Incidence and risk factors for suicide, violent/accidental deaths, and substance abuse deaths in persons living with HIV

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https://chip.dk/Research/Studies/EuroSIDA/Study-group

BACKGROUND

All-cause mortality among persons living with HIV (PLWH) has decreased with the implementation of cART and is now approximately equivalent to the general population [1]. However, rates of suicide remain higher among PLWH compared with the background population [2-4]. Previous studies on suicide among PLWH have been national cohorts or cross-sectional, with no data from more heterogenous populations in Europe [3-5].
Furthermore, deaths due to substance abuse or violence/accident are related by similar patient profiles and as probable misclassifications of suicide.

We aimed to:

- Report the rates of suicide and similar mortality among PLWH in EuroSIDA, a large pan-European observational cohort study.
- Investigate trends between geographic regions and over time.
- Identify risk factors associated with suicide and similar mortality among PLWH.

TABLE 1. PARTICIPANTS CHARACTERISTICS BY OUTCOME GROUP

	All Subjects (N=17701)	Died all causes (n=1658)	Suicide (n=40)	Substance abuse death (n=85)	Violent / accidental death (n=55)
Age at baseline [median (IQR)]	43 (35-50)	46 (38-55)	41.5 (34.5-46.5)	38 (32-44)	40 (32-52)
Age at death [median (IQR)]	-	51 (42-60)	46.5 (40-51.5)	41 (35-49)	45 (35-56)
Gender: Male	12808 (72.4%)	1263 (76.2%)	33 (82.5%)	67 (78.8%)	46 (83.6%)
Ethnicity: White	15261 (86.2%)	1520 (91.7%)	37 (92.5%)	82 (96.5%)	53 (96.4%)
Region					
Central West	4389 (24.8%)	347 (20.9%)	9 (22.5%)	14 (16.5%)	10 (18.2%)
North	3284 (18.6%)	402 (24.2%)	8 (20%)	16 (18.8%)	10 (18.2%)
Central East	2316 (13.1%)	188 (11.3%)	8 (20%)	10 (11.8%)	4 (7.3%)
East	3045 (17.2%)	364 (22%)	6 (15%)	40 (47.1%)	23 (41.8%)
South	4667 (26.4%)	357 (21.5%)	9 (22.5%)	5 (5.9%)	8 (14.5%)
Mode of HIV transmission					
Men who have sex with men (MSM)	6232 (35.2%)	469 (28.3%)	17 (42.5%)	10 (11.8%)	14 (25.5%)
Heterosexual contact	5196 (29.4%)	407 (24.5%)	8 (20%)	7 (8.2%)	13 (23.6%)
Injection drug use (IDU)	5108 (28.9%)	686 (41.4%)	13 (32.5%)	66 (77.6%)	26 (47.3%)
Other, sex unspecified, unknown	1165 (6.6%)	96 (5.8%)	2 (5%)	2 (2.4%)	2 (3.6%)
First AIDS event during follow-up	655 (3.7%)	178 (10.7%)	1 (2.5%)	8 (9.4%)	6 (10.9%)
Any EFV regimen during follow-up	5305 (30%)	458 (27.6%)	11 (27.5%)	24 (28.2%)	20 (36.4%)

REFERENCES
1. Lewden C, Bouteloup V, De Wit S, Sabin C, Mocroft A, Wasmuth JC, et al. All-cause mortality in treated HIV-infected adults with CD4 ≥500/mm3 compared with the general population: evidence from a large European observational cohort collaboration. Int J Epidemiol. 2012;41(2):433-45.
2. Catalan J, Harding R, Sibley E, Clucas C, Croome N, Sherr L. HIV infection and mental health: Suicidal behaviour – Systematic review. Psychology, Health & Medicine. 2011;16(5):588-611.
3. Croxford S, Kitching A, Desai S, Kall M, Edelstein M, Skingsley A, et al. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. Lancet Public Health. 2017;2(1):e35-e46.
4. Ruffieux Y, Lemsalu L, Aebi-Popp K, Calmy A, Cavassini M, Fux CA, et al. Mortality from suicide among people living with HIV and the general Swiss population: 1988-2017. J Int AIDS Soc. 2019;22(8):e25339.
5. Hentzien M, Cabie A, Pugliese P, Billaud É, Poizot-Martin I, Duvivier C, et al. Factors associated with deaths from suicide in a French nationwide HIV-infected cohort. HIV Med. 2018.
6. Kowalska JD, Friis-Møller N, Kirk O, Bannister W, Mocroft A, Sabin C, et al. The Coding Causes of Death in HIV (CoDe) Project: Initial Results and Evaluation of Methodology. Epidemiology. 2011;22(4):516-23.

