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Initiation, changes in use and effectiveness of highly active anti-retroviral therapy in a cohort of injecting drug users

J. M. EGEA[1], R. MUGA[1]*, G. SIRERA[2], B. CLOTET[2], J. TOR[1], M. ARDÈVOL[3], C. REY-JOLY[1] AND A. MUÑOZ[4]

[1] *Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain*
[2] *HIV/Aids Unit, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain*
[3] *Hospital Pharmacy, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain*
[4] *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA*

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SUMMARY

The prevalence of anti-retroviral therapy (ART) use over time and the incidence of AIDS in a cohort of HIV-seroconverting injecting drug users (IDUs) were assessed by means of a hospital-based study of IDUs with a well documented date of HIV infection. Use of ART and clinical endpoints were assessed by hospital records. Three calendar periods (before 1992, 1992–6 and 1997–2000) were defined as corresponding to modalities of ART available. Prevalence of ART usage in each calendar period, changes in medication and, hazard of AIDS in patients reaching the same duration of HIV infection at different calendar periods were analysed. In total, 132 IDUs with a median age of 23 years at seroconversion were followed up for 6·8 years (median) (range 0·2–15·7). At the end of the study, 58 patients (44%) had developed AIDS. Before the introduction of highly active anti-retroviral therapy (HAART) 12% of patients were on ART. Starting in 1997, an increasing proportion were receiving HAART with a prevalence of 39·5% by January 2000. Taking 1992–6 as the reference category the relative hazard of AIDS during 1997–2000 was 0·42 (95% CI, 0·1–1·1) ($P = 0·09$). A 40% penetration of HAART in a cohort of IDUs with known dates of seroconversion resulted in a 58% reduction of the hazard of AIDS.

INTRODUCTION

Cohort studies following large samples of individuals have documented the effectiveness of highly active anti-retroviral therapy (HAART) [1–5]. AIDS mortality has had a downward trend and since 1996 the survival of those HIV-positive individuals undergoing HAART has risen [6]. However, the majority of studies have been conducted on individuals whose transmission category is other than intravenous drug use. In clinical practice, patients with a history of drug use are less likely to have access to anti-retroviral therapies (ART) or to sustain the benefit from HAART than are those from other HIV transmission categories [7].

* Author for correspondence: Department of Internal Medicine, Room 806, Hospital Universitari Germans Trias i Pujol, Carretera Canyet s/n, 08916 Badalona, Barcelona, Spain.

Since the begining of the HIV epidemic, intravenous drug use has been the primary HIV transmission category in Spain and, though a decrease in the incidence of AIDS has been noted in all categories of transmission [8] it is unclear whether this is due to fewer new HIV infections or to the effectiveness of HAART.

Concerns have arisen regarding the degree of compliance and adherence to ART in drug users. However, the United States National Institute of Health (NIH) guidelines states that illegal drug use is not a contraindication for ART [9–11]. Other authors have reported that injecting heroin users undergoing methadone treatment comply with ART therapy as well as other patient categories [12] with the expected adherence vulnerability ablated by interventions designed specifically for this group [13].

Longitudinal data from seroconverting injecting drugs users (IDUs) are necessary to monitor the compliance of these populations with ART and to ensure the effectiveness of ART in individuals who are not regularly included in clinical trials. In this study, we have characterized the pharmaco-epidemiology of ART in HIV-positive IDUs. Subsequently, we have compared the incidence of AIDS in patients reaching comparable durations of HIV infection in three calendar periods corresponding to the availability of different ART regimens. By doing so, we provide a measure of the effectiveness of HAART in our IDU patients [14].

