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Trends in mortality in people living with HIV in an international cohort (RESPOND)

870

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BACKGROUND

- Mortality rates in people living with HIV have declined due to effective antiretroviral treatment (ART) (1). Aging, coinfections, and comorbidities may drive further changes in mortality (2).
- We investigated recent patterns in mortality in the RESPOND cohort consortium to systematically monitor for unexpected trends and identify opportunities to reduce mortality.

METHODS

- The RESPOND cohort consortium was initiated in 2017 and includes over 30,000 people living with HIV from 17 cohorts across Europe and Australia.
- Prospective follow up from 2012 through 2019. Participants before 2017 enrolled retrospectively.
- Mortality classified by the Coding Causes of Death in HIV (CoDe) methodology (3).
- Age-standardized mortality rates were compared over time.
- Multivariable Poisson regression was used to investigate risk factors for all-cause mortality.

RESULTS

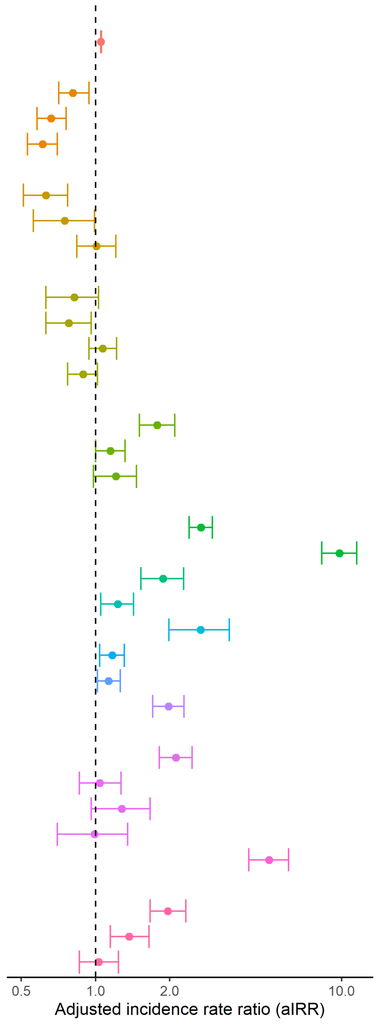
- 33,598 participants, 167,930 PYFU (median 4.8 years; IQR 3.1–8.0); 1700 (5.1%) died.
- Crude, all-cause mortality rate decreased over time.
  - 2012–13: 13.0/1000 PYFU (95%CI 11.8–14.4)
  - 2018–19: 8.6/1000 PYFU (95%CI 7.9–9.5)
- Median age at death increased over time:
  - 2012–13: 52 (IQR 45–62); 2018–19: 56 (IQR 48–65)
- Highest cause-specific crude mortality rate was due to non-AIDS defining malignancy (NADM); see Table 1.
- Age-adjusted Poisson regression showed decreasing mortality from 2012–13 to 2018–19 for deaths due to NADM, AIDS, cardiovascular disease (CVD), liver disease, and other causes, but not unknown/missing (see Figure 2).
- In multivariable analysis including all risk factors where $p<0.1$ in univariable analysis (Figure 1), the strongest predictors of all-cause mortality were poor immunologic/virologic status (current CD4 ≤350 cells/mm^3 + HIV viral load (VL) >200 cp/mL) vs. good immunologic/virologic status (CD4 ≥500 cells/mm^3 + VL <200 cp/mL) and other modifiable risk factors.

(1) Smith CJ, et al. The Lancet. 2014; (2) Pelchen-Matthews A, et al. AIDS. 2018;
(3) Kowalska JD, et al. Epidemiology. 2011

In the RESPOND cohort from 2012 through 2019, cause-specific age-adjusted mortality rates **declined**. **Immunologic/virologic status** was the **strongest predictor of mortality**.

Figure 1. All-cause mortality univariable and multivariable time-updated Poisson regressions

