

# Trend of Mortality Observed in a Cohort of Drug Addicts of the Metropolitan Area of Bologna, North-Eastern Italy, During a 25-Year-Period

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## ABSTRACT

*The aim of our study is to evaluate the temporal trend of deaths in a cohort of i.v. drug users (IVDU) followed in a city of Northern Italy (Bologna), and to assess its relationship with HIV infection and AIDS, and availability of potent anti-retroviral therapy. One thousand and 214 IVDUs (mainly heroin addicts), 916 males and 298 females, attending an out-patient service for treatment and prevention of substance abuse between 1977 and November 1996, were enrolled into our observational cohort, and their vital status was ascertained up to December 31, 2002. The large majority of enrolled subjects were born in the Bologna metropolitan area and surroundings; no extra-European immigrants were present. During the observation period, 271 IVDUs (22.3%) died, 211 males (23.0%), and 60 females (20.1%). No death was recorded before 1984. Main death causes result as follows: AIDS (52.8% of episodes), heroin overdose (22.1%), street accidents (7.4%), decompensated liver cirrhosis (6.3%), and suicide (2.9%). The highest absolute number of deaths was observed between years 1991 and 1996. Crude mortality rate caused by AIDS was 10.0 per 1000 for males and 13.2/1000 for females; the rate of death due to other causes proved 11.1/1000 among males and 5.2/1000 among females. In most recent years, a sharp decrease in the number of AIDS-related deaths, attributable to the increased use of potent antiretroviral regimens, was recorded among IVDUs, although overall mortality rate remained appreciable.*

**Key words:** epidemiology, drug users, HIV infection, overdose, mortality, temporal trend, antiretroviral therapy

## Introduction

A remarkable decrease of HIV-associated disorders, as well as of notified cases of AIDS, has been observed in industrialized countries during the last seven years. Such significant drop of HIV-related morbidity and mortality (mostly occurred thanks to the introduction and diffusion of highly active antiretroviral therapy, or HAART), was also observed among i.v. drug users (IVDUs)<sup>1–3</sup>. However, a significant number of potential Italian patients, still unaware of their HIV serostatus<sup>4</sup>, do not yet make use of antiretroviral treatment: in our previously reported series regarding the year 1997, 29% of active or prior IVDUs were never tested for HIV infection<sup>5</sup>.

A European multicentre study<sup>6</sup> shows how IVDUs with recent HIV seroconversion are subject to an increased risk of mortality due to pneumonia, endocarditis, sepsis, meningitis, encephalitis, and decompensated liver

cirrhosis. Before the availability of HAART, an increased rate of mortality due to heroin overdose and suicide was also recorded among HIV-infected IVDUs<sup>7,8</sup>. Just the use of elevated heroin dosages associated to a suicidal behavior could be partially responsible for this phenomenon in patients with a newly diagnosed HIV disease and lacking of any social and psychological support, especially before the introduction of effective antiretroviral drug combinations (HAART)<sup>9–11</sup>.

In a cohort study of 4,962 IVDUs carried out in Bologna (Italy) between years 1980 and 1990, 332 deaths were observed: 150 of them occurred because of AIDS, 64 of drug overdose, and 39 of accidents<sup>8</sup>. The HIV infection serostatus (28.2% of 1214 subjects were positive) proved to be significantly related also to deaths caused by trauma, heroin overdose, bacterial infections, and acute and

chronic liver disease. The mortality rate of IVDUs proved significantly higher among those subjects who did not receive a HIV serodiagnosis with respect to those subjects who underwent a HIV infection test with negative result (12.1% versus 2.5%)<sup>8</sup>. Again in Bologna, at the end of nineties the risk of a fatal heroin overdose remained remarkably important<sup>12</sup>, while between years 1996 and 1998 Italian national cumulative data showed a progressive decrease of deaths due to this last cause<sup>13</sup>.

In a cohort of 11,432 IVDUs enrolled in Rome (Italy) between years 1980 and 1995, 1,734 deaths were registered (15.2%). The peak of AIDS-associated mortality was observed in 1991 and 1992 (13.2 per 1000 person-years), followed by a decrease occurred in both male and female population since 1993–1994, even earlier than expected according to the availability of (before HAART became available in mid-1996)<sup>14</sup>.

In the Emilia-Romagna region of Italy (of which Bologna is the main administrative centre and largest town), a retrospective study conducted on 4,260 IVDUs followed in Piacenza, Modena and Ferrara during two decades (1975–1995), pointed out a dramatic increase in the rate of deaths caused not only by AIDS; but also by overdose and other causes, especially accidents. The mortality rate observed in this last IVDUs cohort proved particularly high: the calculated standard mortality rate (SMR) was 16.7 for males, and 33.4 for females. The overall probability of survival after 15 years of follow-up was 65%. After drug overdose and AIDS, the other relevant causes of deaths were street accidents, decompensated liver disease, other infectious disorders and malignancies among male IVDUs, while accidents (in particular, homicide), and gastrointestinal tract disorders had a greater prevalence among females<sup>15</sup>.

Finally, in an Italian multicentre study carried out in Turin, Rome, Naples, and Cagliari on IVDUs enrolled between 1980 and 1992, a highly variable mortality rate was detected, ranging from 11.0 per 1000 persons-years in Naples, up to 20.5 per 1000 persons-years in Rome. Again, the most frequent causes of death were represented by drug overdose, AIDS, and accidents, although relevant differences were observed among the four considered cities. A higher mortality rate among IVDUs compared with that of the general population was consistently observed in all considered geographical cohorts<sup>16,17</sup>.