METHODS

Study design and study population

The study population consisted of IDUs with well documented dates of HIV seroconversion, living in two urban areas of metropolitan Barcelona, Spain (Badalona and Santa Coloma de Gramanet). A cohort of IDUs was assembled in a 650-bed tertiary hospital with health-care facilities for the treatment of heroin dependence (detoxification unit) and HIV infection (HIV/AIDS unit). Patients were admitted to the detoxification unit between February 1987 and December 1995. Upon admission they responded to a standard questionnaire including sociodemographic variables, drug use characteristics and clinical data including usage of ART. Blood samples were taken for haematological markers, HIV antibodies (EIA and Western blot) and CD4 cell counts during admission.

To include IDUs cases with well-estimated dates of HIV seroconversion we relied on two criteria. (i) Patients having no more than 2 years separating the last negative and first positive HIV tests. (ii) Patients having an HIV-positive test result not more than 2 years after the start of injecting drug use. In (i) we defined the seroconversion date by taking the midpoint between the last negative and first positive test and in (ii) we defined the seroconversion date by taking the midpoint between the start date of intravenous drug use (as proxy for the last negative date) and the first HIV-positive test.

Prevalence in use of ART over time, transitions from one modality of ART to another, and AIDS survival times were analysed in three periods defined by the availability of ART in Spain: monotherapy with zidovudine before 1992; dual nucleoside therapy from 1992 to 1996, and HAART from 1997 to the end of study (January 2000).

Follow up, outcome and exposure variables

Throughout the study, patients' hospital summaries and charts were consulted to assess ART use as well as changes in medication over time (i.e. switching to other agents or discontinuation of ART) and AIDS diagnosis.

We classified ART use into four categories: (i) none: subjects who underwent no type of ART; (ii) monotherapy: defined as ART with a single nucleoside reverse transcriptase inhibitor, including zidovudine, stavudine, zalcitabine, didanosine, and lamivudine; (iii) dual nucleoside therapy: defined as ART with two or more nucleoside reverse transcriptase inhibitors; and, (iv) HAART defined according to the 1997 US NIH guidelines as ART with two or more nucleoside reverse transcriptase inhibitors with either a protease inhibitor (such as indinavir, saquinavir, ritonavir or nelfinavir) or a non-nucleoside reverse transcriptase inhibitor (such as nevirapine or efavirenz).

AIDS was defined by the clinical conditions described in the 1993 revised US Centers for Disease Control and Prevention (CDC) classification system for HIV infection [15].

Statistical analysis

To describe the epidemiology of ART use, two types

Table 1. *Descriptive statistics of 132 HIV-seroconverting injecting drug users followed at different calendar periods*

	Calendar period		
Variable	Before 1992	1992–6	1997–January 2000
No. seen while AIDS free	112	96	48
Infection duration at beginning of calendar period (median) (years)	0	3·6	7·8
No. of person-years while AIDS-free	482·5	333·6	120·3
Number of AIDS cases	24	28	6
No. of deaths	16	31	6

