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Mortality among HIV-infected women, heterosexual men, and men who have sex with men: insights from an observational cohort study

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Abstract

Background—Mortality among HIV-infected individuals may differ by sex and mode of HIV acquisition. We studied mortality among women, heterosexual men, and men who have sex with men (MSM) in a cohort from Rio de Janeiro, Brazil.

Methods—HIV-infected adults followed at Instituto Nacional de Infectologia Evandro Chagas from 2000–2011 were included. Cox proportional hazards models accounting for competing risks were used to explore risk factors for AIDS and non-AIDS related deaths.

Findings—2224 individuals were included (36·7%[817/2224] women, 24·9%[554/2224] heterosexual men, and 38·4%[853/2224] MSM). Throughout the study period, 103 deaths occurred: 64 due to AIDS-related causes, 31 due to non-AIDS related causes and 8 of unknown causes. In unadjusted analyses, compared to women, hazard of AIDS-related deaths was higher for heterosexual men (hazard ratio [HR] 3·52, 95% confidence interval [95%CI] 1·30–9·08) and for MSM (HR 2·30, 95%CI 0·89–5·94). After adjusting for confounders, excess risk of AIDS-related death observed for heterosexual men was attenuated (aHR 1·99, 95%CI 0·75–5·25, p-

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COMPETING INTERESTS

We declare that we have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

LC, JLC, BG, VGV, PML conceived the study, interpreted the findings and drafted the manuscript. LC performed the statistical analyses with aid from MQ and PML. RDB, MQ and AGP contributed to the study's design, helped with data acquisition, interpretation of the results, and drafting the manuscript. DPC and SRR gathered and revised the data and were involved in the analysis and in revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

value=0.163), but unchanged for MSM (aHR 2·24, 95%CI 0·82–6·11, p-value=0.114). Non-AIDS related mortality did not differ by group.

Interpretation—Compared to women, increased risk of AIDS-related death among heterosexual men was partially mitigated by risk factors for AIDS mortality while excess risk observed among MSM was unchanged. Further study of reasons for AIDS-related mortality disparity by mode of transmission is needed.

Keywords

HIV/AIDS; antiretroviral therapy; sex; mortality; cohort; Brazil; Cox regression models

BACKGROUND

Access to combination antiretroviral therapy (ART) has been shown to prevent HIV transmission (1) and significantly improve prognosis of HIV-infected individuals by decreasing HIV viral load, increasing CD4 cell levels, delaying progression to AIDS, and reducing mortality. Nevertheless, inequalities in health outcomes among HIV-infected individuals continue to be reported in high-, middle- and low-income countries. In particular, sex differences in mortality have been reported in several regions of the world (2–4). A large study from the Antiretroviral Therapy Cohort Collaboration including over 32,000 HIV-infected individuals from Europe and North America showed that HIV-infected women in Europe have lower mortality rates than men before and after ART initiation while no sex differences in all-cause mortality was observed in Canada and the United States (4). In a large multicenter analysis from South Africa, the increased mortality risk among men after initiation of ART persisted after adjustments for socio-demographic and HIV-related clinical characteristics (3). A recent systematic review of 65 studies concluded that females showed improved survival with a pooled risk ratio of death of 0 ·72 (95% confidence interval = 0·69–0·75) compared to men (2).

The varying reports of sex disparities in mortality among HIV-infected populations may be explained by differences by mode of HIV acquisition among men. In particular, HIV-infected adults who report transmission through injection drug use have been shown to have significantly higher risk of mortality compared to other modes of transmission (5). In contrast, differences in mortality between heterosexual men and MSM with HIV infection have not been well described. A recent study from China showed that MSM with HIV infection have faster disease progression to AIDS compared to heterosexual individuals, although their mortality rate was lower (6). Similarly, a Danish study found no difference in mortality rates of HIV-infected MSM, heterosexual men, and women (7). However, a recent study from the United States showed that, in the general population, reporting MSM sexual behavior was associated with over 3-fold increased risk of death from HIV-related causes (8). It is unknown if differences in mode of HIV transmission contribute or modify sex differences in mortality among HIV-infected men and women.

In Brazil, improved survival among HIV-infected individuals has been reported particularly among patients diagnosed after 1996, when free and universal access to ART was instituted (9). However, persistent inequalities have also been observed with HIV-infected injection

drug users presenting higher mortality rates compared to MSM (10). In Brazil, sexual HIV transmission, including both heterosexual activity and MSM, are common. Despite the success of ART, reported AIDS cases have increased among MSM in the last decade (from 34·6% in 2004 to 43·2% in 2013) (11). To date, sex differences in survival have not been evaluated in Brazil. To fill this gap in knowledge, we studied mortality among HIV-infected patients from Rio de Janeiro, Brazil, to determine whether it differs among women, heterosexual men, and MSM in the era of ART.

