Temporal trends in mortality among people who use drugs compared with the general Dutch population differ by hepatitis C virus and HIV infection status

Daniëla K. van Santen[a], Jannie J. van der Helm[a], Bart P.X. Grady[a,c], Anneke S. de Vos[b], Mirjam E.E. Kretzschmar[b,d], Ineke G. Stolte[a,c] and Maria Prins[a,c]

Objectives: We aimed to identify temporal trends in all-cause and cause-specific mortality rates among people who use drugs (PWUD) compared with the general Dutch population and to determine whether mortality trends differed by hepatitis C virus (HCV)/HIV (co) infection status.

Design: Longitudinal cohort study.

Methods: Using data from the Amsterdam Cohort Studies among 1254 PWUD (1985–2012), all-cause and cause-specific standardized mortality ratios (SMRs) were calculated; SMRs were stratified by serological group (HCV/HIV-uninfected, HCV-monoinfected, and HCV/HIV-coinfected) and calendar period. Temporal trends were estimated using Poisson regression.

Results: The overall all-cause SMR was 13.9 (95% confidence interval 12.6–15.3). The SMR significantly declined after 1996, especially due to a decline among women ($P < 0.001$). The highest SMR was observed among HCV/HIV-coinfected individuals during 1990–1996 (SMR 61.9, 95% confidence interval 50.4–76.0), which significantly declined after this period among women ($P = 0.001$). In contrast, SMR for HCV-monoinfected, and HCV/HIV-uninfected PWUD did not significantly change over time. The SMR for non-natural deaths significantly declined ($P = 0.007$), whereas the SMR for HIV-related deaths was the highest during all calendar periods.

Conclusions: We found evidence for declining all-cause mortality among PWUD compared with the general population rates. Those with HCV/HIV-coinfection showed the highest SMR. The decline in the SMR seems to be attributable to the decline in mortality among women. Mortality rates due to non-natural deaths came closer to those of the general population over time. However, HIV-related deaths remain an important cause of mortality among PWUD when compared with the general Dutch population. This study reinforces the importance of harm-reduction interventions and HCV/HIV treatment to reduce mortality among PWUD.

AIDS 2014, **28**:2589–2599

Keywords: causes of death, hepatitis C, HIV, people who use drugs, standardized mortality ratio, trends

[a]Department of Research, Cluster Infectious Diseases, Public Health Service Amsterdam, Amsterdam, [b]Julius Center, University Medical Center Utrecht, Utrecht, [c]Department of Infectious Diseases, Center for Infection and Immunology Amsterdam (CINIMA), Academic Medical Center (AMC), Amsterdam, and [d]Centre for Infectious Disease Control, National Institute of Public Health and the Environment, Bilthoven, the Netherlands.

Correspondence to Daniëla K. van Santen, Nieuwe Achtergracht 100, 1018 WT Amsterdam, the Netherlands.

Tel: +31 20 555 5569; e-mail: dvsanten@ggd.amsterdam.nl

Received: 28 April 2014; revised: 7 August 2014; accepted: 8 August 2014.

DOI:10.1097/QAD.0000000000000450

Introduction

People who use drugs (PWUD) are at an increased risk of premature mortality compared with the general population. In the Netherlands, the start of a major heroin epidemic occurred during the 1970s [1,2]. The prevalence of hepatitis C virus (HCV) peaked during the 1980s, when more than 85% of ever-injectors tested HCV-positive [3,4]. The HIV epidemic commenced during the 1980s [5,6]. In 1985, the prospective Amsterdam Cohort Studies (ACS) among PWUD were initiated to track the HIV epidemic [5].

To minimize the damage PWUD inflict upon themselves and society, harm-reduction interventions were implemented in Amsterdam, the Netherlands, from 1979, making it one of the first countries to do so [7,8]. These included methadone programs and needle exchange programs (NEPs) [7,8]. Especially, the combination of methadone programs and NEP uptake has been associated with a lower risk of HIV and HCV acquisition among people who inject drugs (PWID) [9]. For HIV-infected individuals, combination antiretroviral therapy (cART) became widely available from 1996, which has been shown to substantially reduce HIV-related mortality [10–12]. However, HIV-infected PWID tend to initiate cART at a later stage than other risk groups [13], leading to a diminished probability of survival [14–16]. For HCV-infected PWUD, HCV treatment became relatively easy to access in Amsterdam from 2005, when a special unit was launched to treat HCV-infected PWUD [17], and might have reduced liver-related mortality, which generally requires two to three decades of chronic HCV infection [18].

Previous studies have shown that PWUD have a 4.4–47.6 higher risk of dying than the general population [19–24]. This increased risk of dying differs between studies and countries, which could be ascribed to differences in calendar period of follow-up, study population characteristics, drug-use practices, HIV/HCV incidence and background prevalence, and availability and uptake of harm-reduction interventions [20].

As the ACS have reached 27 years of follow-up, which is one of longest worldwide, we had the unique opportunity to identify changes in mortality rates over different calendar periods. Trends in mortality rates can serve as a proxy for changing health patterns and the effectiveness of health-related interventions that have been implemented.

We hypothesized that because of the introduction and availability of harm-reduction interventions and HCV and HIV therapy, PWUD have reached mortality rates closer to those of the general Dutch population in recent calendar periods. Our study aimed to identify temporal trends in all-cause and cause-specific mortality rates among PWUD compared with the general Dutch population; and to determine whether excess mortality trends differed by HCV/HIV status.

Methods

Study population

The ACS among (injecting and non-injecting) PWUD is an open, prospective cohort study initiated in 1985, aiming to investigate the epidemiology, natural history, and pathogenesis of HIV, and to evaluate the effect of interventions. Participation in the ACS is voluntary and written informed consent is obtained at intake [25]. Recruitment is by means of local methadone outposts, a sexually transmitted diseases clinic, and word of mouth. PWUD visit the Public Health Service of Amsterdam every 4–6 months; they give blood and complete a standardized questionnaire about their health and sexual and drug use behavior during each cohort visit. To encourage continued participation, 12 Euros were paid per follow-up visit. Participants, aged between 20 and 64 years with at least two cohort visits and with both longitudinal HCV and HIV test results (1254/1661), were included in our study. This study was approved by the Medical Ethical Committee of the Amsterdam Medical Centre, the Netherlands.

