Population attributable fractions of mortality in people living with HIV: roles of delayed antiretroviral therapy, hepatitis coinfections and social factors

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Abstract:

Objectives

Despite free access to antiretroviral therapy (ART) from 1996 onward, and treatment for all people living with HIV (PLWHIV) from 2013, mortality in Brazil has not homogeneously decreased. We investigated to what extent delayed ART, hepatitis coinfections and sociodemographic factors predict all-cause mortality in Brazilian PLWHIV.

Design

We included PLWHIV ≥18 years, with complete CD4 count data, followed up between 2007 and 2015 in Brazil.

Methods

After multiple imputation, an extended Cox model helped estimate the effects of fixed and time-varying covariates on mortality.

Results

The study population (n=411,028) were mainly male (61%), Caucasian (55%), ≤40 years (61%), heterosexually HIV-infected (71%), living in the Southeast region (48%) and had basic education (79%). HCV and HBV coinfection prevalences were 2.5% and 1.4%, respectively. During a 4-year median follow-up, 61,630 deaths occurred and the mortality rate was 3.45 [95% confidence interval (CI): 3.42-3.47] per 100 person-years. Older age, male gender, non-Caucasian ethnicity, illiteracy/basic education and living outside the Southeast and Central-West regions were independently associated with increased mortality. The main modifiable predictors of mortality were delayed ART (i.e., CD4<200 cells/mm3 at ART initiation) (adjusted population attributable fraction: 14.20% [95% CI: 13.81-14.59]), being ART-untreated (14.06% [13.54-14.59]), and ART-treated with unrecorded CD4 at ART initiation (5.74% [5.26-6.21]). HCV and HBV coinfections accounted for 2.44% [2.26-2.62] and 0.42% [0.31-0.53] of mortality, respectively.

Conclusions

This study demonstrates that besides early ART and coinfection control, actions targeting males, non-Caucasians and illiterate people and those with basic education are important to reduce avoidable deaths among Brazilian PLWHIV.

Title page

Full title

Population attributable fractions of mortality in people living with HIV: roles of delayed ART, hepatitis coinfections and social factors

Short title

Attributable fractions of mortality in PLWHIV

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Abstract

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Design: We included PLWHIV ≥18 years, with complete CD4 count data, followed up between 2007 and 2015 in Brazil.

Methods: After multiple imputation, an extended Cox model helped estimate the effects of fixed and time-varying covariates on mortality.

Results: The study population (n=411,028) were mainly male (61%), Caucasian (55%), ≤40 years (61%), heterosexually HIV-infected (71%), living in the Southeast region (48%) and had basic education (79%). HCV and HBV coinfection prevalences were 2.5% and 1.4%, respectively. During a 4-year median follow-up, 61,630 deaths occurred and the mortality rate was 3.45 [95% confidence interval (CI): 3.42-3.47] per 100 person-years. Older age, male gender, non-Caucasian ethnicity, illiteracy/basic education and living outside the Southeast and Central-West regions were independently associated with increased mortality. The main modifiable predictors of mortality were delayed ART (i.e., CD4<200 cells/mm^3 at ART initiation) (adjusted population attributable fraction: 14.20% [95% CI: 13.81-14.59]), being ART-untreated (14.06% [13.54-14.59]), and ART-treated with unrecorded CD4 at ART initiation (5.74% [5.26-6.21]). HCV and HBV coinfections accounted for 2.44% [2.26-2.62] and 0.42% [0.31-0.53] of mortality, respectively.

Conclusions: This study demonstrates that besides early ART and coinfection control, actions targeting males, non-Caucasians and illiterate people and those with basic education are important to reduce avoidable deaths among Brazilian PLWHIV.

Keywords

HIV; Hepatitis C; Hepatitis B; Coinfection; Mortality; Socioeconomic Factors.

Introduction

HIV epidemic affects 37.9 million people worldwide, with 770,000 dying from HIV-related causes in 2018 [1]. There are 966,058 people living with HIV (PLWHIV) in Brazil (2019 estimates), with an average of 40,000 new HIV infections annually [2]. The introduction of free antiretroviral therapy (ART) in 1996 under Brazil's Unified Health System (SUS) [3], and treatment for all PLWHIV in 2013 [4], led to a gradual decrease of HIV-related mortality between 2000 and 2014 [5]. The mortality profile of PLWHIV consequently changed, non-HIV-related causes of death becoming more prevalent (e.g., liver and cardiovascular diseases) [6,7].

The main factors of mortality in PLWHIV are late presentation for HIV care [8,9], late diagnosis [8,9] and delayed ART [9,10], as well as discontinuity of care [11] and of treatment [9,10]. Coinfection with hepatitis C virus (HCV) [12–14] and hepatitis B virus (HBV) [12] is also associated with all-cause deaths among PLWHIV. Because of pathophysiologic synergy between the viruses, HCV coinfection accelerates progression to acquired immune deficiency syndrome (AIDS), and HIV infection stimulates liver disease progression [15,16]. Similarly, through a multifactorial interaction mechanism, HBV replication accelerates advanced fibrosis progression, increasing the risk of liver events and death [16].

Mortality among PLWHIV across Brazil has decreased, but not homogenously [5]. A national population-based study showed that CD4 $\leq$200 cells/mm^3 at ART initiation was associated with HIV-related mortality [17]. Moreover, cohort studies in Brazil's Southeast region identified HIV/HCV and HIV/HBV coinfections as further predictors of HIV-related mortality [18].

In previous international studies, older age [19,20], non-Caucasian ethnicity [21] and a low education level [22,23] were all independently associated with increased mortality among PLWHIV. Likewise, a nationwide Brazilian study highlighted that a low education level and living outside the Southeast region were both associated with late presentation for care [24].

Given that early ART is currently the most effective strategy to control HIV-related morbidity and mortality [25], we presume that delayed ART might also be linked to all-cause mortality in Brazilian PLWHIV. Accordingly, we suppose that coinfections and sociodemographic factors might also be associated with all-cause deaths in this population in Brazil.

The objective of our study was to investigate to what extent delayed ART, hepatitis coinfections and sociodemographic characteristics predict all-cause mortality in the country's HIV population. Using a national linkage database, representative of PLWHIV receiving care in Brazil, we identified the covariates associated with all-cause mortality among Brazilian PLWHIV and estimated the population attributable fraction (PAF) of the mortality rate due to each modifiable risk factor, while accounting for known predictors of mortality in this population.