METHODS

Ethics statement

This study was approved by the ethics committee of the Instituto Nacional de Infectologia Evandro Chagas (INI) of the Oswaldo Cruz Foundation, and it was conducted according to the principles expressed in the Declaration of Helsinki. Participants provided written informed consent.

Study site

INI is a national reference for care, research, and training in infectious diseases since 1986. The AIDS laboratory at INI provides primary, specialty, and tertiary care for a cohort of HIV infected individuals in Rio de Janeiro State. A longitudinal observational clinical database has been maintained on patients receiving HIV care which has provided data for several studies (9, 12). Data are updated regularly using outpatient and inpatient clinical documentation and laboratory testing results. Prescription of antiretroviral therapy (drug, dates of use, and dose) is documented by the medical provider and support staff in the clinical records. Trained abstractors record the information onto standardized forms. Collected data are routinely reviewed through internal and external procedures for accuracy.

Study population and definitions

The study population included patients aged ≥18 years who enrolled in the cohort from January 01, 2000 through October 30, 2011 and had a minimum follow up of 60 days. End of follow up was defined as the date of death, last date of a clinic visit or laboratory result (CD4 cell count, HIV RNA measurement, or blood exam) or December 31, 2011, whichever occurred first. Lost to follow-up was defined for those not known to have deceased and not having a clinic visit, an ART prescription or a blood exam after January 01, 2011. These patients were censored at their last date of a clinic visit or laboratory result. Vital status was exhaustively verified using the patients' medical charts, through active contact with individuals and family members, and by linkage with the State of Rio de Janeiro Mortality database (up to December 31 2011) using a previously validated algorithm [8]. Causes of deaths were defined using CoDe ("Coding of Death in HIV") protocol (http://www.cphiv.dk/CoDe/) which is based on a detailed medical chart review and a centralized review process. CoDe forms were completed by two physicians specialized in HIV care while the central review process was performed independently by two qualified reviewers also specialized in HIV care. If agreement on the immediate and underlying causes of death was reached, the cause of death was established. If there was disagreement between the two reviewers, the specific case was referred to one additional reviewer who reviewed the CoDe forms and

established the cause of death. The cause of death was given by the underlying cause and were group in two categories: AIDS related (CoDe 01·1, 01·2, 01), and non-AIDS related (CoDe 02 to 92).

The main variable of interest was constructed using biologic sex and baseline self-reported mode of HIV acquisition, categorized into women, heterosexual men and MSM. Heterosexual men and MSM were mutually exclusive categories; biologic males reporting any sex with men (irrespective of gender identity) were categorized as MSM. Transgender women (n=24) were categorized as MSM for this analysis. Individuals reporting injection drug use/heavy cocaine use were excluded from the analysis (n=235, 48 women, 97 heterosexual men and 90 MSM), as this is a known determinant of increased hazard of death (10). Likewise, men with unknown (n=91) or other (n=19, including vertical transmission, biological accident, blood transfusion and hemophilic) mode of HIV acquisition were excluded from the analysis. Women were assumed to have acquired HIV through heterosexual transmission irrespective of reported sexual practices.

Statistical Analysis

Descriptive statistics for socio-demographic, laboratory and clinical variables were compared using Kruskal Wallis t-test and Chi-squared tests for continuous and categorical variables, respectively. All-cause, AIDS and non-AIDS mortality rates per 1000 person-years (PY) were calculated by group and over time. Cox proportional hazards regression models accounting for competing risks (AIDS-related and non-AIDS-related deaths) were used. Age, CD4 counts, AIDS infections, AIDS malignancies and hospitalizations during follow-up were included in the model as time-updated variables. Unadjusted analyses were conducted for AIDS-related and non-AIDS-related deaths and variables associated with mortality at $p<0·10$ were included in the initial adjusted model, in addition to the exposure variable of interest. The final model retained all covariates with $p<0.05$ in addition to the exposure of interest and time-updated age. R (version 3·0·3), libraries Survival and KMI were used for the analyses.

