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Examining non-AIDS mortality among people who inject drugs

Bradley M. Mathers[a] and Louisa Degenhardt[b,c]

Objective: To systematically review and analyse data from cohorts of people who inject drugs (PWID) to improve existing estimates of non-AIDS mortality used to calculate mortality among PWID in the Spectrum Estimates and Projection Package.

Design: Systematic review and meta-analysis.

Methods: We conducted an update of an earlier systematic review of mortality among PWID, searching specifically for studies providing data on non-AIDS-related deaths. Random-effects meta-analyses were performed to derive pooled estimates of non-AIDS crude mortality rates across cohorts disaggregated by sex, HIV status and periods in and out of opioid substitution therapy (OST). Within each cohort, ratios of non-AIDS CMRs were calculated and then pooled across studies for the following paired sub-groups: HIV-negative versus HIV-positive PWID; male versus female PWID; periods in OST versus out of OST. For each analysis, pooled estimates by country income group and by geographic region were also calculated.

Results: Thirty-seven eligible studies from high-income countries and five from low and middle-income countries were found. Non-AIDS mortality was significantly higher in low and middle-income countries [2.74 per 100 person-years; 95% confidence interval (CI) 1.76–3.72] than in high-income countries (1.56 per 100 person-years; 95% CI 1.38–1.74). Non-AIDS CMRs were 1.34 times greater among men than women (95% CI 1.14–1.57; $N = 19$ studies); 1.50 times greater among HIV-positive than HIV-negative PWID (95% CI 1.15, 1.96; $N = 16$ studies); and more than three times greater during periods out of OST than for periods on OST ($N = 7$ studies).

Conclusions: A comprehensive response to injecting drug must include efforts to reduce the high levels of non-AIDS mortality among PWID. Due to limitations of currently available data, including substantial heterogeneity between studies, estimates of non-AIDS mortality specific to geographic regions, country income level, or the availability of OST should be interpreted with caution.

AIDS 2014, **28** (Suppl 4):S435–S444

Keywords: AIDS, HIV, intravenous, meta-analysis, mortality, review, substance abuse, systematic

Introduction

Compared to their non-drug using peers, people who inject drugs (PWID) are at an elevated risk of mortality from both acute and chronic diseases, many of which are related to their drug use. Much of this excess mortality is attributable to fatal drug overdose and from HIV and other blood-borne viruses transmitted through injecting drug use [1].

Longitudinal studies of PWID provide an opportunity to examine the magnitude, nature and correlates of

[a]The Kirby Institute for Infection and Immunity in Society, Faculty of Medicine, [b]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, and [c]School of Population and Global Health, University of Melbourne, Melbourne, Australia.

Correspondence to Bradley M. Mathers, The Kirby Institute, Wallace Wurth Building, University of New South Wales, Sydney, NSW 2052, Australia.

E-mail: bmathers@kirby.unsw.edu.au
Received: 5 August 2014; revised: 5 August 2014; accepted: 5 August 2014.

DOI:10.1097/QAD.0000000000000435

mortality risk among this group. Previous reviews of drug user cohorts suggest those who are dependent on opioids (both injectors and non-injectors) may have higher mortality rates to those drug users who are dependent on stimulant drugs such as cocaine and amphetamine-type stimulants [2–4].

In a recent systematic review, in 2013, we identified cohort studies of PWID to examine mortality rates and causes of death in this group [5]. We performed random-effects meta-analyses to derive pooled crude mortality rates (CMRs) and standardized mortality ratios (SMRs), and examined participant and study-level variables associated with higher risk of death from all causes and supplementary analyses looking at overdose and AIDS-related mortality. We found AIDS and drug overdose to be the primary causes of death among PWID, and whereas CMRs varied across different settings, overall they were higher in low and middle-income countries (LMICs) compared to high-income countries (HICs).

We undertook a further review and analysis of cohorts of PWID, specifically to examine non-AIDS mortality among HIV-positive and HIV-negative individuals, in an effort to improve existing estimates of mortality used in the UNAIDS Spectrum Estimates and Projection Package model to calculate mortality among PWID.

Methods

For the original review, tailored search strings were used to search Medline, EMBASE and PsychInfo (search terms and strategies have been described previously [5]). Grey literature reporting on mortality was identified using online grey literature databases, library databases and general online searches; the complete list of websites reviewed is provided in a previously published technical report [6]. For the current analysis, we updated the literature search to identify any additional studies published in the period since the earlier review was completed, searching specifically for studies providing data on non-AIDS-related deaths.

