Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain

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ABSTRACT

Aims To assess the relationship between methadone treatment (MT) and overdose and HIV/AIDS mortality among heroin users resident in Barcelona city.

Design All patients who started treatment in any treatment centre between 1992 and 1997 were included in a cohort the first time they were admitted for heroin addiction treatment. Follow-up controls were carried out every 9 months, on average, until 31 December 1999. Variables, both constant and varying over time, were fitted into Cox regression models.

Findings The study recruited 5049 patients, which provided 23 048.2 person-years. Fifty per cent were in MT during the study period; of the total cohort 1005 patients died: 38.4% due to AIDS, 34.7% to overdose and 27% to other causes. Overall mortality decreased from 5.9 deaths per 100 person-years in 1992 to 1.6 in 1999. Globally, life expectancy at birth was 39 years, 38 years lower than that of the general population. The main factor for overdose mortality was not being in MT at the time of death [relative ratio (RR) = 7.1]; other factors were being a current injector at baseline and being HIV positive. For AIDS mortality, the main factor was the calendar year (RR for 1996 versus 1999 = 4.6), the next major factor was more than 10 years of heroin consumption, followed by not being in MT, being unemployed, then having a prison record.

Conclusions The observed mortality decline could be linked to the effectiveness of low-threshold MT. The life expectancy of heroin users increased by 21 years during the study period.

KEYWORDS AIDS, heroin mortality, methadone treatments, overdose mortality.

INTRODUCTION

In the 1990s, in some European countries including Spain, mortality rates among heroin injectors were 20–30 times higher than those of the general population of the same age and sex [1,2]. This was mainly the result of the high HIV/AIDS mortality, which affects Spain more than any other country in Europe [3], and overdose deaths [4]. This led to a rise in young adult mortality [5] which, in turn, led to a fall in the life expectancy of the general population [6].

HIV/AIDS mortality began to decline from 1996 onwards, coinciding with the introduction of highly active antiretroviral treatment (HAART) [7–9].

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Although AIDS mortality decreased with HAART, it is important to take into account the fact that AIDS mortality in intravenous drug users started to decline before the introduction of HAART [10]. On the other hand, the trend in overdose mortality—the main cause of death among heroin users in many countries [11]—was not so uniform [4].

Observational studies in heroin users have identified several factors associated with a higher probability of suffering an overdose [2,11–17]. During the 1990s, methadone maintenance treatment (MT) programmes were used increasingly as instruments for harm-reduction among heroin users, and several studies showed that MT does indeed reduce overdose mortality [11,18]. However, it has been argued that using MT on a routine basis is not as effective as might be expected from the results of studies following a strict protocol. This is due to the risks associated with the first few weeks in MT [19,20], with take-home doses [21,22], the concurrent consumption of other substances [12] or from suicide attempts via methadone poisoning [23]. Due to the rise in drug-related deaths and the presence of methadone in overdose deaths [23–25], some countries have either restricted the use of MT, allowing only methadone detoxification treatments/programmes [26], or they are considering more control over the dispensing of methadone [27–29]. Both these policies could worsen the coverage of treatment of heroin users. The debate over the effectiveness of MT in reducing overdose mortality rates under routine conditions was particularly relevant in the United Kingdom [30,31]. Even though MT has not been shown as a protective factor for AIDS mortality there is some evidence that it does reduce HIV infection in intravenous drug users [32].

In this light, an assessment of the link between a community-based approach to methadone treatment and the overdose and HIV/AIDS mortality trend among heroin users might provide interesting evidence with which to evaluate harm-reduction strategies, particularly in a city which has one of the highest known mortality rates among heroin users [4], where free, broad-coverage, low-threshold MT programmes were developed during the 1990s.

MATERIALS AND METHODS

Heroin users resident in Barcelona city who started treatment in any of the city's treatment centres between 1992 and 1997 were included in a cohort the first time they were admitted into treatment for heroin addiction, regardless of whether they had been treated prior to 1992. The study ended on 31 December 1999.

