

Tuberculosis as primary cause of death among AIDS cases in Rio de Janeiro, Brazil

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SUMMARY

SETTING: Data from the mortality database, Rio de Janeiro City (RJC) Health Department, Rio de Janeiro, Brazil.

OBJECTIVES: To determine the role played by tuberculosis (TB) in Brazil's human immunodeficiency virus (HIV) positive population, we investigated the frequency of TB as the primary cause of death among HIV-positive subjects in RJC.

DESIGN: Information about acquired immune-deficiency syndrome (AIDS) deaths from 1996 to 2005 in individuals aged >12 years was obtained from the Mortality Information System (SIM), and the cause of death was classified according to the International Classification of Diseases (ICD-10), through primary causes coded in Chapter I—B20 to B24 (HIV disease).

RESULTS: There were 8601 AIDS-related deaths in RJC between 1996 and 2005. TB was the primary cause of death in 9.0% of all AIDS-related deaths, while *Pneumocystis carinii* pneumonia (PCP) accounted for 4.7%. TB cases erroneously classified under other infectious diseases may have contributed to an underestimation of the number of TB deaths among HIV-positive patients.

CONCLUSION: Our study showed that TB is the leading cause of AIDS-related deaths and is responsible for twice as many deaths as PCP, in a scenario of free access to antiretrovirals. The potential benefits of TB preventive treatment and of the availability of highly active antiretroviral treatment could not be established by this analysis.

KEY WORDS: tuberculosis; HIV; co-infection; mortality; antiretroviral

THE TUBERCULOSIS (TB) epidemic is fueled worldwide by human immunodeficiency virus (HIV) infection, and HIV poses the greatest threat to TB control.¹ The World Health Organization (WHO) estimated that there were 8.9 million new cases of TB in 2005. Of these, 741 000 were among HIV-infected adults. TB may have caused 1.7 million deaths in 2004 and 248 000 in TB-HIV co-infected individuals.² The Joint United Nations Program on HIV/AIDS (acquired immune-deficiency syndrome) estimated that 2.9 million AIDS deaths would occur in 2006, 65 000 of which in Latin America.³

Brazil has an estimated 600 000 HIV-infected individuals aged between 15 and 49 years.⁴ According to the Brazilian Ministry of Health, 85 000 new TB cases occur annually, causing 6000 deaths.⁵

AIDS-related mortality decreased in Rio de Janeiro City (RJC) in the 2 years following the introduction (in 1997) of highly-active antiretroviral treatment (HAART), which is widely available free of charge. Since 1999, AIDS-related mortality has been stable.⁶ More than 26 000 AIDS cases have been reported since

the beginning of the epidemic,⁷ and approximately 8000 TB cases are reported annually.⁸ Among TB patients seeking care in primary health units in RJC, one study showed that approximately 10% were infected with HIV.⁹

To determine the role played by TB among Brazil's HIV-positive population, we investigated the frequency of TB as the primary cause of death among HIV-positive subjects in RJC. We also looked at the use of HAART by co-infected patients, aiming to use that as a proxy of access to care and to assess relationships between HAART and survival.

METHODS

Information about AIDS deaths in individuals aged >12 years was obtained from the Mortality Information System (SIM); causes of death were classified according to the International Classification of Diseases (ICD-10),¹⁰ through primary causes coded in Chapter I—B20 to B24 (HIV disease), from 1996 to 2005.

The mortality database is standardized; the infor-

Table 1 Total number of deaths and proportional distribution of primary cause of death in AIDS cases, Rio de Janeiro, Brazil, 1996–2005