Role of the Funding Source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

The study population included 2224 patients: 817 (36·7%) women, 544 (24·9%) heterosexual men, and 853 (38·4%) MSM (Table 1, Figure S1). In total, patients contributed 10,142 years of follow-up. Follow-up times for women and heterosexual men were similar (4·1 and 4·1 years, respectively), while for MSM follow-up time was slightly less (3·8 years), though this difference was not statistically significant (p=0·423). Throughout the study period, 103 deaths occurred: 64 due to AIDS-related causes, 31 due to non-AIDS related causes and 8 of unknown causes (Table 1). All-cause mortality rate was 10·2/1000 PY while cause specific mortality rates were 6·3/1000 PY, 3.1/1000 PY and 0.8/1000 PY for

AIDS-related, non-AIDS related and unknown, respectively. All-cause mortality rate was lowest among women (7·9/1000 PY) and the highest among heterosexual men (11·7/1000 PY). Similarly, AIDS-related and non-AIDS related mortalities were lowest among women (4·2/1000 PY and 2·4/1000 PY, respectively) and highest among heterosexual men (8·2/1000 PY and 3·5/1000 PY, respectively). There was no statistically significant trend in all-cause mortality (Table S1). The proportion of patients who died by group was not significantly different though somewhat lower for women. Forty (1·8%) individuals were lost to follow-up, yielding a rate of lost to follow-up of 3·94/1000PY.

Median age at cohort enrollment was lowest for MSM (34·1 years) and highest for heterosexual men (37·5 years, Table 2). Compared to women and heterosexual men, MSM were more likely to be white and have more than 9 years of education. Baseline and nadir CD4 counts were similar among women and MSM, and significantly lower for heterosexual men who also were more likely to have had an AIDS-defining disease at or prior to enrollment. Use of ART was highest for heterosexual men and duration of ART use was similar among groups. Occurrence of an AIDS-defining infection during follow-up was highest for heterosexual men, while AIDS-defining malignancies occurred more frequently among MSM. Hepatitis B was more frequent among MSM while hepatitis C infection did not differ by group. Hospitalizations during study follow-up were more frequent among heterosexual men followed by women and lastly by MSM. Overall, there was a substantial gain in CD4 cell counts among all patients with an overall median of 540 cells/mm^3 in the last year of follow-up. Median last CD4 cell count by group differed slightly, being highest among women (577 cells/mm^3), followed by MSM (533 cells/mm^3) and lastly by heterosexual men (501 cells/mm^3). On the other hand, heterosexual men were more likely to have HIV RNA <400 copies/mL in the last year of follow-up (Table 2).

Assuming women as the reference category, the hazard of AIDS-related death was significantly increased for heterosexual men (HR 3·52, 95%CI 1·30–9·08, *p* value=0·009, Table 3) and borderline increased for MSM (HR 2·30, 95%CI 0·89–5·94, *p* value=0·084). In contrast, the hazard of non-AIDS related death was not significantly different among the groups (HR 1·17, 95%CI 0·36–3·83, *p* value=0·797, for heterosexual men and HR 0·61, 95%CI 0·17–2·15, *p* value=0·440 for MSM compared to women). The final adjusted model for AIDS-related deaths included all statistically significant factors, namely time updated age and CD4 cell counts, last HIV viral load, ART use, and AIDS infection, AIDS malignancy and hospitalization during follow-up. The adjusted model for AIDS-related deaths showed a reduction in the hazard of death for heterosexual men (adjusted HR 1·99, 95%CI 0·75–5·25, *p* value=0·163) compared to women. Conversely, the hazard of AIDS-related death for MSM remained unchanged (adjusted HR 2·24, 95%CI 0·82–6·11, *p* value=0·114). For non-AIDS related deaths, the adjusted hazards for heterosexual men and MSM remained non-significant (heterosexual men, *p* value =0·823, MSM, *p* value=0·326).

DISCUSSION

In this study we found in unadjusted analyses that, compared to women, the hazard of an AIDS-related death was 3·5 times higher for heterosexual men and 2·3 times higher for MSM. After adjustment for confounders, the hazard of AIDS-related death among both

groups of men was twice that of women, with borderline statistical significance. In contrast, deaths due to non-AIDS related causes were not found to be statistically different among the studied groups in both the unadjusted and adjusted analyses. Our observed rates of all-cause mortality were similar to those reported in other regions of Brazil (13), in other high- and low-income settings (14), and in studies that also coded causes of death in HIV in a similar fashion (i.e. used CoDe methodology) (15). Additionally, consistent with our previous studies (9), all-cause, AIDS- and non-AIDS mortality rates did not meaningfully change from 2000 through 2011. In our cohort, AIDS-related causes of death still surpassed non-AIDS related causes, a finding also reported in recent studies from Europe, USA and Australia (15) and England and Wales (16). Finally, we found that sex differences observed for AIDS-related deaths may be modified by sexual mode of HIV transmission.