In a very recent 7-year survey from the US, active drug use proved temporally linked to HIV disease progression and overall mortality<sup>17</sup>.

Our present study aims at:

- i) investigating the past and present mortality trend of a cohort of IVDUs based in Bologna, in an attempt to identify its causes;
- ii) investigating whether HIV infection plays any influence on the rate of mortality due to causes other than AIDS;
- iii) evaluating the AIDS-associated fatality rate among subjects with missed or delayed HIV serodiagnosis, hence

with a possible late diagnosis of the infection only at an advanced stage of the condition.

## Materials and Methods

### *Patients*

An open cohort of 1,214 IVDUs has been assessed for a number of epidemiological and clinical variables. The people involved were mainly i.v. heroin addicts, and included 916 males (75.5%) and 298 females, referring to a specialized outpatient Centre for the treatment and prevention of substance abuse of Bologna (Italy), from the year 1977 up to November 1996. The great majority of enrolled patients at the time of their first visit lived in South-Western districts of the Bologna conurbation (400,000 inhabitants in the city, half a million with the suburbs). The place of birth is a missing datum for one minor part of the people reached by our study; as to the others, most of them were born within the Province of Bologna and no one comes from abroad.

By matching anagraphical data with the registries of the abode or birth municipalities, a retrospective research focusing on whether subjects were still alive on December 31, 2002, has been carried out.

In some cases, neither the year of birth nor the subject's age were available due to patients' refusal to provide their own personal data. Referring to population registries allowed us to retrieve missing information regarding almost all individuals in our cohort: in 60 cases, still assisted by our outpatient services, data are still lacking, but for deceased patients figures were adjusted when causes of death were researched.

### *HIV infection*

At the time of patients' first contact with our dedicated outpatient centre, HIV testing and specific counselling were always offered, but 355 subjects out 1,214 (29.2%) refused this examination. HIV serology became recommended in late 1984, so that the first recognition of a possible underlying HIV infection is related to the first visit at our outpatient Centre, starting from 1984–1985. IVDUs enrolled before 1985 had HIV testing performed starting from this year either at the outpatient units, or at one of the two Infectious Diseases Divisions of Bologna, or local prison facilities. At the time of their next contact with the above-mentioned health care structures, HIV testing and specific counselling were always offered. Data regarding HIV serostatus for IVDUs enrolled after 1985 dates back mainly to the time of first access to IVDA outpatient Centres. Usually, the seroconversion time for patients who were HIV-negative at their first control is not definable, because of the limited availability of patients to be tested or to furnish results.

### *Statistical analysis*

As to the calculations of person-years and rates, the beginning of observation is identified with the year of the first visit at our outpatient Centre for IVDUs. The first

access date of 41 individuals is unknown; for each of them, the enrollment was identified with the first date available in his/her clinical records. The end of observation period was matched with that of death for deceased patients, while it was fixed at December 31, 2002 for living individuals; for two persons who were lost to follow-up, the end-of-observation time is identified with 1997: the year of their last access to the Centre. The cause of death of deceased subjects was drawn by local registries, as expressed by the ICD-IX code<sup>18,19</sup>. Population data were obtained from the official annual statistical update of Bologna; mortality figures were drawn by public health notification registries.

Statistical analysis included specific mortality rates per age, gender and HIV-status, and standardized mortality rate (SMR)<sup>20</sup>, obtained by indirect standardization performed on Bologna rates per each considered year. Chi-square has been used for the analysis of frequency distribution; Student's t test and Analysis of variance were employed to evaluate differences among mean values. The rates per HIV serostatus were calculated by attributing the years of observation of each single subject to his/her own category (HIV-positive, HIV-negative, HIV-unknown), without focusing on the time of seroconversion (which was not always available). As a consequence, not each person's time of HIV-positive or HIV-negative serology, but only the patient serostatus was considered.

The considered study time was analyzed according to a wide range of variables, by dividing it into four different periods, characterized by prominent epidemiologicals, treatment, prognosis, type of medical assistance, and outcome. The first period (years 1977–1983) encompassed the initial service offer, opposition and resistance by patients, no deaths, and absence of HIV-AIDS cases; the second period (1984–1990) was characterized by the rapid spread of AIDS, spontaneous patient access, and early HIV-associated deaths; during the third period (year 1991–1996) the patient access remained sustained, AIDS had the greatest fatality rate, and many deaths occurred; the fourth period (years 1997–2002) was characterized by the availability of highly active antiretroviral therapy (HAART), followed by a sharp drop of AIDS mortality. Our cohort was closed to enrollments at the end of previous period.

## Results

### *Series description – general features*

Overall, 1,214 patients were considered: 916 males and 298 females. The distribution per age classes at the time of enrollment is summarized in Table 1A, where also enrollment period is reported. The age of 60 subjects was not available. Table 1B shows the subjects' enrollment age in different periods. One hundred and 10 IVDUs were enrolled from year 1977 to 1983. At the end of year 1990, patients still alive in our cohort were 607, and in the period 1991–1996 enrolled and alive patients became 1,174. The characterizing features of the above-mentioned time periods are recognizable in the cumulative Table 6.