Reported CMRs and SMRs were extracted along with information on the location of study, recruitment and duration of study follow-up period, number of people in the cohort, percentage of cohort who injected drugs, person-years of follow-up, number of deaths overall and by cause of death. CMRs reported by sex, HIV status, drug injected and opioid substitution therapy (OST) status were also extracted; OST has been demonstrated to reduce mortality among opioid-dependent PWID [2,7]. In a number of cases where standard errors, confidence intervals (CIs) or CMRs were not reported, these were estimated using standard calculations with data that were provided. For the current updated analysis, all studies were reviewed to extract relevant cause of death data to determine non-AIDS-related deaths.

Meta-analyses were performed to derive pooled estimates across cohorts, where data permitted, for the following: non-AIDS CMR among PWID; non-AIDS CMR among male PWID; non-AIDS CMR among female PWID; non-AIDS CMR among HIV-negative PWID; non-AIDS CMR among HIV-positive PWID; non-AIDS CMR among PWID on OST and non-AIDS CMR among PWID off OST.

Within studies, ratios for CMRs were calculated by the following paired sub-groups, and pooled ratios across the studies were again derived using meta-analyses: ratio of non-AIDS CMRs in HIV-negative versus HIV-positive PWID; ratio of non-AIDS CMRs in male versus female PWID; ratio of non-AIDS CMRs during periods on OST versus off OST.

For each of these analyses, in addition to estimating CMRs across all studies, pooled estimates by country income group and by geographic region were also calculated. Countries were categorized as either 'high income' or 'low and middle income' based on World Bank categories [8].

When the number of deaths within a sub-group was zero and CMR, standard error and risk ratios were rendered indeterminate, we set the number of deaths at 0.5 to allow inclusion of these groups in comparative analyses.

Meta-analyses were performed using the 'metan' command in STATA version 12.1 [9]. The 'metan' command uses inverse-variance weighting to calculate random-effects pooled summary estimates, confidence limits, a test for true differences between study effects and an estimate of between-study variance [10,11]. The random-effects model, which allows heterogeneity between and within studies, was applied to all analyses after an a priori decision was made about the marked differences between the study samples, confirmed by observing the heterogeneity chi-square and I-squared statistics.

Results

Our original review included 67 cohort studies [5]; the updated literature search yielded one additional study eligible for inclusion [12]. Of these studies, a total of 42 reported data on cause of death, specifically non-AIDS-related mortality. Table 1 presents a summary of these studies. With the exception of 5 cohorts [47–51], all were from HICs, including 22 cohorts from European countries, 7 from North America, 4 from Australia and 1 from Taiwan.

Table 1. Studies included in current analyses.

