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Trends in AIDS-defining illnesses among people living with HIV in Europe: results from the EuroSIDA study (2003 - 2022)

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BACKGROUND

Implementation of "treat all" policies across Europe have resulted in substantial decreases in AIDS-defining illnesses (ADIs) among people living with HIV (PLWH). However, ADIs continue to present as a significant cause of morbidity and mortality in PLWH. Recent studies of trends and regional differences in specific ADIs and risk factors are limited.

OBJECTIVE To describe temporal trends, types, and risk factors for ADIs across Europe during 2003-2022.

METHODS

- PLWH enrolled in EuroSIDA were followed from the latest of 1/1/2003 or enrolment date (baseline) until first ADI, death, withdrawal, loss-to-follow-up or 31/12/2022.
- Incidence rates of first new ADI or AIDS-related death were calculated as number of events per 1000 person-years of follow-up (PYFU).
- Multivariable Poisson regression with generalised estimating equations was used to compare incidence of ADIs across EuroSIDA regions and over calendar time.

RESULTS

STUDY POPULATION

Baseline characteristics of 20205 persons included in the analysis are given in **Table 1**.

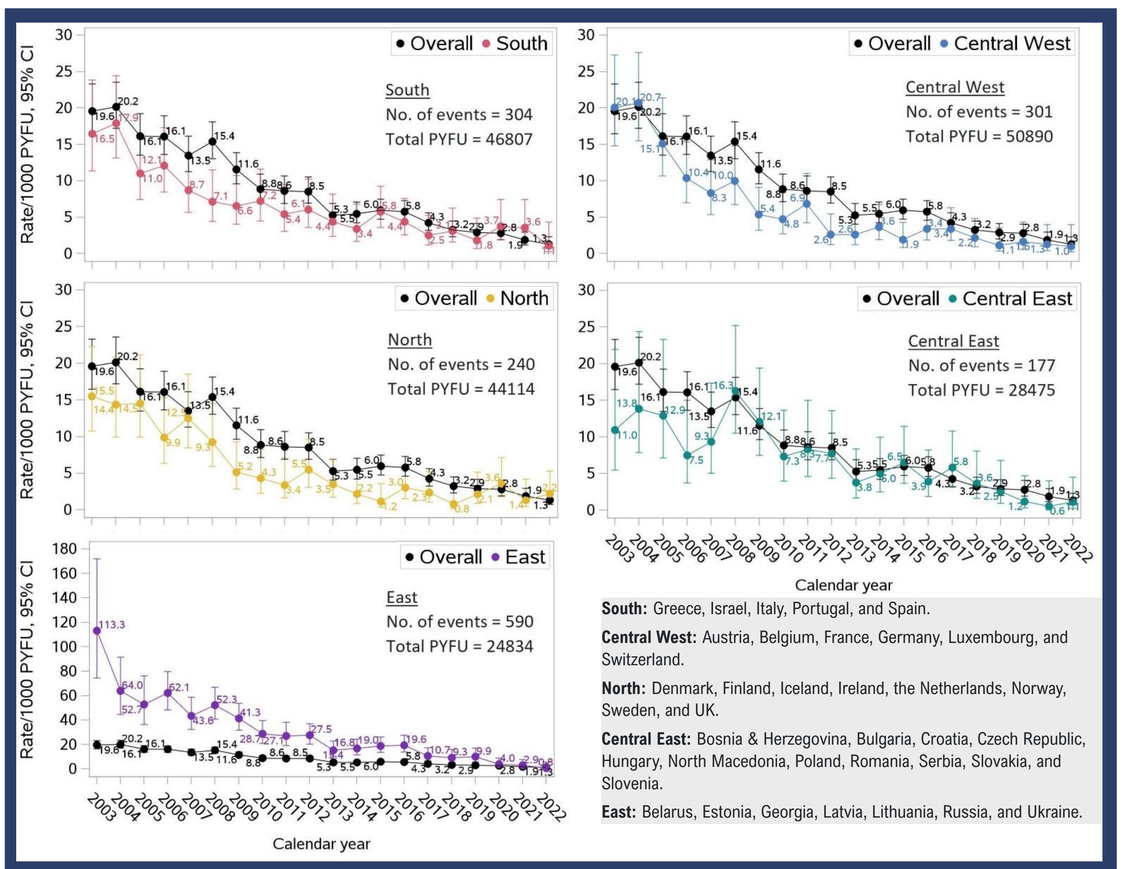
		Overall (*N* = 20205)
Baseline date, median (IQR)		03/2006 (01/2003-07/2014)
Follow-up time per person (years), median (IQR)		9 (5-15)
Region, n (%)	South	4794 (23.7)
	Central West	4883 (24.2)
	North	3920 (19.4)
	Central East	2982 (14.8)
	East	3626 (17.9)
Age (years), median (IQR)		41 (34-49)
Male sex/gender, n (%)		14853 (73.5)
HIV acquisition risk, n (%)	MSM	7509 (37.2)
	People who inject(ed) drugs	5685 (28.1)
	Heterosexual	5648 (28.0)
	Other/unknown	1363 (6.7)
CD4 count (cells/mm^3), median (IQR)		468 (307-662)
Suppressed HIV viral load <200 copies/mL, n (%)		12963 (64.2)
Current ART regimen, n (%)	Optimal*	15178 (75.1)
	Sub-optimal	996 (4.9)
	Not currently on treatment	1151 (5.7)
	ART-naive	2880 (14.3)
Years from HIV diagnosis, median (IQR)		8 (3-14)
Prior ADI, n (%)		4943 (24.5)