The literature suggests some factors that may contribute to sex differences in mortality in the HIV-infected population. Foremost and particularly relevant for AIDS-related deaths, poor clinical and immunological status increase mortality (9) and men are more likely to have more advanced immunodeficiency at start of ART, in particular in middle/low-income settings (17). Consistent with this, in our study several socio-demographic and clinical factors differed most for heterosexual men when compared to women. At cohort enrollment, heterosexual had more advanced immunosuppression as evidenced by a higher frequency of AIDS diagnosis and lowest baseline and nadir CD4 cell counts. Also, throughout follow-up, heterosexual men were more likely to develop AIDS infection, start ART and need inpatient care. Of note, tuberculosis, which has been associated with increased risk of death even after adjustment for disease progression (18), was more frequent among heterosexual men (79/192 [41·1%] of AIDS-infections were tuberculosis) compared to women (69/220 [31·4%]). Indeed, these factors partially explained their increased hazard of death by AIDS-related causes which decreased from a 3·5 unadjusted hazard to an adjusted hazard of 1·99 when accounting for immune status (time updated CD4 counts, last HIV viral load and ART use) and more advanced disease (AIDS infection, AIDS malignancy and hospitalization during follow-up). These results corroborate a nation-wide analysis that showed that the risk of late entry is higher among heterosexual men (19) and suggest that perhaps the remaining increased hazard could have been further mitigated had we captured and adjusted for other markers of late entry.

With regards to the MSM population, our study importantly noted an increased hazard of AIDS-related mortality compared to women. MSM were younger at cohort enrollment, more likely to be white and have more education. Throughout follow-up, compared to women, MSM's immune status was slightly more compromised (as indicated by nadir and last CD4 counts). Despite these differences, the 2·30 increased hazard of AIDS-related death for MSM persisted after adjustment for confounders (adjusted hazard of 2·24). Adherence to ART stands out as one plausible explanation for the increased risk. However, among ART users, 88% of MSM had an undetectable value in their last viral load measurement compared to 80% of women suggesting adherence might be lower among women, a finding that aligns with recent results from public clinics in Rio de Janeiro (20). Additionally, MSM were less likely to start ART which could be linked with an increased risk of AIDS-related deaths. Another explanation could be the high frequency of AIDS-defining malignancies observed among MSM in our sample. Studies have found persistent increased risk for

mortality among HIV-infected patients with history of Kaposi sarcoma, even after adjusting for immune status, ART and co-infections (21). Notably, 2·3% of our MSM population developed an AIDS malignancy compared to 0·7% of women. Moreover, among MSM, Kaposi sarcoma represented 95% (19/20) of the AIDS-related malignancies (the other case was a non-Hodgkin lymphoma). Interestingly, development of an AIDS malignancy during follow-up remained in the final adjusted model for AIDS-related deaths (Table 3) but led to no decrease in the adjusted hazard for MSM.

Studies have shown that MSM have unique health needs that should be addressed with comprehensive culturally-competent clinical care provided by adequately prepared health-care professionals (22). Mental health problems including depression can impact MSM's HIV progression/response to treatment (22) while psychosocial syndemic factors have been shown to impact engagement in care and adherence to ART in Latin America (23). Additionally, MSM remain a vulnerable population for HIV-infection in Latin America (24) with a 14·2% estimated point prevalence of HIV-infection in Brazil (25) that drastically contrasts with the 0·6% HIV-infection prevalence in the Brazilian general population (11). Beyond increased risk of HIV-infection, MSM are subject to stigma that operates at several levels including internalized, interpersonal and structural, all of which stand as barriers to access and utilization of HIV prevention and treatment services (26, 27). Though not HIV-specific, a recent systematic review found that prejudice against nonheterosexual orientation is prevalent in diverse regions of Brazil (28). As noted above, in the present study, MSM were less likely to start ART compared to women despite somewhat lower baseline CD4 cell count. Taken together, our study highlights the need to understand the factors that lead to HIV-infected MSM's increased AIDS-related mortality despite relatively stable immune status and access to care and treatment.

Surprisingly, our study did not find a statistical difference in non-AIDS related mortality by sex among HIV-infected adults. Compared to women, men of reproductive age do not routinely access health services (29) and their health seeking behavior might place them at higher risk for poorer outcomes. Indeed, studies in the general population have shown consistent sex differences in all-cause mortality as well as in other health domains (30). Men also have more comorbid conditions that increase mortality risk such as coronary heart disease and type 2 diabetes mellitus (31, 32) and are more prone to present alcohol related disorders and smoking (33, 34). These observations in turn suggest that non-AIDS related mortality should also differ by sex among HIV-infected individuals, a finding not observed in the present analysis. Advanced HIV disease might pose men at higher risk for AIDS-related deaths thus hindering survival to older age when non-AIDS related causes might prevail. Likewise, the relatively young age of cohort participants (particularly MSM) is another plausible explanation for the low number of non-AIDS events in the present study. Finally, our cohort is relatively small in size which might also have contributed to the small number of outcomes. Future studies using larger cohorts with ageing HIV-infected populations could help elucidate if there is any difference in non-AIDS related mortality for men compared to women and, if so, what are the contributions of HIV-related and traditional/non-HIV related risk factors.