		Sampling frame	*N*	PWID (%)	Men (%)	Drugs used	HIV+ (%)	Recruitment period	End of follow-up period	All-cause mortality		Non-AIDS mortality		
										PYFU	CMR	95% CI	CMR	95% CI
High-income countries														
Australia	Degenhardt *et al.* (2009) [7]	DT	42676	≥70[a]	–	O		1985–2006	2006	425998	0.89	0.86, 0.92	0.88	0.85, 0.91
	DiGiusto *et al.* (2004) [13]	DT	1244	≥70[a]	65	O		1998	2002	394	1.27	0.4, 2.29	1.27	0.16, 2.38
	Tait *et al.* (2008) [14]	DT	894	≥70[a]	60	O		2001–2001	2005	4167	0.54	0.28, 0.72	0.50	0.29, 0.72
Austria	Bauer *et al.* (2008) [15]	DT	114	99[b]	59	O	31	1998–1999	2004	535	5.42	3.45, 7.40	3.55	1.96, 5.15
Canada	Miller *et al.* (2007) [16]	SI	572	100	53	O, S		1966–2004	2004	1608	1.37	0.80, 1.94	1.18	0.65, 1.71
Czech Rep.	Lejckova and Mravcik (2007) [17]	DT	12207	80	68	O, S		1997–2002	2002	38131	0.84	0.75, 0.93	0.93	0.81, 1.05
	Zábransky *et al.* (2011) [18]	OtR	151	100	43	O,S		1996–1998	2008	1660	0.48	0.15, 0.81	0.48	0.15, 0.82
Germany	Golz *et al.* (2001) [19]	DT	178	100	58	–	100	1996–2000	2000	805	4.22	2.80, 5.64	2.48	1.40, 3.57
Italy	Antolini *et al.* (2006) [20]	DT	4644	100	79	O, S		1975–1999	1999	39667	2.01	1.80, 2.16	1.18	1.08, 1.29
	Bargagli *et al.* (2001) [21]	DT	11432	84	82	O		1980–1995	1997	80787	2.15	2.05, 2.25	1.26	1.18, 1.34
	Brancato *et al.* (1995) [22]	DT	138	100	77	O		1985	1994	1272	2.04	1.26, 2.83	1.34	0.70, 1.97
	Ciccolallo *et al.* (2000) [23]	DT	4260	100	78	–		1975–1995	1995	28424	2.26	2.08, 2.43	1.27	1.14, 1.40
	Ferri *et al.* (2007) [24]	DT	10376	72	86	O		1998–2001	2001	15369	–	–	0.99	0.83, 1.15
	Galli and Musicco (1994) [25]	DT	2432	100	78	O	19	1980–1998	1991	16415	2.52	2.28, 2.77	1.64	1.44, 1.83
	Goedert *et al.* (1995) [26]	DT	4962	99[c]	–	O	66	1980–1990	1990	21130	1.57	1.41, 1.75	0.86	0.74, 0.99
	Manfredi *et al.* (2006) [27]	DT	1214	100	76	O	50	1977–1996	2002	13280	2.04	1.8, 2.3	0.96	0.80, 1.13
	Moroni and Galli (1991) [28]	DT	2279	100	–	O		1981–1988	1989	13069	2.43	2.16, 2.69	1.84	1.60, 2.07
	Zaccarelli *et al.* (1994) [29]	DT	2029	100	76	–	32	1985–1991	1991	7872	2.3	1.96, 2.63	1.17	0.93, 1.41
Netherlands	van Haastrecht *et al.* (1996) [30]	DT,other	509	100	62	O, S	34	1985–1992	1993	2229	3.23	2.56, 4.07	2.69	2.01, 3.37
Norway	Eskild *et al.* (1993) [31]	T&C	1009	100	64	O, S	18	1985–1991	1991	3136	2.77	2.22, 3.42	2.65	2.08, 3.22
Spain	Jarrin *et al.* (2007) [32]	Prv.	6575	100	77	–	47	1987–1996	2004	73901	2.02	1.92, 2.12	0.99	0.92, 1.06
	Lumbreras *et al.* (2006) [33]	DT,other	3247	100	77	–	45	1990–1996	2002	26826	2.18	2.00, 2.36	1.13	1.01,1.26
	Sanchez-Carbonell and Seus (2000) [34]	DT	135	88	71	O		1985	1995	1206	3.4	2.36, 4.44	1.66	0.93, 2.39
Sweden	Fugelstad *et al.* (1995) [35]	DT,other	472	100	–	O, S	100	1986–1990	1990	1793	3.85	2.94, 4.76	3.46	2.60, 4.32
	Fugelstad *et al.* (1997) [36]	DT	1640	≥70[b]	69	O, S	13	1981–1988	1992	10772	1.99	1.72, 2.25	1.82	1.56, 2.07
	Fugelstad *et al.* (1998) [37]	DT	101	100	55	O	56	1986–1988	1993	515	7.76	5.54, 10.58	9.97	6.21, 13.73
Taiwan	Huang *et al.* (2011) [12]	Prison	4357	100	88	O	9	2007–2008	2008	6253	2.27	1.90, 2.64	2.27	1.90, 2.64
UK	Copeland *et al.* (2004) [38]	DT	660	100	67	–		1980–2001	2001	6244	2.45	2.06, 2.84	1.14	0.87, 1.40
	Frischer *et al.* (1997) [39]	DT	459	100	99	O	3	1982–1993	1994	2547	2.08	1.52, 2.64	1.96	1.42, 2.51
	Hickman *et al.* (2003) [40]	DT	881	76	75	O		1997–1999	2001	2075	1.59	1.13, 2.23	1.92	1.23, 2.60
	Oppenheimer *et al.* (1994) [41]	DT	128	100	73	O		1969	1991	2349	1.83	1.28, 2.38	1.83	1.28, 2.38
USA	Evans *et al.* (2012) [52]	OtR	644	100	68	O, S	4	1997–2007	2007	4167	0.91	0.62, 1.20	0.91	0.62, 1.20
	Fingerhood *et al.* (2006) [42]	DT	175	100		O, S	100	1994–1998	5 years[d]	743	7.14	5.22, 9.06	3.23	1.94, 4.53
	Goedert *et al.* (2001) [43]	DT	6570	100	66	–	14	1987–1991	1998	28900	4.67	4.42, 4.92	3.53	3.32, 3.75
	McAnulty *et al.* (1995) [44]	OtR, HC	1769	100	73	–		1989–1991	1992	3149	1.05	0.69, 1.41	1.05	0.69, 1.41
	Vlahov *et al.* (2005) [45]	OtR, SB	3593	100	77	O, S	100	1988	2005	25736	4.5	4.24, 4.76	3.29	3.07, 3.51