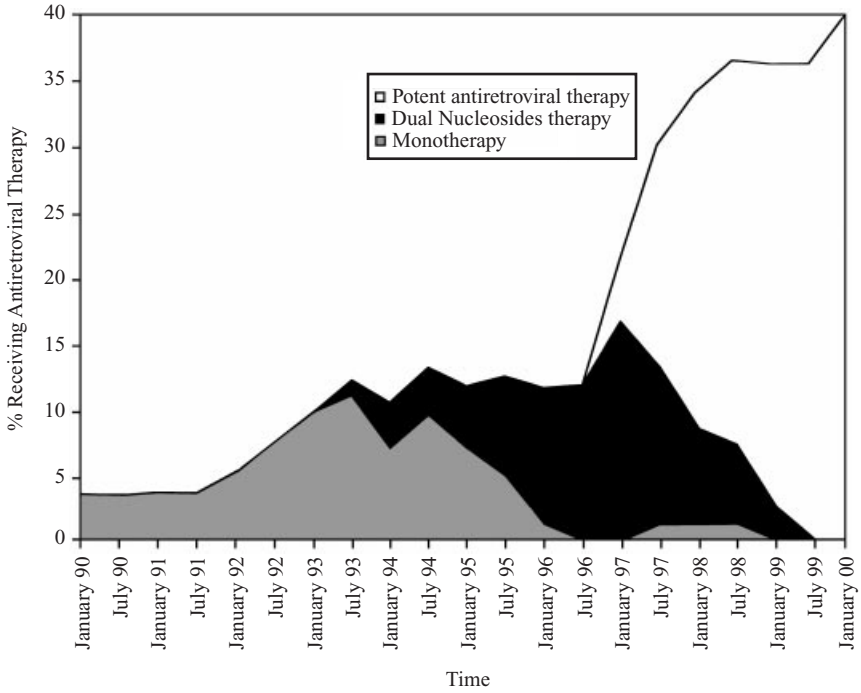

Fig. 1. Use of ART in an HIV-seroconverting cohort of injecting drug users.

of analyses were done. First, simple percentages were calculated to quantify the use of ART regimens during different 6-month periods. Second, transitions (changes from one mode of ART to another in a 6-month period) were monitored. To show the dynamics of the use of ART, the following transitions were analysed: (i) continuation of ART: percentage of cases who either maintained the same regimen or continued under no therapy from one period to the next; (ii) upshifting: among patients undergoing some form of ART, we calculated the percentage who changed from one kind of ART to another, more potent one (i.e. from monotherapy to dual nucleosides or HAART, and from dual nucleosides to HAART); (iii) treatment initiation: at each observation, we recorded the percentage of cases who had not been in treatment and who began some mode of ART and (iv) discontinuation of HAART: we took percentages of those who had been receiving HAART and who abandoned ART or changed to a less potent one.