Table 1. Baseline characteristics of 20205 people living with HIV enrolled in EuroSIDA and under follow-up between 2003 - 2022

*Optimal ART defined as at least 3 antiretroviral agents including an NNRTI, PI, or INSTI, or dual therapy supported by clinical trials: DTG+RPV, XTC+DTG, XTC+DRV/b.

INCIDENCE RATES OF AIDS-DEFINING ILLNESSES

- Overall, 1612 PLWH experienced an ADI during 195120 person-years of follow-up (PYFU), incidence 8.26/1000 PYFU (95% CI 7.87-8.67).
- The incidence of ADIs declined over time in all regions, most pronounced in Eastern Europe (**Figure 1**).



South: Greece, Israel, Italy, Portugal, and Spain.

Central West: Austria, Belgium, France, Germany, Luxembourg, and Switzerland.

North: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden, and UK.

Central East: Bosnia & Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, North Macedonia, Poland, Romania, Serbia, Slovakia, and Slovenia.

East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, and Ukraine.

Figure 1. Crude incidence rates of first new AIDS-defining illnesses between 2003 - 2022 in 20205 people living with HIV enrolled in EuroSIDA

RESULTS (CONT'D)

Univariable and multivariable incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for factors associated with AIDS defining illnesses between 2003 - 2022 are presented in **Figure 2**.

	Univariable IRR (95% CI)	Multivariable IRR (95% CI)
Calendar year period (ref. 2003-2006)		
2007-2010	0.69 (0.61, 0.78)	0.63 (0.55, 0.71)
2011-2014	0.39 (0.34, 0.45)	0.38 (0.33, 0.45)
2015-2018	0.27 (0.23, 0.32)	0.30 (0.26, 0.36)
2019-2022	0.13 (0.10, 0.16)	0.16 (0.12, 0.20)
Geographical region (ref. Central West)		
South	1.10 (0.93, 1.29)	1.11 (0.93, 1.31)
North	0.92 (0.77, 1.09)	1.05 (0.88, 1.26)
Central East	1.05 (0.87, 1.27)	1.19 (0.97, 1.47)
East	4.02 (3.48, 4.63)	2.90 (2.37, 3.55)
Sex/gender and HIV acquisition risk (ref. MSM)		
Males who inject drugs	2.74 (2.39, 3.14)	1.28 (1.06, 1.55)
Females who inject drugs	2.45 (2.05, 2.92)	1.18 (0.93, 1.48)
Heterosexual males	1.48 (1.24, 1.76)	1.04 (0.86, 1.25)
Heterosexual females	1.45 (1.23, 1.69)	0.90 (0.76, 1.08)
Other/unknown	1.30 (1.04, 1.63)	0.95 (0.75, 1.21)
CD4 count at baseline, cells/mm3 (ref. >=500)		
<100	8.97 (7.43, 10.83)	7.00 (5.55, 8.82)
100-199	3.47 (2.92, 4.13)	3.01 (2.47, 3.67)
200-299	2.05 (1.74, 2.42)	2.02 (1.69, 2.43)
300-499	1.40 (1.22, 1.61)	1.38 (1.20, 1.59)
Unknown	5.51 (4.53, 6.71)	1.76 (1.37, 2.27)
ART regimen time-updated (ref. optimal)		
Sub-optimal ART	1.16 (0.93, 1.45)	1.13 (0.90, 1.41)
Not currently on treatment	4.76 (4.14, 5.47)	2.82 (2.40, 3.32)
ART-naive	5.33 (4.65, 6.11)	1.97 (1.61, 2.42)