(*continued overleaf*)

Table 1 (*continued*)

	Sampling frame	*N*	PWID (%)	Men (%)	Drugs used	HIV+ (%)	Recruitment period	End of follow-up period	All-cause mortality		Non-AIDS mortality		
									PYFU	CMR	95% CI	CMR	95% CI
Vlahov *et al.* (2008) [46]	OtR, SB	2089	100	62	O, S	5	1997–1999	2002	8629	0.71	0.54, 0.88	0.72	0.54, 0.90
Middle-income countries													
Brazil Cardoso *et al.* (2006) [47]	NSP	478	100	79	S	49	2000–2001	2001	612	2.77	1.45, 4.09	1.14	0.30, 1.99
India Solomon *et al.* (2009) [48]	DT,other	1158	100	100	O	25	2005–2006	2008	1998	4.25	3.35, 5.16	3.55	2.73, 4.38
Poland Moskalewicz and Sieroslawski (1996) [49]	DT	656	100	74	O		1983–1992	1992	3594	2.28	1.81, 2.83	2.20	1.71, 2.68
Thailand Quan *et al.* (2007) [50]	DT	346	100	93	O, S		1999	2002	571	3.85	2.42, 5.83	2.98	1.56, 4.39
Vietnam Quan *et al.* (2010) [51]	DT	894	100	100	O	23	2005	2007	710	6.3	4.60, 8.50	4.37	2.83, 5.90

CI, confidence interval; CMR, crude mortality rate; DT, drug treatment; HC, health clinics; NSP, needle and syringe programme; O, opioids; OtR, outreach; Prv., HIV prevention service; PWID, people who inject drugs; PYFU, person-years of follow-up; S, stimulants; SB, snowballing; SI, supervised injecting facilities; T&C, HIV testing and counselling services.
[a]The proportion of patients who were injectors was not reported but was assumed to at least 70 percentage due to the predominance of this route of administration among opioid dependent people in this country.
[b]Not explicitly stated, but implied in this study.
[c]Data on history of drug use was available for 62% of patients, of these 99% had a history of injection.
[d]Patients were followed for 5 years after date of enrolment.
Some CMR and PYFU are calculated.

The cohorts included ranged in size from 100 to over 42 000 participants, contributing a total of 929 238 person-years of follow-up. Men formed the majority of participants in all the studies (median 74% men). Cohorts varied markedly across a number of important characteristics, including: the location of recruitment, whether through drug treatment services, prison, or via 'community'-based recruitment; HIV prevalence at baseline; the extent of exposure to effective drug treatment; and availability of antiretroviral therapy (ART) to the cohorts.

Opioids were reported as participants' sole primary drug of injection in the majority of studies ($n = 20$), 13 cohorts included both stimulant and opioid users and 1 Brazilian study included stimulant users only. It was, however, commonly noted in study descriptions that poly-drug use was likely to occur.

Twenty-one studies reported non-AIDS mortality disaggregated by HIV status at baseline, 22 provided data disaggregated by sex and 7 reported on mortality for periods on and off OST. Results from the analyses of non-AIDS-related mortality are presented in the remainder of this study.

There was substantial variability in non-AIDS mortality between studies (Fig. 1). The results of meta-analyses examining non-AIDS mortality among cohorts of PWID are presented in Table 2. Non-AIDS mortality was significantly higher in LMICs (2.74 per 100 person-years; 95% CI 1.76, 3.72) than in HICs (1.56 per 100 person-years; 95% CI 1.38, 1.74). Non-AIDS mortality was higher in Asia (3.16 per 100 person-years; 95% CI 2.19, 4.13) than other geographic regions, with the lowest pooled non-AIDS mortality rate for Australasia (0.75 per 100 person-years; 95% CI 0.41, 1.82).