Laboratory methods

At entry, the ACS participants were tested for HIV antibodies by ELISA and at every follow-up visit if previously negative. In 2005, participants with at least two cohort visits between December 1985 and January 2005 were retrospectively tested for HCV antibodies with a third-generation ELISA (AxSym HCV version 3.0; Abbott, Wiesbaden, Germany). Individuals who were anti-HCV-negative at entry were tested for HCV antibodies at the most recent visit. On finding HCV seroconversion (defined as the presence of HCV antibodies in a previously HCV-seronegative individual), we tested samples between the first and the most recent visit to obtain the most exact seroconversion interval. From 2005 onwards, HCV testing occurred prospectively.

Definitions and statistics

Information about vital status was obtained by matching the ACS data at regular intervals against the municipal and national population registries in the Netherlands. Causes of death (CODs) were systematically obtained from hospital records, general practitioners, the national HIV Monitoring Foundation, or coroners. The CODs were divided into four categories: HIV-related deaths; liver-related deaths; natural causes other than HIV or liver-related deaths (e.g. cardiovascular-related deaths, non-AIDS-related cancers); and non-natural causes (i.e. overdose, accidents, homicide, and suicide).

Follow-up time was calculated from the first cohort visit until: loss to follow-up, last known date to be alive, death, or cohort censoring date (i.e. 31 December 2012). Calendar periods were defined as follows: period 1 (1985–1989) – pre-cART and before adequate methadone dose (≥60 mg/day) was generally available in Amsterdam; period 2 (1990–1996) – pre-cART with adequate methadone substitution therapy; period 3 (1997–2000) – early cART era; period 4 (2001–2005) – late cART era; period 5 (2006–2012) – late cART and HCV treatment era.

Four HCV/HIV serological groups were defined: HCV/HIV-uninfected, HIV-monoinfected, HCV-monoinfected, and HCV/HIV-coinfected. HIV and HCV status were treated as time-dependent variables. For HIV and HCV seroconverters, the midpoint between the last negative and the first positive antibody test was used to estimate the moment of seroconversion. After the last cohort visit, the serological group was carried forward until the end of follow-up. In a sensitivity analysis, a more stringent censoring strategy was applied (i.e. censoring took place at the end of the calendar period of the last cohort visit) to check whether results were robust.

Crude mortality rates (CMRs) per 1000 person-years, including 95% confidence intervals (CIs), were calculated. Standardized mortality ratios (SMRs) were used to compare the mortality rate among the PWUD with the mortality rate in the general Dutch population. SMR is the ratio of the observed deaths among PWUD from the ACS and the expected number of deaths. Expected deaths were calculated by multiplying the person-years accrued from our study population by the mortality rate of the general Dutch population matched by age group, sex, and calendar period.

Mortality rates of the general Dutch population were obtained from the Human Mortality Database (HMD) (www.mortality.org), and the numbers of deaths per COD were obtained from Statistics Netherlands (www.cbs.nl). To calculate the mortality rate of the general Dutch population per calendar period, age group, and sex, the following formula was used:

$$\mathrm{MR} = \frac{\mathrm{Total\_deathsGP} - \mathrm{Total\_deathsACS}}{\mu\mathrm{PopulationGP} - \mathrm{PopulationACS}}$$

where MR is the mortality rate; GP the general population; and μ the average.

The SMRs for each calendar period, serological group, and COD were calculated using univariable Poisson regression models with the natural logarithm of the expected deaths as offset term; the exponential of the coefficient of the Poisson model is the SMR. Multivariable Poisson models, with the same offset term, were used to obtain the effect of calendar period and serological group on the SMR and are expressed in SMR ratios; SMR ratios can be interpreted as a relative SMR. *P* values for trends were obtained from the multivariable models. Multivariable models were corrected for age group, sex and serological group. We additionally checked for interactions between calendar period and the other covariates. For the calculation of the SMR per cause of death, PWUD were included in the analysis irrespective of their HCV/HIV status. Stata version 11.2 was used (Stata Statistical Software: Release 11; Stata Corp LP, College Station, Texas, USA).

Results

Out of 1254 PWUD, at entry, 63.9% ($n = 801$) were men, their median age was 30 years [interquartile range (IQR) 26–36], and 72.4% ($n = 908$) had ever injected drugs (Table 1). The median follow-up time was 15.0 years (IQR 9.5–20.9). At the study entry, the proportion of those who ever injected was similar among those included (i.e. at least two cohort visits) and excluded in this study. However, individuals included in our study were older, more often of Dutch nationality, less often homeless and a higher proportion of them were men compared to the excluded PWUD.

The characteristics and demographical distribution of PWUD changed across the calendar periods (Table 1). During the first calendar period, 82.4% of PWUD were aged between 20 and 34 years compared with only 11.9% in the most recent calendar period. The percentage of participants who ever injected drugs or injected drugs during the calendar period decreased over time. During the first calendar period, 20.2% were HCV/HIV-uninfected, 1.3% HIV-monoinfected, 52.3% HCV-monoinfected, and 26.3% HCV/HIV-coinfected. During the latest calendar period, 38.8% were HCV/HIV-uninfected, 1.8% HIV-monoinfected, 45.6% HCV-monoinfected, and 13.9% HCV/HIV-coinfected. During 18 575 person-years of total follow-up time, 96 PWUD seroconverted for HIV and 54 for HCV.

Overall mortality rates

Among 1254 PWUD, 406 deaths were observed during the study period. The overall CMR for all-cause mortality was 21.9 per 1000 person-years (95% CI 19.8–24.1). The overall effect of calendar period on the CMR was significant ($P = 0.003$) (Table 2). The highest CMR was observed between 1990 and 1996 (27.5 per 1000 person-years; 95% CI 23.1–32.6) (Table 2). The CMR declined from 27.5 in 1990–1996 to 17.4 in 2001–2005, and was followed by a slight increase to 23.7 in the period 2006–2012 (Fig. 1a).

The overall SMR was 13.9 (95% CI 12.6–15.3), meaning that drug users from the ACS had a 13.9 times higher mortality rate compared with the age, sex, and

Table 1. General characteristics of 1254 drug users on active follow-up from the Amsterdam Cohort Studies (ACS) with at least two follow-up visits by calendar period (1985–2012).