Incidence of AIDS

The outcome of interest was the patients' progression

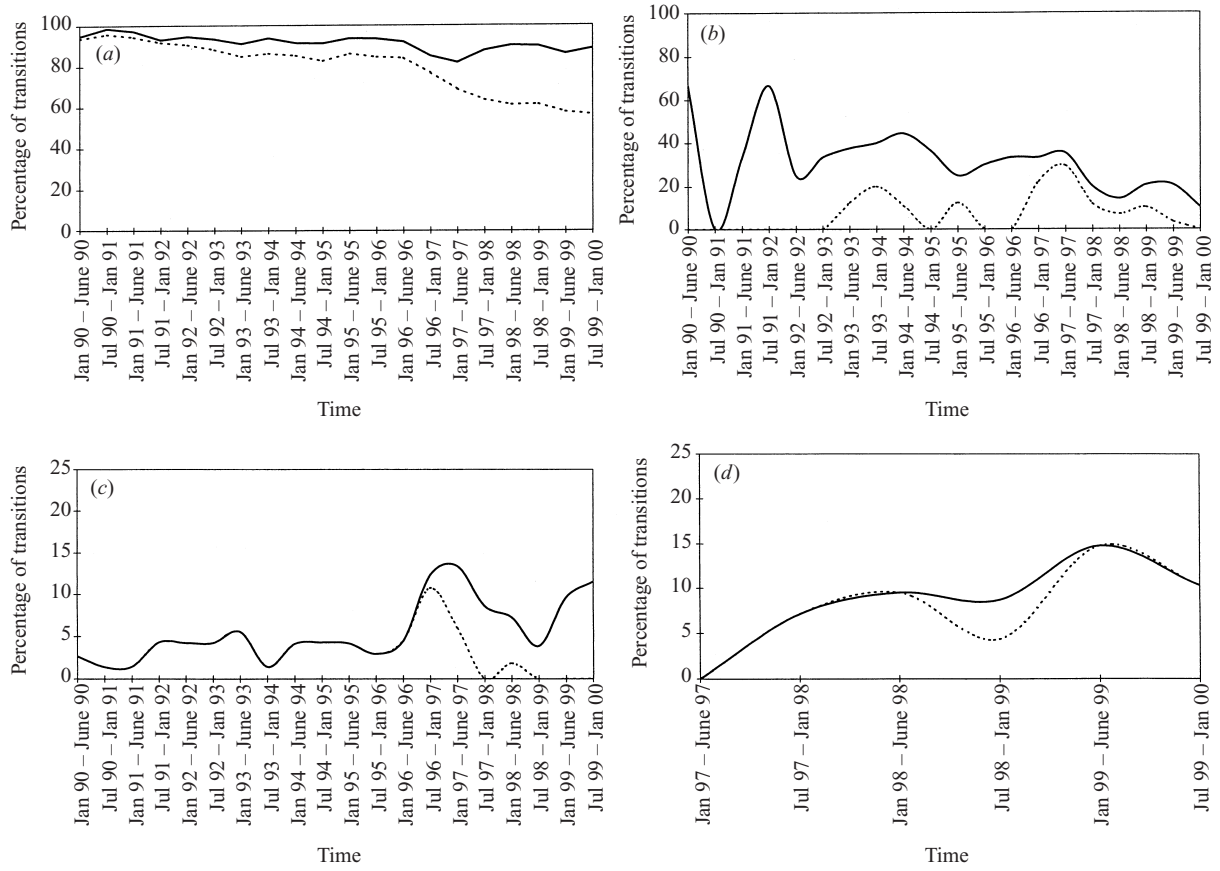

Fig. 2. Dynamics of the use of ART in an HIV-seroconverting cohort of injecting drug users. Modalities of ART available at each analysed semester were: no therapy (N), monotherapy (M), dual nucleosides therapy (C) and HAART (P). Relationship between modalities of ART and transitions between semesters were as follows:

		Subsequent mode of treatment			
		N	M	C	P
Previous mode of treatment	N	N–N	N–M	N–C	N–P
	M	M–N	M–M	M–C	M–P
	C	C–N	C–M	C–C	C–P
	P	P–N	P–M	P–C	P–P

(*a*) -----, Proportion remaining in no therapy (N–N) among all; ——, proportion remaining in same therapy [(N–N)+(M–M)+(C–C)+(P–P)] among all. (*b*) -----, Proportion upshifting among ART users [(M–C)+(M–P)+(C–P)]; ——, proportion shifting among ART users [(M–C)+(M–P)+(C–P)+(M–N)+(C–N)+(C–M)+(P–N)+(P–M)+(P–C)]. (*c*) -----, Proportion of untreated patients going into mono or dual nucleosides therapy [(N–M)+(N–C)]; ——, proportion of untreated patients going into therapy [(N–M)+(N–C)+(N–P)]. (*d*) -----, Proportion abandoning ART after HAART initiation (P–N); ——, proportion discontinuing HAART [(P–N)+(P–M)+ (P–C)].

to AIDS for HIV-positive IDUs reaching the same duration of HIV infection at different calendar periods. Up to the end of 1992, only zidovudine was used and thus we denote the period prior to 1992 as monotherapy. In 1993 didanosine was introduced and was typically used in combination with zidovudine. This period of combination of two nucleoside reverse transcriptase inhibitors (NRTIs) extended from 1993 to the end of 1996, including didanosine, zalcitabine, stavudine and lamivudine. Protease inhibitors (PI) (ritonavir, saquinavir and indinavir) were introduced towards the end of 1996, thus defining the period of HAART from the beginning of 1997 to the date of analysis (January 2000): typically two NRTIs and one PI or one non-NRTI (nevirapine or efavirenz).