Methods

Databases

Despite national coverage, the four country's databases (reflecting disease reporting, HIV laboratory tests, ART and death notification) [26–29], used in this study, do not have a common identification number. Accordingly, we performed a probabilistic record linkage using individual data (name, mother's maiden name, date of birth and city of birth) for

the period January 1, 2007 to December 31, 2015, applying a Bloom filter [30]. We then checked for consistencies and duplicates, and removed all personal identification.

Ethical considerations

The ethics review board of the Faculty of Health Sciences at the University of Brasilia approved the study and provided a waiver of informed consent for secondary use of data. The Ministry of Health of Brazil agreed to data access exclusively for the study period.

Study population

The study population comprised all PLWHIV registered in SUS aged ≥18 years old at the beginning of follow-up, with at least one recorded CD4 count between January 1, 2007 and December 31, 2015, and with complete data for gender, region of residence and hepatitis coinfections.

Study design

We performed a survival analysis with entry date (baseline) at the first available CD4 count date. The end of follow-up date was defined as the latest available news date (HIV laboratory test or death), with censoring at December 31, 2015 due to data availability.

Outcome

The outcome was all-cause deaths occurring between January 1, 2007 and December 31, 2015.

Covariates

Time-fixed covariates were age at baseline, gender, ethnicity, education level, HIV transmission mode, region of residence, and HCV and HBV coinfections. Education level was classified into three groups: illiteracy, basic education (defined here as primary/lower secondary education) and higher education (defined here as upper secondary/third-level education) [31].

HCV coinfection was defined as detectable anti-HCV antibodies and HCV-RNA, or International Classification of Diseases (ICD-10) codes B17.1/B18.2 as the cause of death. HBV coinfection was defined as detectable anti-HBV antibodies or hepatitis B virus surface antigen, or ICD-10 codes B16/B17.0/B18.0/B18.1 as the cause of death [32].

Time-varying covariates were CD4 count and ART status (treated versus untreated). All measures available for both covariates during the follow-up period were included. In addition, to test the effect of delayed ART, a combined time-varying variable was created using the interaction between ART status and the last available CD4 count (with 200 cells/mm^3 threshold) before ART initiation.

Missing data

Missing data concerned three of the covariates: ethnicity, education level and HIV transmission mode (we did not impute missing data concerning unrecorded CD4 counts before ART initiation, as this regarded individuals already on ART at baseline). Missing values for the three mentioned covariates were imputed before analysis using multiple imputation by chained equations (MICE) [33], under a missing at random assumption. All observed variables were used in the imputation process, generating 25 imputed sets.

Statistical analyses

Global and regional mortality rates were computed as the number of all-cause deaths occurring during the study period divided by the number of person-years (PY) (i.e., the sum, for all patients, of the number of years between baseline and end of follow-up).

An extended proportional hazard Cox model based on Breslow's estimates [34] was applied after multiple imputation. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated by combining regression coefficients and standard errors from the model estimated for each of the imputed data sets. Since all covariates tested were very significantly associated with the outcome (Wald test p-value $<10^{-3}$) in univariable and multivariable analyses, the final multivariable model included all fixed covariates and the combined time-varying covariate.

The proportional risks assumption was tested graphically using scaled Schoenfeld residuals, log-log curves, and by comparing the Kaplan-Meier survival function with the model-predicted survival function [35].

Finally, for each of the modifiable factors, we estimated the PAF, defined as the proportion of mortality which could be avoided by risk factor modification [36,37]. We calculated adjusted PAF based on the final Cox multivariable model estimates across multiply imputed data sets using the punafcc Stata command for each category of interest. The punafcc command calculates the unattributable fraction, which is a mean between-scenario HR (the real-world scenario of individuals at risk and not at risk, and a fantasy scenario where no one is at risk), which is then subtracted from 1 to provide the PAF [38,39].

RStudio 2015 (RStudio, Inc., Boston, MA) and Stata/SE 14.2 (StataCorp LP, College Station, USA) were used for data treatment and for statistical analyses.

Subgroup and sensitivity analyses

Subgroup analyses were performed for HIV/HCV-coinfected and non-HIV/HCV-coinfected individuals. Sensitivity analyses were performed for a region-by-region analysis, and by calendar period (pre- and post-2013, the year when treatment for all PLWHIV was implemented).

Results

Descriptive analysis

The study included 411,028 PLWHIV followed up in SUS between January 2007 and December 2015. There were 3,311,425 observations, with a mean of 8 records per person, and at least one record per person per year.

The study population were mainly aged between 18 and 39 years old (61.0%) (median age: 36 years [interquartile range (IQR): 29-44 years]), male (61.0%), and residents in the Southeast region (48.2%). Moreover, 2.5% and 1.4% were HCV- and HBV-coinfected, respectively. At baseline, 74.7% had a CD4 count ≥200 cells/mm^3 and 78.6% were ART-untreated. Among those with complete data, 54.7% were Caucasian, 79.3% had basic education, and 70.5% were heterosexually HIV-infected (Table 1).

Deceased individuals had a higher median age (40 years [IQR: 32-48 years]). Among those aged ≥50 years, 22.8% died. Furthermore, 16.4% of men and approximately 15% of PLWHIV in each of Brazil's 5 regions also died. HCV and HBV coinfections accounted for 34.5% and 22.8%, respectively, of those who died. At baseline, 24.7% of those treated with CD4 <200 cells/mm^3 at ART initiation died. From complete data,

14.3% of non-Caucasians, 20.7% of illiterate people and 35.1% of those HIV-infected through injecting drug use (IDU) died (Table 1).

Survival analysis

Among the 411,028 PLWHIV – accounting for 1,788,381 PY from 2007 to 2015 – there were 61,630 all-cause deaths. Median follow-up time was 4.24 years. Global mortality rate was 3.45 [95% CI: 3.42-3.47] deaths per 100 PY. Mortality rate by region of residence varied from 3.26 [3.22-3.29] to 4.45 [4.32-4.59] deaths per 100 PY in the Southeast and North regions, respectively (Figure 1).

Univariable analyses

All covariates were significantly associated with mortality in the univariable models (p-value$<10^{-3}$) (Table 2).

Multivariable analysis

In the multivariable analysis, the time-fixed covariates associated with an increased mortality were older age ('40-49 years' and '≥50 years' (adjusted HR (aHR) [95% CI]: 1.22 [1.20-1.24] and 1.73 [1.69-1.77] versus '18-39 years', respectively), male gender (1.52 [1.49-1.55]), non-Caucasian ethnicity (1.15 [1.13-1.18] versus Caucasian), illiteracy and basic education (1.66 [1.57-1.75] and 1.27 [1.23-1.31] versus higher education, respectively). The HIV transmission modes associated with higher mortality were IDU (1.75 [1.65-1.85]) and heterosexual (1.26 [1.23-1.29]), versus transmission between men who have sex with men (MSM)/bisexual. Both HIV/HCV (1.73 [1.67-

1.79]) and HIV/HBV (1.25 [1.18-1.32]) coinfections were independently associated with an increased mortality (Table 2).