The treatment centres cited provide free care and the data included in this paper include all MT carried out in Barcelona during the period under study, with MT co-existing with other treatment programmes (i.e. naltrexone, drug free and detoxification programmes). MT began in Barcelona in 1991, with 469 MT places available. The number of MT places rose to 1200 in 1992, and stood at 2500 from 1996 onwards. Since 1994 MT has been low-threshold, with no time or methadone dose limits and no penalization for consumption of illegal drugs. The objective was to provide palliative therapy, and 60% of doses were unsupervised (take-home doses were supplied for several days at a time, depending on the patient). From the outset, the methadone was dispensed as a liquid medication taken orally with auxiliary programmes, organized by specialized professionals, available to patients including: complete physical and analytical checks, psycho-pathological assessments, social support and educational work programmes [33,34].

At recruitment, subjects underwent a clinical examination, blood cell count and serological tests to detect HIV, HBV and HBC antibodies. They were also interviewed, given a personal identification code for the purpose of the study, and socio-demographic variables and drug consumption history, including injecting behaviour, were also recorded. For certain variables these baseline data focused on the 30 days prior to the interview; the information was compiled at the treatment centre itself, and stored in a central database with encrypted identifiers. Linkage between databases was carried out using an identifier constructed from the first three letters of each surname, full first name, date of birth and sex [35]. Particular attention was paid to guaranteeing absolute confidentiality.

Follow-up visits were scheduled every 6 months after the baseline visit, and were carried out on average every 9 months. They recorded the type of treatment assigned, the number of days spent in each type of treatment, the date the treatment ended and the results of blood tests. The AIDS Register was consulted to check for the possible existence of an AIDS diagnosis, and its date. If the subject was not in treatment/was not attending the MT programme at the time of follow-up, the local census data were then consulted to check whether they had moved away from Barcelona, and vital status was also obtained, together with the date and cause of death from the National Death Register, when applicable. When necessary (death due to non-natural causes) the records of the Forensic Institute were also consulted.

Analysis

Patients who moved out of Barcelona were censored at the date of the move (7% of total cohort). Those not detected as deceased were considered to be still alive at the end of the study period. Yearly mortality rates,

standardized for age and sex, were calculated using the population aged 15–54 years, taken from the local 1996 census. Life expectancy at birth was calculated based on the age at admission to treatment, for those aged between 15 and 54 years. For those aged under 15, we adopted the corresponding rate for the population of Barcelona. In order to determine the rates for those over than 54 years old we observed the trend in the cumulative conditional probability of being alive, and based on those rates, we applied an exponential parametric model in order to be able to estimate the rates for other ages (55–90 years). To evaluate trends, 1993 was taken as the reference year due to the low number of person-years during the first year of the study.

Statistical analysis was carried out using the SPSS-PC and EGRET packages. To analyse mortality-associated factors, Cox proportional risk regression models with variables both constant and varying over time were fitted [36]. Variables considered constant over time included those relating to baseline data and HIV serological status. Subjects were coded positive if they were diagnosed as HIV positive either at entry, or during follow-up. The non-constant variables were: observational period, age, years of consumption and being in MT. For these non-constant variables, the person-time for each individual was calculated using days as the time unit in each category. Two models were fitted: the first model analysed deaths by overdose and included the whole cohort, and the second model included only those subjects who had ever injected heroin; these subjects were analysed for AIDS mortality. Variables found to be significant ($P < 0.05$) in bivariate analysis were included into the multivariate model, along with those considered to be potential confounders.

RESULTS

The study recruited 5049 patients, who provided 23 048.2 person-years of follow-up. At entry into the study, 77% were men, with a mean age of 29 years; 18% lived in a deprived area, more than 60% were unemployed and more than 50% had been in prison. Thirty-nine per cent had been consuming heroin for more than 10 years, 91% consumed daily, 79% had injected drugs at some stage and 59% had done so during the 30 days prior to the baseline interview. Fifty-one per cent were diagnosed as HIV positive and of these, 17% were diagnosed with AIDS either at entry or during follow-up. During follow-up, 50% of subjects were admitted to MT. They spent at least 3 days in MT during follow-up; the rest were treated with drug-free programmes (Table 1). In 1992, the total number of person-years in methadone treatment was 114; this figure rose sharply to 1225 person-years in 1998, then remained constant. Subjects in MT started treatment with methadone on an average of three occasions (range 1–8) and underwent treatment for a mean of 805 days (range 3–2913). They received a mean daily dose of 71 mg of methadone, and 97% of them spent at least 1 day on a take-home schedule.