Calendar Period	No. Cases	No. Developing AIDS	Relative Hazards	95% Confidence Interval
Before 1992	112	24	1·41	(0·7–2·8)
1992–1996	96	28	1	–
1997–January 2000	48	6	0·42	(0·1–1·1)

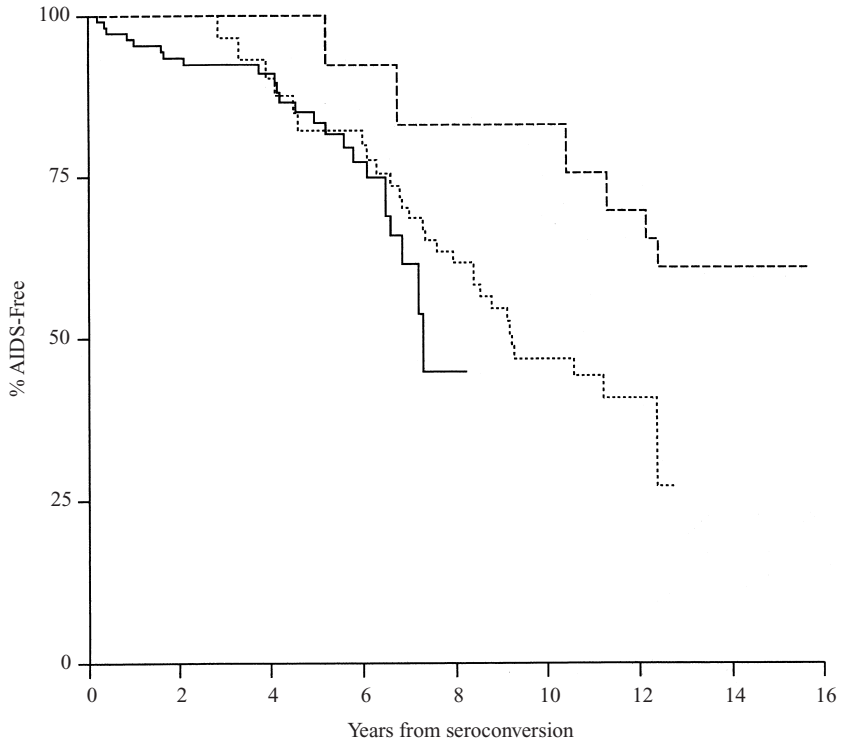

Fig. 3. Kaplan–Meier curves and RH for AIDS in an HIV-seroconverting cohort of injecting drug users according to calendar periods.

Individuals contributed as many records for data analysis as calendar periods in which they were observed at risk for events of interest. Each contribution was characterized by (i) the length of time infected with HIV when entering a given period, (ii) infection duration when exiting a given period, and (iii) the status with respect to event of interest at exit from the period (e.g. AIDS). Because a patient could contribute at different times in more than one calendar period, staggered entries were employed. In the survival analysis, the individual only contributed to risk sets between entering and exiting and thus we compared hazards of events of interest in different calendar periods in IDUs with the same infection duration [14, 16–17]. Estimation of survival curves was obtained using the Kaplan–Meier method, incorporating staggered entries. Since in a given calendar period patients entered with different HIV infection durations, the method reconstructs survival functions over the full range of values of years from seroconversion. The estimator is to be interpreted as the one to be obtained if conditions of that period are always present. Comparison of survival functions was done by estimating and testing relative hazards (RH) by using a Cox proportional hazards model with staggered entries [17]. If modalities of treatment associated with a calendar period are more effective than those in the reference period, RH indicates the factor by which the event hazard is reduced.

RESULTS

Among 836 patients admitted to a detoxification treatment unit between February 1987 and December 1995, 146 had a well-determined date of HIV

Calendar Period	No. Cases	No. Developing AIDS	Relative Hazards	95% Confidence Interval
Before 1992	66	18	1·36	(0·6–3·3)
1992–1996	48	15	1	–
1997–January 2000	13	1	0·23	(0·02–2·3)