### *Age and sex*

Overall follow-up accounted for 10,030.50 person-years for male subjects, and 3,249.75 person-years for females: cumulated follow-up accounted for 13,280.25 person-years. Mean age did not differ between enrolled males and females, when considering both the entire follow-up, and single time periods. A temporal trend to increased patients' age occurred through time: the difference among mean age at enrollment during different time periods turned out to be significantly different ( $p < .0001$ ; Table 1B). The age at which each person started to take up IVD was asked, but not provided for nearly one half of involved subjects;

### *HIV serostatus*

When assessing HIV serostatus, IVDUs HIV-positive were 426, and HIV-negative subjects were 433 (Table 2). In particular, HIV infection was found in 297 men (32% of males), and in 298 women (43% of females). Moreover, among tested individuals, HIV-positive male patients accounted for 46%, while females were 61%, leading to a statistically different distribution ( $\chi^2=14,2667$ ;  $p=0.0002$ ).

The record of HIV positive serostatus was documented in 8% of patients early HIV-negative; the great majority of them was deducted from death certifications.

### *Analysis of deaths*

Overall IVDUs subjects dead on December 31, 2002 were 271 (22.3% of all enrolled individuals): 211 males (23% of enrolled males), and 60 females (20.1% of the female cohort). The mean patient age at the time of death was comparable by gender:  $33.2 \pm 6.6$  years among males, and  $33.5 \pm 6.0$  years among females ( $\chi^2=1,091$ ,  $p=n.s.$ ). The overall 1,214 enrolled IVDUs accounted for 13,280.25 years-person (a mean of nearly 11 years per patient), while the 271 deceased individuals contributed for 1,258 years-person (an average of less than five years per patient). Table 3 resumes all data concerning deaths, classified per age group and sex, with person-years and rates per 1000. The overall death distribution does not show any significant difference between males and females. The time of initial i.v. drug addiction, when available, does not provide evidence of significant relation between age of start of IVDUs and eventual lethal outcome.

The cause of each single death has been retrieved for 267 of the 271 deceased patients (98.5%). No deaths were registered in this cohort in the years preceding 1984. Figure 1 shows the different causes of death per year, in the period 1984–2002. Overall AIDS-related deaths total 143 (52.8%), followed by those due to heroin overdose (60: 22.1%), liver cirrhosis (17: 6.3%), road accidents (20: 7.4%), suicide (8: 2.9%), homicide (3: 1.1%), infectious endocarditis and other heart disorders (6: 2.2%), neoplasm (lung's or lymphoma, 5 deaths, 1.8%), and pneumonia (2: 0.7%). Three causes of death occurred only once: wasting syndrome, bleeding endocranic aneurism, and fire accident. The cause of death could not be found

**TABLE 1**  
BOLOGNA IVDU COHORT. CASE DISTRIBUTION ACCORDING TO SEX, ENROLLING PERIOD, AND AGE AT ENROLLMENT (SECTION A); COMPARISON OF DIFFERENT PERIODS AND ENROLLMENT AGES (SECTION B)

<b>Section A</b>					
Sex	Enrolling	Period			
	Age groups	I	II	III	All
Women	0–14	1	1		2
	15–19	6	9	5	20
	20–24	7	45	33	85
	25–29	4	38	49	91
	30–34	2	20	26	48
	35–44	1	10	27	38
	45–49			2	2
	50–54			1	1
	Nn	1	3	7	11
Total women		22	126	150	298
Mean age		22.71	26.06	29.01	27.29
Standard error		1.342	0.487	0.557	0.377
Men	0–14		2		2
	15–19	21	18	10	49
	20–24	41	130	95	266
	25–29	16	125	143	284
	30–34	6	55	97	158
	35–44	1	22	67	90
	45–49		2	10	12
	50–54		1	3	4
	>55	1		1	2
nn	2	19	28	49	
Total men		88	374	454	916
Mean age		22.88	26.17	29.28	27.37
Standard error		0.609	0.287	0.324	0.219
<b>Section B</b>					
Sex	Enrolling	Period			
	Age groups	I	II	III	All
Total		110	500	604	1214
Mean age		22.85	26.14	29.21	27.35
Standard deviation		5.7196	5.4080	6.6763	
Standard error		0.553	0.247	0.280	0.189
95% confidence limits	lower	21.7542	25.6562	28.6629	
	upper	23.9467	26.6283	29.7624	
Median		22	25	28	
Minimum		14	10	17	
Maximum		56	53	62	
	Anova variation	Deviance (SS)	gf	Variance (MS)	p (F)
	among periods	4837.661	2	2418.831	
	within periods	42735.203	1151	37.129	
	total	47572.864	1153	41.260	<0.001

in four patients only. Table 4 reports the causes of death stratified according to gender, with the associated rate per 1000 person-years.

When examining deaths, according to whether they are due to AIDS or not, it can be highlighted that 111 fatal episodes non AIDS related occurred to males (41% of

**TABLE 2**  
BOLOGNA IVDU COHORT: SUBJECT DISTRIBUTION ACCORDING TO INITIAL HIV SEROSTATUS AND SEX

HIV at enrollment	Sex				Total
	Females		Males		
Negative	83	27.9%	350	38.2%	433
Positive	129	43.3%	297	32.4%	426
(not available)	86	28.9%	269	32.3%	355
Total	298	100%	916	100%	1214

**TABLE 3**  
BOLOGNA IVDU COHORT. DISTRIBUTION OF DEATHS OVER THE FOUR GIVEN AGE GROUPS, CLASSIFIED BY GENDER. PERSON-YEARS (P-Ys) FOLLOW-UP, AND MORTALITY RATE PER 1,000 P-Ys SUBJECTS ARE ALSO PRESENTED

Age groups	Males			Females			Total Deceased
	Deceased	P-ys	Rate/ 1000 p-ys	Deceased	P-ys	Rate/ 1000 p-ys	
< 25	11	943.5	11.66	1	334.0	2.99	12
25–34	130	485.5	26.68	39	1590.0	24.53	169
35–44	57	3109.0	18.33	16	1015.75	15.75	73
≥ 45	13	608.0	21.38	4	195.0	20.46	17
Total	211	10030.5	21.04	60	3249.75	18.46	271

overall men), while only 17 to females (28.3% of deceased women). The general distribution of causes of death was significantly different according to patient gender ( $p < 0.001$ ): AIDS-related deaths proved significantly more frequent among females, while overdose-related ones occurred predominantly among males ( $\chi^2=11,042$ ;  $p < 0.001$ ). AIDS-related deaths have been compared with all other cumulative causes of death, and disease caused deaths with violence caused ones, in Table 5.