During follow-up, 1005 patients died: 386 due to AIDS (38.4%), 349 to overdose (34.7%) and 270 (27%) to other causes, mostly violent (7% of the total) and diseases of the digestive system (6% of the total), mainly cirrhosis. Of those dying due to overdose, 41% were HIV positive, 86% presented opiates or its metabolites in their body fluids, 34% cocaine or its metabolites and 59% benzodiazepines. Seventy-six per cent presented more than one psychoactive substance, while in 4% no post-mortem toxicological analysis was performed. In relation to MT, 81% of overdose deaths (274 subjects) had never been on MT and only 11 users died while in MT. Of these, only one of them died within the first 3 weeks (14th day), the other 10 had been in MT for more that 162 days. Of those dying due to AIDS, 75% were registered as AIDS cases and 25% were HIV positive without a clinical diagnosis of AIDS (pre-AIDS cases).

The overall mortality rate for the entire period was 4.4 per 100 person-years. Overdose mortality fell progressively throughout the entire period of observation, from 3.1 per 100 person-years in 1992 to 0.6 per 100 person-years in 1999. AIDS mortality increased from 1.3 per 100 person-years in 1992, reaching a maximum of 3.4 per 100 person-years in 1995, with an important decline from 1996 onwards (Fig. 1). Mortality due to other causes fell less than the above two causes—declining from 1.2 per 100 person-years in 1992 to 0.7 per 100 person-years in 1999. These other causes were the main cause of death in 1999.

Life expectancy at birth for this cohort (Fig. 2) over the study period was 39 years, 38 years lower than that for the population of Barcelona. However, it rose steadily from 32 years in 1993, to 53 in 1997—the last year for

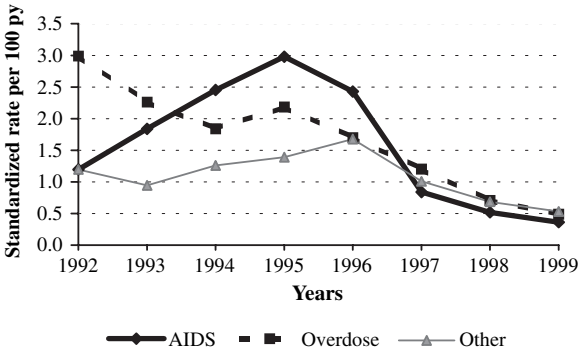

Figure 1 Trends in the standardized mortality rate per 100 person-years for ages 15–54 years, stratified by cause of death, Barcelona, 1992–1999

Table 1 Characteristics and death in a cohort of heroin users, Barcelona 1992–99.

Mean age at cohort entry ± SD (range) 29.3 ± 6 (15–54)
Mean days of follow-up ± SD (range) 1667.3 ± 785.4 (1–2920)

	n (%)	*Deaths*	*Person–years of follow-up*
Variables constant over time			
Gender			
Female	1185 (23.5)	207	5600.0
Male	3864 (76.5)	798	17448.2
Area of residence			
Other	3871 (81.7)	706	17938.1
Deprived area	868 (18.3)	174	3744.8
Prison record			
No	2204 (47)	363	10305.4
Yes	2484 (53)	542	10980.4
Employment status			
Employed	1715 (36.7)	261	8125.5
Unemployed	2953 (63.3)	615	13227.6
Drugs injection			
Never	946 (20.6)	86	4222.9
Yes, but not at the moment	955 (20.8)	130	4377.4
Currently	2695 (58.6)	641	12232.5
Year of starting treatment			
1997	510 (10.1)	26	1217.1
1996	589 (11.7)	61	1870.9
1995	814 (16.1)	131	3146.8
1994	864 (17.1)	164	4002.9
1993	958 (19.0)	270	4967.1
1992	1314 (26.1)	353	7843.2
HIV serological status			
Negative	2061 (49)	159	10008.3
Positive	2142 (51)	670	9533.1
Variables changing over time			
Age (years)			
≤ 25	1444 (28.7)	113	3667.4
> 25	3593 (71.3)	892	19380.8
Years of heroin consumption			
0–5	1452 (29.6)	90	2632.7
5–10	1534 (31.3)	246	7311.2
> 10	1913 (39.0)	633	12359.1
Being in MT			
Yes	2530 (50.1)	119	5399.5
No	2519 (49.1)	887	17648.6
Period of observation			
1999		62	3811.4
1998		87	3916.2
1997		132	3848.9
1996		224	3544.8
1995		226	3100.5
1994		143	2478.6
1993		95	1736.8
1992		36	610.9

Table 2 Variables associated with overdose death among heroin users, Barcelona 1992–99.