Our results highlight directions for future studies. Studies from Latin America with larger cohorts are urgently needed. Latin America's HIV epidemic is unique being comprised of a high proportion of MSM along with high rates of heterosexual transmission. Additionally, cohort collaborations should be encouraged. For our study population of over 2,000 individuals, only 31 deaths occurred due to non-AIDS related causes. Studies comparing mortality of HIV-infected individuals with that of the general population can help gain a better understanding of the treated history of HIV infection, to monitor and predict the progress of the HIV epidemic and to plan health services in the post ART era. Cause-specific mortality studies (35) are another fundamental extension as the results here presented can (and most likely will) differ when specific causes (such as external causes/violence) are considered. The importance of separating men by sexual behavior has been acknowledged in an Antiretroviral Therapy Cohort Collaboration study that included over 32,000 HIV-infected individuals from Europe and North America (4). In this particular study, authors decided to exclude the MSM population because of their improved outcomes when compared to heterosexuals. It is interesting and intriguing that we found exactly the opposite to be true in our study, with both groups of men showing increased risk of AIDS-related deaths. Global studies could help elucidate if MSM populations are subject to different environments that shapes their risks and behaviors and how these influence their health outcomes.

Our study has strengths and limitations that should be acknowledged. First, the use of an open cohort to study mortality implies that an assumption regarding those lost to follow-up needs to be made. For the present, we used information from a patients' medical chart (including dates of visits and of laboratory procedures) as well as linkage with the State of Rio de Janeiro Mortality database to determine which patients had died. As such, we were able to assume with confidence that those lost to follow-up were not dead allowing us to estimate a rate of lost to follow-up that was not different among the studied groups. We excluded patients reporting injection drug use/heavy cocaine use given its known association with mortality (5). This allowed us to study mortality among women, heterosexual men and MSM without the confounding effect of drug use but precluded an analysis of this particular risk factor which may differ by sex and/or sexual mode of transmission. Causes of death were classified using the CoDe methodology ensuring an accurate and consistent review of the clinical conditions preceding death and, as such, minimizing information bias. That said, the requirement that deaths be classified using the CoDe system hindered us from using more recent data that has not yet been reviewed with this protocol. Additional limitations include the small number of cohort participants identified as transgender women (n=24) and consequently the inability to explore this group separately from MSM; lack of generalizability to other HIV-infected populations from Brazil considering this a non-probabilistic sample; and lack of information regarding known and unknown confounding factors such as ART adherence, among others. Finally, as discussed in Cochran et al (8), studies that evaluate mortality among MSM in the general population are rare because mortality datasets do not provide information on sexual orientation. Unfortunately, this is exactly the case for Brazil precluding the comparison of the mortality rates among MSM in our cohort and MSM in the general population.

In summary, our results show that in a middle-income country with universal access to care and treatment, men showed increased risk of AIDS-related death compared to women. The increased risk of AIDS-related death among heterosexual men was partially attenuated by known risk factors for AIDS mortality. For MSM, the increased risk of death was unchanged after adjusting for disease progression highlighting the need to explore other causes for the increased risk of AIDS-related mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

We performed a bibliographic search of MEDLINE via PubMed electronic database for publications restricted to the following languages: English, Spanish, and Portuguese. We filtered for publications dated after 1998 and the last search was run on 17 May 2016. We used the following search strategy: ("hiv"[MeSH Terms] OR "acquired immunodeficiency syndrome"[MeSH Terms]) AND ("mortality"[MeSH Terms] OR "survival"[MeSH Terms]) AND (gender[tw] OR "sex"[MeSH Terms] OR sex[tw] OR ("male"[MeSH Terms] AND "female"[MeSH Terms])) AND (English[la] OR Portuguese[la] OR Spanish[la]) AND "adult"[MeSH Terms] AND "humans"[MeSH Terms] AND 1998[PDAT] : 2016[PDAT]. In addition to original publications, we found a recent systematic review that showed women to have decreased risk of death compared to men. Differential mortality between heterosexual men and men who have sex with men, however, has not been well described with only a few studies addressing the issue with contrasting findings. It is unknown if differences in mode of HIV acquisition can contribute or modify sex differences in mortality among HIV-infected men and women.

