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Predictors of immunodeficiency-related death in a cohort of low-income people living with HIV: a competing risks survival analysis

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SUMMARY

We conducted a survival analysis with competing risks to estimate the mortality rate and predictive factors for immunodeficiency-related death in people living with HIV/AIDS (PLWH) in northeast Brazil. A cohort with 2372 PLWH was enrolled between July 2007 and June 2010 and monitored until 31 December 2012 at two healthcare centres. The event of interest was immunodeficiency-related death, which was defined based on the Coding Causes of Death in HIV Protocol (CoDe). The predictor variables were: sociodemographic characteristics, illicit drugs, tobacco, alcohol, nutritional status, antiretroviral therapy, anaemia and CD4 cell count at baseline; and treatment or chemoprophylaxis for tuberculosis (TB) during follow-up. We used Fine & Gray's model for the survival analyses with competing risks, since we had regarded immunodeficiency-unrelated deaths as a competing event, and we estimated the adjusted sub-distribution hazard ratios (SHRs). In 10 012·6 person-years of observation there were 3·1 deaths/100 person-years (2·3 immunodeficiency-related and 0·8 immunodeficiency-unrelated). TB (SHR 4·01), anaemia (SHR 3·58), CD4 <200 cells/mm^3 (SHR 3·33) and being unemployed (SHR 1·56) were risk factors for immunodeficiency-related death. This study discloses a 13% coverage by highly active antiretroviral therapy (HAART) in our state and adds that anaemia at baseline or the incidence of TB may increase the specific risk of dying from HIV-immunodeficiency, regardless of HAART and CD4.

Key words: Cohort studies, HIV, mortality, risk factor.

INTRODUCTION

Two decades after the introduction of highly active antiretroviral therapy (HAART) [1] with its impact on the overall mortality of people living with HIV/AIDS (PLWH), there has been a decrease in the ratio between deaths related and unrelated to immunodeficiency in several cohorts throughout developed countries [2]. A number of European countries currently present a predominance of deaths caused by non-AIDS-defining infections and cancers, liver disease and drug abuse [3–5]. However, immunodeficiency-related

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conditions remain the leading causes of death in many parts of the world [2], particularly in low-income regions, such as Brazil [6, 7].

In Brazil, HAART has been widely available since 1996. This has resulted in the reduction of infectious and parasitic diseases, and in the consequent increase in the proportion of deaths unrelated to HIV immunodeficiency [6, 7]. Nevertheless, the Brazilian mortality pattern has not changed as expressively as in other countries [2, 7]. In Brazil, HIV/AIDS mortality rates rose by 2% per year from 2005 to 2015. Last year there were 33 800 new HIV infections and 21 000 deaths from HIV/AIDS, along with a 50% coverage by HAART in the country [8]. Therefore, it is essential that deaths related to HIV immunodeficiency and its predictive factors are correctly identified in order that interventions may be aimed at reducing lethality from this disease.

Studies have detected a strong association between the risk of immunodeficiency-related death and clinical factors, such as low CD4 cell count, low weight, anaemia and tuberculosis (TB) [9–11]. This association has also been verified with lifestyle, such as the use of illicit drugs, tobacco or alcohol [12, 13]. However, the diversity of classification systems used to relate death to HIV immunodeficiency may cause bias in these estimates [14]. In much of the research studies, the definition of death related and unrelated to HIV immunodeficiency is based on the International Classification of Diseases (ICD), but the ICD does not cover the entire spectrum of diseases and conditions related to HIV and its treatments [4, 14]. In addition, estimates on the pattern of mortality in PLWH may be biased by competing risk from other causes of death, which may prevent observation of the cause-specific risk of death from immunodeficiency [15].

There are few evidences from South America, among which two studies from the southeast of Brazil used an international standardized protocol for classifying deaths [6, 7] – the Coding causes of Death in HIV (CoDe) [4]. One of these studies addressed the bias from the concurrent risk of immunodeficiency-unrelated deaths [6]. Northeast Brazil is poorer than the southeast, presenting different estimates on HIV/AIDS. In the southeast, AIDS diagnosis and mortality rates are decreasing, currently standing at 18·6 and 5·7/100 000 population, respectively, while in the northeast both rates have increased to levels of 15·2 and 4·3/100 000 [16].