Overdose	*n (p-y†)*	*Mortality rate per 100 p-y†*	*Crude RR† (95% CI)†*	*Adjusted RR*† (95% CI)†*
Variables constant over time‡				
Drugs injection				
Never	946 (4222.9)	0.9	1	1
Yes, but not at the moment	955 (4377.4)	0.9	0.94 (0.59–1.50)	0.8 (0.57–1.43)
Currently	2695 (12 232.5)	2.0	2.3 (1.61–3.22)	2.0 (1.29–3.04)
HIV serological status				
Negative	2061 (10 008.3)	1.1	1	1
Positive	2142 (9533.1)	1.5	1.3 (1.04–1.7)	1.4 (1.02–1.80)
Variables changing over time				
Period of observation				
1999		0.5	1	1
1998		0.8	1.4 (0.8–2.4)	1.3 (0.66–2.45)
1997		1.3	2.4 (1.4–4.0)	1.6 (0.83–2.95)
1996		1.8	3.3 (2.0–5.4)	1.7 (0.88–3.17)
1995		2.4	4.3 (2.7–7.0)	1.9 (1.02–3.76)
1994		1.9	3.4 (2.1–5.8)	1.3 (0.66–2.70)
1993		2.5	4.5 (2.7–7.6)	1.4 (0.66–3.04)
1992		3.1	5.6 (2.9–11.0)	0.5 (0.13–1.82)
Being in MT†				
Yes	2530 (5399.5)	0.2	1	1
No	2519 (17 648.6)	1.9	9.4 (5.1–17.1)	7.1 (3.77–13.45)

‡Collected at baseline. *Model adjusted for gender, age and years of consumption. †p-y: person-years; RR: relative ratio; 95% CI: 95% confidence interval; MT: methadone treatment.

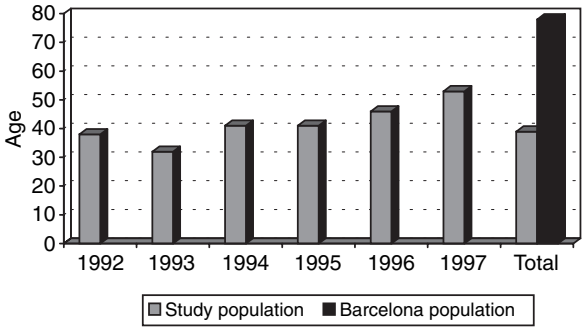

Figure 2 Life expectancy of heroin users by year of starting treatment (1992–1997) and life expectancy of the general population of Barcelona

which it was calculated—still 25 years lower than that of the general population.

In the multivariate analysis, not being in MT at the time of death was the factor most strongly associated with the risk of dying from overdose [relative ratio (RR) 7.1] (Table 2). On the other hand, the risk of dying was double among current injectors at the baseline interview and slightly higher among HIV positive subjects (RR 1.4). Regarding the period of death, there was a slight decline between 1995 and 1999, which was not significant.

Among heroin injectors (Table 3) the risk of dying of AIDS in 1996 was significantly higher (RR = 4.6 in relation to 1999). At the same time, people with more than 10 years of consumption had a 2.7 times higher risk than those with less than 5 years' consumption. Additionally, patients who were not in MT at the time of death had 60% more risk than users in MT. A higher risk of dying from AIDS was observed among the unemployed (RR = 1.4) and those with a prison record (RR = 1.2).

DISCUSSION

This study reveals an important decline in mortality among heroin users in Barcelona, from 1995 onwards. In fact, in 1999 the standardized rate was almost five times lower than in 1995. As a consequence of this decline, the life expectancy at birth has risen by 21 years, although in 1999 it was still 25 years lower than that of the general population. Not only had AIDS mortality declined—as already documented [37]—but overdose deaths had also fallen, a previously unknown phenomenon, where the protective effects of MT was proved to have played a significant role.