Calendar period ($N = 1254$)	Total *n* (%)	1985–1989 541	1990–1996 853	1997–2000 823	2001–2005 699	2006–2012 498
Age median (IQR)[a]	30 (26–36)	29 (25–33)	32 (28–36)	36 (31–41)	39 (32–44)	44 (39–49)
Age group in years [*n* (%)][a]						
20–34	886 (70.65)	446 (82.44)	554 (64.95)	331 (40.22)	209 (29.90)	59 (11.85)
35–49	356 (28.39)	93 (17.19)	291 (34.11)	470 (57.11)	441 (63.09)	332 (66.67)
50–64	12 (0.96)	2 (0.37)	8 (0.94)	22 (2.67)	49 (7.01)	107 (21.49)
Sex [*n* (%)]						
Men	801 (63.88)	293 (54.16)	512 (60.09)	559 (67.92)	489 (69.96)	338 (67.87)
Women	453 (36.12)	248 (45.84)	341 (39.98)	264 (32.08)	210 (30.04)	160 (32.13)
Nationality [*n* (%)][a]						
Dutch	934 (74.48)	401 (74.12)	628 (73.62)	655 (79.59)	567 (81.12)	408 (81.93)
Non-Dutch	320 (25.52)	140 (25.88)	225 (26.38)	168 (20.41)	132 (18.88)	90 (18.07)
Homeless [*n* (%)][a]						
Yes	116 (9.34)	9 (1.66)	71 (8.38)	62 (7.60)	68 (9.91)	33 (7.02)
No	1126 (9.34)	532 (98.34)	776 (91.62)	754 (92.40)	618 (90.09)	437 (92.98)
Ever injected drugs [*n* (%)]						
Yes	908 (72.41)	450 (83.18)	695 (81.48)	586 (71.20)	465 (66.52)	338 (67.87)
No	346 (27.59)	91 (16.82)	158 (18.52)	237 (28.80)	234 (33.48)	160 (32.13)
Injected drugs in the preceding 6 months [*n* (%)][a,b]						
Yes	668 (73.98)	349 (77.56)	496 (72.20)	292 (50.52)	179 (38.91)	86 (26.88)
No	235 (25.88)	101 (22.44)	191 (27.80)	286 (49.48)	281 (61.09)	226 (72.44)
Borrowed needles [*n* (%)][a,c]						
Yes	234 (35.03)	157 (44.99)	99 (19.96)	45 (15.41)	14 (7.82)	3 (3.49)
No	434 (64.97)	192 (55.01)	397 (80.04)	247 (84.59)	165 (92.18)	83 (96.51)
Methadone dosage in mg [*n* (%)][a]						
0	208 (17.33)	20 (4.05)	159 (18.84)	226 (27.80)	222 (32.13)	137 (29.72)
1–60 mg	310 (25.83)	40 (8.10)	414 (49.05)	260 (31.98)	166 (24.02)	103 (22.34)
>60 mg	253 (21.08)	21 (4.25)	249 (29.50)	297 (36.53)	302 (43.70)	219 (47.51)
Unknown[d]	429 (35.75)	413 (83.60)	22 (2.61)	30 (3.69)	1 (0.14)	2 (0.43)
HCV/HIV serogroup [*n* (%)][a]						
HCV/HIV-uninfected	428 (34.13)	109 (20.15)	199 (23.33)	294 (35.72)	291 (41.63)	193 (38.76)
HIV-monoinfected	16 (1.28)	7 (1.29)	9 (1.06)	9 (1.09)	10 (1.43)	9 (1.81)
HCV-monoinfected	564 (44.98)	283 (52.31)	421 (49.36)	356 (43.26)	292 (41.77)	227 (45.58)
HCV/HIV-coinfected	246 (19.62)	142 (26.25)	224 (26.26)	164 (19.93)	106 (15.16)	69 (13.86)
Chronic hepatitis B						
Yes	72 (5.99)	46 (8.94)	63 (7.76)	36 (4.57)	22 (3.32)	14 (3.04)
No	468 (91.05)	748 (92.23)	751 (95.42)	640 (96.68)	446 (96.96)	
Seroconversion during follow-up (*n*)						
HIV seroconversion	96	23	56	9	5	3
HCV seroconversion	54	19	25	4	6	0

HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range. Missing values at study entry for: 'methadone dosage' = 54; 'chronic hepatitis B' = 52; 'homeless' = 12; 'injected drugs in the preceding 6 months' = 5. Missing values are not included in the percentages.
[a]At study entry in the cohort (total) and at the first visit during the calendar period.
[b]Out of those who ever injected drugs.
[c]Out of those who injected drugs in the last 6 months preceding the first visit during that calendar period.
[d]Unknown dosage among those enrolled in a methadone program.

calender-matched general Dutch population. During 1985–1990, the SMR was 15.8 (95% CI 9.7–25.9), it increased to 25.5 (95% CI 21.5–30.3) in 1990–1996, followed by a decline to 14.1 (95% CI 11.2–17.8) in 1997–2000, 9.9 (95% CI 7.9–12.3) in 2001–2005, and 10.8 (95% CI 9.0–13.1) in 2006–2012 (Fig. 1b, Table 3). The SMR decreased with increasing age ($SMR_{20-34} = 22.9$, 95% CI 18.7–28.2; $SMR_{35-49} = 15.5$, 95% CI 13.7–17.5; $SMR_{50-64} = 7.3$, 95% CI 5.8–9.3) and was higher among women ($SMR_{men} = 12.8$, 95% CI 11.3–14.4; $SMR_{women} = 16.6$, 95% CI 14.0–19.6).

In multivariable analysis, a significant interaction between calendar period and sex ($P = 0.03$) was observed. The SMR significantly decreased in later calendar periods among women [adjusted SMR ratio $(aSMRr)_{2006-2012} = 0.6$, 95% CI 0.4–0.9, compared to 1990–1996; $P < 0.001$] (Table 3), while remaining stable among men. HCV-monoinfected (aSMRr = 1.9, 95% CI 1.4–2.8) and HCV/HIV-coinfected (aSMRr = 7.0, 95% CI 5.0–9.8) PWUD had a significantly higher SMR compared with HCV/HIV-uninfected PWUD ($P < 0.001$) (Table 3).

All-cause mortality per serological group

Hepatitis C virus/HIV-uninfected people who use drugs

Although the overall effect of calendar period was not significant ($P = 0.16$), the CMR for HCV/HIV-uninfected PWUD slightly increased from 2001 to 2005 onwards (Fig. 1c, Table 2). The overall SMR was 4.7

Table 2. All-cause crude mortality rates (overall and by HCV/HIV serological group) and cause-specific crude mortality rates among 1254 people who use drugs from the Amsterdam Cohort Studies by calendar period (1985–2012).