When analyzing the entire time span split into four different periods (as mentioned above), not a single death occurred in the period 1977–1983. Between 1984 and

1990, 40 deaths were registered among 459 enrolled subjects (8.7%): 13 of them were attributed to AIDS, and 27 due to other causes. Between 1991 and 1996, of 1,174 IVDU 172 deceased (14.6%): 109 dead because of AIDS, and 63 due to all other possible causes. Between 1997 and 2002, among 1002 living subjects we observed 59 deaths (5,9%): 21 because of AIDS, and 38 due to all other cumulative causes (Table 6).

Table 7 presents the mortality rate per 1000 person-years according to gender and grouped age of death, as well considering HIV/AIDS, and all the other causes of death.

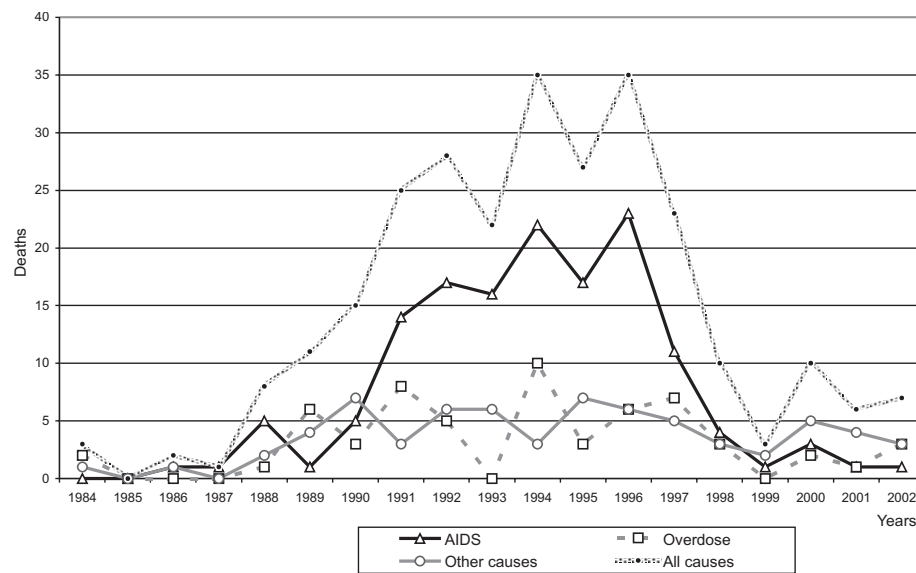


Fig. 1. Bologna IVDU cohort. Deaths per main causes during the whole time of observation. The cohort had no deaths until 1983.

**TABLE 4**  
BOLOGNA IVDU COHORT. ALL DEATHS OCCURRED IN OUR COHORT ARE REGISTERED ACCORDING TO THEIR RECOGNIZED CAUSES. BOTH ABSOLUTE FIGURES AND MORTALITY RATE PER 1,000 PATIENTS-YEARS (P-Y) ARE SHOWN

Sex	Females		Males		Total	
	Deceased	Rate/1000 p-ys	Deceased	Rate/1000 p-ys	Deceased	Rate/1000 p-ys
Cause of death						
AIDS	43	13.231	100	9.970	143	10.768
Overdose	6	1.846	54	5.384	60	4.518
Hepatitis, cyrrhosis	3	0.923	14	1.396	17	1.280
Heart diseases		0	6	0.598	6	0.452
Road accidents	5	1.539	15	1.495	20	1.506
Suicide	1	0.308	7	0.698	8	0.602
Neoplasm	1	0.308	4	0.399	5	0.377
Respiratory pathologies		0	2	0.199	2	0.150
Undefined cause		0	2	0.199	2	0.150
Other violent causes		0	4	0.399	4	0.301
Unknown causes	1	0.308	3	0.299	4	0.301
Total	60	18.463	211	21.036	271	20.406

**TABLE 5**  
BOLOGNA IVDU COHORT. DEATH DISTRIBUTION ACCORDING TO SETS OF DEATH CAUSES: AIDS, NON-AIDS, AND DISEASE/VIOLENT DEATH

Sex	Females		Males		Total	
	Deceased	Rate/1000 p-ys	Deceased	Rate/1000 p-ys	Deceased	Rate/1000 p-ys
AIDS	43	13.231	100	9.970	143	10.768
Non-AIDS	16	4.923	108	10.767	128	9.337
Unknown	1	0.308	3	0.299	4	0.301
Total	60	18.463	211	21.036	271	20.406
Diseases	47	14.463	126	12.562	173	13.027
Violent causes	12	3.693	80	7.976	92	6.928
Unknown or undefined causes	1	0.308	5	0.499	6	0.452
Total	60	18.463	211	21.036	271	20.406

**TABLE 6**  
BOLOGNA IVDU COHORT. DYNAMIC TRENDS OBSERVED IN OUR PATIENTS: ENROLLMENTS AND DEATHS OCCURRED DURING THE FOUR GIVEN TIME PERIODS