Year	Deaths <i>n</i>	TB (B20.0) %	PCP (B20.6) %	Other infectious diseases (B20, except for B20.0 and B20.6) %	Malignant neoplasms (B21) %	Specified diseases (B22) e.g., HIV, dementia, wasting, etc.	Other conditions (B23) %	Unspecified diseases (B24) %
1996	1388	11.1	5.8	37.5	3.8	5.1	5.5	31.1
1997	1078	8.7	4.4	44.3	3.3	6.3	1.2	31.7
1998	900	8.1	5.3	47.6	2.9	9.6	0.3	26.2
1999	743	8.0	5.2	54.5	3.7	11.4	0.8	16.5
2000	782	9.3	3.7	57.9	4.1	9.7	0.6	14.6
2001	712	9.4	3.3	55.3	3.1	12.8	1.7	14.5
2002	776	9.4	4.4	50.6	3.0	13.3	1.4	17.9
2003	778	9.0	4.1	54.3	3.2	10.3	1.2	18.0
2004	766	8.0	3.6	52.8	3.7	12.7	2.1	17.2
2005	678	6.8	5.9	55.6	3.1	11.2	2.8	14.5

Source: Mortality Information System, Rio de Janeiro, Brazil, 1996–2005.

AIDS = acquired immune-deficiency syndrome; TB = tuberculosis; PCP = *Pneumocystis carinii* pneumonia; HIV = human immunodeficiency virus.

mation entered is collected from the declaration of death recorded by a physician after the outcome. Coding of the primary cause of death followed the ICD-10 algorithms.

Information on HAART was obtained from the RJC antiretroviral (ARV) drug database, beginning with each subject's starting date of HAART. Information on specific drug usage, changes in regimens, immune and virological responses and adherence to therapy were not available. In Brazil, ARVs are only available from the public sector.

Linkage of the databases was performed using the software Reclink.¹¹

Statistical analyses were performed using Epi Info 6.04d (Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS 9.0 (SPSS Inc, Chicago, IL, USA). Comparison of proportions was done using the χ^2 test ($\alpha = 0.05$). Data were analyzed by year of death, and when homogeneous, pooled analyses were applied.

The study was approved by the Ethics Research Committee of the Rio de Janeiro City Health Department.

RESULTS

Between 1996 and 2005, there were 8601 AIDS-related deaths in RJC. TB was the primary cause of

Table 2 Demographics of AIDS-related deaths, comparing tuberculosis and other primary causes of death, Rio de Janeiro, Brazil, 1996–2005

Characteristics	TB %	Other causes %	<i>P</i> value
Male	71.7	70.5	0.49
Age <35 years	38.7	32.4	<0.001
Schooling <8 years	60.8	52.7	<0.001
Race non-white	63.7	46.1	<0.001

Source: Mortality Information System, Rio de Janeiro, Brazil, 1996–2005.
AIDS = acquired immune-deficiency syndrome; TB = tuberculosis.

death in 9.0% of all AIDS-related deaths, while *Pneumocystis carinii* pneumonia (PCP) accounted for 4.7% (Table 1). The percentage of TB-HIV deaths decreased slowly from 1996 (11.1%), the last year without HAART in Brazil, to 6.8% in 2005. 'Other' infectious diseases accounted for 54.3% (all cases under the B20 coding, with the exception of B20.0, which is the code for TB-HIV co-infection). Table 1 also shows the proportional distribution of the three-digit ICD-10 coding for AIDS-related deaths. The contribution of infectious diseases to AIDS deaths in RJC has remained high over the years.

Patients who died from TB were younger (38.7% vs. 32.4% aged <35 years, $P < 0.001$), less educated (60.8% vs. 52.7%, $P < 0.0001$) and more likely to be non-white (63.7% vs. 46.1%, $P < 0.0001$) than patients who died from other causes (Table 2).