PLWH in the northeast of Brazil present multiple causes of death with profiles from the HAART and pre-HAART eras [17], and a very high incidence of TB co-infection (2·8/100 person-years) [18]. Therefore, this study aimed to identify risk factors for immunodeficiency-related death in a cohort of PLWH in this region. We classified the deaths using the CoDe protocol [4], and then we conducted a competing risks survival analysis with the Fine & Gray model [19], which weights the immunodeficiency-unrelated deaths as a competing event.

METHODS

This was a cohort study with a survival analysis of an adult population of PLWH attending specialized care services for HIV/AIDS in the state of Pernambuco, in the northeast of Brazil. The study was located in two hospitals from the Brazilian integrated health system (Sistema Único de Saúde; SUS), Hospital Universitário Oswaldo Cruz (HUOC) and Hospital Correia Picanço (HCP), which encompassed 70% of PLWH in our state at the time of recruitment.

The study was approved by the Ethics Committee of the Universidade Federal de Pernambuco (CEP/CCS/UFPE 254/05), and all participants underwent the informed consent process prior to being enrolled in the study. This report follows the STROBE checklist.

The study population consisted of outpatients and inpatients at HUOC and HCP, of whom <5% refused to participate, resulting in a consecutive sample of 2372 PLWH enrolled from July 2007 to June 2010 and followed until December 2012. The participants were aged $\geqslant$17 years, and no criteria were established for exclusion or withdrawal from the study.

The outcome was the event of death, classified as immunodeficiency-related or immunodeficiency-unrelated. The monitoring and collection of data regarding mortality were conducted periodically with searches on the Pernambuco Mortality Information System (SIM) database, which thus prevented follow-up losses until the study ended on 31 December 2012. We collected the date of death, and the immediate, intermediate and underlying causes of death (ICD-10 codes) from SIM, using the probabilistic linkage program RecLink III [20]. Following this, causes of death were re-coded in our dataset and classified as immunodeficiency-related or immunodeficiency-unrelated, according to the CoDe Protocol [4].

The CoDe Protocol was developed by the Copenhagen HIV Programme – Centre for Health and Infectious Disease Research (CHIP), and is publicly available free of charge on the CHIP homepage

(www.cphiv.dk/CoDe). The CoDe comprises two processes, the first uses a Case Report Form to collect sociodemographic and clinical data from the death case, and the second is a Review Form consisting of a matched case review to determine the sequence of events that led to death, to codify the causes of death, and to classify them as immunodeficiency-related or -unrelated. In the present study, we only applied the CoDe Review Form, since we had no data to apply to the Case Report Form [4]. Two specialist professionals (C.C.B. and J.D.L.B.) independently classified each case, based on the underlying, intermediate and immediate causes of death recorded by SIM. Discordant cases were defined by another specialist (M.F.P.M.A.).

According to the CoDe Protocol [4], deaths from external causes were considered definitely unrelated to immunodeficiency, while cases with an AIDS-defining condition or Hodgkin's lymphoma as an underlying, intermediate or immediate cause were classified as definitely related to immunodeficiency. The remaining cases were all considered as non-sudden deaths, and thus were classified as either related or unrelated to immunodeficiency, depending on the CD4 cell count of <200 or ⩾200 cells/mm^3, respectively. To this end, we assessed the CD4 cell counts closest to death from the year preceding death. The 103 cases with no information on CD4 cell counts within 365 days before death were classified through consensus by the three reviewers, based only on the causes of death.

The independent variables as predictors of immunodeficiency-related death included *sociodemographic* (sex, age group, individual monthly income, literacy, work, social support); *life habits* (alcohol, smoking, illicit drugs) and *clinical characteristics* at baseline (HAART, CD4 cell count, anaemia, nutritional status) or during the cohort (treatment for TB, chemoprophylaxis for TB).

Age was categorized into age groups (<40 or ⩾40 years) and income as <1 or ⩾1 minimum salary. The mean values of the Brazilian minimum salary were as follows: US$185.64 (2007); US$246.88 (2008); US$198.13 (2009); US$295.82 (2010); US$327.92 (2011); US$332.98 (2012). Social support was considered absent if the patient was homeless or living alone. Alcohol consumption was categorized according to criteria from the Centers for Disease Control and Prevention [21], as non-drinker, light drinker (up to 2 drinks/day for men and 1 drink/day for women) and excessive drinker (>2 drinks/day for men and 1 drink/day for women). Smoking was classified as: non-smoker, ex-smoker (not smoking at the time of interview nor during the previous 6 months) and current smoker (smoking at the time of the interview or had given up smoking for <6 months). Illicit drug use was considered if the individual reported ever having used marijuana, cocaine or crack.