With respect to region of residence, living in the North, Northeast and South regions was associated with higher mortality (1.27 [1.22-1.33], 1.13 [1.09-1.18] and 1.06 [1.02-1.10] versus living in the Central-West region, respectively). Furthermore, the time-varying factors associated with an increased mortality were being ART-untreated (1.78 [1.75-1.83]), ART-treated with CD4 <200 cells/mm^3 at ART initiation (2.53 [2.47-2.59]) and ART-treated with unrecorded CD4 at ART initiation (1.33 [1.30-1.36]) versus ART-treated with CD4 ≥200 cells/mm^3 at ART initiation (Table 2).

Proportional hazards assumption

The proportional hazards assumption was supported for all fixed covariates in the final multivariable model through graphical diagnosis (data not shown).

Population attributable fractions (PAF)

After adjusting for covariates in the multivariable model, PAF showed that 2.44% [95% CI: 2.26-2.62] and 0.42% [0.31-0.53] of the mortality rate was attributable to HCV and HBV coinfections, respectively. Moreover, delayed ART (CD4 <200 cells/mm^3 at ART initiation) accounted for 14.20% [13.81-14.59] of the mortality rate, ART-untreated for 14.06% [13.54-14.59], and ART-treated with unrecorded CD4 at ART initiation for 5.74% [5.26-6.21] (Table 2).

Subgroup analyses

Among the 10,313 HIV/HCV-coinfected individuals (57,039 PY), 3,558 all-cause deaths occurred during the study period – i.e., a mortality rate of 6.24 [95% CI: 6.04-6.45] deaths per 100 PY – for a median follow-up time of 6.44 years.

HIV/HCV-coinfected individuals had a higher mortality than non-HIV/HCV-coinfected individuals for the following variables: older age ('40-49 years' (aHR [95% CI]: 1.38 [1.28-1.49] and '≥50 years' (2.03 [1.85-2.22]) versus '18-39 years'), and HIV/HCV/HBV triple coinfection (1.55 [1.36-1.76]). However, among HIV/HCV-coinfected individuals, living in the Southeast and South regions was associated with lower mortality (0.68 [0.56-0.82] and 0.74 [0.62-0.90] versus living in the Central-West region, respectively) (Table 3).

As for modifiable factors in the HIV/HCV-coinfected subgroup, being ART-treated with CD4 <200 cells/mm^3 at ART initiation accounted for 7.92% [95% CI: 6.51-9.31] of the mortality rate, followed by being ART-untreated (7.12% [5.20-9.01]) and ART-treated with unrecorded CD4 at ART initiation (3.52% [0.87-6.10]). HIV/HCV/HBV triple coinfection accounted for 1.20% [1.13-1.27] of mortality (Table 3).

Sensitivity analyses

Sensitivity analyses revealed all the same predictors of mortality identified in the global analysis in all PLWHIV.

In the region-by-region analysis, mortality in older people was higher in the Central-West region ('40-49 years' (aHR [95% CI]: 1.33 [1.23-1.44]) and '≥50 years' (1.87 [1.71-2.05]) versus '18-39 years') than elsewhere. Mortality was higher in the North region for HCV (2.53 [1.90-3.37]) and HBV (1.59 [1.27-1.99]) coinfections, as well as for ART-untreated (2.58 [2.36-2.81]), ART-treated with CD4 <200 cells/mm^3 at ART initiation

(3.50 [3.19-3.83]) and ART-treated with unrecorded CD4 at ART initiation (2.04 [1.79-2.32]) versus ART-treated with CD4 ≥200 cells/mm^3 at ART initiation. Being HIV-infected through IDU (1.96 [1.56-2.47]) (versus MSM/bisexual) was associated with higher mortality in the Northeast region. Finally, male gender (1.65 [1.59-1.72]), non-Caucasian ethnicity (1.27 [1.22-1.33]), illiteracy (2.26 [2.02-2.53]) and basic education (1.39 [1.30-1.48]) (versus higher education) were associated with higher mortality in the South region (Table 4).

Analyses by calendar period showed that the mortality risk in ART-untreated individuals (versus ART-treated with CD4 ≥200 cells/mm^3 at ART initiation) post-2013 (3.56 [3.41-3.71]) was twice as high as pre-2013 estimates (1.66 [1.62-1.71]) (data not shown).

Discussion

This is the largest study to date investigating all-cause mortality of PLWHIV followed up in Brazil's public health system between 2007 and 2015. Furthermore, it is the only study to estimate the proportion of deaths attributable to specific factors, which could be avoided by implementing targeted healthcare and health surveillance policies. The primary result is that delayed ART (i.e., CD4<200 cells/mm^3 at ART initiation) was the main modifiable predictor of mortality in PLWHIV in Brazil, accounting for approximately 1 in 6 deaths. As this result is independent of the other cofactors explored here, interventions ensuring early ART initiation for all PLWHIV – irrespective of CD4 counts – could decrease the mortality rate in Brazil's HIV population by 14%.

Given that the mortality profile of PLWHIV has changed in the last few years [12], delayed ART was not only the leading predictor of all-cause deaths in PLWHIV in our study, but also among HIV/HCV-coinfected individuals, accounting for 8% of the

mortality rate in this subgroup. Delayed ART has been associated elsewhere with an increased mortality in the HIV population due to HIV-related [10,40] and non-HIV-related events [41,42]. Initiating ART with a CD4 <200 cells/mm^3 is also a proxy of late diagnosis and late presentation for care, which were both related to mortality in this population [43].

Despite insufficient data in our study for the period following the implementation of the government's 'treatment for all' policy, the mortality risk post-2013 in ART-untreated PLWHIV was twice that of pre-2013 level. As expected therefore, over the whole study period, being ART-untreated was a strong predictor of mortality.

Moreover, HCV and HBV coinfections were important modifiable factors of mortality in our study population, accounting for 2.44% and 0.42% of the mortality rate, respectively. These results are consistent with previous studies showing that HCV coinfection was associated with increased all-cause and HCV-related mortality in PLWHIV [18,19], as a consequence of cirrhosis, end-stage liver disease and hepatocellular carcinoma [44]. HBV coinfection was associated with lower CD4 count at ART initiation [45] and with higher mortality, despite early treatment in PLWHIV [46]. In our study, HIV/HCV/HBV triple coinfection accounted for 2.62% of the mortality rate, probably due to exacerbation of liver fibrosis [47].