Periods	I	II	III	IV	Total
Years	1977–1983	1984–1990	1991–1996	1997–2002	1977–2002
Survivors at prior time interval	–	110	570	1002	
Newly enrolled subjects	110	500	604	0	1214
IVDUs alive in the period	110	610	1174	1002	
IVDUs deceased in the relevant period	0	40	172	59	271
Fatality rate (%) in the relevant period	0%	6.6%	14.6%	5.9%	22.3%
Subjects lost at follow-up	0	0	0	2	2
Subjects alive at the end of follow-up	110	570	1002	941	941

When analyzing the separated time periods (as mentioned above), the mortality rate per 1000 patients-year was 0/1000 (no deaths), 19.5/1000, 32.2/1000, and 10.2/1000 respectively: in the overall period 1977–2002, the

mean mortality rate proved 20.4/1000. The highest fatality index was reached in the period 1991–1996, when it accounted for 33.5/1000 among women, and 31.8/1000 among men.

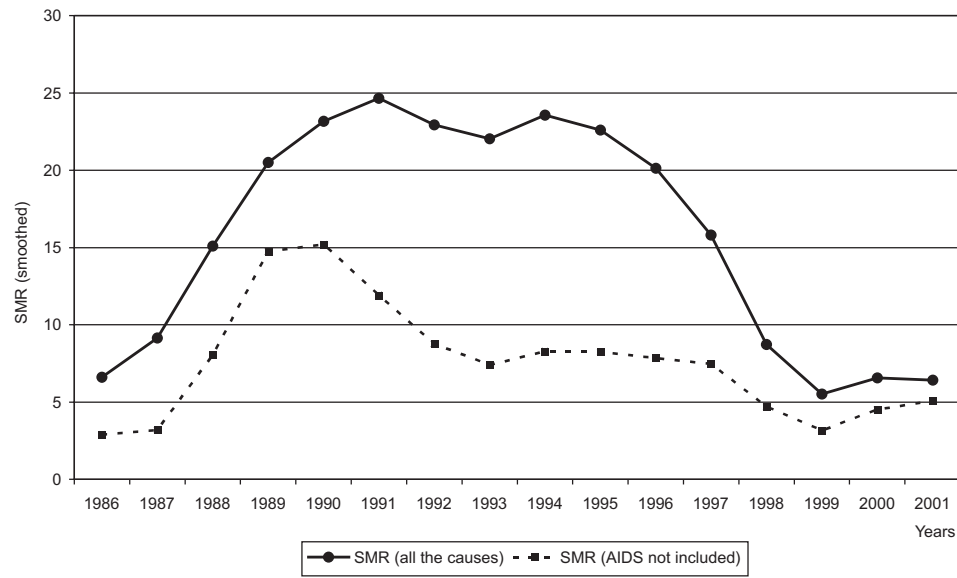


Fig. 2. Bologna IVDU cohort. Mortality trend from 1986 to 2001. Yearly SMR for all death causes. Indirect standardization based on Bologna population rates for each year (upper line), smoothed using weighted adjacent year values. Lower line shows the contribution to SMR of death causes other than AIDS; the area comprised between the two slopes identifies AIDS contribution to deaths.

Figure 2 shows the smoothed temporal trend of standardized mortality rate (SMR) for all causes, 1986 to 2002 (upper line). The lower line shows the SMR calculated without considering AIDS-associated deaths, so that the area between the two curves represents the absolute contribution of AIDS to excess mortality during the relevant period. The decrease of deaths due to other causes shows a drop paralleling that of AIDS-related fatality events, but excess mortality remains higher than the values observed in the pre-AIDS era.

When considering our series according to first HIV serostatus, we obtained a rate of 37,00/1000 for HIV-in-

fected patients, compared with 17,00/1000 for non-HIV-infected IVDU, and 7,85/1000 for individuals with undetermined HIV serostatus. In the whole time period, the mortality index was higher for male HIV-positive patients compared with HIV-positive females, but women aged 25–44 years, as subgroup, had the greatest risk of death for AIDS. When excluding AIDS, all other causes of death largely predominated among males, especially for people aged 25–44 years. In more detail, the highest risk of death was found in the group aged 25–34 years, while only a few deaths were observed Table 9 presents mortality rate analyzed according to HIV serostatus and subdi-

TABLE 7  
BOLOGNA IVDU COHORT. DEATH DISTRIBUTION PER CAUSES (AIDS/NON-AIDS), AGE GROUPS, AND SEX

Sex	Non AIDS			AIDS		Unknown		Total
	Death age	Deceased	Rate/1000 p-ys	Deceased	Rate/1000 p-ys	Deceased	Deceased	Rate/1000 p-ys
Females	<25	1	2.99	0	0.00		1	2.99
	25–34	8	5.03	28	17.61	1	37	24.53
	35–44	5	4.92	14	13.78		19	15.75
	>44	2	10.23	1	5.12		3	20.46
	Total	16	4.92	43	13.23	1	60	18.46
Males	<25	11	11.66	1	1.06		12	11.66
	25–34	60	12.37	61	12.57	2	123	26.80
	35–44	30	9.65	32	10.29	1	63	18.33
	>44	7	11.51	6	9.87		13	21.38
	Total	108	10.77	100	9.97	3	211	21.04
Females+Males	All together	124	9.34	143	10.77	4	271	20.41