A total of 21 studies reported data on non-AIDS mortality disaggregated by sex; 2 of these studies included men only [48,51]. Non-AIDS CMRs were greater for male than for female PWID in 14 out of the 19 cohorts that included PWID of both sexes (Table 2). In the five studies in which women had greater non-AIDS CMRs than men, these differences were not statistically significant (at 95% CI). Pooled across the 19 studies that allowed the comparison, non-AIDS CMRs were 1.34 times greater among male PWID than among female PWID (95% CI 1.142, 1.570). Pooled estimates of these rate ratios were greater than 1 for HICs and LMICs, and across all regions.

Twenty-one studies reported non-AIDS mortality disaggregated by participants' HIV status. In the majority of these studies, individuals were assigned to HIV-positive or HIV-negative groups based on their HIV status measured at baseline. Four studies were of cohorts comprising HIV-positive participants only [19,35,42,45]. Notably, in five studies, a number of AIDS-related deaths were reported among individuals who were recorded as HIV-negative at

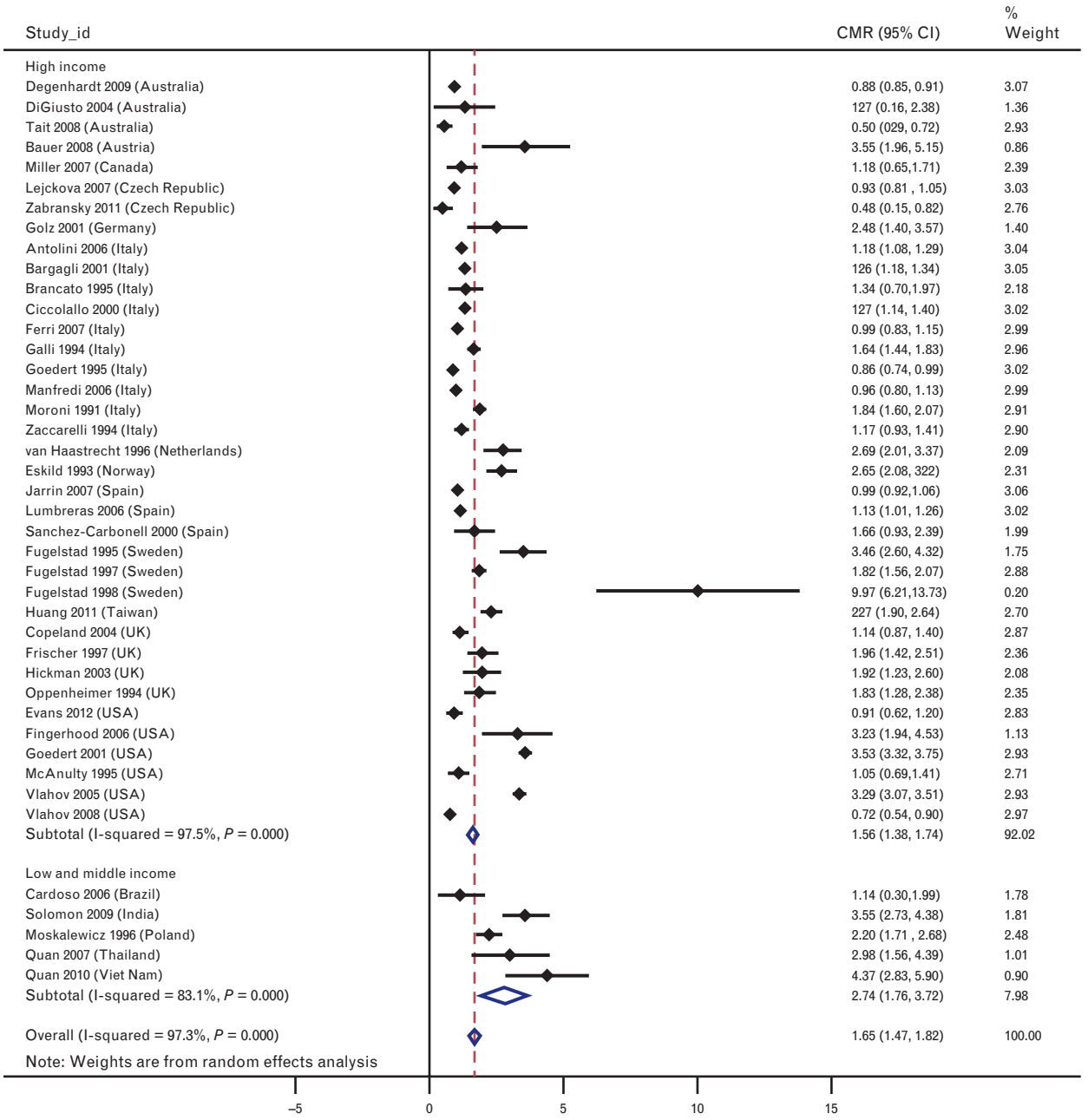

Fig. 1. Forest plot showing non-AIDS-related crude mortality rates and overall estimates from meta-analysis.

