external causes and genitourinary diseases and, mainly, the persistent role played by TB as a cause of death, affecting differentially on AIDS mortality in Rio de Janeiro, which has been unacceptably above the national average. Interestingly, São Paulo has shown a sustained decline in TB and AIDS mortality rates over time, indicating that the state is in a far more favorable situation than Rio de Janeiro in terms of controlling both epidemics.

Despite the substantial decrease in the incidence of opportunistic diseases that followed the implementation of cART in different economic contexts globally[16], infections are still the leading cause of mortality among PLWHA in Brazil[17]. Accordingly, the analysis of the specific components of mortality confirms the protagonism of infectious diseases among PLWHA in the country.

We recently described TB maintenance as a cause of mortality among PLWHA nationwide[11]. This infection remains one of the most important causes of death among PLWHA across the globe, especially in developing regions[18], having a major impact on the survival of patients with HIV in Brazil as a whole[19] and even more notably in Rio de Janeiro[20].

Presented data show that the persistence of TB in PLWHA in Rio de Janeiro is similar to what has been demonstrated collectively in the states showing an increase in AIDS mortality. Importantly, the average annual reduction in TB among the general population of Rio de Janeiro was lower than in other regions, showing that this cause of death remains virtually unchanged in the population throughout the state.

In accordance with phenomenon described herein, the analysis of a PLWHA cohort in Rio de Janeiro evidenced that at least 10% of newly diagnosed AIDS patients presented for HIV care with active TB, thus not taking advantage from preventive therapy with isoniazid, which has been shown to reduce the risk of TB isolated or in combination with death among HIV-infected patients with access to cART[21].

Reporting of infections and invasive bacterial diseases as the immediate cause of death in almost half of TB/HIV co-infected patients in Rio de Janeiro[22] suggests that these individuals could benefit from measures such as increased anti-pneumococcal immunization and the use of cotrimoxazole, as well as actions aimed primarily at TB control, such as improved screening with skin testing and preventive therapy.

The proportional increase described for GEN among PLWHA that we described complies with previous national research, in which this trend was attributed to the higher frequency of renal failure among HIV-infected individuals in contrast to the general population[14]. Here, the differential increase of GEN among PLWHA in Rio de Janeiro was evidenced, although this finding does not contribute to the understanding of the high AIDS mortality in the state due to the low rate at which these conditions occur. The same is true regarding external causes.

Possible bottlenecks for reducing AIDS mortality in Rio de Janeiro include late presentation to clinical care for HIV - largely attributed to delayed diagnosis of infection and

associated with increased risk of clinical events and progression to death, as well as reduction in the effectiveness of cART[23].

Although at a frequency comparable to that described for developed regions, 54% of participants in a PLWHA cohort in Rio de Janeiro presented for clinical care with a CD4 count < 350 cells/mm3, that is, with immediate recommendation to start antiretroviral therapy[24].

Although the proportion of late presentation in Rio de Janeiro does not differ from that observed nationwide[25], this picture is particularly worrying in the state, a large urban center marked by the fragmented and inefficient structure of its health system, which clearly reduces the capacity of its public health system to diagnose, treat and retain these patients in clinical care for HIV[24].

In this context, the fragmentation of the public health system and the overburden on specialized services found in Rio de Janeiro[26] pose limitations to HIV testing, the prompt linkage of infected people to health services and their retention in continuous care, critical steps for optimization of the benefits of antiretroviral therapy and the mitigation of AIDS mortality.

Another relevant aspect regarding the issue of AIDS mortality in Rio de Janeiro, as evidenced in its capital city, is the growing proportion of patients whose HIV diagnosis is made in urgent and emergency care systems, many of whom are already showing pronounced immunodeficiency and evolving to death without prior testing[27].

Although the proportion of deaths with ill-defined causes has been declining in the country, its value remains relatively high in most states[28]. As a result, complementary analyzes were performed by redistributing these deaths, aiming to minimize their potential impact on the ASMR; however, the variations obtained were only marginal. GLMM was chosen to be used in the analysis, adopting the states with random effects to account for any sources of variability at this level.

One of the positive aspects of the study is the evaluation of all DC issued in the national territory over a period of 15 years, which made it possible to contrast the temporal trends in causes of death for individuals with HIV/AIDS codes to those verified for individuals without such mention, as well as to compare the profiles obtained for the different Brazilian states.

Limitations of the study include the potential underweighting of the HIV/AIDS group, since B20-B24 codes are not reported in at least 25% of DC issued to HIV-infected patients, as noted among participants in two large urban cohorts of PVHA[29]. Other limitations include the low accuracy of DC and the influence of unrecognized confounding variables typical of population-based studies.

The findings described here need to be consolidated by approaches at individual level, examining potential factors that differentially impact the survival of these patients, in order to substantiate public policies aimed at addressing the HIV/AIDS epidemic in the state.

In conclusion, TB persistence and high infectious disease mortality rates play a central role in AIDS mortality in Rio de Janeiro and may reflect delays in identifying HIV infection and/or presenting for care and treatment. The strategy of testing and treatment seems

to be insufficient by bumping into clear gaps such as the fragility of the public health system, highlighting the need for structural changes to deal more effectively with the epidemic in the state.

CONCLUSION

GEN, EC and especially TB have been differentially affecting the survival of HIV patients in Rio de Janeiro in a scenario of high occurrence of infectious diseases, a finding that supports the need to improve control measures specific to the HIV/AIDS epidemic, in parallel with the restructuring of the public health system in Rio de Janeiro.

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