Methadone maintenance treatment and mortality in HIV-positive people who inject opioids in China

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Objective To examine the effect of methadone maintenance treatment (MMT) on mortality in people injecting opioids who receive antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection in China.

Methods The study involved a nationwide cohort of 23 813 HIV-positive (HIV+) people injecting opioids who received ART between 31 December 2002 and 31 December 2011. Mortality rates and demographic, disease and treatment characteristics were compared in patients who received either ART and MMT or ART only. Factors associated with mortality were identified by univariate and multivariate analysis.

Findings Overall, 3057 deaths occurred during 41 959 person–years of follow-up (mortality: 7.3 per 100 person–years; 95% confidence interval, CI: 7.0–7.5). Mortality 6 months after starting ART was significantly lower with ART and MMT than with ART only (6.6 versus 16.9 per 100 person–years, respectively; $P < 0.001$). After 12 months, mortality was 3.7 and 7.4 per 100 person–years in the two groups, respectively ($P < 0.001$). Not having received MMT was an independent predictor of death (adjusted hazard ratio: 1.4; 95% CI: 1.3–1.6). Other predictors were a low haemoglobin level and a low CD4+ T-lymphocyte count at ART initiation and treatment at facilities other than infectious disease hospitals.

Conclusion Patients would benefit more from both MMT and HIV treatment programmes and would face fewer barriers to care if cross-referrals between programmes were promoted and ART and MMT services were located together.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

In Asian countries, including China, most epidemics of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) have stabilized. In 2011, the estimated prevalence of HIV infection in China was 0.058%, a rate similar to or lower than that observed in neighbouring countries. Furthermore, an estimated 780 000 people were living with HIV/AIDS and 28.4% of them were thought to have been infected by injecting illicit drugs.[1] China now has the world's largest number of people who inject illicit drugs[2] and it is well known that the country's epidemic of HIV infection originated in and spread rapidly in this group because of unsafe practices, such as sharing needles.[2–4] The epidemic soon spread through commercial plasma donation, sexual contact and mother-to-child transmission.[3]

In response, since 2004 the Chinese government has implemented comprehensive strategies for treating both HIV infection and drug dependence involving, respectively, a National Free Antiretroviral Treatment Programme and a National Methadone Maintenance Treatment Programme.[1,5–7] The National Free Antiretroviral Treatment Programme (NFATP) operates in a variety of settings, including infectious disease hospitals, general hospitals and local clinics run by the Chinese Center for Disease Control and Prevention. By April 2012, the programme had provided antiretroviral therapy (ART) to a total of 166 371 HIV-positive (HIV+) patients.[8] Already, the 10-year-old programme is seeing some success: mortality rates and viral loads have decreased more among enrolled patients than among those not undergoing treatment.[9–12] Similarly, the National Methadone Maintenance Treatment Programme has reduced drug dependence and involvement in drug-related crime among clients, increased the employment rate and improved social functioning.[6] This programme has helped 357 586 opioid-dependent individuals since 2004;[8] it is, in fact, the largest network for methadone maintenance treatment in the world.[13]

In China and globally, the introduction of ART has dramatically reduced AIDS-related mortality and the rate at which HIV+ patients progress to AIDS. However, in low- and middle-income countries, the proportion of HIV+ people injecting illicit drugs who receive ART is often disproportionally low.[14] For example, people who inject illicit drugs account for an estimated 28.4% of all HIV+ individuals in China, but only 15.5% of ART patients inject illicit drugs.[1,12,15] Thus, despite the increasing availability of ART, which is a life-saving therapy, HIV-related and all-cause mortality remain high among people who inject illicit drugs and are HIV+.

Studies in various countries, including Brazil,[16] Denmark[17] and the United States of America,[18] have shown that individuals on ART who become infected with HIV by injecting illicit drugs have a higher risk of death than those infected by other transmission routes. The lower uptake of ART and the poorer outcomes observed among HIV+ people who inject illicit drugs are thought to be attributable to a variety of factors, such as delays in starting treatment, poor adherence to ART, continuing drug dependence and a high prevalence of comorbidities, such as depression and hepatitis C.[19]

Internationally, there is growing evidence that treatment of opioid dependence, such as methadone maintenance treatment (MMT), not only stabilizes drug dependence and its associated psychosocial conditions, but also promotes adherence to ART and improves virological responses among HIV+ people.[18,20–23] Although China's national ART and MMT programmes have been shown to benefit their respective target populations when assessed independently,[6,9–11,24,25] the advantages of coincident ART and MMT for HIV+ people who inject opioids have not yet been examined in China, though they have

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been observed in other settings.[13,20,23,26,27] The aim of this study, therefore, was to determine whether MMT reduces mortality in HIV+ people who inject opioids and are receiving ART through China's national ART programme.