Mortality in persons aged 50 years old and over was almost twice that in those aged between 18 and 39 years old. Previous studies showed that age-related comorbidities were more prevalent in PLWHIV because of chronic systemic inflammation and exposure to ART [48], resulting in excess mortality at older age [20]. Additionally, older HIV/HCV-coinfected individuals in our study faced higher mortality than non-HIV/HCV-coinfected

people, probably because most of Brazil's HCV population are over 40 years old [49], and because liver disease takes longer to reach advanced stages [50].

In line with previous studies showing that men had higher HIV-related mortality than women [17,51,52], male gender was associated with an increased all-cause mortality in this study, especially among non-HIV/HCV-coinfected individuals. Our result suggests a remaining disproportionate risk of death for HIV-infected men, as reported before [52]. This could be explained by the relationship encountered between male gender and late presentation for care [53], HIV late diagnosis [54], and delayed ART [52].

With respect to HIV transmission mode, mortality in people infected through IDU was almost twice as high as in those infected through MSM/bisexual intercourse. Nevertheless, the proportion of HIV infection through IDU in our study diminished from 2.5% in 2007 to 0.4% in 2015, confirming a tendency towards a decreasing impact of this predictor of mortality [17], historically associated with IDU until the 1990s in Brazil [55]. The effect of IDU transmission mode in our population reflects previous findings where IDU-based HIV infection was associated with a higher risk of late diagnosis and higher HIV-related mortality than sexual transmission [56].

Indeed, heterosexual HIV transmission was associated with higher mortality in our population than MSM/bisexual transmission. Elsewhere, heterosexual HIV transmission was independently associated with late presentation for care and late presentation with advanced disease [53]. Given that MSM in general are at higher risk of acquiring HIV due to their sexual behaviors [57], and that HIV is more prevalent among them [58], they are tested more often. Accordingly, they are usually diagnosed early and have better linkage to care [59]. The fact that heterosexual transmission has been the primary reported

mode of HIV infection in Brazil since 2000 [2] underlines the need for HIV testing in heterosexual couples.

We also found that non-Caucasian ethnicity – previously linked to HIV-related mortality in Brazil [60,61] – was associated with higher all-cause mortality. In other international studies, non-Caucasians had higher all-cause mortality [62,63], lower life expectancy [64] and higher levels of HIV care discontinuity [21] than PLWHIV of Caucasian ethnicity. The lack of any association between non-Caucasian ethnicity and mortality in the HIV/HCV-coinfected subgroup in our study may be due to the lower prevalence of recorded non-Caucasian ethnicity among Brazilian HIV/HCV-coinfected individuals [65].

Furthermore, we found that illiteracy and basic education were strong predictors of mortality, which strengthens previous evidence showing that low education level is associated with higher mortality among PLWHIV [18,23]. Education level has been associated with healthy behaviors, improved self-assessed health, greater life expectancy, lower morbidity and lower mortality from different causes [66]. In addition, it may reflect socioeconomic status, which was related to increased HIV-related mortality in other cohorts [67] and considered a determinant of survival in PLWHIV [68].

With regard to region of residence, we revealed geographical and social inequalities in terms of PLWHIV mortality in Brazil. The North region was associated with higher mortality, probably because the extension of the HIV epidemic through rural Amazon areas continues to complicate access to care [69]. Besides, as HBV is endemic in this region [70,71], HIV/HCV coinfection and HIV/HCV/HBV triple coinfection may be diagnosed late and therefore have a greater impact, as revealed in the region-by-region analysis.

The Northeast region was also associated with higher mortality in our study. A previous study found a greater proportion of non-HIV-related causes of death than HIV-related causes among deceased PLWHIV in this region [72], possibly reflecting more accurate reporting of deaths there. Our region-by-region analysis showed that PLWHIV infected through IDU faced higher mortality in the Northeast than elsewhere. This is surprising, as historically HIV incidence among people who use drugs has been higher in the Southeast and South regions [73,74]. The fact that risk reduction policies are better implemented in the Southeast region [75], and the possibility that these policies are not yet sufficiently extended to the country's other regions, may explain this.

Living in the South region was associated with higher mortality in the global analysis, presumably because of the stronger impact of certain sociodemographic factors (male gender, non-Caucasian ethnicity and illiteracy/basic education), highlighted in the region-by-region analysis. This is consistent with previous research revealing that the HIV epidemic is generalized throughout most of this region [76,77]. Indeed, the HIV mortality rate there has been higher than national estimates since 2008 [2].

By contrast, living in the Southeast and South regions was associated with lower mortality among HIV/HCV-coinfected people. This might be explained by better health infrastructure [78], as well as sociodemographic and environmental conditions [24] in these regions, which may translate into improved early diagnosis and greater linkage to care [79].

The major strength of our study is its representativeness of the entire HIV population in Brazil, including people that present late for care and for treatment. Our results provide valuable information to minimize sociodemographic inequalities and therefore improve survival in the Brazilian PLWHIV population.

Other study strengths and limitations concern the use of secondary data. While information systems may be subject to underreporting and data misclassification [80], secondary databases may be an efficient strategy to represent a real-world cohort and diminish the risk of bias related to time-varying factors [81]. In order to reduce the under-ascertainment of coinfection prevalence based on disease notification [82], we also included deaths related to HCV and to HBV in the case definition of hepatitis coinfections. With regard to incomplete data, multiple imputation estimates allowed us to minimize selection bias [33]. As we accounted for all-cause deaths, underestimation of mortality in our study is unlikely.

In conclusion, besides modifiable factors (i.e., delayed ART and hepatitis coinfections), sociodemographic characteristics were significant predictors of all-cause mortality in PLWHIV in Brazil. This highlights the importance of actions targeting specific populations (males, non-Caucasians, illiterate people and those with basic education), which goes beyond early ART and coinfections control, in order to reduce avoidable deaths among Brazilian PLWHIV.

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Melina E SANTOS performed the research, analyzed the data and wrote the paper. Camelia PROTOPOPESCU and Patrizia CARRIERI designed the study and guided the research. Rachel A RIBEIRO and Antony STEVENS performed the record linkage. Gerson F M PEREIRA contributed to the data access, as did Adele S BENZAKEN who also provided ideas for drafting the paper. Marie L NISHIMWE and Issifou YAYA contributed to the data management. Wildo N ARAÚJO contributed to the study's conception and design. All authors approved the final version. Fábio MESQUITA, MD, PhD, and team leader of HIV and Viral Hepatitis at the WHO Country Office in Myanmar, contributed to the study and gave valuable input to the paper. Finally, our thanks to Jude SWEENEY for the English revision and editing of this manuscript.