baseline. Across the 16 studies from which data were available, the non-AIDS crude mortality was 1.5 times higher among HIV-positive than HIV-negative PWID (95% CI 1.14, 1.96) [25,33,43,47,51] (Table 3). This held true across pooled HICs and LMICs, Western Europe and Asia; in the three North American studies included [43,46,52] and a single Italian study [27], CMRs were higher among HIV-negative than HIV-positive PWID.

Seven studies reported non-AIDS mortality separately for periods during which individuals received OST and when not-receiving OST [7,12,13,35–37,53]. Mortality during time spent on OST was significantly lower than time spent off OST (CMR ratio 0.31; 95% CI 0.18, 0.54) (Table 3).

Discussion

We found 42 cohort studies of PWID, from 18 countries, reporting data on non-AIDS mortality. The cohorts varied markedly in terms of recruitment methods, HIV prevalence and the pattern of drug use among the cohort,

Table 2. Pooled crude mortality rates for non-AIDS-related mortality.

	No. of studies	Pooled CMR per 100 PYFU (95% CI)	I^2 (P value)
Overall	42	1.65 (1.47, 1.82)	97% (<0.001)
HIC	37	1.56 (1.38, 1.74)	98% (<0.001)
LMIC	5	2.74 (1.76, 3.72)	83% (<0.001)
Western Europe	27	1.42 (1.28, 1.56)	92% (<0.001)
Eastern Europe	1	2.20 (1.72, 2.69)	–
Asia	4	3.16 (2.19, 4.13)	78% (<0.001)
Latin America	1	1.14 (0.30, 1.99)	–
North America	7	1.96 (0.87, 3.05)	99% (<0.001)
Australasia	3	0.75 (0.41, 1.09)	84% (<0.001)

CI, confidence interval; HIC, high-income country; LMIC, low and middle-income country; PYFU, person-years of follow-up.

the period in which people were followed up, and likely exposure to effective treatment for drug dependence and HIV. It is highly likely that these differences, along with variation in other characteristics both within and between cohorts, were responsible for the substantial heterogeneity observed in all the analyses of non-AIDS mortality conducted for this study.

Our findings suggest non-AIDS CMRs are considerably lower in HICs than in less wealthy countries. In our previous analysis of all-cause mortality, although differences in pooled CMRs between country income groups were statistically significant, pooled SMRs were not. We posited that the higher CMRs observed in LMICs may reflect higher overall mortality in the general population in these countries, which is adjusted for through the calculation of SMRs [5]. It is possible that differences in mortality rates in the general population between HICs and LMICs contribute to the differences observed for pooled non-AIDS CMRs here.

It is important to note that data on non-AIDS mortality were available from only five studies in middle-income countries. These are unlikely to be representative of the diversity in risk and mortality present across LMICs.

The pooled regional estimates suggest rates of non-AIDS-related mortality might be lower among PWID in Australasia compared to other regions and substantially higher in Asia, but again, the limited number of studies from regions outside of North America and Western Europe do not allow robust regional comparisons.

Mortality from causes other than AIDS appears to be consistently higher among men compared to women who inject. The same direction of difference in mortality between men and women was also seen in the previous analysis examining all-cause mortality. Of note is the observation from that analysis that while pooled all-cause CMRs were higher for men than for women, all-cause SMRs were higher for women than for men, suggesting that women who inject experience much higher rates of excess mortality relative to their age-matched non-drug-using peers than is the case for men who inject.

People who inject drugs, who are HIV-positive, appear to experience substantially greater levels of mortality from non-AIDS-related causes then HIV-negative PWID. Explanations for such a difference were unable to be explored directly through the current analysis. Further research to understand this observation might examine whether or not HIV-positive PWID have poorer physical health, are more likely to experience social disadvantage or are more likely to engage in various risky behaviours that might contribute to HIV acquisition as well as fatal outcomes such as drug overdose.