The use of HAART was defined if the patient was using a combination of three different antiretroviral drugs at the beginning of the cohort. The nutritional status was based on the body mass index (BMI), using weight and height measured at baseline, and was categorized as underweight (<18·5 kg/m^2), normal (18·5–24·9 kg/m^2) or overweight/obese (⩾25 kg/m^2), according to World Health Organization criteria [22]. The CD4 cell counts at baseline were categorized as <200 or ⩾200 cells/mm^3. The diagnosis of anaemia at baseline was defined if the haemoglobin concentration (Hb) was <12 g/dl for women and <14 g/dl for men, according to EuroSIDA criteria [23]. The CD4 cell count and Hb at baseline were considered as the first measurements within the first year of follow-up.

The variable 'treatment for tuberculosis' was defined as the treatment prescribed by the attending physician, according to the Brazilian Ministry of Health protocol (assessing clinical findings and/or acid-alcohol-resistant bacillus in sputum and/or culture for *Mycobacterium tuberculosis*) [24]. Asymptomatic individuals with a positive tuberculin skin test (TST) are recommended for latent tuberculosis infection (LTBI) treatment, based on the Brazilian Ministry of Health protocol, which recommends the use of 300 mg isoniazid for 6 months [24]. The variable 'chemoprophylaxis for tuberculosis' was categorized as: 'not indicated and not treated' (a negative TST), 'indicated and treated' (a positive TST and treated for LTBI), 'indicated and not treated' (a positive TST and not treated for LTBI), 'no tuberculin skin test' [25].

Sociodemographic, lifestyle habits and clinical data were collected at the time of enrolment, from interviews and information from hospital records. Information was also collected periodically during follow-up from these same sources regarding the treatment for TB, results of TST and treatment for LTBI. Weight and height were measured at baseline with calibrated, standardized instruments.

Samples for the CD4 cell count and *M. tuberculosis* culture were collected in the laboratory of the respective hospitals and sent to the Pernambuco Central Laboratory (Lacen-PE) or the Julião Paulo da Silva Municipal Laboratory (for the CD4 cell counts of HUOC patients). The Hb, sputum smear and TST

were conducted within the respective services. Results of the Hb and CD4 cell counts were obtained from hospital records. All information and results from clinical and laboratory measurements were collected and recorded on a standardized instrument developed specifically for this study.

Processing and analysing data

Survival analyses were conducted using the statistical method for the sub-distribution of hazards, proposed by Fine & Gray [19], which estimates the sub-distribution hazard ratios (SHRs), calculating the median of follow-up time until failure by the event of interest, and attributing a weighted risk to other causes of failure (competing event), rather than censoring. According to Pintile [15], the standard survival analysis based on the Kaplan–Meier method always overestimates the true probabilities of the event of interest in a competing risks situation. Indeed, we aimed to estimate the risk of HIV-related death, thus individuals who died from HIV-unrelated causes could not to be observed during the total periods under risk of HIV-related death, increasing the ratio between the number of HIV-related deaths and total follow-up periods in the cohort.

For our analysis, the dependent variable was the time period between entry to the study and immunodeficiency-related death (event of interest); and the competing event was the time until immunodeficiency-unrelated death. All independent variables (sociodemographic, lifestyle, clinical) were analysed as categorical variables. An additional category 'no information' was created for variables with more than 5% missing data (CD4 and Hb).

In the bivariate analysis, we estimated the association between each independent variable and immunodeficiency-related deaths, using the SHR, a confidence interval (CI) of 95% and the P value. The variables with $P \leqslant 0{\cdot}25$ in the bivariate analysis were included in the multivariate regression models. We ran a saturated model with all covariates with a P value of at least 0·25 in the bivariate analysis, and a final model, using the backward stepwise selection method, hence the variables with $P<0{\cdot}05$ were maintained in the final model. Additionally, we performed a sensitivity analysis by repeating the same analytical steps with the subgroup of patients whose CD4 count results were available. Stata v. 12.0 software (StataCorp., USA) was used to perform the analyses.