It should be noted that the data presented here come from a cohort study, not from a controlled community trial. Thus we are dealing with an assessment of the effectiveness of low-threshold MT operating routinely in the framework of a 'policy of harm-reduction'. Despite the

Table 3 Variables associated with AIDS death among injecting heroin users, Barcelona 1992–99.

AIDS	*n (p-y†)*	*Mortality rate per 100 p-y†*	*Crude RR† (95% CI)†*	*Adjusted RR*† (95% CI)†*
Variables constant over time‡				
Employment status				
Employed	1127 (5309.5))	1.2	1	1
Unemployed	2199 (9779.8)	1.9	1.6 (1.2–2.1)	1.4 (1.15–1.76)
Prison record				
No	1447 (6747.1)	1.2	1	1
Yes	2014 (8957.5)	2.3	1.8 (1.4–2.4)	1.2 (1.02–1.47)
Variables changing over time				
Age (years)				
< 25	1015 (2590.9)	0.8	1	1
> 25	2487 (13255.9)	2.0	2.5 (1.6–3.9)	1.4 (0.99–2.09)
Years of heroin consumption				
0–5	884 (1578.3)	0.7	1	1
5–10	1096 (4787.9)	1.2	1.7 (0.9–3.3)	1.4 (0.87–2.20)
> 10	1448 (9122.3)	2.3	3.3 (1.8–6.1)	2.7 (1.71–4.31)
Period of observation				
1999		0.5	1	1
1998		0.6	1.4 (0.6–2.9)	1.04 (0.61–1.78)
1997		1.0	2.2 (1.1–4.3)	1.9 (1.16–3.20)
1996		3.1	6.7 (3.6–12.3)	4.6 (2.81–7.41)
1995		3.2	7.0 (3.8–12.9)	4.3 (2.57–7.07)
1994		2.8	6.0 (3.2–11.3)	3.5 (2.04–6.02)
1993		2.5	4.9 (2.5–9.7)	3.5 (1.93–6.34)
1992		1.6	3.3 (1.02–9.6)	2.5 (1.04–5.99)
Being in MT+				
Yes	1823 (3934.5)	1.4	1	1
No	1679 (11912.3)	1.9	1.4 (1.1–1.9)	1.6 (1.23–2.03)

‡Collected at baseline. *Model adjusted for gender. †p-y: person-years; RR: relative ratio; 95% CI: 95% confidence interval; MT: methadone treatment.

fact that, in such a design, we cannot control treatment assignment or treatment compliance, cohort studies provide compelling designs for studying risk factors in real-life conditions. However, some limitations of the study should be taken into account: (1) people not detected in any register (mortality register, census, etc.) were considered alive, leading probably to an underestimate of the mortality rate; and (2) it was impossible to analyse the route of heroin administration, HIV serological status and other variables as 'varying over time', although we do not believe this would significantly affect our results. The impact of MT on the mortality rates of heroin users was so great that it is difficult to believe that these or other uncontrolled variables could explain the phenomenon. In fact, according to the RR found, it is estimated that 86% of the overdoses and 38% of AIDS deaths occurring among non-MT users could have been avoided had they been in treatment.

The sustained decline in overdose mortality over the period 1992–99 contrasts with the slight decline in the number of overdoses observed in the specific mortality register based on forensic data [6]. Furthermore, as in other countries, these registers reveal a rise in the number of deaths with methadone in body fluids [23]. A cross-sectional analysis of these registers would have given rise to controversies similar to those in the United Kingdom over the efficacy of MT programmes as a measure for controlling mortality [30,31]. In these studies, the population at risk cannot be determined, and hence it is not possible to ascertain whether a fall in the number of deaths was due to a fall in the number of users or to a decline in factors leading to a reduction in the risk of overdose, for example intravenous use. Nor can it be ascertained whether the rise in the number or proportion of overdose deaths in which methadone is detected is due to a 'killer' effect of the substance or, as seems more likely, to a rise in heroin users who take heroin despite being in MT. In our case, being a cohort study, it was possible to calculate the RR adjusted for various factors whose effects could well be confused with that of MT (age, sex, HIV infection, administration route, etc.). Furthermore, we knew when a user was in treatment (MT or drug-free treatment) or not. The treatment *per se* has been shown to be protective against death because the user takes less

heroin and injects himself less often, this is especially true for MT [38], and this is one of the reasons why methadone could be effective in reducing overdose mortality. In our study we considered people in drug-free treatment as if they were not in treatment (i.e. non-MT). Thus, if drug-free treatments had been more effective than no treatment at all in reducing mortality, evaluating MT as the only treatment would produce an underestimation of its effect.