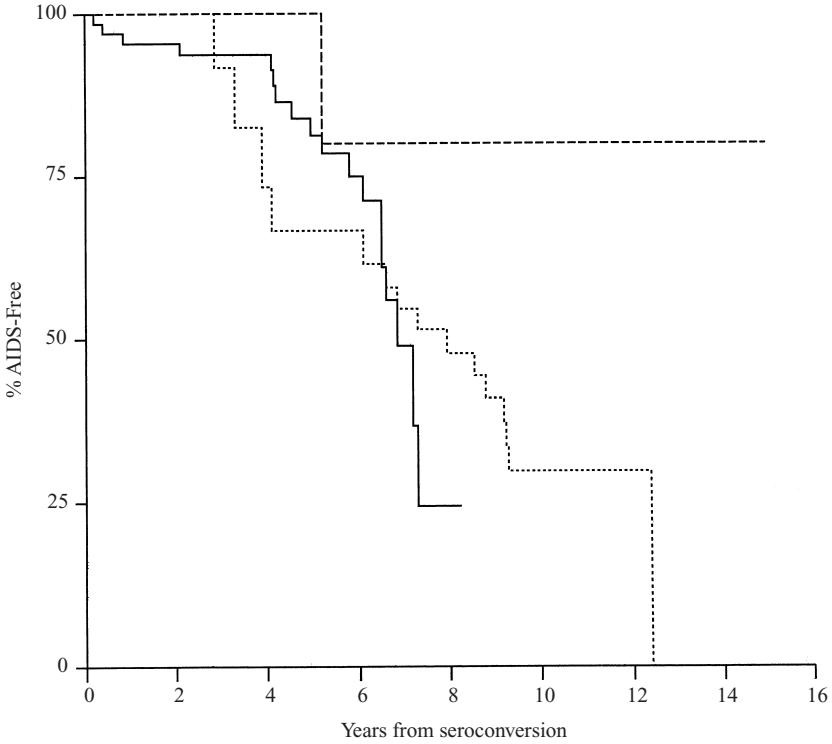

Fig. 4. Kaplan–Meier curves and RH for AIDS in an HIV-seroconverting cohort of injecting drug users never exposed to ART according to calendar periods.

seroconversion and 132 (90 % of the study population) were followed up. Twenty-seven out of 132 (20·5 %) were women. Age at seroconversion (median) was 23 years (Inter-quartile Range (IQR), 20–26 years) and the interval time of seroconversion (median) was 1 year (IQR, 0·7–1·7 years). By December 1986, 50 % of the sample had seroconverted (IQR, April 1985–October 1989). From HIV seroconversion to AIDS diagnosis, death, or date of analysis, 936 person-years of follow-up had been accumulated (median duration of follow up 6·8 years). Eleven percent of the study population was followed up for less than 2 years.

Table 1 shows the number of seroconverters seen for each calendar period as well as the number of AIDS diagnosis and deaths. At the end of the study, 58 cases (44 %) of AIDS had been diagnosed, 34 % (20/58) of them with some form of tuberculosis.

Figure 1 shows the prevalence of ART/monotherapy usage (< 5 %) before 1992; the 12 % of patients treated with either monotherapy or dual nucleoside ART in the second period and, the rapid rise in the use of HAART starting in January 1997 and reaching 39·5 % by January 2000.

Changes in use of ART over time

Figure 2(*a*) shows the percentage of HIV-positive IDUs whose treatment remained the same, and that of those receiving no ART. Up to December 1996, a moderate downward trend was observed in the proportion of patients not receiving ART but a dramatic decline was subsequently observed at the time HAART was introduced. Figure 2(*b*) shows the

percentage of patients switching from one mode of ART to another. Prior to 1996, downshifting, which included ART discontinuation or abandonment, was common.

Figure 2(*c*) shows the dynamics of ART initiation. Before 1996, shifting from no ART to monotherapy or dual nucleoside ART was constant. After 1997, HIV-positive individuals who had not been exposed to ART formed the largest number of transitions to ART. In Figure 2(*d*) we show the percentage of discontinuation of HAART.