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Figure 1

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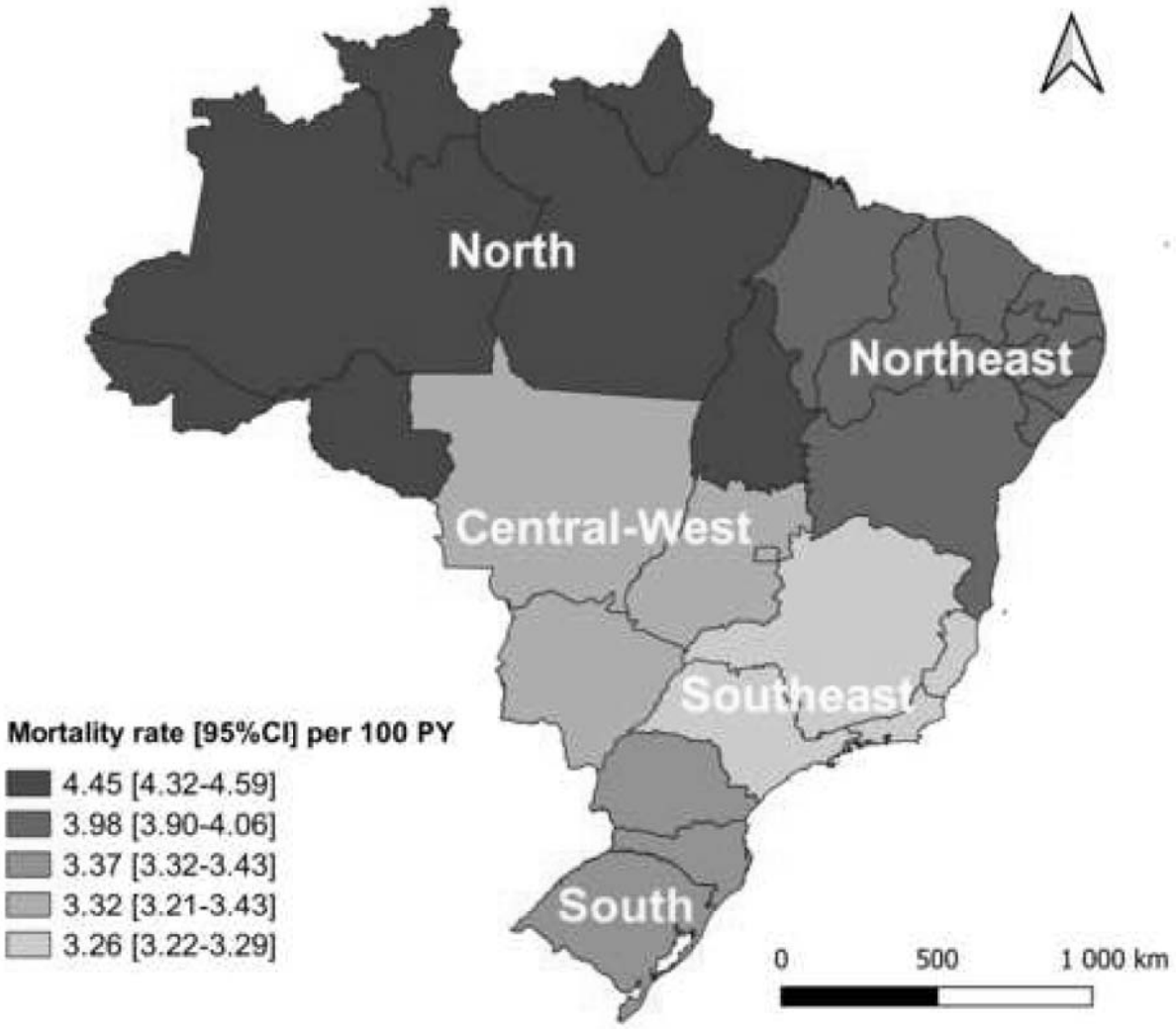

Figure 1. Mortality rate by region of residence per 100 person-years (PY) in the study population (Brazil, 2007-2015, N= 411,028)

Table 1

Table 1. Characteristics of individuals and all-cause deaths in the study population, and according to HIV/HCV coinfection (Brazil, 2007-2015, N= 411,028)

Covariates	Study population N (%)*		HIV/HCV coinfected N (%)*		Not HIV/HCV coinfected N (%)*	
	Total individuals (N= 411,028)	All-cause deaths (n= 61,630)**	Total individuals (N= 10,313)	All-cause deaths (n= 3,558)**	Total individuals (N= 400,715)	All-cause deaths (n= 58,072)**
Age (years)§						
Median [IQR]	36 [29-44]	40 [32-48]	41 [36-47]	43 [37-48]	36 [29-44]	39 [32-48]
18-39	250,816 (61.0)	30,361 (12.1)	4,420 (42.9)	1,250 (28.3)	246,396 (61.5)	29,111 (11.8)
40-49	102,393 (24.9)	18,100 (17.7)	4,213 (40.8)	1,550 (36.8)	98,180 (24.5)	16,550 (16.9)
≥50	57,819 (14.1)	13,169 (22.8)	1,680 (16.3)	758 (45.1)	56,139 (14.0)	12,411 (22.1)
Gender§						
Female	160,346 (39.0)	20,509 (12.8)	2,865 (27.8)	858 (30.0)	157,481 (39.3)	19,651 (12.5)
Male	250,682 (61.0)	41,121 (16.4)	7,448 (72.2)	2,700 (36.3)	243,234 (60.7)	38,421 (15.8)