Another argument which could be used to explain the smaller decline in overdose mortality rates in the specific overdose register is the low representativeness of the cohort under study with respect to Barcelona heroin users in general. However, this explanation seems unlikely, given the size and characteristics of the cohort. In fact, in 1995 around 72% of heroin users interviewed in the street had been in treatment previously [39], and there was a wide incorporation of users into MT during the second half of the nineties. The discrepancy could be explained by the fact that users who had never been in treatment present higher prevalence of risk behaviours for overdose [11], as well as by the fact that the specific register collects deaths occurring in the city whether or not they were resident there. Furthermore, if we compare the 1993 overdose mortality rate in our cohort (2.3 per 100 person-years) with the one calculated with the data from the 1993 specific mortality register and a city capture–recapture estimate of heroin users [40] (2.1 per 100 users), we can see the similarity of both rates, supporting the fitness of our cohort.

National death registers have served as the basis for many studies on MT effectiveness. However, they are usually not particularly useful for several reasons: changes in the definitions of overdose and AIDS over time, changes in the *International Classification of Diseases* (ICD) upon which these statistics are based and the validity problems of many of these registers with respect to the adequate coding of underlying cause of death among those dying of overdose [41–43]. In the present study, quality of cause of death coding was specifically sought—agreement between the Death Certificate signed by the doctor, the forensic report, and the AIDS register was checked—to overcome these problems.

The extremely high prevalence of HIV and AIDS cases in our cohort, compared with other European cohorts [10,44,45], explains the high mortality rates in the present study (more than 2.5 per 100 person-years over several years). Our cohort reflects the high prevalence of AIDS in Spain, the highest in Europe, and the fact that in Spain injection was the principal risk behaviour for AIDS [3]. Age, and above all length of drug consumption, may rather be markers of the duration of HIV infection. Similarly, employment status and having been in prison may be considered markers of the lack of social integration and the difficulty in obtaining any benefit from the health resources available. Looking at RR for years of observation in the MT adjusted model (Table 3), it seems clear that the implementation of HAART in 1997 has had a significant impact (between 1996 and 1997 AIDS mortality fell by 59%) and, even though we could not directly test the link with HAART, we can see the relation over the period as in other studies evaluating the efficacy of HAART [7]. Nevertheless, this HAART effect adds to an already declining AIDS mortality trend observed before its introduction, a fact which has already been described by other authors [10]. With our study results we could attribute this previous decline in AIDS mortality to MT, because when 'being in MT' was not included in the model, the highest RR for AIDS mortality was for the year 1995 (data not shown). Also, the RR for the period effect was double, compared to when 'being in MT' was introduced. However, from 1997 onwards, the RRs are very similar in both models, suggesting probably that the HAART effect was so strong that the effect of being in MT almost disappeared.

Methadone treatment has been widely criticized, especially in relation to non-controlled, low-threshold MT, but according to our study results, where such a low-threshold MT was being delivered, such an MT approach can be useful to prevent both overdose and AIDS mortality. We cannot deny that MT effectiveness improves when used as part of more complex programmes including other interventions [33,46]; however, these complementary interventions substantially increase the cost of treatment, and their implantation may compete with the idea of a generalization of low-threshold MT [47]. In such cases, policy makers should assign priorities depending on available funding and the epidemiological situation.

In conclusion we can state that, despite the clear decline in mortality among heroin users following the increase in low-threshold MT (and the introduction of HAART), the life expectancy of this sector of the population is still lower than that of their contemporaries. In order to sustain the increase in the life expectancy of heroin users in the future, risk reduction policies should not be reduced or relaxed. Indeed, the opposite is necessary in order to explore new strategies to prevent both fatal and non-fatal overdoses, as well as hepatitis and bodily injuries.

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