**TABLE 8**  
BOLOGNA IVDU COHORT. MORTALITY RATE PER 1,000 PERSONS-YEARS ANALYZED ACCORDING TO GENDER, SUBDIVIDED INTO THREE GROUPS: HIV-INFECTED PATIENTS, HIV-NEGATIVE SUBJECTS, AND SUBJECTS WITH UNKNOWN HIV SEROSTATUS

Gender	HIV-infected patients	HIV-negative subjects	Subjects with unknown HIV serostatus	Total
Males	39.26	18.06	8.47	21.04
Females	32.08	12.42	5.86	18.46
Total	37.00	17.00	7.85	20.41

**TABLE 9**  
BOLOGNA IVDU COHORT. MORTALITY RATE ACCORDING TO HIV SEROSTATUS AND MOST RELEVANT CAUSES OF DEATH. »MISCELLANEOUS« REFERS TO THE LESS FREQUENT CAUSES CONSIDERED AS A WHOLE. HIV-INFECTED SUBJECTS INCLUDE PATIENTS WHOSE HIV SEROSTATUS WAS IDENTIFIED ONLY FROM THEIR DEATH CAUSE CERTIFICATE

Causes of death	HIV-infected subjects		HIV-negative subjects		Subjects with unknown HIV serostatus	
	Deceased subjects	Rate Per 1000 p-ys	Deceased subjects	Rate Per 1000 p-ys	Deceased subjects	Rate Per 1000 p-ys
AIDS	143 (*)	107.7	–	–	–	–
Heroin overdose	20	15.1	26	19.6	14	10.5
Liver cirrhosis	11	8.3	3	2.3	3	2.3
Road accidents	8	6.0	6	4.5	6	4.5
Miscellaneous	12	9.0	11	8.3	8	6.0
Total	194	146.1	46	34.6	31	23.3

(\*) The subjects known as HIV-negative and the subjects with unknown HIV serostatus who died because of AIDS are reported in this group, as mentioned in the text.

vided following the four more frequent causes of death; the »miscellaneous« patient group includes the four IVDUs whose death cause is unknown before 25 years of age, and after the age of 45 (Tables 7 and 8).

Table 9 presents mortality rate analyzed according to HIV serostatus and subdivided following the four more frequent causes of death: the »miscellaneous« patient group includes the four IVDUs whose death disease is unknown. Among the 143 patients deceased because of AIDS, we registered 32 IVDUs who were HIV-negative upon enrollment, and 3 subjects who did not undergo HIV testing, but who became known as HIV-infected when death cause was obtained. Two more HIV-unknown subjects, who resulted HIV-positive at death, died because of liver diseases.

Among IVDUs who deceased because of overdose, 33.3% had HIV infection, 43.3% was HIV-negative (not statistically significant difference), while the HIV serostatus of the remaining 23.3% was not ascertained. At death, the prevalence of HIV infection is significantly higher among females (81.7%) than among males (68.7%;  $p < 0.001$ ). Mortality rates per 1000 person-years for HIV-infected, HIV-negative, HIV-unknown patients, stratified according to gender, are shown in Table 8. Among 271 deceased IVDUs, those infected with HIV were 194 (71.6%), including 145 males and 49 females. HIV-negative IVDUs were 46 (16.9%), including 41 males and five females; deceased IVDUs with unknown HIV serostatus were 31 (11.4%), including 25 males and six females. The

patients, whose serostatus was negative or unknown, and who resulted HIV infected from death cause, are 37. As already mentioned, 35 of them died because of AIDS; as well two HIV-unknown, proved HIV-positive at death, died because of liver diseases. At the time of death, this last patient group was aged 25 to 34 years in 66% of cases, while the remaining IVDUs of this subgroup were aged 35–44 years. All these patients died between 1991 and 1997.

## Discussion and Conclusion

In a 25-year-long observation study, the wide time span of our follow-up allows us to assess the mortality trend along well distinguished periods: the pre-AIDS era, the HIV pandemic era, and the HAART era (with the introduction and consolidation of HAART as the standard of antiretroviral care for HIV disease).

Several Authors point out that, if the availability of potent HAART regimens has improved the prognosis of HIV disease since end-1996 or early 1997, this effect applies only to those IVDU who have undergone serodiagnosis turning out positive to the test, then have accepted antiretroviral treatment, and have followed it with satisfactory adherence levels<sup>17,21–25</sup>.

Our data show that an initially slow, but later progressive increase in the number of deaths has taken place since 1984 (the year when the first death of our cohort was registered). After the first AIDS-related death was



reported, in 1986, the increase in the mortality rate of our cohort became increasingly important until 1994, with the last peak observed in the year 1996 (immediately before the introduction of HAART). Since 1997, with the implementation of potent HAART regimens, a dramatic drop of AIDS-associated deaths has been observed in our cohort of IVDUs. In more details, exceptionally high standardized mortality rates (SMR) were reached between 1988–1997, followed by a significant reduction from 1998. A limited increase observed in 2000, was however not confirmed over the following two years. As to the causes of death in our extensive observational cohort, death due to AIDS and drug overdose were remarkably predominant among males, applying to HIV positive, HIV negative and HIV unknown alike.

Previous experiences carried out by us<sup>12</sup>, proved that overdose-associated deaths in Bologna since 1994 have accounted for a steadily increasing fraction of the overall Emilia-Romagna regional reported cases. Based on all the above-mentioned comprehensive data, we don't think we can read a decrease in the risk of death from heroin overdose in our cohort until 1997, while in Italy some cumulative data have shown a progressive reduction of this cause of death already since 1996<sup>13</sup>. We would like to stress that death in the female component of our cohort is largely related to AIDS-associated causes, all other causes showing a lower frequency among women. For a correct interpretation of these data, it is necessary to consider the higher prevalence of HIV serostatus among women with respect to men, in our cohort.