Covariates	Study population N (%)*		HIV/HCV coinfected N (%)*		Not HIV/HCV coinfected N (%)*	
	Total individuals (N= 411,028)	All-cause deaths (n= 61,630)**	Total individuals (N= 10,313)	All-cause deaths (n= 3,558)**	Total individuals (N= 400,715)	All-cause deaths (n= 58,072)**
Ethnicity§						
Caucasian	152,379 (54.7)	19,337 (12.7)	4,978 (65.4)	1,544 (31.0)	147,401 (54.4)	17,793 (12.1)
Non-Caucasian	126,174 (45.3)	18,091 (14.3)	2,632 (34.6)	820 (31.2)	123,542 (45.6)	17,271 (14.0)
*Missing****	*132,475 (32.2)*	*24,202 (39.3)*	*2,703 (26.2)*	*1,194 (33.6)*	*129,772 (32.4)*	*23,008 (39.6)*
Education level§						
Higher education	39,298 (17.5)	2,747 (7.0)	782 (12.4)	175 (22.4)	38,516 (17.6)	2,572 (6.7)
Basic education	177,955 (79.3)	24,033 (13.5)	5,358 (85.3)	1,639 (30.6)	172,597 (79.1)	22,394 (13.0)
Illiteracy	7,266 (3.2)	1,505 (20.7)	144 (2.3)	65 (45.1)	7,122 (3.3)	1,440 (20.2)
*Missing****	*186,509 (45.4)*	*33,345 (54.1)*	*4,029 (39.1)*	*1,679 (47.2)*	*182,480 (45.5)*	*31,666 (54.5)*
HIV transmission mode§						

Covariates	Study population N (%)*		HIV/HCV coinfected N (%)*		Not HIV/HCV coinfected N (%)*	
	Total individuals (N= 411,028)	All-cause deaths (n= 61,630)**	Total individuals (N= 10,313)	All-cause deaths (n= 3,558)**	Total individuals (N= 400,715)	All-cause deaths (n= 58,072)**
MSM/bisexual	67,144 (28.0)	7,951 (11.8)	1,408 (18.4)	431 (30.6)	65,736 (28.3)	7,520 (11.4)
Heterosexual	168,960 (70.5)	29,000 (17.2)	5,402 (70.4)	1,788 (33.1)	163,558 (70.5)	27,212 (16.6)
IDU	3,729 (1.5)	1,307 (35.1)	860 (11.2)	339 (39.4)	2,869 (1.2)	968 (33.7)
*Missing****	*171,195 (41.7)*	*23,372 (37.9)*	*2,643 (25.6)*	*1,000 (28.1)*	*168,552 (42.1)*	*22,372 (38.5)*
Region of residence[§]						
Central-West	26,259 (6.4)	3,654 (13.9)	310 (3.0)	130 (41.9)	25,949 (6.5)	3,524 (13.6)
Southeast	198,332 (48.2)	30,352 (15.3)	6,262 (60.7)	2,151 (34.4)	192,070 (47.9)	28,201 (14.7)
North	29,017 (7.1)	4,301 (14.8)	91 (0.9)	50 (55.0)	28,926 (7.2)	4,251 (14.7)
Northeast	61,684 (15.0)	9,293 (15.1)	248 (2.4)	98 (39.5)	61,436 (15.3)	9,195 (15.0)
South	95,736 (23.3)	14,030 (14.7)	3,402 (33.0)	1,129 (33.2)	92,334 (23.1)	12,901 (14.0)

Covariates	Study population N (%)*		HIV/HCV coinfected N (%)*		Not HIV/HCV coinfected N (%)*	
	Total individuals (N= 411,028)	All-cause deaths (n= 61,630)**	Total individuals (N= 10,313)	All-cause deaths (n= 3,558)**	Total individuals (N= 400,715)	All-cause deaths (n= 58,072)**
HCV coinfection§§						
Not HCV coinfected	400,715 (97.5)	58,072 (14.5)	NA	NA	NA	NA
HCV coinfected	10,313 (2.5)	3,558 (34.5)				
HBV coinfection§§						
Not HBV coinfected	405,331 (98.6)	60,330 (14.9)	9,793 (95.0)	3,296 (33.7)	395,538 (98.7)	57,034 (14.4)
HBV coinfected	5,697 (1.4)	1,300 (22.8)	520 (5.0)	262 (50.4)	5,177 (1.3)	1,038 (20.1)
CD4 count (cells/mm^3)§§§						
CD4 ≥200	307,191 (74.7)	31,327 (10.2)	7,826 (75.9)	2,360 (30.2)	299,365 (74.7)	28,967 (9.7)
CD4 <200	103,837 (25.3)	30,303 (29.2)	2,487 (24.1)	1,198 (48.2)	101,350 (25.3)	29,105 (28.7)
ART status§§§						

Covariates	Study population N (%)*		HIV/HCV coinfected N (%)*		Not HIV/HCV coinfected N (%)*	
	Total individuals (N= 411,028)	All-cause deaths (n= 61,630)**	Total individuals (N= 10,313)	All-cause deaths (n= 3,558)**	Total individuals (N= 400,715)	All-cause deaths (n= 58,072)**
ART-untreated	322,973 (78.6)	46,862 (14.5)	6,979 (67.7)	2,390 (34.3)	315,994 (78.9)	44,472 (14.1)
ART-treated	88,055 (21.4)	14,768 (16.8)	3,334 (32.3)	1,168 (35.0)	84,721 (21.1)	13,600 (16.1)
ART status according to CD4 count (cells/mm^3) at ART initiation§§§						
ART-treated/CD4 ≥200	1,753 (0.4)	130 (7.4)	18 (0.2)	5 (27.8)	1,735 (0.4)	125 (7.2)
ART-untreated	322,973 (78.6)	46,862 (14.5)	6,979 (67.7)	2,390 (34.3)	315,994 (78.9)	44,472 (14.1)
ART-treated/CD4<200	1,442 (0.3)	356 (24.7)	18 (0.2)	8 (44.4)	1,424 (0.3)	348 (24.4)
ART-treated/ unrecorded CD4	84,860 (20.7)	14,282 (16.8)	3,298 (31.9)	1,155 (35.0)	81,562 (20.4)	13,127 (16.1)

ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug use; IQR, interquartile range; MSM, men who have sex with men; NA, not applicable.

* The distribution of explanatory covariates does not include missing values.

** The proportion of all-cause deaths is calculated according to covariate category.

*** The proportion of *missing values* is shown among total individuals and all-cause deaths.

§ Fixed covariate, measured at baseline.

§§ Fixed covariate, measured at baseline or at death (i.e., death notification).

§§§ Time-varying covariate, descriptive statistics given for baseline.