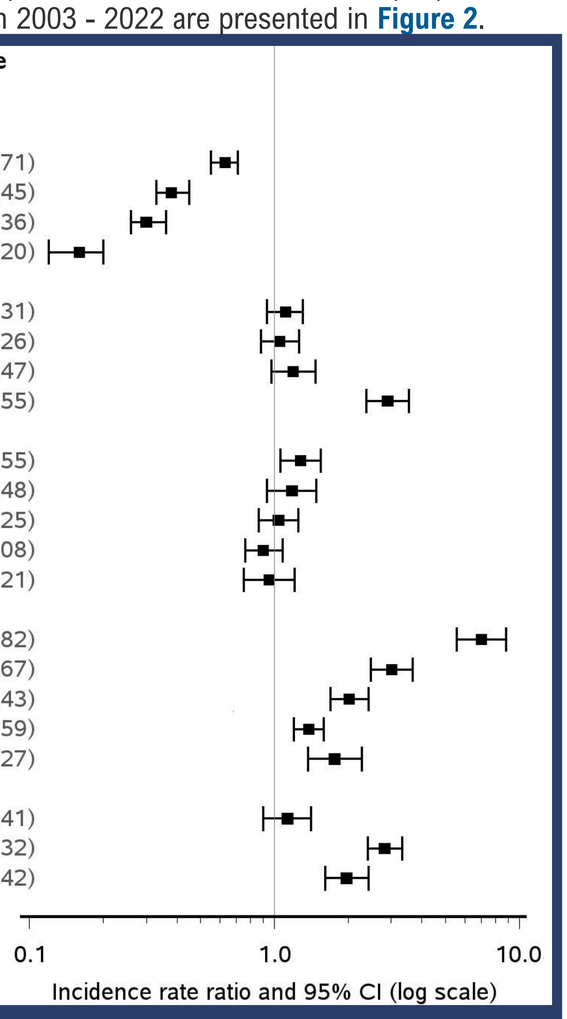


Figure 2. Factors associated with AIDS defining illnessess
Analysis adjusted for baseline variables: sex/gender and HIV acquisition risk, race/ethnicity, time from HIV diagnosis, CD4-cell count, CD4-nadir, prior ADI; and time-updated variables: age, ART regimen, hepatitis B and C status, prior cardio-vascular disease, prior diabetes mellitus, prior non-AIDS-defining malignancy, prior end-stage liver disease, prior chronic kidney disease.

- After adjustment, the decrease over time remained significant (p<0.0001) and the rate of ADIs in Eastern Europe was nearly 3 times more compared to Central West (p<0.0001) (**Figure 2**).
- A sensitivity analysis excluding those with previous ADIs at baseline showed similar results.

TYPES OF AIDS-DEFINING ILLNESSES

Figure 3 illustrates the type of ADIs experienced over the study period.