Since 1998, in our observational study, we witnessed a significant reduction of both AIDS-related deaths (still quite high in 1997), and overdose-caused deaths, which dropped to a half in 1998 compared to 1996 and 1997. Such a notable reduction in frequency could be related to a concurrent increase of substitutive methadone treatment, carried out in most of IVDUs outpatient services of Bologna over the same period of time. In the Emilia-Romagna region, the implementation of the so-called »*damage reduction strategy*« had already significantly contributed to foster a decrease in overdose-related deaths in such cities as Modena or Ferrara, where methadone treatment had been massively introduced among IVDUs since early 90s<sup>15</sup>. Since 1997 the global mortality trend for all non-AIDS-related deaths has paralleled the decrease in AIDS-associated fatalities. A very recent study from Baltimore (USA) longitudinally followed i.v. drug abusers with a concurrent HIV infection since 1998 (when HAART was already available since three years). The authors observed that active drug use was temporally linked to HIV disease progression and overall mortality<sup>17</sup>.

Over two thirds of all deceased subjects in our cohort were HIV-infected. Nearly half of all deaths were related to AIDS. Awareness of the infection can be regarded both as a possible concurrent reason for adopting risky behaviour or even for suicide (from overdose to car accidents, suffered or committed aggressions, reported self-dam-

age), and as a cause of increased caution which can lead to approach and trust in outpatient health care services. In our series, the progressively increasing patient's age at enrollment observed throughout the study period, is linked to the ageing of IVDU population who refer to dedicated outpatient services. These data are not related with any evidence that proportionally younger patient population is at modified risk of IVDU.

During the whole analyzed period, the mortality rate for all causes is higher for male HIV-infected IVDUs than for female HIV-infected IVDUs, but women aged 25 to 44 years represented the subgroup at higher risk of AIDS-related death, as confirmed by a very recent study from Canada<sup>24</sup>. When excluding AIDS, all diseases involved as a cause of death in our cohort were predominantly present in the male component of our patients group, notably in the age interval ranging from 25 to 44 years. In more details the highest mortality risk applies to the 25–34 age group, while it is at its lowest before 25, and after 45 years of age.

Should HAART maintain its remarkable effectiveness in future years, a further increase of life expectancy of HIV-infected subjects could be foreseen<sup>17,24–26</sup>. This favorable condition may induce the IVDU population to refer to dedicated outpatient centres, and adhere to both HAART and substitutive pharmacological strategies aimed at »drug damage containment«, and may therefore benefit from a further reduction of overdose-related deaths. On the other hand, we cannot exclude that a progressively lowering HIV morbidity may allow a long-term increase of incidence of chronic concurrent diseases commonly affecting the same IVDU population, as causes of mortality (i.e. decompensated liver cirrhosis, cancer)<sup>6</sup>. Moreover, we also cannot exclude that part of these patients will continue and/or resume the use of drugs while undergoing treatment for HIV disease, hence remaining prone to incur in lethal overdose episodes.

In conclusion, we would strongly recommend repeated HIV serology for all IVDUs and persons adopting HIV-risky sexual practices, who have undergone previous HIV tests with negative results. This is meant to avoid that patients regarded as HIV negative, who then got infected while carrying on their risky practices through the exchange of syringes or through sexual contacts, may end up with their infection not being diagnosed until their HIV infection progresses into advanced clinical signs and symptoms, related to a more severe immunological and neurological deterioration, more unlikely to be treated successfully. The favorable perspective offered by the large-scale availability of multiple HAART combinations for HIV-infected IVDUs makes it absolutely necessary nowadays to apply a more strict and effective epidemiological monitoring of the population at-risk, especially of IVDUs<sup>27</sup>. It is in fact worth reminding that in Italy there is wide recorded evidence of general lack of awareness of the HIV serostatus of current and past sexual partners in many patients who have been later tested and resulted positive for HIV and/or AIDS.