For this study, there was no previous sample size calculation. The power of the study was calculated *a posteriori* to detect the differences between the incidence of immunodeficiency-related death in patients who had and who had not CD4 <200 cells/mm^3 (90·5% *vs.* 49·6%), anaemia (81% *vs.* 49·4%) and treatment for TB (87% *vs.* 66%). Our sample size has a power of at least 94% (96% for association with CD4 <200 cells/mm^3, 94% for anaemia, and 95% for treatment for TB).

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national (National Council of Health, Brazil) and institutional committees (approval by the Ethics Committee of the Centro de Ciências da Sáude/Universidade Federal de Pernambuco 254/05) on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

The cohort included 2372 PLWH, who were enrolled between July 2007 and June 2010 and followed until 31 December 2012, resulting in 10 012·6 person-years of observation. The mean age of participants was 39·3 years (S.D. = 9·7), 62·5% were male and 72·6% were using HAART at the beginning of the cohort. The median of income was R$ 380·00 (Q_1–Q_3 70·00–511·50, $n = 2328$). The other continuous variables presented mean values as follow: BMI 23·4 kg/m^2 (S.D. = 4·3, $n = 2309$); CD4 at baseline 442·4 cells/mm^3 (S.D. = 294·4, $n = 2076$); Hb at baseline 12·5 g/dl (S.D. = 1·5, $n = 833$) for women and 13·8 g/dl (S.D. = 1·9, $n = 1348$) for men. No information was provided on the CD4 cell counts in 16% of observations, and in 8% of the Hb values, during the first year of the cohort. Among the cases of death, 56 (17·8%) presented only one CD4 count, which functioned as the CD4 at baseline as well as the more recent CD4 count before death.

There were 315 (13·3%) deaths from all causes; 232 (73·6%) deaths were classified as immunodeficiency-related, according to CoDe criteria. AIDS-defining infections were the most common causes of immunodeficiency-related deaths (30%), of which TB was the most common (70%). The median time from the most recent CD4 cell count until immunodeficiency-related death was 192 days ($n = 215$), and until immunodeficiency-unrelated death was 174 days ($n = 78$). It can be observed in Table 1 that some of the studied

Table 1. *Comparison of sociodemographic, life habits and clinical characteristics between immunodeficiency-related and -unrelated deaths in a cohort of 2372 PLWH, 2007–2012*

Variables	Immunodeficiency-related deaths *n* (%)	Immunodeficiency-unrelated deaths *n* (%)	Survivors *n* (%)	*P* value
Baseline characteristics				
Sex				0·013
Female	72 (31·0)	23 (27·7)	795 (38·6)	
Male	160 (69·0)	60 (72·3)	1262 (61·3)	
Age group, years				0·000
17–39	140 (60·3)	27 (32·5)	1080 (52·5)	
⩾40	92 (39·7)	56 (67·5)	977 (47·5)	
Social support				0·623
Lives with family or partner	188 (81·0)	64 (77·1)	1667 (81·4)	
Lives alone. in a shelter or on the streets	44 (19·0)	19 (22·9)	382 (18·6)	
Literacy				0·014
Yes	190 (82·6)	72 (86·7)	1822 (89·0)	
No	40 (17·4)	11 (13·3)	244 (10·9)	
In work				0·000
Yes	29 (12·9)	17 (20·7)	526 (25·9)	
No	196 (87·1)	65 (79·3)	1507 (74·1)	
Monthly individual income				0·058
⩾1 minimum salary	104 (45·6)	44 (54·3)	1088 (53·9)	
<1 minimum salary	124 (54·4)	37 (45·7)	931 (46·1)	
Alcohol				0·001
Non-drinker	174 (75·3)	54 (65·8)	1276 (62·3)	
Light drinker	37 (16·0)	16 (19·5)	554 (27·1)	
Excessive drinker	20 (8·7)	12 (14·6)	217 (10·6)	
Smoking				0·011
Non-smoker	89 (38·5)	37 (44·6)	933 (45·5)	
Current smoker	93 (40·3)	26 (31·3)	591 (28·8	
Ex-smoker for ⩾6 months	49 (21·2)	20 (24·1)	528 (25·7)	
Illicit drugs				0·063
Never used	153 (66·2)	56 (67·5)	1495 (72·9)	
Used at some point	78 (33·8)	27 (32·5)	555 (27·1)	
Using HAART				0·718
Yes	32 (13·8)	11 (13·2)	248 (12·1)	
No	200 (86·2)	72 (86·7)	1809 (87·9)	
CD4 cell count				0·000
⩾200 cells/mm^3	58 (25·0)	59 (71·1)	1471 (71·5)	
1–199 cells/mm^3	86 (37·1)	9 (10·8)	314 (15·3)	
Not informed	88 (37·9)	15 (18·1)	272 (13·2)	
Anaemia				0·000
No	39 (16·8)	40 (48·2)	1250 (60·8)	
Yes	143 (61·6)	34 (41·0)	675 (32·8)	
Not informed	50 (21·5)	9 (10·8)	132 (6·4)	
Nutritional status				0·000
Normal	137 (59·0)	45 (54·2)	1193 (59·1)	
Underweight	43 (18·5)	8 (9·6)	171 (8·5)	
Overweight/obese	29 (12·5)	30 (36·1)	653 (32·4)	
Characteristics during the cohort				
Treatment for tuberculosis				0·000
No	132 (56·9)	68 (81·9)	1887 (91·7)	
Yes	100 (43·1)	15 (18·1)	170 (8·3)	
Chemoprophylaxis for tuberculosis				0·000
Not indicated and not treated for LTBI	57 (24·6)	28 (33·7)	741 (36·0)	
Indicated and treated for LTBI	5 (2·2)	4 (4·8)	139 (6·8)	
Indicated and not treated for LTBI	11 (4·7)	2 (2·4)	126 (6·1)	
No tuberculin skin test	159 (68·5)	49 (59·0)	1051 (51·1)	