Added value of this study

We found that, compared to women, the risk of an AIDS-related death was 3·5 times higher for heterosexual men and 2·3 times higher for MSM. After adjustment for confounders, the hazard of AIDS-related death for both groups of men was nearly than twice that of women. In contrast, deaths due to non-AIDS related causes were not found to differ among the studied groups. Our findings indicate that sex differences exist for AIDS-related deaths and may be modified by sexual mode of HIV acquisition.

Implications of all the available evidence

Combined with existing evidence of increased risk of death for men compared to women, our results show that, in a middle-income country with a concentrated epidemic, this risk persists irrespective of mode of HIV acquisition. Our results suggest that future studies need to explore factors leading to increased risk of AIDS-related death among men and that these factors may differ by mode of HIV acquisition.

Table 1

Overall and cause-specific mortality rates for the study population, INI cohort, 2000–2011.

	Women	Heterosexual Men	MSM	Total	p-value*
Number of patients (%)	817 (36·7)	554 (24·9)	853 (38·4)	2224	
Years of follow-up (person-years)	3,795	2,553	3,794	10,142	
Median person-years of follow-up (IQR)	4·1 (2·0,6·4)	4·1 (2·1,6·4)	3·8 (1·8,6·3)	4 (2·0,6·4)	0·423
Number of deaths (%)	30 (3·7)	30 (5·4)	43 (5·0)	103 (4·6)	0·247
All cause mortality rate per 1000PY (IQR)	7·9 (5·5, 11·3)	11·7 (8·2, 16·8)	11·3 (8·4, 15·3)	10·2 (8·4, 12·3)	0·008
AIDS-related death	16	21	27	64	
Rate per 1000PY (IQR)	4·2 (2·6, 6·9)	8·2 (5·4, 12·6)	7·1 (4·9, 10·4)	6·3 (4·9, 8·1)	0·004
Non-AIDS related death	9	9	13	31	
Rate per 1000PY (95%CI)	2·4 (1·2, 4·6)	3·5 (1·8, 6·8)	3·4 (2·0, 5·9)	3·1 (2·1, 4·3)	0·002
Unknown death	5	0	3	8	
Rate per 1000PY (95%CI)	1·3 (0·5, 3·2)	0	0·8 (0·3, 2·5)	0·8 (0·4, 1·6)	0·001
Lost to follow-up [a]	13 (1·6)	14 (2·5)	13 (1·5)	40 (1·8)	0·328
Rate per 1000PY (95%CI)	3·43 (1·99, 5·90)	5·48 (3·25, 9·26)	3·43 (1·99, 5·90)	3·94 (2·89, 5·38)	1

*Kruskal Wallis t-test and Chi-squared tests for continuous and categorical variables, respectively.

[a]For those not deceased, defined as not having a clinic visit, an ART prescription nor any blood exams after January 01 2011.

Abbreviations used:
MSM: men who have sex with men
IQR: interquartile range
CI: confidence interval

Table 2

Socio-demographic, laboratory and clinical characteristics of the study population, INI cohort, 2000–2011.

	Women	Heterosexual Men	MSM	Total	p-value*
Number of patients (%)	817 (36·7)	554 (24·9)	853 (38·4)	2224	
Age at enrollment [a]					
Median (IQR)	36·1 (29·3, 43·2)	37·5 (30·5, 45·1)	34·1 (27·4, 41·3)	35·6 (28·7, 42·7)	<0·001
<30	290 (35·5)	203 (36·6)	297 (34·8)	790 (35·5)	<0·001
30–39	208 (25·5)	142 (25·6)	193 (22·6)	543 (24·4)	
40–49	93 (11·4)	81 (14·6)	57 (6·7)	231 (10·4)	
50+	226 (27·7)	128 (23·1)	306 (35·9)	660 (29·7)	
Race					
Non-white	479 (58·6)	298 (53·8)	327 (38·3)	1104 (49·6)	<0·001
White	338 (41·4)	256 (46·2)	526 (61·7)	1120 (50·4)	
Education (years)					
Up to 9	513 (62·8)	337 (60·8)	227 (26·6)	1077 (48·4)	<0·001
More than 9	304 (37·2)	217 (39·2)	626 (73·4)	1147 (51·6)	
AIDS at or prior to enrollment [b]	186 (22·8)	181 (32·7)	230 (27·0)	597 (26·8)	<0·001
CD4 count at enrollment (cells/mm^3) [c]					
Median (IQR)	394 (224, 596)	297 (165, 450)	371 (220, 552)	364 (207,547·8)	<0·001
>350	447 (57·6)	203 (39·1)	444 (54·2)	1094 (51·8)	<0·001
201–350	162 (20·9)	157 (30·3)	192 (23·4)	511 (24·2)	
51–200	141 (18·2)	128 (24·7)	147 (17·9)	416 (19·7)	
<=50	26 (3·4)	31 (6·0)	36 (4·4)	93 (4·4)	
HIV RNA at enrollment (copies/mL) [c]					
<=100000	665 (81·4)	429 (77·4)	678 (79·5)	1772 (79·7)	0·043
>100000	56 (6·9)	60 (10·8)	89 (10·4)	205 (9·2)	
Missing	96 (11·8)	65 (11·7)	86 (10·1)	247 (11·1)	
Nadir CD4 count (cells/mm^3) [d]					
Median (IQR)	212 (85, 311)	140 (52, 251)	201 (76, 319)	189 (72, 299)	<0·001
>350	152 (18·6)	60 (10·8)	160 (18·8)	372 (16·7)	<0·001