	Total	1985–1989	1990–1996	1997–2000	2001–2005	2006–2012	*P* value
Overall CMR by calendar period							
Person-years	18 575	1198	4736	3454	4594	4598	
Number of deaths (*n*)	406	16	130	71	80	109	
Number of PWUD[a]	1254	541	923	1031	1029	899	
CMR (95% CI)	21.86 (19.83–24.09)	13.36 (8.18–21.80)	27.45 (23.11–32.60)	20.59 (16.31–25.98)	17.42 (13.99–21.68)	23.70 (19.65–28.60)	0.003
CMR by serological group							
HCV/HIV-uninfected [*n* (%)]	40 (100)	0	5 (12.50)	5 (12.50)	13 (32.50)	17 (42.50)	
CMR (95% CI)	7.44 (5.46–10.14)	0 (0–15.23)[b]	5.40 (2.25–12.97)	5.30 (2.21–12.74)	7.99 (4.64–13.76)	10.38 (6.45–16.69)	0.160
HIV-monoinfected [*n* (%)]	8 (100)	1 (12.50)	2 (25.00)	0	2 (25.00)	3 (37.50)	
CMR (95% CI)	37.96 (18.98–75.90)	60.22 (8.48–427.52)	50.46 (12.62–201.74)	0 (0–99.96)[b]	40.18 (10.04–160.65)	44.25 (14.27–137.21)	0.523
HCV-monoinfected [*n* (%)]	137 (100)	7 (5.11)	32 (23.36)	22 (16.06)	27 (19.71)	49	
CMR (95% CI)	15.23 (12.88–18.00)	11.14 (5.31–23.37)	13.21 (9.34–18.68)	13.07 (8.60–19.85)	12.86 (8.82–18.75)	22.65 (17.12–29.97)	0.047
HCV/HIV-coinfected [*n* (%)]	221 (100)	8 (3.62)	91 (41.18)	44 (19.91)	38 (17.19)	40 (18.10)	
CMR (95% CI)	55.37 (48.53–63.18)	25.73 (12.87–51.45)	67.52 (54.98–82.92)	55.97 (41.67–75.22)	46.98 (33.83–63.90)	54.86 (40.24–74.79)	0.029
CMR by cause of death							
HIV-related [*n* (%)]	87 (21.43)	1 (6.25)	52 (40.00)	12 (16.90)	12 (15.00)	10 (9.17)	
CMR (95% CI)	4.68 (3.79–5.78)	0.83 (0.12–5.92)	10.98 (8.37–14.41)	3.47 (1.97–6.12)	2.61 (1.48–4.60)	2.17 (1.17–4.04)	<0.001
Liver-related [*n* (%)]	30 (7.39)	1 (6.25)	6 (4.62)	6 (8.45)	5 (6.25)	12 (11.01)	
CMR (95% CI)	1.61 (1.13–2.31)	0.83 (0.12–5.92)	1.27 (0.56–2.82)	1.74 (0.78–3.88)	1.09 (0.45–2.61)	2.60 (1.48–4.60)	0.376
Natural [*n* (%)]	111 (27.34)	2 (12.50)	21 (16.15)	18 (25.35)	24 (30.00)	46 (42.20)	
CMR (95% CI)	5.97 (4.96–7.20)	1.67 (0.42–6.68)	4.43 (2.89–6.80)	5.22 (3.29–8.30)	5.22 (3.50–7.79)	10.00 (7.49–13.36)	0.001
Non-natural [*n* (%)]	107 (26.35)	11 (68.75)	42 (32.31)	21 (29.78)	19 (23.75)	14 (12.84)	
CMR (95% CI)	5.76 (4.76–6.96)	9.18 (5.08–16.58)	8.87 (6.55–12.00)	6.09 (4.00–9.34)	4.14 (2.64–6.48)	3.04 (1.80–5.14)	0.001
Unknown	71 (17.49)	1 (6.25)	9 (6.92)	14 (19.72)	20 (25.00)	27 (24.77)	

CI, confidence intervals; CMR, crude mortality rate; HCV, hepatitis C virus; *n*, number of deaths; PWUD, people who use drugs.
[a]The number of PWUD per calendar period also includes those PWUD who were not on active follow-up but contributed follow-up time until censoring.
[b]Calculation based on exact binomial methods.