PLWH, People living with HIV/AIDS; HAART, highly active antiretroviral therapy; LTBI, latent tuberculosis infection. Mean values in dollars for Brazilian minimum salary: US$185.64 (2007); US$246.88 (2008); US$198.13 (2009); US$295.82 (2010); US$327.92 (2011); US$332.98 (2012).

characteristics presented significantly different frequencies between groups of survivors, immunodeficiency-related and -unrelated deaths.

The overall mortality rate in the cohort was 3·1/100 person-years, comprising 2·3/100 person-years for immunodeficiency-related deaths and 0·8/100 person-years for immunodeficiency-unrelated deaths. Patients who died from conditions unrelated to immunodeficiency had a longer contribution of time-at-risk than those who died from immunodeficiency: the mean of 859·6 *vs.* 626·7 person-years ($P = 0{\cdot}0003$), respectively. The incidence rate of immunodeficiency-related death per year of entry to the cohort is presented in Table 2, showing a rising trend until 2009, followed by a fall in 2010.

In the bivariate survival analysis with competing risks (Table 3), only the variables 'social support' and 'HAART' did not obtain a P value <0·25. Table 4 presents two multivariate models, of which there is a saturated model with all the other variables, and a final model with the selected variables. After applying the backward stepwise method, the variables 'age group', 'sex', 'literacy', 'income', 'smoking' and 'illicit drug' were excluded from the final model. The adjusted SHRs indicated the following risk factors for immunodeficiency-related death (in descending order of their SHR): treatment for TB during cohort, anaemia or a CD4 count <200 cells/mm^3 in the first year of the cohort, and being unemployed at baseline.

Table 5 presents a sensitivity analysis by replicating the same bivariate and multivariate analyses considering only the subsample of patients with available CD4 counts. In this subsample ($n = 373$), the variables maintained in the final multivariate model were: treatment for TB during cohort, BMI, anaemia and CD4.

Table 2. *Incidence rate of immunodeficiency-related death per year of entrance in a cohort of 2372 PLWH, 2007–2012*

	N	Mortality rate
2007	66	1·64/100 person-years
2008	111	2·3/100 person-years
2009	47	5·5/100 person-years
2010	8	4·0/100 person-years

PLWH, People living with HIV/AIDS.