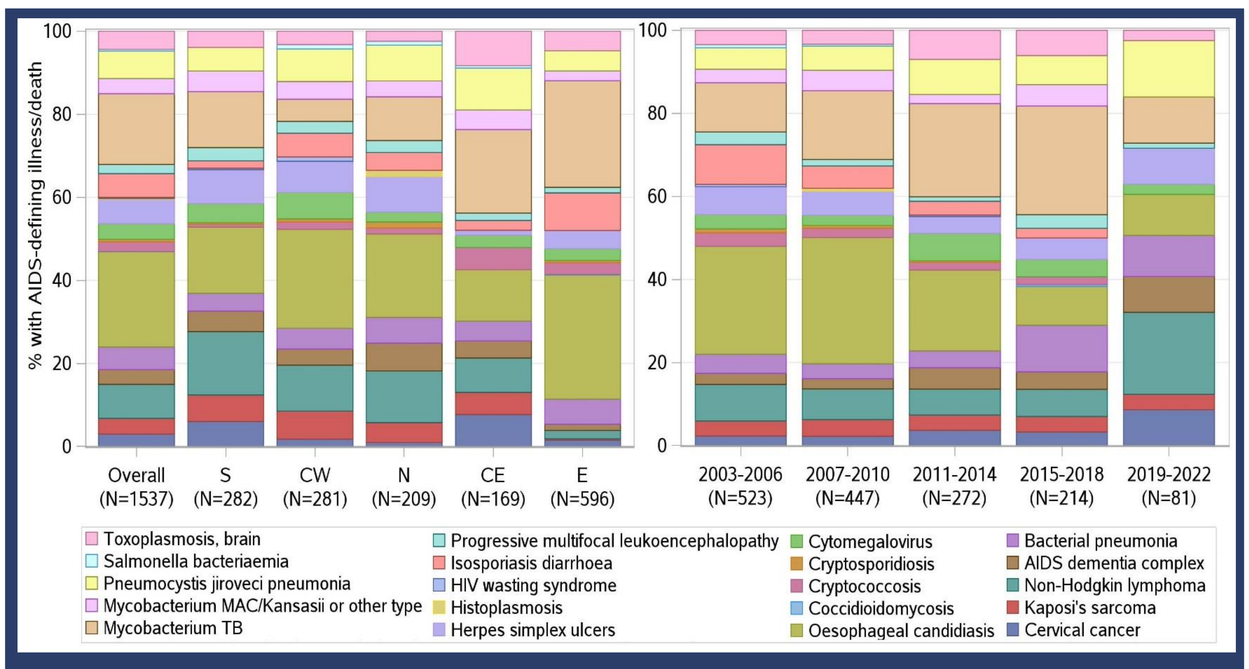


Figure 3. Types of first new AIDS-defining illness according to region (left) and time of onset (right)
S=South, CW=Central West, N=North, CE=Central East, E=East.
Note: if >1 ADI diagnosis is reported on the same day, all are counted.

- Overall, temporal trends shifted from predominantly opportunistic infections in 2003-2006 (85.3% of all diagnoses, including 26.0% oesophageal candidiasis and 11.9% tuberculosis) to relatively more malignancies in 2019-2022 (32.1% vs 14.7% in 2003-2006).
- Oesophageal candidiasis (28.4%) and tuberculosis (25.7%) were dominating in Eastern Europe, whereas proportion of malignancies was smaller; 3.9% compared to 15.0% overall.

LIMITATIONS

- Changes in the study population over time that may affect the risk of AIDS.
- Differences in the stage of disease at time of enrolment.
- Some previously collected variables, e.g. prophylactic treatment for PCP was collected only up to 2016 in EuroSIDA.
- Risk of survival-related selection bias for enrolment into EuroSIDA.

CONCLUSIONS

Incidence of ADIs decreased over time across Europe with the most pronounced reduction observed in Eastern Europe. However, rates of ADIs in this region remain higher compared with other regions, also after adjustment.

Despite recommendations on universal access to HIV-services all over Europe, our findings suggest the presence of inequalities in access to healthcare, HIV-management and ADIs prevention, which requires further investigation.

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