Methods

The study involved a nationwide cohort of HIV+ people injecting opioids who received ART between 31 December 2002 and 31 December 2011. In accordance with World Health Organization recommendations,[28] the current eligibility criterion for ART in China is a CD4+ T-lymphocyte (CD4+ cell) count below 350 cells/μL; before 2008, it was a count below 200 cells/μL. In China, recommended first-line ART regimens for all eligible HIV+ patients, including those injecting opioids, involve combinations of zidovudine, stavudine, lamivudine, nevirapine and efavirenz.[29] Criteria for enrolment in MMT have been described previously.[6] Programme guidelines suggest an initial methadone dose of no more than 50 mg per day for all patients, which is subsequently adjusted as appropriate.[30]

Eligibility for inclusion in this study was simply having been enrolled in China's national ART programme at any time between 31 December 2002 and 31 December 2011. Individuals were excluded from the study if one of the following applied: (i) during medical or police registration, he or she reported acquiring an HIV infection through a transmission route other than opioid injection; (ii) ART had been received before the start of the study period; or (iii) the start date for ART was missing from the individual's records in the ART programme data system. Participants were divided into two subgroups depending on whether or not they had received MMT at any time during ART: the ART + MMT subgroup and the ART-only subgroup, respectively. Those who initiated and discontinued MMT before receiving ART were included in the ART-only subgroup. Active drug users were not identified separately in either subgroup.

Data collection

The data for this study were obtained from the real-time, web-based data system[31] of the Chinese National Center for AIDS/STD Control and Prevention, which contains three interlinked, but independently operated, data subsystems: (i) the ART-for-adults subsystem; (ii) the HIV/AIDS case reporting subsystem; and (iii) the MMT subsystem. All HIV+ individuals who met the appropriate eligibility criterion for ART described above[29] and who received ART via the national ART programme were registered in the ART-for-adults data subsystem. This subsystem contains identification and demographic data for all patients and detailed information on their ongoing clinical management and ART, including the drugs used, the doses administered and HIV viral load.[32] Staff at local Center for Disease Control and Prevention facilities track all individuals who have tested positive for HIV in China using the national HIV/AIDS case reporting data subsystem. Records created in this subsystem contain identification data, detailed demographic data and information on health status, health history and survival.[31] All opioid-dependent individuals who take part in China's national MMT programme are registered and tracked in the MMT data subsystem. Client records contain identification and demographic data and are updated daily with information on methadone treatment.[6] Data on all individuals included in this study were initially obtained from the ART data subsystem. Then, that information was supplemented with data from the HIV/AIDS case reporting subsystem. Finally, additional data were obtained from the MMT data subsystem on all study subjects with records in that subsystem. The data sets in each subsystem were linked using unique, national, 15- or 18-digit Chinese citizen identification numbers.

An intent-to-treat approach was adopted for exposure to both ART and MMT. Thus, subjects were regarded as having received ART or MMT if they had been given at least one dose of an ART drug or methadone, respectively, regardless of their level of adherence or treatment duration. All subjects included in the final study cohort were followed through the ART programme and the observation time was the time between the date of ART initiation and one of three outcomes: (i) the end of the study (i.e. the patient was still alive and receiving ART); (ii) death while on ART; or (iii) discontinuation of ART or loss to follow-up. A subject was categorized as having discontinued ART or being lost to follow-up if no follow-up data had been recorded for more than 3 months. However, although their records in the ART data subsystem were not up to date, these patients could still be tracked through the HIV/AIDS case reporting data subsystem for events such as death. The outcome of interest in the study was all-cause mortality.

Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables are described using medians and interquartile-ranges (IQRs). Statistical tests were not used to compare the characteristics of subgroups because the large sample sizes resulted in the detection of statistically significant differences that were probably not clinically meaningful. Rather, a difference greater than 5% between subgroups was considered meaningful. The observation time was presented in person–years. The mortality rate was calculated as the total number of deaths divided by the total observation time, both overall and in different study subpopulations. Risk factors for mortality were examined using Cox proportional hazards regression analysis. Factors identified as having a significant influence on mortality on univariate analysis (i.e. $P < 0.05$) and factors known to be clinically meaningful were included in multivariate regression models, from which adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained. Although missing data are presented in the tables, all analyses were run using only cases for which data were complete. All P-values presented are two-sided and $P < 0.05$ was indicative of statistical significance. Differences in mortality rates over time were calculated by dividing the total number of subjects who died in each 6-month interval by the sum of the individual observation times for subjects followed up during the corresponding interval. All statistical analyses were performed using SAS v. 9.1.3 software (SAS Institute, Cary, United States of America).

Ethics approval

This study was reviewed and approved by the institutional review board of the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention. As all data included here were collected during the regular administration of China's national ART and MMT programmes and since all participants in these programmes provided signed informed consent at the time of enrolment, no further informed consent was sought.

Results

The ART-for-adults data subsystem contained records on a total of 152 749 patients for the period from 31 December 2002 to 31 December 2011. Of these patients, 128 607 (84.2%) were excluded because their HIV infection was acquired through a route other than opioid injection. An additional 293 patients (< 0.1%) were excluded because they were not ART-naïve when they enrolled in the ART programme. Finally, 36 patients (< 0.1%) were excluded because the ART start date was missing from their records in the ART-for-adults subsystem. Thus, the final cohort consisted of 23 813 HIV+ ART patients who injected opioids.

Of the 23 813 patients, 18 652 (78.3%) were assigned to the ART-only subgroup because they did not receive MMT during the study period. It should be noted that 906 patients in this subgroup had started and discontinued MMT before ART. The ART + MMT subgroup included 5161 participants (21.7% of 23 813) who had enrolled in both ART and MMT programmes concurrently at some time during the study period. Of this subgroup, 3335 (64.6% of 5161) were enrolled in the MMT programme before ART initiation: they had been in the MMT programme for a median of 1.20 years (IQR: 0.40–2.43) and had enrolled at a median age of 33.8 years (IQR: 30.3–37.8). An additional 669 patients (13.0% of 5161) began MMT less than 6 months after initiating ART and 1157 (22.4% of 5161) began MMT more than 6 months after ART.

As shown in Table 1, the median age of participants in our study cohort was 34.0 years (IQR: 30.0–39.0 years). The majority were male (87.6%), Han Chinese (54.1%), had been educated to middle school level or higher (52.1%) and were married or cohabitating (54.1%). At the time of ART initiation (i.e. ART baseline), the median CD4+ cell count in study participants was 177.0 cells/μL (IQR: 80.0–264.0) and the median haemoglobin concentration was 13.4 g/dL (IQR: 11.5–15.0). A large proportion of patients (48.3%) were receiving a regimen that contained zidovudine, lamivudine, and nevirapine or efavirenz and 64.0% were being treated in a general hospital. By the end of the study, 16 321 patients (68.5%) were still alive and receiving ART, 3057 (12.8%) had died while still in the ART programme and 4435 (18.6%) had discontinued their ART regimen or were lost to follow-up.

Differences between subgroups

We observed several differences greater than 5% in demographic characteristics between the ART + MMT and ART-only subgroups (Table 1). Compared with members of the ART-only subgroup, fewer patients in the ART + MMT subgroup belonged to an ethnic minority (28.6 versus 35.7%), had been educated to a primary school level or lower (27.1 versus 36.2%) and were married or cohabiting (45.2 versus 56.5%). In addition, the ART + MMT subgroup contained a greater proportion of patients with a CD4+ cell count above 200 cells/μL at ART baseline (46.6 versus 40.2%) and a greater proportion who were being treated at the Center for Disease Control and Prevention clinics (19.5 versus 12.3%).