DISCUSSION

Our estimates on PLWH in the northeast of Brazil demonstrated that deaths attributed to immunodeficiency occurred at a rate of 2·3 deaths/100 people per year between 2007 and 2012. Immunodeficiency-related deaths were more frequent than immunodeficiency-unrelated deaths with a ratio of almost 3:1. Most of the patients who died from immunodeficiency were not taking HAART at inclusion in the study, although most of them presented a CD4 cell count <200 cells/mm^3. Considering immunodeficiency-unrelated deaths as competing events, the adjusted hazard for immunodeficiency-related death was 1½ times higher in patients who were unemployed; 3½ times higher in those who presented a CD4 count <200 cells/mm^3 or anaemia at baseline; and four times higher in patients who received treatment for TB during the cohort.

Immunodeficiency is still a major cause of death of PLWH in some developed countries [2, 26], such as Spain, where 53% of deaths were related to immunodeficiency in a recent cohort [14]. However, several European regions have reported deaths from other causes as being the most common [3–5, 27]. In a Swiss cohort, 84% of deaths between 2005 and 2009 were immunodeficiency unrelated at a rate of 0·8/100 person-years, while immunodeficiency-related deaths at 0·14/100 person-years occurred [5]. Survival estimates may be discordant in different epidemiological and socioeconomic contexts. In the southeast of Brazil, 49% of deaths in PLWH were attributed to immunodeficiency between 2005 and 2007 (1·24/100 person-years) [6], and 62%, between 2007 and 2009 (1·35/100 person-years) [7]. Our study was conducted in a low-income region of the country and encountered even higher estimates which were in accordance with a very high proportion of patients not taking HAART (86%).

The high frequencies of low CD4 cell counts and anaemia, and co-infection with TB in patients who died due to HIV immunodeficiency may largely explain the excessive mortality rate, as they were the strongest predictors of immunodeficiency-related death, regardless of HAART at study inclusion. In a cohort of PLWH in the southeast of Brazil it was observed that a low CD4 cell count [hazard ratio (HR) 5·96] and AIDS diagnosis at the baseline (HR 8·25) significantly increased the risk of death related to immunodeficiency [7]. However, the effects of TB and anaemia were not investigated [7]. Levels of CD4 cells reflects the susceptibility to opportunistic diseases in PLWH [28], of which TB is the leading cause of death [26, 29]. In the HIV/TB co-infection, the viral load increases while the CD4 cell count diminishes [30] and both infections progress [31, 32].

Table 3. *Bivariate model of sub-distribution hazards from sociodemographic and life habit variables for immunodeficiency-related death, considering other deaths as competing event in 2372 PLWH, 2007–2012*

Variables	SHR	(95% CI)	*P* value
Sociodemographic and life habits variables			
Sex			
Female	1·00		
Male	1·35	(1·02–1·78)	0·035
Age group, years			
17–39	1·00		
⩾40	0·71	(0·55–0·93)	0·011
Social support			
Lives with family or partner	1·00		
Lives alone, in a shelter or on the streets	1·05	(0·72–1·40)	0·974
Literacy			
Yes	1·00		
No	1·65	(1·18–2·33)	0·004
Monthly individual income			
⩾1 Minimum salary	1·00		
<1 Minimum salary	1·40	(1·08–1·82)	0·011
Smoking			
Never smoked	1·00		
Current smoker	1·60	(1·19–2·13)	0·002
Ex-smoker for ⩾6 months	0·97	(0·68–1·37)	0·860
Illicit drugs			
Never used	1·00		
Used at some point	1·32	(1·01–1·73)	0·044
Alcohol			
Non-drinker	1·00		
Light drinker	0·50	(0·35–0·71)	0·000
Excessive drinker	0·65	(0·41–1·02)	0·060
In work			
Yes	1·00		
No	2·31	(1·57–3·40)	0·000
Clinical variables			
Using HAART at baseline			
<1 year	1·00		
⩾1 year	0·82	(0·56–1·19)	0·299
CD4 cell count at baseline			
⩾200 cells/mm^3	1·00		
1–199 cells/mm^3	6·55	(4·72–9·10)	0·000
Not informed	7·78	(5·59–10·82)	0·000
Anaemia at baseline			
No	1·00		
Yes	6·27	(4·41–8·90)	0·000
Not informed	11·74	(7·70–17·92)	0·000
Nutritional status at baseline			
Normal (eutrophic)	1·00		
Underweight	2·14	(1·52–3·03)	0·000
Overweight	0·40	(0·26–0·58)	0·000
Treatment for tuberculosis during the cohort			
No	1·00		
Yes	6·41	(4·95–8·30)	0·000
Chemoprophylaxis for tuberculosis during the cohort			
Not indicated and not treated for LTBI	1·00		
Indicated and treated for LTBI	0·47	(0·19–1·18)	0·109
Indicated and not treated for LTBI	1·14	(0·60–2·15)	0·683
No tuberculin skin test	1·94	(1·44–2·62)	0·000

PLWH, People living with HIV/AIDS; SHR, sub-distribution hazard ratio; CI, confidence interval; HAART, highly active antiretroviral therapy; LTBI, latent tuberculosis infection.