The review also found that OST reduces non-AIDS mortality risk during periods when individuals were receiving treatment. Previous research has also shown that specific periods in and out of treatment vary in risk, with the first weeks in or out of treatment being the riskiest for elevated mortality [7]. Although it is known that OST availability varies considerably across countries, the data on OST coverage are limited at best [54], and typically cannot be extrapolated back to the periods in which these cohort studies were undertaken, making it difficult to make pooled estimates of the potential variation in non-AIDS mortality according to country-level OST coverage.

Examining differences in mortality from cohort studies is subject to a number of limitations. The studies identified for inclusion in the current analysis were predominantly from HICs, in particular, countries in Western Europe. It would clearly be unwise to assume that mortality is consistent across populations of injectors, pointing to a need for new research in countries where injecting is known to occur, but little or no research has examined this.

The occurrence of AIDS-related deaths among those designated HIV-negative in a number of studies highlights the limitation of relying on HIV status measured at baseline only. This results in those who contract HIV during the follow-up period being assigned to the HIV-negative group for the duration of the study. Future research in this area would benefit from assessing and recording individuals HIV status at multiple time points.

Table 3. Pooled crude mortality rates for non-AIDS mortality by sex, HIV serostatus at baseline and periods on versus periods off opioid substitution therapy.

	Females			Males			Ratio CMR-male/CMR-female		
Sex	No.of studies	Pooled CMR per 100 PYFU (95% CI)	I^2 (P value)	No. of studies	Pooled CMR per 100 PYFU (95% CI)	I^2 (P value)	No. of studies	Rate ratio (95% CI)	I^2 (P value)
Overall	19	0.91 (0.68, 1.14)	88% (<0.001)	21	1.35 (1.19, 1.52)	85% (<0.001)	19	1.34 (1.14, 1.57)	44% (0.022)
HIC	17	0.92 (0.68, 1.15)	88% (<0.001)	17	1.22 (1.09, 1.36)	81% (<0.001)	17	1.33 (1.13, 1.57)	49% (0.012)
LMIC	2	0.59 (−0.67, 1.85)	0% (0.698)	4	3.25 (2.30, 4.19)	55% (<0.1)	2	3.16 (0.43, 23.35)	0% (0.869)
Western Europe	14	0.97 (0.70, 1.25)	91% (<0.001)	13	1.31 (1.17, 1.44)	76% (<0.001)	13	1.35 (1.12, 1.61)	58% (0.005)
Asia	1	1.2 (−2.11, 4.52)	–	3	3.64 (2.98, 4.29)	0% (0.544)	1	2.68 (0.16, 43.89)	–
Latin America	1	0.49 (−0.87, 1.85)	–	1	1.84 (0.48, 3.21)	–	1	3.76 (0.22, 65.67)	–
North America	3	0.82 (0.43, 1.21)	28% (<0.25)	3	1.07 (0.80, 1.33)	0% (0.816)	3	1.25 (0.72, 2.18)	24% (0.268)
Australasia	1	0.45 (0.12, 0.78)	–	1	0.49 (0.22, 0.77)	–	1	1.09 (0.43, 2.76)	–
	HIV-positive			HIV-negative			Ratio CMR-HIV-positive/CMR-HIV-negative		
HIV serostatus	No. of studies	Pooled CMR per 100 PYFU (95% CI)	I^2 (P value)	No. of studies	Pooled CMR per 100 PYFU (95% CI)	I^2 (P value)	No. of studies	Rate ratio (95% CI)	I^2 (P value)
Overall	21	2.51 (1.96, 3.05)	97% (<0.001)	16	1.66 (1.23, 2.09)	98% (<0.001)	16	1.50 (1.15, 1.96)	86% (<0.001)
HIC	18	2.34 (1.80, 2.89)	97% (<0.001)	14	1.49 (1.05, 1.93)	98% (<0.001)	14	1.47 (1.05, 1.93)	88% (<0.001)
LMIC	3	5.65 (3.69, 7.61)	0% (0.849)	2	3.22 (2.46, 3.99)	0% (0.341)	2	3.22 (2.46, 3.99)	0% (0.690)
Western Europe	13	2.05 (1.62, 2.47)	92% (<0.001)	11	1.35 (1.02, 1.68)	95% (<0.001)	11	1.63 (1.17, 2.27)	87% (<0.001)
Asia	2	5.65 (3.69, 7.61)	0% (0.849)	2	3.22 (2.46, 3.99)	0% (0.341)	2	1.73 (1.15, 2.61)	0% (0.690)
Latin America	1	0	–	1	0	–	–	–	–
North America	5	2.53 (1.10, 3.96)	97% (<0.001)	3	1.73 (−.176, 3.64)	99% (<0.001)	3	0.90 (0.75, 1.09)	0% (0.732)
	Periods on OST			Periods off OST			Ratio CMR-on-OST/ CMR-off-OST		
OST status	No. of studies	Pooled CMR per 100 PYFU (95% CI)	I^2 (P value)	No. of studies	Pooled CMR per 100 PYFU (95% CI)	I^2 (P value)	No. of studies	Rate ratio (95% CI)	I^2 (P value)
Overall	7	0.71 (0.40, 1.03)	94% (<0.001)	7	3.15 (2.04, 4.25)	97% (<0.001)	7	0.31 (0.18, 0.54)	91% (<0.001)