As shown in Table 2, 3057 deaths were identified over 41 959 person–years of observation time, which corresponds to an overall mortality rate of 7.3 per 100 person–years (95% CI: 7.0–7.5) in our cohort of HIV+ people injecting opioids who received ART. The highest mortality rates were observed in individuals with a haemoglobin level below 9 g/dL (17.5 per 100 person–years; 95% CI: 15.9–19.2) and those with a CD4+ cell count at ART baseline below 50 cells/μL (12.0 per 100 person–years; 95% CI: 11.2–12.7). A total of 2519 deaths were identified over 30 558 person–years of observation time in our ART-only subgroup, which corresponds to a mortality rate of 8.2 per 100 person–years (95% CI: 7.9–8.6). By contrast, only 538 deaths occurred in 11 401 person–years of observation time in our ART + MMT subgroup, which corresponds to a mortality rate of 4.7 per 100 person–years (95% CI: 4.3–5.1). Fig. 1 shows the change in mortality rate over time in the two subgroups. At 6 months after ART baseline, mortality in the ART-only subgroup was over twofold greater than in the ART + MMT subgroup: 16.9 versus 6.6 per 100 person–years, respectively. The difference becomes smaller at 12 months (7.4 versus 3.7 per 100 person–years) and disappears thereafter.

Factors affecting survival

The results of the multivariate analysis carried out to identify risk factors for death among study participants are shown in Table 2. Factors significantly associated with an increased risk of death include: older age; male sex; being single, divorced or widowed; a CD4+ cell count of 200 cells/μL or less at ART baseline; a baseline haemoglobin level of 12 g/dL or less; being treated at a Center for Disease Control and Prevention clinic; and not participating in the MMT programme.

Discussion

Our main finding is that MMT reduced the risk of death in HIV+ people injecting opioids who were receiving ART, particularly in the first 6 months of treatment: during this period, study participants receiving only ART had a mortality rate more than twice as high as those receiving ART and MMT (16.9 versus 6.6 per 100 person–years, respectively). The primary reasons for lower mortality in those receiving MMT are thought to be: (i) better adherence to the ART regimen due to regular, daily contact with health-care workers at methadone clinics; (ii) reduced active opioid injection; and (iii) the stabilizing effect of methadone on behaviour associated with opioid injection, which promotes social reintegration. These factors have already been well documented in a variety of settings.[14,19,20,33–35]

The literature also supports our finding that a low CD4+ cell count at the start of ART is a strong independent predictor of death.[10,12] A low baseline CD4+ cell count, which indicates advanced immunosuppression, is a concern for all patients in China's national ART programme.[15] It is interesting to note that the median CD4+ cell count at ART baseline was higher in our ART + MMT subgroup than in the ART-only subgroup (192 versus 172 cells/μL, respectively), though the difference was not large. This observation indicates that people who were injecting opioids and were engaged in the MMT programme often enrolled in the ART programme at an earlier stage of HIV infection. Thus, participation in China's national MMT programme may mitigate the increased risk of death in people injecting opioids in China. In addition, China's national MMT programme is helping these people to overcome the many barriers they face in engaging with and remaining in the ART programme.[12] Regular, often daily, interactions with health-care providers in the MMT programme:

Table 1. **People injecting opioids who were infected with the human immunodeficiency virus and received antiretroviral therapy (ART), with or without methadone maintenance treatment (MMT), China, 2002–2011**