Mean values in dollars for Brazilian minimum salary: US$185.64 (2007); US$246.88 (2008); US$198.13 (2009); US$295.82 (2010); US$327.92 (2011); US$332.98 (2012).

Table 4. *Multivariate regression models of the sub-distribution hazards of immunodeficiency-related death, considering other deaths as competing event in 2372 PLWH, 2007–2012*

	Saturated multivariate model ($n = 2372$)			Final multivariate model ($n = 2372$)		
Variables	SHR	(95% CI)	*P* value	SHR	(95% CI)	*P* value
Sociodemographic and life habits variables						
Sex						
Female	1·00					
Male	0·91	(0·67–1·24)	0·567			
Age group, years						
17–39	1·00					
⩾40	0·88	(0·66–1·18)	0·400			
Literacy						
Yes	1·00					
No	1·27	(0·88–1·82)	0·205			
Monthly individual income						
⩾1 Minimum salary	1·00					
<1 Minimum salary	0·81	(0·61–1·08)	0·161			
Smoking						
Never smoked	1·00					
Current smoker	1·40	(1·00–1·96)	0·051			
Ex-smoker for ⩾6 months	0·99	(0·69–1·42)	0·948			
Illicit drugs						
Never used	1·00					
Used at some point	1·13	(0·83–1·52)	0·437			
Alcohol						
Non-drinker	1·00			1·00		
Light drinker	0·60	(0·41–0·90)	0·012	0·66	(0·45–0·98)	0·038
Excessive drinker	0·58	(0·37–0·90)	0·016	0·68	(0·45–1·05)	0·080
In work						
Yes	1·00			1·00		
No	1·47	(0·99–2·19)	0·056	1·56	(1·05–2·32)	0·027
Clinical variables						
CD4 cell count at baseline						
⩾200 cells/mm^3	1·00			1·00		
1–199 cells/mm^3	3·52	(2·45–5·07)	0·000	3·33	(2·35–4·74)	0·000
Not informed	4·63	(3·26–6·58)	0·000	4·63	(3·31–6·48)	0·000
Anaemia at baseline						
No	1·00			1·00		
Yes	3·62	(2·51–5·23)	0·000	3·58	(2·49–5·14)	0·000
Not informed	5·75	(3·69–8·97)	0·000	5·93	(3·85–9·14)	0·000
Nutritional status at baseline						
Normal	1·00			1·00		
Underweight	1·18	(0·81–1·72)	0·399	1·16	(0·78–1·69)	0·433
Overweight	0·67	(0·45–1·01)	0·054	0·64	(0·43–0·95)	0·029
Treatment for TB during the cohort						
No	1·00			1·00		
Yes	3·85	(2·80–5·29)	0·000	4·01	(2·95–5·44)	0·000
Chemoprophylaxis for TB during the cohort						
Not indicated and not treated for LTBI	1·00					
Indicated and treated for LTBI	0·95	(0·38–2·40)	0·922			
Indicated and not treated for LTBI	0·89	(0·47–1·69)	0·729			
No tuberculin skin test	0·97	(0·70–1·35)	0·849			

PLWH, People living with HIV/AIDS; SHR, sub-distribution hazard ratio; CI, confidence interval; LTBI, latent tuberculosis infection.