The distribution of patients on HAART is shown in Table 3. By the year 2000, around 50% of those who died had been on HAART at some time in their lives, and this percentage is sustained until 2005. Looking at all years pooled together (1997–2005), 27.3%

Table 3 Distribution of patients on HAART by year of death related to TB or PCP, Rio de Janeiro, Brazil, 1996–2005

Year	Total <i>n</i> (%)	TB (B20.0) <i>n</i> (%)	PCP (B20.6) <i>n</i> (%)
1996	0	0	0
1997	108 (10.0)	3 (3.2)	3 (6.3)
1998	155 (28.3)	20 (27.4)	5 (10.4)
1999	255 (42.5)	17 (28.8)	14 (35.9)
2000	316 (44.9)	31 (42.5)	5 (17.2)
2001	351 (54.6)	33 (49.3)	8 (33.3)
2002	389 (50.5)	23 (31.5)	12 (35.3)
2003	392 (50.3)	33 (47.1)	12 (37.5)
2004	391 (49.1)	23 (37.7)	12 (42.9)
2005	331 (48.8)	27 (58.7)	10 (25.0)

Source: Rio de Janeiro antiretroviral drug database.

HAART = highly-active antiretroviral treatment; TB = tuberculosis; PCP = *Pneumocystis carinii* pneumonia.

of TB-related deaths were among patients on HAART (median 18 months) vs. 20.1% of those who died from PCP (median 20 months). In total, 33.8% of the cases had been treated with HAART (median time 22 months).

DISCUSSION

Our results show the magnitude of the impact of TB on survival in people with HIV. Even in a city with a low HIV burden such as RJC (<1% among pregnant women), the high burden of TB can reduce survival among people living with HIV despite free access to care and ARV drugs. One explanation is the occurrence of TB prior to HIV diagnosis, with TB initiating an HIV/AIDS diagnosis.

Although we have worked with secondary databases to assess the burden of TB in AIDS-related mortality, our data support other findings of the TB-HIV profile in RJC. For example, the percentage of HIV-positive cases among those with active TB was stable, at around 8%, throughout the study.¹²

The pattern of death among AIDS cases in RJC, when using only the three-digit ICD-10 coding B20 to B24, remains primarily composed of infectious diseases. A similar pattern is found in the developing world, where limited access to antiretroviral treatment (ART) prevents the reduction in mortality seen in the industrialized nations,¹³ where viral hepatitis, non-AIDS-related malignancies and cardiovascular events are now more common causes of death.¹⁴⁻¹⁶ Thus, infectious diseases are still a large component of AIDS-related mortality in RJC. More attention should be given to strategies that lead to earlier diagnosis of HIV in the general population, to wider prescription of those preventive treatments available and to the appropriate timing of starting HAART, all with the aim of reducing infectious disease-related mortality.¹⁷

Although it is well known that HAART reduces the incidence of opportunistic diseases, TB can occur at high CD4 cell counts, in contrast to PCP, which occurs mainly in patients with CD4 cell counts <200 cells/mm³. This may explain the lower proportion of PCP in our cases compared to TB, although we were unable to find a difference in the duration of treatment with HAART between the two conditions.

One limitation of our approach of secondary databases is that, by looking only at ICD-10 coding on the death certificate, it is not possible to address diagnostic misclassification or simultaneous diagnosis of TB with other illnesses. Therefore, TB cases who were erroneously classified under other infectious diseases could contribute to an underestimation of the number of TB-related deaths among HIV-positive patients. On the other hand, the availability of such a database allows us to quickly assess the burden of a disease on mortality, which, from the point of view of public health planning, is of great importance. It also helps

formulate policies to implement prophylactic treatment, as can be done in the case of TB.

Furthermore, we did not have access to CD4 cell counts or viral load results, which could be used as covariates in our analysis. Nor were we able to analyze the use of TB preventive treatment by such subjects.

We previously reported that in almost 30% of the AIDS cases that were entered in the National Diseases Surveillance System in 2002, the diagnosis of AIDS came from death certificates.⁶ We were also able to show that among TB-HIV cases occurring in 2003 in RJC, 50% were on HAART before the diagnosis of TB.¹⁸ These previous findings showed that a proportion of our TB-HIV cases did not have the benefit of an opportune HIV diagnosis, thus eliminating any potential protective effect of HAART. On the other hand, another study in RJC has shown the protective effects of HAART and isoniazid preventive treatment on TB occurrence,¹⁹ suggesting that, besides receiving HAART, when HIV-infected patients are tested and treated for latent TB infection, a tremendous reduction in TB incidence may occur.