Characteristic	No. (%) of participants		
	All	ART only	ART + MMT
Demographic characteristic			
Age, years			
15–29	4 574 (19.2)	3 642 (19.5)	932 (18.1)
30–39	14 265 (59.9)	11 114 (59.6)	3151 (61.1)
≥ 40	4 974 (20.9)	3 896 (20.9)	1 078 (20.9)
Median (IQR), years	34.0 (30.0–39.0)	34.0 (30.0–39.0)	35.0 (31.0–39.0)
Gender			
Male	20 868 (87.6)	16 436 (88.1)	4 432 (85.9)
Female	2 945 (12.4)	2 216 (11.9)	729 (14.1)
Ethnicity			
Han Chinese	12 892 (54.1)	9 555 (51.2)	3 337 (64.7)
Ethnic minority	8 126 (34.1)	6 652 (35.7)	1 474 (28.6)
Missing data	2 795 (11.7)	2 445 (13.1)	350 (6.8)
Educational level			
Primary school or lower	8 154 (34.2)	6 754 (36.2)	1 400 (27.1)
Middle school or higher	12 416 (52.1)	9 156 (49.1)	3 260 (63.2)
Missing data	3 243 (13.6)	2 742 (14.7)	501 (9.7)
Marital status			
Single, divorced or widowed	10 796 (45.3)	7 989 (42.8)	2 807 (54.4)
Married or cohabitating	12 876 (54.1)	10 543 (56.5)	2 333 (45.2)
Missing data	141 (0.6)	120 (0.6)	21 (0.4)
Clinical characteristic at ART initiation			
CD4+ cell count (cells/μL)			
< 50	3 927 (16.5)	3 359 (18.0)	568 (11.0)
50–200	9 265 (38.9)	7 157 (38.4)	2 108 (40.8)
> 200	9 907 (41.6)	7 503 (40.2)	2 404 (46.6)
Missing data	714 (3.0)	633 (3.4)	81 (1.6)
Median (IQR)	177.0 (80.0–264.0)	172.0 (73.0–262.0)	192.0 (109.5–267.0)
Haemoglobin concentration (g/dL)			
< 9	1 515 (6.4)	1 239 (6.6)	276 (5.3)
9–12	5 131 (21.5)	4 047 (21.7)	1 084 (21.0)
> 12	15 485 (65.0)	11 981 (64.2)	3 504 (67.9)
Missing data	1 682 (7.1)	1 385 (7.4)	297 (5.8)
Median (IQR)	13.4 (11.5–15.0)	13.4 (11.5–15.1)	13.4 (11.7–14.8)
ART			
Treatment regimen			
Zidovudine, lamivudine and nevirapine or efavirenz	11 495 (48.3)	8 890 (47.7)	2 605 (50.5)
Stavudine, lamivudine and nevirapine or efavirenz	9 271 (38.9)	7 261 (38.9)	2 010 (38.9)
Other or missing data	3 047 (12.8)	2 501 (13.4)	546 (10.6)
Treatment facility			
Infectious disease hospital	3 739 (15.7)	2 970 (15.9)	769 (14.9)
General hospital	15 237 (64.0)	12 007 (64.4)	3 230 (62.6)
CDC clinic	3 290 (13.8)	2 286 (12.3)	1004 (19.5)
Other or missing data	1 547 (6.5)	1 389 (7.4)	158 (3.1)
Follow-up status			
Main outcome			
Alive and still on ART	16 321 (68.5)	12 590 (67.5)	3 731 (72.3)
Died while on ART	3 057 (12.8)	2 519 (13.5)	538 (10.4)
Discontinued ART	4 435 (18.6)	3 543 (19.0)	892 (17.3)
Total	23 813 (100.0)	18 652 (100.0)	5 161 (100.0)

CDC, Chinese Center for Disease Control and Prevention; IQR, interquartile range.
[a] All values in the table represent absolute numbers and percentages unless otherwise stated.

Table 2. **Risk factors for death in people injecting opioids and infected with human immunodeficiency virus who received antiretroviral therapy, with or without methadone maintenance treatment, China, 2002–2011**