Mean values in dollars for Brazilian minimum salary: US$185.64 (2007); US$246.88 (2008); US$198.13 (2009); US$295.82 (2010); US$327.92 (2011); US$332.98 (2012);

Table 5. *Sensitivity analysis: multivariate regression model of the sub-distribution hazards of immunodeficiency-related death, considering other deaths as competing event, in a subsample of 373 PLWH with available CD4 counts, 2007–2012*

Predictor variables	Adjusted SHR	95% CI	*P* value
Treatment for TB during the cohort			
No	1·00		
Yes	4·55	(3·15–6·58)	0·000
Anaemia at baseline			
No	1·00		
Yes	3·23	(2·14–4·87)	0·000
Not informed	5·51	(3·04–9·97)	0·000
CD4 cell count at baseline			
⩾200 cells/mm^3	1·00		
1–199 cells/mm^3	3·82	(2·70–5·43)	0·000
Nutritional status			
Normal	1·00		
Underweight	0·95	(0·58–1·56)	0·840
Overweight/obese	0·57	(0·35–0·91)	0·020

PLWH, People living with HIV/AIDS; SHR, sub-distribution hazard ratio; CI, confidence interval.

Thus, it is extremely important to investigate TB as an independent risk factor for deaths in PLWH in our endemic area [2]. In our study, TB/HIV co-infection differentiated a group with a fourfold risk of death from immunodeficiency, in agreement with a Cambodian study [29]. Moreover, TB is associated with severe anaemia which is a strong predictor of both TB and death in PLWH [33]. Anaemia is associated to a substantial reduction in the survival of PLWH [34–36], irrespective of co-infections and levels of CD4 cells [10, 34]. Severe anaemia may increase mortality by several times, such as a rate of 15 times, as observed in an African study [37]. Our study adds that the presence of anaemia at the beginning of the follow-up increases the cause-specific risk of dying from HIV immunodeficiency by three times.

During the HAART era, factors related to lifestyle, such as alcohol intake, reduce the long-term survival of PLWH [13]. On the other hand, light or moderate alcohol intake [38], as well as employment [39], may be associated to longer survival rates in PLWH. More specifically, some cohort studies have reported a twofold risk of AIDS-related deaths in patients who were unemployed [40]. Employment may indicate differences in accessing healthcare and its quality [39]. Accordingly, in our study the risk of dying from HIV immunodeficiency was one-third lower in light drinkers and workers compared to non-drinkers and non-workers. We would expect that underweight patients [10], not taking HAART [26] and those who were most vulnerable to TB (positive TST without treatment for LTBI) [29] would present a greater risk of immunodeficiency-related death. However, our analyses have not encountered such an association. Possibly this study did not have the statistical power to detect these issues.

The differences between the groups of immunodeficiency-related and -unrelated deaths regarding CD4 count <200 cells/mm^3 (40% *vs.* 10%) and anaemia (60% *vs.* 40%), reinforced the hazards ratios of these predictors for immunodeficiency-related death. However, in the patients who died from immunodeficiency, no CD4 data was available for almost 40%, and no Hb data for 20%, while TST was only available for less than half of the patients. These missing data may hinder observing the actual differences in the hazards. In the subsample of patients with available CD4 counts, non-workers and light drinkers lost their effect, showing that these socioeconomic variables are sensitive to the availability of laboratory tests. This finding might be explained by an interrelation between socioeconomic condition, the severity of HIV infection and access to healthcare facilities. Accordingly, patients not having CD4 or Hb data had higher SHR than those with low CD4 cell count or anaemia.

We created the 'not informed' categories to avoid a selection bias from exclusion of missing data. However, in patients without CD4 results a misclassification on the cause of death may have occurred. Nevertheless, 70% of deaths could be attributed to HIV immunodeficiency. On the other hand, we addressed the overestimation on immunodeficiency caused by the ICD-10 system [14] using the CoDe Review Form. Furthermore, we applied Fine & Gray's method to address the bias from competing risks [15]. Therefore, we believe that our analyses brought a more reliable understanding regarding HIV lethality in northeast Brazil, and corroborated that the introduction of HAART with free access in the public health services does not seem to have assured a wide coverage by HAART nor did it reduce mortality trends in PLWH in our region as in other regions of Brazil [6, 7, 17] and in other countries [2, 12].

CONCLUSIONS

Even in the HAART era, 75% of PLWH who died in our region did so due to immunodeficiency, where the

leading cause was TB. Anaemia at baseline or incidence of TB increase the specific risk of dying from immunodeficiency by several times. We recommend a careful management of anaemia and TB as important HIV comorbidities, and efforts to investigate the reasons that have limited the effectiveness of HAART on the survival estimates of PLWH in our region. We encourage researchers to use the CoDe and competing risks methods in studies regarding mortality in PLWH worldwide.

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DECLARATION OF INTEREST

None.

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