Hazards of AIDS in patients reaching the same duration of HIV infection at different calendar periods

Figure 3 shows the Kaplan–Meier curves for AIDS-free time corresponding to estimates obtained from individuals seen in a given period after HIV seroconversion, including patients exposed and non-exposed to ART. Taking 1992–6 as the reference category period, the RH of AIDS was substantially reduced in the era of HAART (1997–2000) (RH, 0·42; 95% CI, 0·1–1·1) ($P = 0{\cdot}09$). To further investigate the contribution of interventions other than ART (e.g. the widespread use of prophylaxis for opportunistic infections) in the reduction of AIDS rates, we made a Kaplan–Meier analysis in HIV-positive IDUs never exposed to ART ($n = 77$). Divergent curves would suggest the effectiveness of health-care interventions other than ART in reducing the hazard of AIDS. Although not statistically significant, the RH of AIDS in the period 1997–January 2000 was reduced among those HIV-positive IDUs never exposed to ART (RH, 0·23; 95% CI, 0·02–2·3) ($P = 0{\cdot}2$) (Fig. 4).

DISCUSSION

Injecting drug use has been the main category of HIV transmision in Spain since the beginning of the epidemic [18]. In Catalonia, from 1981 to September 1999, 12728 AIDS cases were diagnosed of which 7364 (58%) were due to injecting drug use. In our setting, the health-care system guarantees access to ART but it has been reported that patients with a history of drug use are less likely to undergo ART than those included in other categories of transmission [19–22].

This study shows the successful introduction of HIV-infected IDUs to HAART and from the public health perspective results are encouraging because the incidence of AIDS fell by 58% with the introduction of HAART [4, 23–25]. One previous study in a cohort of HIV-positive IDUs from Baltimore (USA) reported a prevalence of HAART use of 14% [26]. Although the percentage of HIV-positive IDUs on HAART is still less than 50%, the increase with respect to previous calendar periods is noteworthy. Until September 1996, only three anti-retrovirals (AZT, ddC, ddI) were licensed in Spain, and the proportion of HIV-positive IDUs on ART was below 15%. Since January 1997 we have observed a sharp rise in the percentage of HIV-positive IDUs receiving ART. However, the increased prevalence of ART use cannot be solely attributed to the introduction of HAART, it also includes a variety of interventions involving HIV-positive IDUs in care and therapies [9, 10]. In particular, the widespread use of prophylaxis for opportunistic infections may have been conducive to the involvement of IDUs in HAART.

Longitudinal studies on patients with HIV/AIDS have shown that the introduction of HAART is likely to increase both AIDS-free time and overall survival [27, 28]. Here we have reported hazards of AIDS in HIV-positive IDUs reaching the same duration of HIV infection at different calendar periods in order to assess the effectiveness of ART at the population level rather than at the individual level, as would be the case in clinical trials [14]. Despite the fact that the number of patients is limited, results suggest that the benefits from HAART in IDUs could reach the same level as reported in other categories of HIV transmission [2–6]. In this study, less than 15% of those HIV-positive IDUs starting HAART abandoned therapies or changed to less potent HIV regimens, suggesting successful ART compliance in this population. In this respect, factors related with less than optimum prescriptions of ART have been associated with lower age, ongoing drug addiction or the inexperience of doctors treating HIV-positive individuals [19, 26, 29].

This study does not establish whether or not HIV-positive IDUs involved in ART have a less severe drug dependence than those who are not on ART. However, treatment of drug dependence also favours compliance to prophylaxis of opportunistic infections and treatment of tuberculosis as well as patient retention within the health-care system [13]. Therefore, improving access to detoxification among HIV-

positive heroin users may facilitate the use of ART. In this hospital cohort the observed decrease in hazards of AIDS in the HAART era (1997–2000) relative to the pre-HAART era (1992–6) is not biased due to differential availability of methadone programmes because it was equally available in both periods.

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