	Women	Heterosexual Men	MSM	Total	p-value*
201–350	282 (34·5)	142 (25·6)	268 (31·4)	692 (31·1)	
51–200	241 (29·5)	217 (39·2)	270 (31·7)	728 (32·7)	
<=50	142 (17·4)	135 (24·4)	155 (18·2)	432 (19·4)	
Last CD4 count (cells/mm^3) [e]					
Median (IQR)	577 (394, 791)	501 (311, 683)	533 (363, 741)	540 (360, 742)	< 0·001
>350	623 (76·3)	363 (65·5)	625 (73·3)	1611 (72·4)	< 0·001
201–350	88 (10·8)	104 (18·8)	121 (14·2)	313 (14·1)	
51–200	57 (7)	44 (7·9)	50 (5·9)	151 (6·8)	
<=50	11 (1·3)	15 (2·7)	22 (2·6)	48 (2·2)	
Missing	38 (4·7)	28 (5·1)	35 (4·1)	101 (4·5)	
Last HIV RNA (copies/mL) [e]					
<400	573 (70·1)	421 (76)	590 (69·2)	1584 (71·2)	0·013
>= 400	203 (24·8)	100 (18·1)	220 (25·8)	523 (23·5)	
Missing	41 (5)	33 (6)	43 (5)	117 (5·3)	
Hepatitis B diagnosis [f]	25 (3·1)	27 (4·9)	61 (7·2)	113 (5·1)	0·001
Hepatitis C diagnosis [f]	60 (7·3)	34 (6·1)	42 (4·9)	136 (6·1)	0·119
ART use [g]	683 (83·6)	486 (87·7)	677 (79·4)	1846 (83)	< 0·001
Median time of ART use (IQR) [g]	3·5 (0·8, 6·5)	3·5 (1·2, 6·4)	3·1 (0·5, 6·9)	3·4 (0·8, 6·6)	0·198
AIDS infection during follow-up [h]	220 (26·9)	192 (34·7)	219 (25·7)	631 (28·4)	< 0·001
AIDS malignancy during follow-up [h]	6 (0·7)	12 (2·2)	20 (2·3)	38 (1·7)	< 0·001
Any hospitalization during follow-up [i]	257 (31·5)	205 (37)	248 (29·1)	710 (31·9)	0·007

*Kruskal Wallis t-test and Chi-squared tests for continuous and categorical variables, respectively.

[a]Calculated as the difference between date of enrolment and date of birth.

[b]AIDS-defining disease (CDC 1993 definition) prior to or at enrollment.

[c]Nearest result six months prior to or after enrollment.

[d]Lowest CD4 cell count available during follow-up.

[e]Defined as the last result within the last year a patient's follow-up.

[f] Hepatitis B infection was defined by the presence of hepatitis B surface antigen (HBsAg) and hepatitis C infection was defined by the presence of hepatitis C antibodies at any time during follow-up.

[g] ART use was defined as the use of at least three antiretroviral drugs (two nucleoside reverse transcriptase inhibitors and either a protease inhibitor and/or a non-nucleoside reverse transcriptase inhibitor and/or an integrase inhibitor) for a minimum period of 90 days. Years of ART use were calculated from start of treatment to date of death or censoring.

[h] Diagnosis of an AIDS-defining infection or AIDS-defining malignancy during follow-up were captured from the patient's medical chart. To avoid bias (by controlling for a covariate that could be the cause of death) AIDS defining infections and malignancies were considered only if they happened at least 30 days prior to end of follow-up.

[h] Hospital admission was defined as any hospitalization during follow-up. Hospitalizations that ended in death were excluded from the count.