METHODS

Participants enrolled in EuroSIDA were followed from the latest of enrollment or January 2007 through 2018. Cause of death was classified using CoDe methodology [6]. Cause-specific Cox regression analysis was used to assess risk factors associated with each cause. Univariate analyses were conducted for each risk factor. Factors chosen a priori (age, calendar year of follow-up, and region) and significant in univariate analysis (p<0.1) were included in multivariable.

RESULTS

The characteristics of the 17,701 included participants, stratified by outcome group, are shown in table 1. Participants were followed for a median of 7.66 PYFU (IQR 4.15-12.00). There were 1,658 deaths during 137,918 PYFU (crude MR: 12.0 per 1,000 PYFU; 95%CI 11.5, 12.6). There were 40 suicides (crude MR: 0.3 per 1000 PYFU; 95%CI 0.2, 0.4), 85 deaths due to substance abuse (crude MR: 0.6 per 1000 PYFU; 95%CI 0.5, 0.8), and 55 deaths due to violence/accident (crude MR: 0.4 per 1000 PYFU; 95%CI 0.3, 0.5)

In multivariable analyses:

- Individuals within 12 months after their first AIDS diagnosis showed 9x higher risk of suicide compared to no prior AIDS diagnosis (aHR 9.73; 95%CI 2.21, 42.9) (fig. 1).
- Participants in Eastern Europe and those who acquired HIV by injection drug use (IDU) demonstrated the highest risk of mortality due to both violence/accident and substance abuse (figures 2 &3).
- Male participants showed more than double the risk violent/accidental death (aHR 2.63; 95%CI 1.22, 5.69) (fig. 3).

LIMITATIONS

- Key risk factors not collected (psychiatric medication, mental illness, active alcohol or substance use) may lead to unmeasured confounding.
- The low number of outcomes limited power to detect some associations and precluded more complex analysis, e.g. stratification, tests for interaction, or the inclusion of more risk factors in multivariable analysis.
- The proportion of unknown/missing causes of mortality (349, 21%) also limited power. Deaths in later years were more likely to have unknown causes, likely due to delays in reporting, and the highest proportions of unknown causes were in Central West (28%) and Northern Europe (26%) compared to Central East (15%), East (15%), and South (18%).

CONCLUSIONS

- Increased risk of suicide was associated with a recent AIDS diagnosis.
- Increased risk of death due to substance abuse or violence/accident were both associated with Eastern European region and IDU mode of HIV transmission.
- There is little research in the contemporary cART era examining suicide in the immediate period following AIDS diagnosis. These results indicate a need for further research on mental health effects and support directly following an initial AIDS diagnosis.
- Eastern Europe should be an area of focus for preventing substance abuse and violent/accidental mortality among PLWH, as increased mortality risk appears to be independent from expected associations with age and mode of HIV transmission. It is important to investigate and identify what specific drivers of mortality explain these regional differences.

Figure 1
Risk factors associated with Suicide mortality

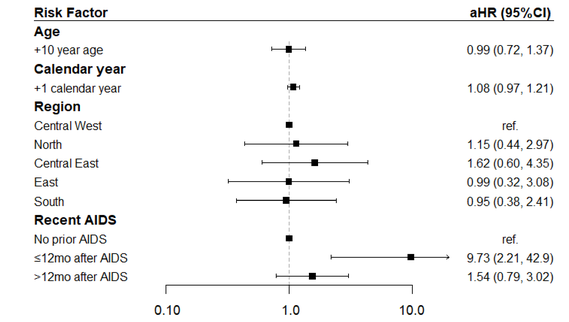

Figure 2
Risk factors associated with Substance Abuse mortality

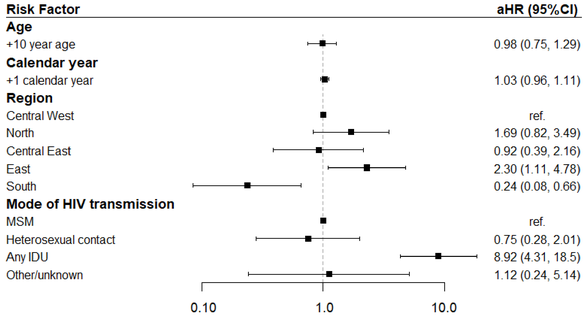

Figure 3
Risk factors associated with Violent/Accident mortality