## REFERENCES

1. PEZZOTTI, P., P. A. NAPOLI, S. ACCIAI, S. BOROS, R. URCIOLI, V. LAZZERI, G. REZZA, AIDS, 13 (1999) 249. — 2. GAZZARD, B., Int. J. Clin. Pract. 103 Suppl. (1999) 45. — 3. LAZZARINI, I., M. LANZAFAME, M. TREVENZOLI, S. VENTO, E. CONCIA, Lancet, 353 (1999) 841. — 4. NAPOLI, P. A., M. DORRUCI, D. SERRAINO, P. PEZZOTTI, S. FRANCESCHI, S. VELLA, G. REZZA, Eur. J. Epidemiol., 14 (1998) 41. — 5. SABBATANI, S., E. DI CRESCENZO, Infez. Med., 1 (1999) 24. — 6. PRINS, M., I.H. AGUADO, J. R. ROBERTSON, B. BROERS, N. CARRE, D. J. GOLDBERG, R. ZANGERLE, R. A. COUTINHO, A. VAN DER HOECK, AIDS, 11 (1997) 1747. — 7. ZACCARELLI, M., P. GATTARI, G. REZZA, S. CONTI, L. SPIZZICHINO, D. VLAHOV, G. IPPOLITO, V. LELLI, C. VALENZI, AIDS, 8 (1994) 345. — 8. GOEDERT, J. J., G. PIZZA, F. M. GRITTI, P. COSTIGLIOLA, A. BOSCHINI, A. BINI, C. LAZZARI, A. PALARETI, Int. J. Epidemiol., 24 (1995) 1204. — 9. VAN HAASRECHT, H. J. A., G. H. C. MIENTRES, J. A. R. VAN DEN HOEK, R. A. COUTINHO, AIDS, 8 (1994) 1721. — 10. GLASS, R. M., JAMA, 259 (1988) 1369. — 11. STARACE, F., Int. J. Soc. Psych., 39 (1993) 64. — 12. SABBATANI, S.: Le droghe, il rischio, la prevenzione e la conoscenza. Quale strategia per il contrasto delle tossicodipendenze. In Italian. (Editrice Compositori, Bologna, 1999). — 13. Relazione Annuale della D.G.S.A. (year 1998). In Italian. (Dipartimento della Pubblica Sicurezza. Ministero dell'Interno, Rome, 1999). — 14. BARGAGLI, A. M., A. SPERATI, M. DAVOLI, F. FORASTIERE, C. A. PERUCCI, Addiction, 96 (2001) 1455. — 15. CICCOLALLO, L., G. MORANDI, R. PAVARIN, C. SORIO, E. BUIATTI, Epidemiol. Prev., 24 (2000) 75. — 16. Epidemiological Studies on Effects of Drug Abuse Group, Epidemiol. Prev., 25 (1997) 265. — 17. LUCAS, G. M., M. GRISWOLD, K. A. GEBBO, J. KERULY, R. E. CHAISSON, R. D. MOORE, Am. J. Epidemiol., 163 (2006) 412. — 18. Repubblica Italiana. D.P.R. 10 settembre 1990 n. 285. »Approvazione del regolamento di polizia mortuaria«, Gazzetta Ufficiale (Suppl. ordinario) 239 (1990) 3. — 19. Classificazione delle malattie, traumatismi e cause di morte. IX revisione - 1975. Metodi e norme, serie C, n. 10. (Istituto Centrale di Statistica (ISTAT), Rome, 1984). — 20. LILENFELD, A. M., D. E. LILIENTHAL: Fondamenti di epidemiologia. (Piccin, Padua, 1986). — 21. VAN DER WERF, M. J., J. SCHINKELM, G. VAN SANTEN, U. VERGOUWE, R. A. WIX, E. J. VAN AMELJDEN, AIDS, 13 (1999) 1280. — 22. BASSETTI, S., M. BATTEGAY, H. FURRER, M. RICKENBACH, M. FLEPP, L. KAISER, A. TELENTI, P. VERNAZZA, E. BERNASCONI, P. SUDRE, J. Acquir. Immune. Defic. Syndrome, 21 (1999) 114. — 23. CELENTANO, D. D., D. VLAHOV, S. COHN, V. M. SHADLE, O. OBASANJO, R. D. MOORE, JAMA, 280 (1998) 544. — 24. SPITTAL, P. M., R. S. HOGG, K. LI, K. J. CRAIB, M. RECSKY, C. JOHNSTON, J. S. MONTANER, M. T. SCHECHTER, E. WOOD. AIDS Care, 18 (2006) 101. — 25. SCHINKEL, J., R. A. COUTINHO, E. J. VAN AMELJDEN, AIDS, 12 (1998) 1247. — 26. Notiziario dell'Istituto Superiore di Sanità, 11 Suppl. 1 (1998) 1. — 27. BOSELLI, F., G. CHIOSSI, A. GALLINELLI, Sex. Transm. Dis., 30 (2003) 707.

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## SMANJENJE SMRTNOSTI U SKUPINI OVISNIKA O DROGAMA NA PODRUČJU GRADA BOLONJE, ITALIJA

### SAŽETAK

Cilj ovog istraživanja je ocijeniti trenutni trend smrtnosti u skupini intravenoznih ovisnika o drogama (eng. intravenous drug users, IVDU) praćenih u gradu sjeverne Italije, Bolonji i procijeniti povezanost s HIV infekcijama i AIDS-om, te dostupnost učinkovite antiretroviralne terapije. 1214 IVDUa (uglavnom ovisnika o heroinu), 916 muškaraca i 298 žena, koji su dolazili u ambulante radi liječenja i prevencije ovisnosti u razdoblju od 1977. godine i studenog 1996. godine, ili su uključeni u našu promatranu skupinu te je njihov vitalni status bio proučavan sve do 31. 12 2002. godine. Velika većina ispitanika uključenih u istraživanje bili su rođeni na području grada Bolonje i njegovoj okolini, imigranti izvan područja Europe nisi bili uključeni. Tijekom perioda promatranja 271 IVDU (22.3%) je umro, 211 muškaraca (23.0%) i 60 žena (20.1%). Niti jedan smrtni slučaj nije zabilježen prije 1984. godine. Glavni uzroci smrti su slijedeći: AIDS (52.8% slučajeva), predoziranje heroinom (22.1%), ulične nesreće (7.4%), ciroza jetre (6.3%), i samoubojstvo (2.9%). Najveći sveukupni broj smrtnih slučajeva primijećen je između 1991. i 1996. godine. Gruba stopa smrtnosti uzrokovana AIDS-om bila je 10.0 na 1000 za muškarce i 13.2 na 1000 za žene, a utvrđena stopa smrtnosti iz drugih razloga 11.1/1000 među muškarcima i 5.2/1000 među ženama. Posljednjih je godina zabilježen nagli pad u broju smrtnih slučajeva povezanih s AIDS-om kod IVDUa, što se pripisuje učinkovitim antiretroviralnim režimima, iako je sveukupna stopa smrtnosti i dalje ostala značajna.