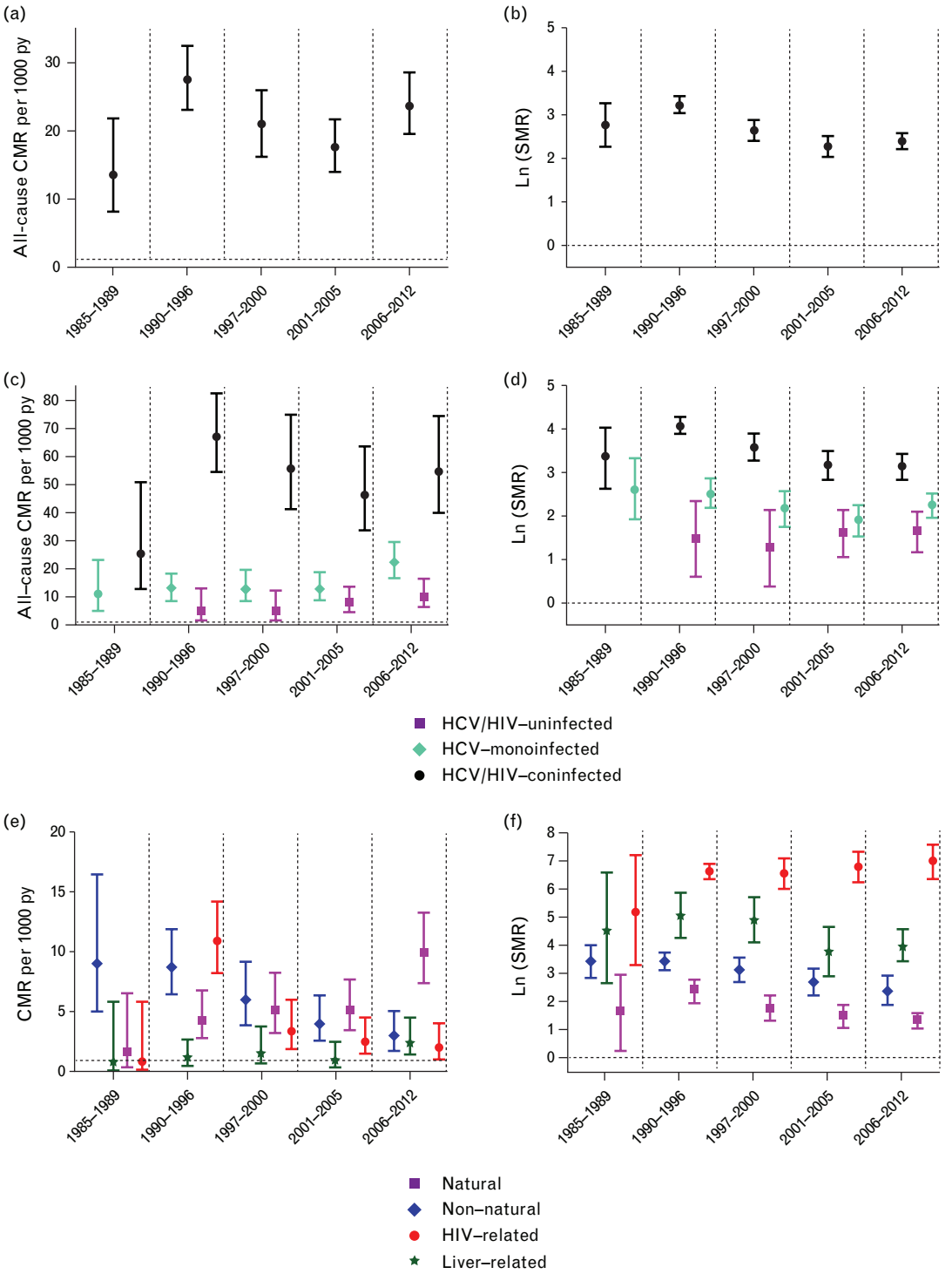

Fig. 1. (a–f) Crude mortality rates (CMRs) (a) overall, (c) per serological group, and (e) per cause of death stratified by calendar period; and standardized mortality ratios (SMRs) (b) overall, (d) per serological group, and (f) per cause of death stratified by calendar period among people who use drugs from the Amsterdam Cohort Studies (1985–2012). On the left side, all graphs show the CMRs and on the right side all graphs show the natural logarithm of the SMRs. The SMRs depicted on the graphs are transformed to the natural logarithm in order to fit either all serological groups or causes of death into one graph. Note: Most of the graphs have different scales in order to fit each of the CMR or SMR into one graph. (a) All-cause CMR per 1000 py per calendar period among 1254 PWUD; (b) all-cause SMR per calendar period among 1254 PWUD; (c) all-cause CMR per 1000 py per calendar period and serological group; (d) all-cause SMR per calendar period and serological group; (e) cause-specific CMR per 1000 py per calendar period; (f) cause-specific SMR per calendar period. (*) CMRs and SMRs for HIV-monoinfected are not shown given the small number of individuals and few endpoints. Ln, natural logarithm; py, person-years.

Table 3. Multivariable Poisson models for all-cause standardized mortality ratios (overall and stratified per HCV/HIV serological group) among 1254 people who use drugs from the Amsterdam Cohort Studies (1985–2012).

	All-cause mortality[a]					Per serological group								
						HCV/HIV-uninfected		HCV-monoinfected		HCV/HIV-coinfected[a]				
	SMR (95% CI)	aSMRr (95% CI)	*P*	aSMRr (95% CI)	*P*	aSMRr (95% CI)	*P*	aSMRr (95% CI)	*P*	aSMRr (95% CI)	*P*	aSMRr (95% CI)	*P*
		Women		Men						Women		Men	
Calendar period			<0.001		0.569		0.543		0.227		<0.001		0.382
1985–1989	15.84 (9.70–25.85)	0.54 (0.23–1.26)		0.59 (0.29–1.18)		NE		0.92 (0.40–2.09)		0.28 (0.07–1.16)		0.62 (0.26–1.44)	
1990–1996	25.52 (21.49–30.31)	1		1		1		1		1		1	
1997–2000	14.12 (11.19–17.82)	0.46 (0.28–0.77)		0.87 (0.61–1.26)		0.86 (0.25–3.01)		0.88 (0.50–1.55)		0.33 (0.17–0.64)		0.93 (0.59–1.46)	
2001–2005	9.87 (7.93–12.29)	0.28 (0.16–0.49)		0.82 (0.58–1.18)		1.23 (0.43–3.52)		0.80 (0.46–1.41)		0.29 (0.15–0.56)		0.63 (0.38–1.05)	
2006–2012	10.83 (8.98–13.07)	0.60 (0.39–0.94)		0.92 (0.64–1.33)		1.30 (0.45–3.71)		1.38 (0.81–2.37)		0.30 (0.15–0.58)		0.77 (0.46–1.32)	
Serological group					<0.001	NA		NA		NA		NA	
HCV/HIV-uninfected	4.73 (3.47–6.45)		1										
HCV-monoinfected	9.52 (8.06–11.26)		1.93 (1.36–2.75)										
HCV/HIV-coinfected	35.91 (31.47–40.97)		6.97 (4.96–9.80)										

Serological group, age group and sex were included as covariates in the all-cause mortality multivariable model. Age group and sex were included as covariates in the stratified models per serological group. Statistically significant interaction terms were also included as covariates in the model. HIV-monoinfected people were not included in the multivariable model due to limited numbers. aSMRr, adjusted SMR ratio; CI, confidence interval; HCV, hepatitis C virus; NA, not applicable; NE, no events; SMR, standardized mortality ratio.
[a]Significant interaction between calendar period and sex.

(95% CI 3.5–6.5) (Table 3). As illustrated in Fig. 1d, the SMR slightly increased after 2000, although the overall effect of calendar period was not statistically significant in multivariable analysis ($P = 0.54$) (Table 3).

HIV-monoinfected people who use drugs

The overall CMR for HIV-monoinfected PWUD was 37.9 (95% CI 19.0–75.9) (Table 2) and the overall SMR was 26.3 (95% CI 13.2–52.6). Given the small number of HIV-monoinfected PWUD and deaths among them, the SMRs per calendar period were not calculated for them.

Hepatitis C virus-monoinfected people who use drugs

The CMR for HCV-monoinfected PWUD was borderline significantly different across the calendar periods ($P = 0.05$) and was the highest between 2006 and 2012 (CMR = 22.7, 95% CI 17.1–30.0) (Fig. 1c, Table 2). The overall SMR was 9.5 (95% CI 8.1–11.3) (Table 3). As illustrated in Fig. 1d, the SMR decreased until 2001–2005 and was followed by a slight increase in 2006–2012, although the overall effect of calendar period was not statistically significant in the multivariable analysis ($P = 0.23$) (Table 3).