CONCLUSIONS

Analysis of the primary cause of death among AIDS cases using a secondary database showed that TB is the leading cause of AIDS-related deaths and is responsible for twice as many deaths as PCP. Infectious diseases still pose a great burden among HIV-positive patients in RJC, in contrast with other regions of the world where patients also have access to HAART. The TB burden may be underestimated due to potential misclassification among causes of death labeled as 'other'. The potential benefits of TB preventive treatment and HAART availability could not be established by this analysis.

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RÉSUMÉ

CONTEXTE : Les données provenant de la base de données du Département de Santé de Rio de Janeiro City, Brésil.

OBJECTIFS : Pour déterminer le rôle joué par la tuberculose (TB) dans notre population séropositive pour le virus de l'immunodéficience humaine (VIH), nous avons investigué la fréquence de la TB comme cause primaire de décès parmi les sujets séropositifs pour le VIH à Rio de Janeiro City.

SCHEMA : On a obtenu les informations concernant les décès par syndrome d'immunodéficience acquise (SIDA) chez les sujets âgés de >12 ans entre 1996 et 2005 grâce au Système d'Information de la Mortalité (SIM) ; la cause du décès a été classifiée selon la Classification Internationale des Maladies (ICD-10) en fonction des causes primaires codées au chapitre 1-B20 à B24 (maladies VIH).

RÉSULTATS : A Rio de Janeiro City, Brésil, il y a eu entre 1996 et 2005, 8601 décès liés au SIDA. Le TB a été la cause primaire de décès dans 9% de tous les décès liés au SIDA, alors que la pneumonie à *Pneumocystis carinii* (PCP) a été en cause dans 4,7% des cas. Les cas de TB classés par erreur sous d'autres maladies infectieuses pourraient contribuer à une sous-estimation du nombre de décès par TB chez les patients séropositifs pour le VIH.

CONCLUSION : Notre étude a montré que la TB est la cause principale des décès liés au SIDA et qu'elle est responsable de deux fois plus de décès que la PCP dans un contexte d'accès libre aux médicaments antirétroviraux. Les avantages potentiels du traitement préventif de la TB et de la disponibilité du HAART n'ont pas pu être déterminés par cette analyse.

RESUMEN

MARCO DE REFERENCIA : La base de datos sobre mortalidad del departamento de salud de la ciudad de Río de Janeiro, Brasil.

OBJETIVOS : Para determinar la repercusión que tiene la tuberculosis (TB) en la población con serología positiva para el virus de la inmunodeficiencia humana (VIH), se investigó la frecuencia de TB como principal causa de defunción en las personas VIH positivas en la ciudad de Río de Janeiro.

MÉTODO : Se obtuvo información sobre las defunciones de personas >12 años de edad con síndrome de inmunodeficiencia adquirida (SIDA), entre 1996 y 2005, a partir del sistema de información sobre mortalidad y se catalogó la causa de defunción según la clasificación internacional de las enfermedades (CIE-10) utilizando los códigos del grupo B20 a B24 (enfermedad por VIH) del capítulo I.

RESULTADOS : Entre 1996 y 2005 ocurrieron 8601 defun-

ciones relacionadas con el sida en la ciudad de Río de Janeiro. La TB constituyó la causa principal de defunción en 9,0% de todos los casos de defunciones asociadas con el SIDA, en comparación con el 4,7% representado por la neumonía por *Pneumocystis carinii* (PCP). Los casos de TB clasificados erróneamente como otras enfermedades infecciosas pueden contribuir a subestimar el número de muertes por TB en pacientes con serología positiva para el VIH.

CONCLUSIÓN : El presente estudio pone en evidencia que la TB es la principal causa de defunción asociada con el SIDA y provoca el doble de muertes que la PCP, en un medio con acceso gratuito a los medicamentos antirretrovíricos. Este análisis no permite establecer la posible utilidad del tratamiento preventivo de la TB ni del suministro del HAART.