CI, confidence interval; CMR, crude mortality rate; HIC, high-income country; LMIC, low and middle-income country; OST, opioid substitution therapy; PYFU, person-years of follow-up.

Ascertaining cases of death within a cohort can also present challenges, particularly in settings without established death notification and registration systems. Reliable information on cause of death may also be unavailable and misattribution of AIDS or non-AIDS-related causes may occur.

The cohorts included in this analysis spanned significant eras of the HIV epidemic including the introduction, increasing availability and improving efficacy of ART, progress which has had an enormous impact on morbidity and survival among people living with HIV.

Few of the studies included in this review met endorsed criteria for reporting cohort studies (such as the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) consensus statement [55]). Important data, including standard parameters such as 'person years of follow-up', were for many studies inconsistently reported, absent or could not easily be calculated, particularly for estimates disaggregated by different characteristics.

Searches to identify studies of this nature in the peer-reviewed literature are fallible. Recent research may be difficult to access, given the typical delay from when research is conducted to being published in peer-reviewed journals. There is also a well recognized under-representation of research from LMICs in the peer-reviewed literature [56,57]. As described for our earlier review, we attempted to address these limitations by using multiple methods to source literature including surveying a broad network of experts in the field about unpublished studies. We primarily reviewed English-language documents, though the abstracts of non-English language peer-reviewed articles were reviewed when available in English and translation was undertaken when papers appeared relevant.

We also draw attention to the limitations of using meta-analytical methods to aggregate results from observational studies. These methods were originally developed for synthesizing findings from randomized controlled trials, which have the benefit that preconditions and sample factors that might influence observed outcomes can be controlled or adjusted for [58]. Controlling such factors is not possible in observational studies, and as highlighted, the settings and characteristics of the cohorts included in the current review are diverse. Recognizing this marked heterogeneity, we sought to explore factors important to mortality by looking at within-study differences between groups (by sex, HIV status and OST exposure) and then pooling the relative differences across studies.

To better examine the potential for non-AIDS mortality to be higher among HIV-positive injectors, there is a need for cross-national work involving more sophisticated analyses of these kinds of longitudinal cohorts. This might involve the development of consortia of cohort investigators across varied countries who would pool harmonized data across cohorts, and examine multiple issues including but not limited to competing risk analyses of non-AIDS and HIV-related mortality, and better investigation of potential sources of confounding.

In conclusion, non-AIDS-related causes of death and drug overdose in particular remain significant contributors to the high levels of mortality experienced by PWID. A comprehensive response to injecting drug use must include efforts that are effective in reducing mortality by these causes. Non-AIDS-related mortality should be considered in estimates of disease burden and in projections of survival among PWID.

Current knowledge about mortality among PWID is largely informed by evidence from HICs. Data that are available suggest substantial differences in mortality between HICs and LMICs. Multiple factors are likely to contribute to the differing levels of risk observed and warrant further investigation in these neglected settings.

Across a diversity of settings, men who inject drugs and PWID who are HIV-positive are at elevated risk of non-AIDS mortality compared to women and HIV-negative PWID, respectively. The limited number of studies and the marked heterogeneity of the cohorts considered in this review, however, limit our ability to make generalizable assertions, quantifying the risk conferred by these factors.

Exposure to OST significantly reduces non-AIDS mortality and remains essential to an effective and comprehensive public health strategy, addressing injecting drug use that must also be responsive to identified risk.

Acknowledgements

Conflicts of interest

There are no conflicts of interest to declare.

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