Hepatitis C virus/HIV-coinfected people who use drugs

The CMR for HCV/HIV-coinfected PWUD significantly differed across the calendar periods ($P = 0.03$) and was the highest between 1990 and 1996 (CMR = 67.5, 95% CI 55.0–82.9), which is also the highest CMR observed in this study (Fig. 1c, Table 2). The CMR for HCV/HIV-coinfected PWUD was more than twice that of the CMR for all PWUD and had a pattern similar to the CMR for all PWUD over time (Fig. 1a and c, Table 2). The overall SMR was 35.9 (95% CI 31.5–41.0) (Table 3). HCV/HIV-coinfected PWUD had the highest SMR during all calendar periods compared with the other serological groups and especially during the period 1990–1996 (SMR = 61.9, 95% CI 50.4–76.0) (Fig. 1d). As illustrated in Fig. 1d, the SMR declined after 1990–1996 and remained stable in the two most recent periods. In multivariable analysis, the effect of calendar period was significantly different among women and men ($P = 0.03$). Among women, the SMR was significantly lower in the last three calendar periods compared with 1990–1996 ($P < 0.001$), whereas the SMR remained relatively stable over time among men (Table 3).

Mortality per cause of death

The most common CODs were natural deaths ($n = 111$), followed by non-natural ($n = 107$), HIV-related ($n = 87$), and liver-related deaths ($n = 30$).

Natural causes

The CMR for natural deaths significantly increased over time ($P = 0.001$) – from 1.7 (95% CI 0.4–6.7) between 1985 and 1989 to 10.0 (95% CI 7.5–13.4) between 2006 and 2012 (Fig. 1e, Table 2). The overall SMR was 5.0 (95% CI 4.1–6.0) and was the lowest of the cause-specific

SMR. As illustrated in Fig. 1f, the SMR for natural causes decreased after 1990–1996 (Fig. 1f), although the overall effect of calendar period was not significant ($P = 0.38$) (Table 4).

Non-natural causes

In contrast to the CMR for natural causes, the CMR for non-natural deaths significantly decreased over time ($P = 0.001$) – from 9.2 (95% CI 5.1–16.6) in 1985–1989 to 3.0 (95% CI 1.8–5.1) in 2006–2012 (Fig. 1e, Table 2). The overall SMR for non-natural deaths was 21.3 (95% CI 17.6–25.7), and we observed a steady decline of the SMR over time ($P = 0.007$) (Fig. 1f, Table 4).

HIV-related causes

The CMR for HIV-related deaths reached its peak in the period 1990–1996 (CMR = 11.0, 95% CI 8.4–14.4), followed by a statistically significant decline after 1996 ($P < 0.001$) (Fig. 1e, Table 2). The overall SMR was 798.2 (95% CI 647.0–984.9). As illustrated in Fig. 1f, we observed a higher HIV-related SMR after 1990, although the overall effect of calendar period was not significant in the multivariable analysis for men ($P = 0.30$) and bordeline signficant for women ($P = 0.06$) (Table 4).

Liver-related causes

The overall CMR for liver-related deaths was 1.6 (95% CI 1.1–2.3) and did not significantly differ across the calendar periods ($P = 0.38$) (Table 2). The overall SMR for liver-related deaths was 72.4 (95% CI 50.6–103.5). As illustrated in Fig. 1f, the SMR for liver-related deaths decreased after 2000, although the overall effect of calendar period was not significant in the multivariable analysis ($P = 0.11$) (Table 4).

Finally, in a sensitivity analysis with a more stringent censoring strategy, comparable results were observed.

Discussion

We investigated whether mortality among PWUD from the ACS has come closer to that of the general Dutch population in recent calendar periods. As hypothesized, we observed a decline in mortality among PWUD compared with the general Dutch population after 1996. However, despite this decline, mortality rates among PWUD are still 11 times higher than those of the general population in the most recent calendar period. Of interest, mortality due to non-natural deaths came closer to the general Dutch population over time.

The decline in the SMR among PWUD seems to be mainly attributable to the decline in mortality after 1996 among HCV/HIV-coinfected women; this is in line with a study among PWID in Norway, which showed that compared to men, women had a lower risk of mortality in the long term, although in the short term – within 3 years of inclusion in the study –, women had a higher risk of mortality [26]. One explanation for the different mortality trends among men and women might be that women sought HIV and/or drug treatment earlier than men and were less likely to be imprisoned [26]. Furthermore, the decline among HCV/HIV-coinfected PWUD might be explained by the availability of cART from 1996 onwards. In line with our findings, a study among HIV seroconverters showed that overall and cause-specific mortality rates decreased after the introduction of cART [27]. However, the benefits of cART appeared to be less pronounced for PWUD than for MSM [27]. Nonetheless, cART availability alone cannot explain the decrease of the SMR observed, as a more constant SMR would be expected because the positive effects of cART have also reduced mortality among HIV-infected individuals in the general Dutch population. Hence, the decline of the SMR after 1996 is also likely to be attributable to the significant decline in non-natural deaths over time. This is in contrast to the findings from

Table 4. Multivariable Poisson models for cause-specific standardized mortality ratios among 1254 people who use drugs from the Amsterdam Cohort Studies (1985–2012).

	SMR-ratios by cause of death									
	Natural		Non-natural		HIV-related[a]				Liver-related[b]	
	aSMRr (95% CI)	*P*	aSMRr (95% CI)	*P*	aSMR r (95% CI) Women	*P*	aSMR r (95% CI) Men	*P*	aSMR r (95% CI)	*P*
Calendar period		0.383		0.007		0.055		0.298		0.105
1985–1989	1[c]		1		1[c]		1[c]		1[c]	
1990–1996			0.94 (0.48–1.84)							
1997–2000	0.73 (0.39–1.36)		0.84 (0.40–1.80)		0.53 (0.20–1.38)		1.11 (0.48–2.53)		0.89 (0.30–2.5)	
2001–2005	0.67 (0.37–1.23)		0.47 (0.21–1.06)		0.26 (0.08–0.88)		2.08 (0.97–4.46)		0.33 (0.10–1.06)	
2006–2012	0.60 (0.34–1.06)		0.31 (0.13–0.74)		0.50 (0.16–1.58)		1.76 (0.67–4.60)		0.38 (0.15–0.97)	

Serological group, age group and sex were included as covariates in the multivariable models. Statistically significant interaction terms were also included as covariates in the model. aSMRr, adjusted SMR ratio; CI, confidence interval; HCV, hepatitis C virus; SMR, standardized mortality ratio.
[a]Significant interaction between calendar period and sex.
[b]Only sex was included as a covariate given the limited number of events (number of deaths = 30).
[c]The first and the second calendar period are grouped together due to low number of deaths.

the 2008 Annual Report by the European Monitoring Centre for Drugs and Drug Addiction, in which a rebound of overdose mortality was observed in many European countries from 2003 to 2005 [28]. The observed decline in non-natural deaths in our study could be explained by a decrease in the popularity of injecting drug use in Amsterdam over time [29,30]. During 2006–2012, only 26.9% of the ACS participants injected drugs compared with 77.6% during 1985–1989. Also, PWID might have become safer injectors over time, reducing the risk of overdose. These changes in injecting risk behavior could be ascribed to harm-reduction interventions and demographical changes, as recently demonstrated in our modeling study [31]. To summarize, a combination of factors such as availability of comprehensive harm-reduction interventions, HIV and HCV therapy and changing drug patterns among PWUD probably led to the reduction in mortality observed in the present study, especially among HCV/HIV-coinfected women. In addition, HIV-infected PWUD who survived the pre-cART period might have been the PWUD exhibiting less risk behavior and the lowest risk of dying.