Abbreviations used:
MSM: men who have sex with men
IQR: interquartile range
HIV: human immunodeficiency virus
ART: antiretroviral therapy
AIDS: acquired immunodeficiency syndrome

Table 3

Cox proportional hazard models for mortality by cause of death, INI Cohort, 2000–2011.

	AIDS-related death* (n=64)		non-AIDS related death*(n=31)	
	HR (95%CI)	**aHR (95%CI)**	**HR (95%CI)**	**aHR (95%CI)**
Sex-risk category				
Women	Ref.	Ref.	Ref.	Ref.
Heterosexual men	**3·52 (1·30, 9·08)**	1·99 (0·75, 5·25)	1·17 (0·36, 3·83)	0·87 (0·26, 2·92)
MSM	2·30 (0·89, 5·94)	2·24 (0·82, 6·11)	0·61 (0·17, 2·15)	0·52 (0·14, 1·94)
Age (per year)	**1·03 (1·00, 1·06)**	**1·04 (1·01, 1·08)**	0·97 (0·92, 1·03)	0·97 (0·92, 1·03)
Race				
White	Ref.		Ref.	
Non-white	1·53 (0·79, 2·95)		1·17 (0·42, 3·24)	
Education				
Up to 9 years	**2·16 (1·09, 4·27)**		**3·35 (1·07, 10·53)**	
More than 9 years	Ref.		Ref.	
AIDS diagnosis [a]	**2·75 (1·43, 5·30)**		**1·59 (0·57, 4·49)**	
CD4+ T lymphocyte (per 100 cells/mm^3) [b]	**0·40 (0·30, 0·52)**	**0·51 (0·38, 0·66)**	**0·69 (0·52, 0·91)**	**0·75 (0·58, 0·96)**
Last HIV RNA (copies/mL) [c]				
< 400	Ref.		Ref.	Ref.
>= 400	**10·1 (5·02, 20·2)**	**6·30 (2·88, 13·7)**	**7·41 (2·63, 20·89)**	**4·64 (1·48, 14·5)**
Hepatitis B [d]			NA	
No	Ref.			
Yes	0·98 (0·24, 4·09)			
Hepatitis C [d]			NA	
No	Ref.			
Yes	0·72 (0·17, 2·98)			
ART use [e]	**0·26 (0·12, 0·57)**	**0·11 (0·05, 0·28)**	**0·24 (0·08, 0·79)**	**0·08 (0·02, 0·35)**
AIDS infection during follow-up [f]	**10·9 (5·33, 22·3)**	**7·44 (3·23, 17·1)**	**12·6 (4·00, 39·8)**	**6·87 (1·85, 25·5)**
AIDS malignancy during follow-up [f]	**10·1 (3·55, 28·5)**	**3·77 (1·14, 12·5)**	NA	
Hospitalization during follow-up [g]	**11·7 (5·51, 24·9)**	**2·85 (1·19, 6·81)**	**15·5 (4·36, 54·9)**	**8·92 (2·01, 39·7)**

Age, CD4+ T lymphocyte counts, AIDS infection/malignancy and hospitalizations were included in the model as time-updated variables. Bold implies statistically significant results assuming the significance threshold of 5%.

*As per CoDe classification.

[a] AIDS-defining disease (CDC 1993 definition) prior to or at enrollment.

[b] Time-updated CD4 counts were determined from cohort entry for every six months thereafter, when there was no CD4 count available, the value was linearly interpolated from the two adjacent values.

[c] Defined as the last result within the last year a patient's follow-up; 5% of patients had missing values which were randomly imputed following the distribution of un/detectable viral load for the entire sample.

[d] Hepatitis B infection was defined by the presence of hepatitis B surface antigen (HBsAg) and hepatitis C infection was defined by the presence of hepatitis C antibodies at any time during follow-up.

[e] ART use was defined as the use of at least three antiretroviral drugs (two nucleoside reverse transcriptase inhibitors and either a protease inhibitor and/or a non-nucleoside reverse transcriptase inhibitor and/or an integrase inhibitor) for a minimum period of 90 days.

[f] Diagnosis of an AIDS-defining infection or AIDS-defining malignancy during follow-up were captured from the patient's medical chart. To avoid bias (by controlling for a covariate that could be the cause of death) AIDS defining infections and malignancies were considered only if they happened at least 30 days prior to end of follow-up.

[g] Hospital admission was defined as any hospitalization during follow-up. Hospitalizations that ended in death were excluded from the count.

Abbreviations used:
ART: antiretroviral therapy
AIDS: acquired immunodeficiency syndrome
HR: hazard ratio
aHR: adjusted hazard ratio
CI: Confidence interval
NA: not applicable