Covariate	Level	IRR (95% CI)	aIRR (95% CI)
Age (per one year)		1.05 (1.05–1.06)	1.05 (1.05–1.06)
Time period (ref. 2012–2013)			
	2014–2015	0.84 (0.73–0.97)	0.81 (0.71–0.94)
	2016–2017	0.71 (0.62–0.81)	0.66 (0.58–0.76)
	2018–2019	0.66 (0.58–0.76)	0.61 (0.53–0.7)
Race/Ethnicity (ref. White)			
	non-White	0.38 (0.31–0.46)	0.63 (0.51–0.77)
	Unknown	0.63 (0.47–0.83)	0.75 (0.56–0.99)
	Prohibited	0.76 (0.64–0.9)	1.01 (0.84–1.21)
Region (ref. Central West)			
	Central East	0.84 (0.65–1.06)	0.82 (0.63–1.03)
	East	1.31 (1.08–1.56)	0.78 (0.63–0.96)
	North / Australia	0.89 (0.79–1.01)	1.07 (0.94–1.22)
	South	0.84 (0.74–0.96)	0.89 (0.77–1.02)
HIV transmission risk (ref. MSM)			
	Injection drug use	3.08 (2.73–3.47)	1.78 (1.51–2.1)
	Heterosexual contact	1.11 (0.98–1.25)	1.15 (1–1.32)
	Other/unknown/missing	1.49 (1.22–1.81)	1.21 (0.98–1.47)
CD4/HIV RNA status (ref. Good)			
	Intermediate	2.99 (2.69–3.32)	2.68 (2.4–2.98)
	Poor	9.01 (7.74–10.46)	9.78 (8.29–11.5)
Diabetes (ref. no diabetes)		3.51 (2.89–4.22)	1.88 (1.53–2.28)
Chronic kidney disease (ref. no CKD)		2.64 (2.29–3.03)	1.23 (1.05–1.43)
End-stage renal disease (ref. no ESRD)		5.23 (3.96–6.75)	2.67 (1.99–3.5)
Hypertension (ref. no HTN)		1.73 (1.57–1.9)	1.17 (1.04–1.31)
Dyslipidemia (ref. no dyslipidemia)		1.57 (1.43–1.73)	1.13 (1.02–1.26)
Cardiovascular disease (ref. no CVD)		4.2 (3.67–4.79)	1.98 (1.71–2.29)
Hepatitis C history (ref. antibody negative)			
	chronic untreated	3.6 (3.21–4.02)	2.12 (1.82–2.47)
	cured	1.63 (1.38–1.92)	1.04 (0.86–1.27)
	spontaneously resolved	2.08 (1.6–2.64)	1.28 (0.96–1.67)
	treatment failure	1.51 (1.09–2.03)	0.99 (0.7–1.35)
End-stage liver disease (ref. no ESLD)		10.29 (8.59–12.23)	5.08 (4.2–6.08)
Smoking history (ref. never smoker)			
	current smoker	2.2 (1.89–2.58)	1.97 (1.67–2.33)
	previous smoker	1.84 (1.54–2.19)	1.37 (1.15–1.65)
	unknown smoking history	0.99 (0.84–1.18)	1.03 (0.86–1.24)

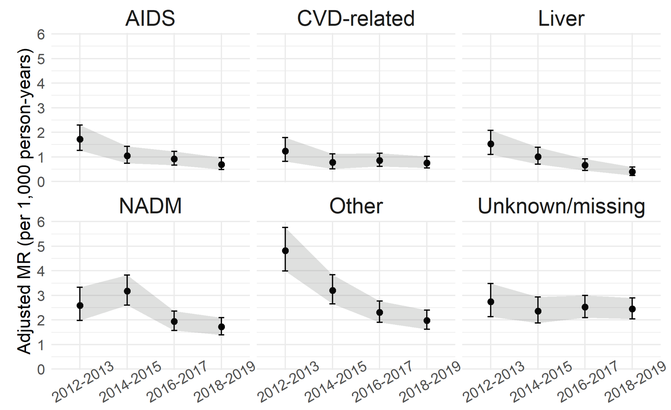


Multivariable analysis also adjusted by Gender, Hepatitis B; aIRR n.s.

Table 1: Cause-specific crude mortality rates (MR) per 1000 person-years

	N events	crude MR (95%CI)
NADM	370	2.20 (1.98 - 2.44)
AIDS	169	1.01 (0.85 - 1.16)
CVD	142	0.85 (0.71 – 1.00)
Liver	133	0.79 (0.66 - 0.94)
Other	469	2.79 (2.55 - 3.06)
Unknown/missing	417	2.48 (2.25 - 2.73)

Figure 2: Age-standardized mortality rates (MR)



LIMITATIONS

- Many unknown/missing causes of death.
- Retrospective enrollment may lead to selection bias.

CONCLUSIONS

- Age-adjusted mortality rates due to specific causes declined from 2012–13 to 2018–19.
- Mortality due to NADM was greater than AIDS-, CVD-, or liver-related mortality.
- Median age at death has increased over time but is still relatively young compared to the background population.
- All-cause mortality was strongly associated with modifiable risk factors, especially immunologic/virologic status and chronic conditions, indicating areas for improvement.

The RESPOND Study Group:
https://www.chip.dk/Studies/RESPOND/Study-Group