Of interest, the HIV-related CMR among PWUD significantly and substantially decreased after 1996, whereas the HIV-related SMR did not significantly change over time. HIV-related mortality is dependent on the incidence and prevalence of HIV in a population. Therefore, given our higher proportion of HIV-infected PWUD compared with the general Dutch population, as expected, we observed a high HIV-related SMR. However, even though the proportion of HIV-infected PWUD in our study population decreased over calendar time, no decrease was observed in the HIV-related SMR. Therefore, the HIV-related mortality in the general Dutch population probably decreased at a faster rate than it did for PWUD from the ACS. HCV-coinfection, which is common among our study population, might play a role as it has been shown that HCV/HIV-coinfected individuals have a higher risk of death from HIV/AIDS than HIV-monoinfected individuals [12,32]. Also, even though the benefits of cART have been observed in all risk groups [33], the HIV-positive individuals from exposure groups other than PWUD might have easier access to care, be more adherent to cART, have a better socioeconomic status, and a healthier lifestyle.

In line with the two studies [22,34] we found that HCV/HIV-coinfected PWUD have a higher SMR than HIV-monoinfected and HCV-monoinfected PWUD. Our overall SMR (35.9) for HCV/HIV coinfection was higher than the SMR (12.8) described by Hernando *et al.* [22], but was very similar to the findings by McDonald *et al.* (34.0) [34]. The difference in SMR between the studies might be explained by differences in the study period. Hernando *et al.*'s study comprises data from the cART era (1997–2010), whereas both our and McDonald *et al.*'s study had follow-up both during the pre-cART and the cART era [22,34].

The SMR for liver-related deaths did not significantly change over time. This could be attributed to an increase in liver-related deaths in the general Dutch population [35]. Furthermore, HCV/HIV-coinfected PWUD might have died of HIV-related causes before experiencing the consequences of HCV [4]. However, the burden of HCV-related disease among PWUD in our study was made visible by the increased liver-related CMR during the latest calendar period.

We found that the CMR for natural causes significantly increased over time. This can be partly explained by ageing of our cohort participants and the lower risk of HIV-related mortality among PWUD in the cART era. However, if CODs are misclassified (i.e. underlying HCV and HIV-related cause of death is not recognized), this might contribute to the increasing CMR for natural deaths. Nevertheless, the SMR for natural causes did not significantly change over time.

Several limitations of our study should be mentioned. First, even though we adjusted for age group, sex, calendar period, and serological group, other determinants, such as active drug use, alcohol consumption, hepatitis B, or smoking, were not taken into account. Second, PWUD who were ever positive for HCV antibodies were considered HCV-positive for the whole study period, thus spontaneous or treatment-induced HCV clearance was not taken into account. Although the minority, especially in HCV/HIV-coinfected individuals, clears the virus spontaneously, this definition of HCV positivity might have led to an underestimation of the SMR for PWUD with a chronic HCV infection. However, active PWID who clear the virus are at risk of HCV re-infection. Third, although coverage and components of harm-reduction interventions changed during the study period, they were already implemented before the ACS started; therefore we do not have a proper comparison with a period without such interventions. Furthermore, our sample of PWUD might not be representative for the general PWUD Dutch population.

In conclusion, in line with our hypothesis, significant declines in all-cause and non-natural morality rates were observed among PWUD compared with the general Dutch population. Women with an HCV/HIV coinfection contributed to the decline in the all-cause SMR over time. However, PWUD are still at an increased risk of dying even when uninfected with HCV and HIV. Our results also suggest that, despite the availability of cART, HIV-related deaths remain an important cause of mortality among PWUD when compared with the general Dutch population. This study reinforces the

importance of a high coverage of comprehensive harm-reduction interventions combined with timely HIV and HCV treatment uptake to reduce excess mortality among PWUD.

Acknowledgements

The authors wish to thank the participants of the ACS for their contribution, research nurses of the ACS Wendy van der Veldt and Laura del Grande for data collection and cohort management, Camiel Welling for his help coding causes of death, Gerben-Rienk Visser and Linda May for data management support, Ronald Geskus for critically reviewing the manuscript, Marcel Buster for his help on the SMR, and Claire Buswell for editing the final manuscript. The ACS on HIV infection and AIDS is a collaboration between the Public Health Service of Amsterdam, the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation, the University Medical Center Utrecht, the Jan van Goyen Clinic, and the Netherlands HIV Monitoring Foundation.

Author contributions: D.K.vS. performed the statistical analyses, interpreted the data, and wrote the manuscript. J.J.vdH. and I.G.S. provided substantial contributions to the analyses and interpretation of the data as well as the manuscript. B.P.X.G. provided data management support and feedback on the interpretation of the data and the draft manuscript. M.E.E.K. and A.S.dV. provided feedback on the interpretation of the data and the draft manuscript. M.P. designed and supervised the overall study, and substantially contributed to the analyses, interpretation of the data and manuscript. All authors contributed to subsequent drafts and approved the final version of the manuscript.

Funding: The ACS is supported by the Center for Infectious Disease Control of the Netherlands National Institute for Public Health and the Environment (RIVM) and this study was supported by ZonMW, the Netherlands, Organization for Health Research and Development [125020005].

Conflicts of interest

None of the authors has a conflict of interest.