Characteristic	No. (%) of participants[a]	No. (%) of deaths	Person–years of observation	Mortality rate[b] (95% CI)	Multivariate analysis[c]	
					Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Demographic characteristic						
Age, years						
15–29	4 574 (19.2)	507 (16.6)	8 857	5.7 (5.2–6.2)	1.0	1.0
30–39	14 265 (59.9)	1 913 (62.6)	25 836	7.4 (7.1–7.7)	1.3 (1.1–1.4)	1.4 (1.2–1.6)
≥ 40	4 974 (20.9)	637 (20.8)	7 267	8.8 (8.1–9.4)	1.4 (1.2–1.6)	1.6 (1.4–1.9)
Gender						
Male	20 868 (87.6)	2 777 (90.8)	36 497	7.6 (7.3–7.9)	1.5 (1.3–1.7)	1.8 (1.6–2.1)
Female	2 945 (12.4)	280 (9.2)	5 463	5.1 (4.5–5.7)	1.0	1.0
Ethnicity						
Han Chinese	12 892 (61.3)	1 620 (69.1)	24 927	6.5 (6.2–6.8)	1.2 (1.1–1.3)	1.0 (0.9–1.1)
Other	8 126 (38.7)	726 (30.9)	12 504	5.8 (5.4–6.2)	1.0	1.0
Educational level[d]						
Primary school or lower	8 154 (39.6)	782 (34.2)	12 062	6.5 (6.0–6.9)	1.0	NA
Middle school or higher	12 416 (60.4)	1 503 (65.8)	24 210	6.2 (5.9–6.5)	1.0 (0.9–1.1)	NA
Marital status						
Single, divorced or widowed	10 796 (45.6)	1 625 (53.3)	19 404	8.4 (8.0–8.8)	1.3 (1.2–1.4)	1.5 (1.3–1.6)
Married or cohabiting	12 876 (54.4)	1 421 (46.7)	22 398	6.3 (6.0–6.7)	1.0	1.0
Clinical characteristic at ART initiation						
CD4+ cell count (cells/μL)						
< 50	3 927 (17.0)	967 (32.5)	8 067	12.0 (11.2–12.7)	2.8 (2.5–3.0)	1.8 (1.5–2.0)
50–200	9 265 (40.1)	1 302 (43.7)	18 490	7.0 (6.7–7.4)	1.6 (1.4–1.7)	1.4 (1.2–1.5)
> 200	9 907 (42.9)	709 (23.8)	14 729	4.8 (4.5–5.2)	1.0	1.0
Haemoglobin concentration (g/dL)						
< 9	1 515 (6.8)	452 (16.1)	2 577	17.5 (15.9–19.2)	3.6 (3.2–4.0)	3.2 (2.8–3.7)
9–12	5 131 (23.2)	999 (35.7)	9 491	10.5 (9.9–11.2)	2.2 (2.0–2.4)	2.1 (1.9–2.3)
> 12	15 485 (70.0)	1 351 (48.2)	27 569	4.9 (4.6–5.2)	1.0	1.0
ART						
Treatment regimen						
Zidovudine, lamivudine and nevirapine/efavirenz	11 495 (55.4)	1 097 (41.3)	16 146	6.8 (6.4–7.2)	1.0	1.0
Stavudine, lamivudine and nevirapine/efavirenz	9 271 (44.6)	1 560 (58.7)	20 766	7.5 (7.1–7.9)	1.3 (1.2–1.4)	0.9 (0.8–1.0)
Treatment facility						
Infectious disease hospital	3 739 (16.8)	448 (15.2)	7 698	5.8 (5.3–6.4)	1.0	1.0
General hospital	15 237 (68.4)	1 908 (64.6)	25 777	7.4 (7.1–7.7)	1.2 (1.1–1.3)	2.2 (1.9–2.5)
CDC clinic	3 290 (14.8)	598 (20.2)	6 138	9.7 (9.0–10.5)	1.6 (1.4–1.9)	3.0 (2.5–3.6)
Study subgroup						
MMT programme participation						
No (ART-only subgroup)	18 652 (78.3)	2 519 (82.4)	30 558	8.2 (7.9–8.6)	1.6 (1.5–1.8)	1.4 (1.3–1.6)
Yes (ART + MMT subgroup)	5 161 (21.7)	538 (17.6)	11 401	4.7 (4.3–5.1)	1.0	1.0
Total	28 813 (100.0)	3 057 (100.0)	41 959	7.3 (7.0–7.5)	NA	NA

ART, antiretroviral therapy; CDC, Center for Disease Control and Prevention; CI: confidence interval; HR: hazard ratio; MMT, methadone maintenance treatment; NA, not applicable.

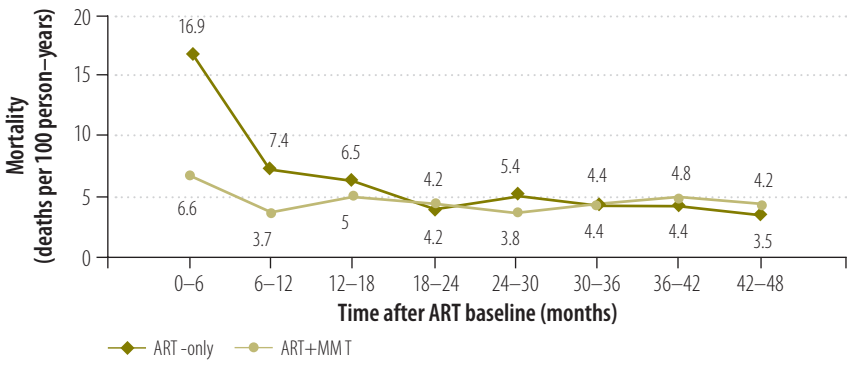
[a] The analyses involved only study participants for whom complete data were available.