Table 2

Table 2. Factors associated with all-cause mortality in the study population (univariable and multivariable analyses, extended Cox model with multiple-imputation, Brazil, 2007-2015, N= 411,028)

Covariates	All-cause deaths (n= 61,630)				
	HR [95% CI]	p-value	aHR [95% CI]	p-value	aPAF (%) [95% CI]
Age (years)[§]					
18-39 (ref)	1		1		
40-49	1.27 [1.24-1.29]	$<10^{-3}$	1.22 [1.20-1.24]	$<10^{-3}$	NA
≥50	1.76 [1.73-1.80]	$<10^{-3}$	1.73 [1.69-1.76]	$<10^{-3}$	
Gender[§]					
Female (ref)	1		1		NA
Male	1.44 [1.42-1.46]	$<10^{-3}$	1.52 [1.49-1.55]	$<10^{-3}$	
Ethnicity[§]					
Caucasian (ref)	1		1		NA
Non-Caucasian	1.19 [1.17-1.21]	$<10^{-3}$	1.15 [1.13-1.18]	$<10^{-3}$	

Covariates	All-cause deaths (n= 61,630)				
	HR [95% CI]	p-value	aHR [95% CI]	p-value	aPAF (%) [95% CI]
Education level[§]					
Higher education (ref)	1		1		
Basic education	1.37 [1.33-1.41]	$<10^{-3}$	1.27 [1.23-1.31]	$<10^{-3}$	NA
Illiteracy	2.09 [1.98-2.20]	$<10^{-3}$	1.66 [1.57-1.75]	$<10^{-3}$	
HIV transmission mode[§]					
MSM/bisexual (ref)	1		1		
Heterosexual	1.17 [1.15-1.20]	$<10^{-3}$	1.26 [1.23-1.29]	$<10^{-3}$	NA
IDU	2.00 [1.90-2.12]	$<10^{-3}$	1.75 [1.65-1.85]	$<10^{-3}$	
Region of residence[§]					

Covariates	All-cause deaths (n= 61,630)				
	HR [95% CI]	p-value	aHR [95% CI]	p-value	aPAF (%) [95% CI]
Central-West (ref)	1		1		
Southeast	0.99 [0.96-1.03]	0.608	1.01 [0.97-1.04]	0.658	
North	1.30 [1.24-1.36]	$<10^{-3}$	1.27 [1.22-1.33]	$<10^{-3}$	NA
Northeast	1.18 [1.14-1.23]	$<10^{-3}$	1.13 [1.09-1.18]	$<10^{-3}$	
South	1.02 [0.98-1.06]	0.335	1.06 [1.02-1.10]	0.002	
HCV coinfection§§					
Not HCV coinfected (ref)	1		1		
HCV coinfected	1.91 [1.85-1.97]	$<10^{-3}$	1.73 [1.67-1.79]	$<10^{-3}$	2.44 [2.26-2.62]
HBV coinfection§§					
Not HBV coinfected (ref)	1		1		
HBV coinfected	1.38 [1.30-1.45]	$<10^{-3}$	1.25 [1.18-1.32]	$<10^{-3}$	0.42 [0.31-0.53]

Covariates	All-cause deaths (n= 61,630)				
	HR [95% CI]	p-value	aHR [95% CI]	p-value	aPAF (%) [95% CI]
ART status according to CD4 count (cells/mm^3) at ART initiation[§§§]					
ART-treated / CD4 ≥200 (ref)	1		1		
ART-untreated	1.76 [1.72-1.80]	$<10^{-3}$	1.78 [1.75-1.83]	$<10^{-3}$	14.06 [13.54-14.59]
ART-treated / CD4 <200	2.70 [2.63-2.76]	$<10^{-3}$	2.53 [2.47-2.59]	$<10^{-3}$	14.20 [13.81-14.59]
ART-treated / unrecorded CD4	1.38 [1.35-1.41]	$<10^{-3}$	1.33 [1.30-1.36]	$<10^{-3}$	5.74 [5.26-6.21]

aHR, adjusted hazard ratio; aPAF, adjusted population attributable fraction; ART, antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IDU, injecting drug use; MSM, men who have sex with men; NA, not applicable.

[§] Fixed covariate, measured at baseline.

[§§] Fixed covariate, measured at baseline or at death (i.e., death notification).

[§§§] Time-varying covariate.

Table 3

Table 3. Factors associated with all-cause mortality according to HIV/HCV coinfection (multivariable analysis, extended Cox model with multiple imputation, Brazil, 2007-2015, N= 411,028)

Covariates	All-cause deaths (n= 61,630)					
	HIV/HCV coinfected (n= 3,558)			Not HIV/HCV coinfected (n= 58,072)		
	aHR [95% CI]	p-value	aPAF (%) [95% CI]	aHR [95% CI]	p-value	aPAF (%) [95% CI]
Age (years)[§]						
18-39 (ref)	1			1		
40-49	1.38 [1.28-1.49]	$<10^{-3}$	NA	1.21 [1.19-1.24]	$<10^{-3}$	NA
≥50	2.03 [1.85-2.22]	$<10^{-3}$		1.71 [1.68-1.75]	$<10^{-3}$	
Gender[§]						
Female (ref)	1		NA	1		NA
Male	1.25 [1.15-1.35]	$<10^{-3}$		1.54 [1.51-1.57]	$<10^{-3}$	
Ethnicity[§]						

Covariates	All-cause deaths (n= 61,630)					
	HIV/HCV coinfected (n= 3,558)			Not HIV/HCV coinfected (n= 58,072)		
	aHR [95% CI]	p-value	aPAF (%) [95% CI]	aHR [95% CI]	p-value	aPAF (%) [95% CI]
Caucasian (ref)	1		NA	1		NA
Non-Caucasian	1.02 [0.94-1.11]	0.559		1.16 [1.13-1.18]	$<10^{-3}$	
Education level[§]						
Higher education (ref)	1			1		
Basic education	1.14 [1.00-1.31]	0.049	NA	1.27 [1.23-1.32]	$<10^{-3}$	NA
Illiteracy	1.60 [1.22-2.09]	0.001		1.66 [1.57-1.76]	$<10^{-3}$	
HIV transmission mode[§]						
MSM/bisexual (ref)	1			1		
Heterosexual	1.08 [0.97-1.20]	0.160	NA	1.27 [1.24-1.30]	$<10^{-3}$	NA
IDU	1.20 [1.05-1.38]	0.009		1.95 [1.83-2.09]	$<10^{-3}$	
Region of residence[§]						

Covariates	All-cause deaths (n= 61,630)					
	HIV/HCV coinfected (n= 3,558)			Not HIV/HCV coinfected (n= 58,072)		
	aHR [95% CI]	p-value	aPAF (%) [95% CI]	aHR [95% CI]	p-value	aPAF (%) [95% CI]
Central-West (ref)	1			1		
Southeast	0.68 [0.56-0.82]	$<10^{-3}$		1.02 [0.99-1.06]	0.225	
North	1.37 [0.97-1.92]	0.072	NA	1.28 [1.22-1.34]	$<10^{-3}$	NA
Northeast	0.79 [0.60-1.03]	0.086		1.14 [1.10-1.19]	$<10^{-3}$	
South	0.74 [0.62-0.90]	0.002		1.08 [1.03-1.12]	$<10^{-3}$	
HBV coinfection[§§]						
Not HBV coinfected (ref)	1			1		
HBV coinfected	1.55 [1.36-1.76]	$<10^{-3}$	2.62 [1.78-3.45]	1.20 [1.13-1.27]	$<10^{-3}$	0.29 [0.19-0.40]
ART status according to CD4 count (cells/mm^3) at ART initiation[§§§]						