References

1. Buster M. *Centrale Methadon Registratie Jaarverslag 1993*. Amsterdam: GG&GD; 1994.
2. Van Brussel GH. **Methadone treatment by general practitioners in Amsterdam.** *Bull N Y Acad Med* 1995; **72**:348–358.
3. van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S, *et al*. **Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users.** *Eur J Epidemiol* 2007; **22**:183–193.
4. Matser A, Urbanus A, Geskus R, Kretzschmar M, Xiridou M, Buster M, *et al*. **The effect of hepatitis C treatment and human immunodeficiency virus (HIV) co-infection on the disease burden of hepatitis C among injecting drug users in Amsterdam.** *Addiction* 2012; **107**:614–623.
5. Buning EC, Coutinho RA, Van Brussel GH, van Santen GW, van Zadelhoff AW. **Preventing AIDS in drug addicts in Amsterdam.** *Lancet* 1986; **1**:1435.
6. Van Haastrecht HJ, Van den Hoek JA, Bardoux C, Leentvaar-Kuypers A, Coutinho RA. **The course of the HIV epidemic among intravenous drug users in Amsterdam, The Netherlands.** *Am J Public Health* 1991; **81**:59–62.
7. Buning EC, Van Brussel GH, Van Santen G. **The 'methadone by bus' project in Amsterdam.** *Br J Addict* 1990; **85**:1247–1250.
8. Van den Hoek JA, Van Haastrecht HJ, Coutinho RA. **Risk reduction among intravenous drug users in Amsterdam under the influence of AIDS.** *Am J Public Health* 1989; **79**:1355–1357.
9. van den Berg C, Smit C, Van Brussel G, van den Berg C, Smit C, Van Brussel G, *et al*. **Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users.** *Addiction* 2007; **102**:1454–1462.
10. Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC, Porter K. **Changes in the risk of death after HIV seroconversion compared with mortality in the general population.** *JAMA* 2008; **300**:51–59.
11. 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**:433–445.
12. van der Helm J, Geskus R, Sabin C, Meyer L, Del Amo J, Chene G, *et al*. **Effect of HCV infection on cause-specific mortality after HIV seroconversionbefore and after 1997.** *Gastroenterology* 2012; **144**:751–760e2.
13. Smit C, Lindenburg K, Geskus RB, Brinkman K, Coutinho RA, Prins M. **Highly active antiretroviral therapy (HAART) among HIV-infected drug users: a prospective cohort study of sexual risk and injecting behaviour.** *Addiction* 2006; **101**:433–440.
14. Mehta SH, Kirk GD, Astemborski J, Galai N, Celentano DD. **Temporal trends in highly active antiretroviral therapy initiation among injection drug users in Baltimore, Maryland, 1996–2008.** *Clin Infect Dis* 2010; **50**:1664–1671.
15. CASCADE Collaboration. **Changes in the uptake of antiretroviral therapy and survival in people with known duration of HIV infection in Europe: results from CASCADE.** *HIV Med* 2000; **1**:224–231.
16. van Asten LC, Boufassa F, Schiffer V, Brettle RP, Robertson JR, Hernandez Aguado I, *et al*. **Limited effect of highly active antiretroviral therapy among HIV-positive injecting drug users on the population level.** *Eur J Public Health* 2003; **13**:347–349.
17. Lindenburg CE, Lambers FA, Urbanus AT, Schinkel J, Jansen PL, Krol A, *et al*. **Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project.** *Eur J Gastroenterol Hepatol* 2011; **23**:23–31.
18. Grebely J, Dore GJ. **What is killing people with hepatitis C virus infection?** *Semin Liver Dis* 2011; **31**:331–339.
19. Bargagli AM, Hickman M, Davoli M, Perucci CA, Schifano P, Buster M, *et al*. **Drug-related mortality and its impact on adult mortality in eight European countries.** *Eur J Public Health* 2006; **16**:198–202.
20. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. **Mortality among people who inject drugs: a systematic review and meta-analysis.** *Bull World Health Organ* 2013; **91**:102–123.
21. Aldaz P, Moreno-Iribas C, Egues N, Irisarri F, Floristan Y, Sola-Boneta J, *et al*. **Mortality by causes in HIV-infected adults: comparison with the general population.** *BMC Public Health* 2011; **11**:300–308.
22. Hernando V, Perez-Cachafeiro S, Lewden C, Gonzalez J, Segura F, Oteo JA, *et al*. **All-cause and liver-related mortality in HIV positive subjects compared to the general population: Differences by HCV co-infection.** *J Hepatol* 2012; **57**:743–751.

23. Jimenez-Trevino L, Saiz PA, Garcia-Portilla MP, Diaz-Mesa EM, Sanchez-Lasheras F, Buron P, *et al*. **A 25-year follow-up of patients admitted to methadone treatment for the first time: mortality and gender differences.** *Addict Behav* 2011; **36**:1184–1190.
24. Evans JL, Tsui JI, Hahn JA, Davidson PJ, Lum PJ, Page K. **Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO study.** *Am J Epidemiol* 2012; **175**:302–308.
25. Van den Hoek JA, Coutinho RA, Van Haastrecht HJ, van Zadelhoff AW, Goudsmit J. **Prevalence and risk factors of HIV infections among drug users and drug-using prostitutes in Amsterdam.** *AIDS* 1988; **2**:55–60.
26. Gjersing L, Bretteville-Jensen AL. **Gender differences in mortality and risk factors in a 13-year cohort study of street-recruited injecting drug users.** *BMC Public Health* 2014; **14**:440–451.
27. Smit C, Geskus R, Walker S, Sabin C, Coutinho R, Porter K, Prins M. **Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion.** *AIDS* 2006; **20**:741–749.
28. Vicente J, Giraudon I, Matias J, Hedrich D, Wiessing L. **Rebound of overdose mortality in the European Union 2003–2005: findings from the 2008 EMCDDA Annual Report.** *Euro Surveill* 2009; **14**:1–2.
29. van Ameijden EJ, Coutinho RA. **Large decline in injecting drug use in Amsterdam, 1986–1998: explanatory mechanisms and determinants of injecting transitions.** *J Epidemiol Community Health* 2001; **55**:356–363.
30. van der Knaap N, Grady BP, Schim van der Loeff MF, Heijman T, Speksnijder A, Geskus R, Prins M. **Drug users in Amsterdam: are they still at risk for HIV?** *PLoS One* 2013; **8**:e59125.
31. de Vos AS, van der Helm JJ, Matser A, Prins M, Kretzschmar ME. **Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction?** *Addiction* 2013; **108**:1070–1081.
32. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, *et al*. **Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study.** *Lancet* 2000; **356**:1800–1805.
33. Wood E, Hogg RS, Lima VD, Kerr T, Yip B, Marshall BD, Montaner JS. **Highly active antiretroviral therapy and survival in HIV-infected injection drug users.** *JAMA* 2008; **300**:550–554.
34. McDonald SA, Hutchinson SJ, Bird SM, Mills PR, Dillon J, Bloor M, *et al*. **A population-based record linkage study of mortality in hepatitis C-diagnosed persons with or without HIV coinfection in Scotland.** *Stat Methods Med Res* 2009; **18**:271–283.
35. Logtenberg-van der Grient H, Boland G, Mostert M, Schalm S. **Onnodige sterfte door hepatitis B en C.** *Medisch Contact* 2012; **8**:456–459.