Covariates	All-cause deaths (n= 61,630)					
	HIV/HCV coinfected (n= 3,558)			Not HIV/HCV coinfected (n= 58,072)		
	aHR [95% CI]	p-value	aPAF (%) [95% CI]	aHR [95% CI]	p-value	aPAF (%) [95% CI]
ART-treated / CD4 ≥200 (ref)	1			1		
ART-untreated	1.43 [1.30-1.58]	$<10^{-3}$	7.12 [5.20-9.01]	1.81 [1.77-1.85]	$<10^{-3}$	14.55 [14.00-15.09]
ART-treated / CD4 <200	1.85 [1.66-2.05]	$<10^{-3}$	7.92 [6.51-9.31]	2.58 [2.51-2.64]	$<10^{-3}$	14.60 [14.20-15.00]
ART-treated / unrecorded CD4	1.12 [1.03-1.22]	0.009	3.52 [0.87-6.10]	1.34 [1.31-1.38]	$<10^{-3}$	5.80 [5.31-6.28]

aHR, adjusted hazard ratio; aPAF, adjusted population attributable fraction; ART, antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug use; MSM, men who have sex with men; NA, not applicable.

[§] Fixed covariate, measured at baseline.

[§§] Fixed covariate, measured at baseline or at death (i.e., death notification).

[§§§] Time-varying covariate.

Table 4

Table 4. Factors associated with all-cause mortality in the study population by region of residence (multivariable analyses, extended Cox model with multiple imputation, Brazil, 2007-2015, N= 411,028)

Covariates	All-cause deaths (n= 61,630)				
	Central-West (n= 3,654)	**Southeast (n= 30,352)**	**North (n= 4,301)**	**Northeast (n= 9,293)**	**South (n= 14,030)**
	aHR [95% CI]	**aHR [95% CI]**	**aHR [95% CI]**	**aHR [95% CI]**	**aHR [95% CI]**
Age (years)[§]					
18-39 (ref)	1	1	1	1	1
40-49	1.33 [1.23-1.44]	1.21 [1.18-1.24]	1.18 [1.10-1.27]	1.13 [1.08-1.19]	1.29 [1.24-1.34]
≥50	1.87 [1.71-2.05]	1.72 [1.67-1.77]	1.65 [1.51-1.80]	1.53 [1.44-1.62]	1.84 [1.76-1.93]
Gender[§]					
Female (ref)	1	1	1	1	1
Male	1.49 [1.38-1.61]	1.47 [1.43-1.51]	1.45 [1.35-1.56]	1.55 [1.47-1.62]	1.65 [1.59-1.72]
Ethnicity[§]					

Covariates	All-cause deaths (n= 61,630)				
	Central-West (n= 3,654)	Southeast (n= 30,352)	North (n= 4,301)	Northeast (n= 9,293)	South (n= 14,030)
	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]
Caucasian (ref)	1	1	1	1	1
Non-Caucasian	1.15 [1.06-1.25]	1.12 [1.09-1.16]	1.14 [1.04-1.26]	1.11 [1.04-1.18]	1.27 [1.22-1.33]
Education level[§]					
Higher education (ref)	1	1	1	1	1
Basic education	1.24 [1.06-1.44]	1.25 [1.19-1.30]	1.25 [1.12-1.39]	1.18 [1.07-1.30]	1.39 [1.30-1.48]
Illiteracy	1.45 [1.13-1.86]	1.65 [1.52-1.80]	1.58 [1.31-1.89]	1.44 [1.26-1.64]	2.26 [2.02-2.53]
HIV transmission mode[§]					
MSM/bisexual (ref)	1	1	1	1	1
Heterosexual	1.33 [1.20-1.46]	1.27 [1.23-1.32]	1.16 [1.05-1.27]	1.27 [1.20-1.35]	1.23 [1.16-1.30]
IDU	1.95 [1.41-2.70]	1.65 [1.53-1.79]	1.52 [0.95-2.42]	1.96 [1.56-2.47]	1.84 [1.65-2.04]

Covariates	All-cause deaths (n= 61,630)				
	Central-West (n= 3,654)	Southeast (n= 30,352)	North (n= 4,301)	Northeast (n= 9,293)	South (n= 14,030)
	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]
HCV coinfection§§					
Not HCV coinfected (ref)	1	1	1	1	1
HCV coinfected	2.39 [1.99-2.85]	1.71 [1.63-1.79]	2.53 [1.90-3.37]	1.74 [1.43-2.11]	1.68 [1.57-1.78]
HBV coinfection§§					
Not HBV coinfected (ref)	1	1	1	1	1
HBV coinfected	1.36 [1.10-1.67]	1.26 [1.17-1.35]	1.59 [1.27-1.99]	1.22 [1.00-1.49]	1.14 [1.02-1.28]
ART status according to CD4 count (cells/mm^3) at ART initiation§§§					

Covariates	All-cause deaths (n= 61,630)				
	Central-West (n= 3,654)	Southeast (n= 30,352)	North (n= 4,301)	Northeast (n= 9,293)	South (n= 14,030)
	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]
ART-treated / CD4 ≥200 (ref)	1	1	1	1	1
ART-untreated	1.95 [1.77-2.15]	1.68 [1.63-1.73]	2.58 [2.36-2.81]	2.11 [1.99-2.23]	1.59 [1.51-1.67]
ART-treated / CD4 <200	2.37 [2.14-2.63]	2.56 [2.47-2.65]	3.50 [3.19-3.83]	2.39 [2.25-2.55]	2.43 [2.31-2.56]
ART-treated / unrecorded CD4	1.23 [1.12-1.36]	1.33 [1.29-1.37]	2.04 [1.79-2.32]	1.30 [1.21-1.40]	1.25 [1.19-1.31]

aHR, adjusted hazard ratio; aPAF, ART, antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug use; MSM, men who have sex with men.

[§] Fixed covariate, measured at baseline.

[§§] Fixed covariate, measured at baseline or at death (i.e., death notification).

[§§§] Time-varying covariate.