[b] Per 100 person–years.

[c] Cox proportional hazards regression analysis.

[d] Some variables were not included in the regression analysis and, consequently, no results are presented for them. 95% CIs were calculated on assumption of a Poisson distribution.

Fig. 1. **Mortality in people injecting opioids and infected with the human immunodeficiency virus who received antiretroviral therapy (ART), with or without methadone maintenance treatment (MMT), by time from ART initiation, China, 2002–2011**



(i) promote the cessation of injecting drug use; (ii) increase adherence to the ART regimen; (iii) ensure regular monitoring of the CD4+ cell count; and (iv) increase opportunities for discussing treatment options, for managing medication side-effects and comorbid conditions and for psychosocial counselling.[20,34,36,37] Thus, the higher CD4+ cell counts we found at ART baseline in patients receiving ART and MMT were not unexpected.

Our finding that a low haemoglobin level at ART initiation is a strong predictor of death has also been reported previously in the literature.[38,39] Anaemia is known to be an independent predictor of death and disease progression in patients with HIV/AIDS.[39–41]

Because of the way China's healthcare system is structured, the national ART programme provides treatment for HIV infection through a variety of channels, such as hospitals specializing in infectious diseases, general hospitals and local Center for Disease Control and Prevention facilities. We found that the type of facility providing treatment was an independent predictor of death in HIV+ people injecting opioids who were receiving ART in China. This observation is consistent with the results of a previous study in China, which showed that the type of facility providing care for HIV+ patients was associated with their survival probability.[11] Although this previous study involved patients living in rural areas who were not injecting illicit drugs (as opposed to ours, which only included those who were injecting opioids in urban settings), it confirms that treatment outcomes vary in accordance with the type of facility. In the present study, mortality was lowest among patients treated at infectious disease hospitals. We believe this was probably because specialized doctors and staff with better training and more experience in providing ART were available, monitoring was more effective, and the facility was located in a better-equipped urban setting.

Our study had several limitations. First, because it was a descriptive, observational study, no inferences about causality can be made. Second, although we attempted to reduce the influence of confounding variables by using multivariate analysis, there remains a risk of confounding by unmeasured variables. For example, seropositivity for hepatitis C virus and depressive symptoms are known to be poor prognostic factors for patients with HIV/AIDS and may have influenced our results.[19] Third, the categorization of ART recipients as opioid injectors was based on patients' self-reported history of opioid use at the time their HIV infection was detected. Hence, some participants may have been inappropriately excluded from our final cohort due to information bias. Fourth, the missing values for some variables in our data set could have resulted in an under- or overestimation of mortality rates and of the importance of associated risk factors. Finally, although ART and MMT providers follow guidelines published by the Chinese Ministry of Health, their clinical decisions are not standardized and may be influenced by, for example, the provider's potentially biased opinions about poor compliance among drug users. Despite these limitations, the generalizability and reproducibility of our findings are likely to be high because the study involved a large cohort of participants drawn from a national treatment programme.

In summary, our finding that ART and MMT had a joint beneficial effect on mortality in Chinese HIV+ people injecting opioids suggests that there is an urgent need for changes in ART and MMT programmes. Cross-referrals between these programmes should be encouraged so that a greater proportion of people who inject opioids can benefit from receiving the two treatments. An even better approach may be to house ART and MMT care services at the same location – a model that has already proved to be more effective worldwide, both clinically and in terms of cost.[14,23,27,42–44] The next step in reducing barriers to treatment and in improving poor outcomes in HIV+ people who inject illicit drugs in China should be to study the feasibility of integrating ART and MMT services. ■

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ملخص

العلاج الصياني بالميثادون ومعدل الوفيات لدى الأشخاص الإيجابيين لفيروس العوز المناعي البشري الذين يتعاطون المواد الأفيونية المفعول عن طريق الحقن في الصين

الغرض دراسة تأثير العلاج الصياني بالميثادون (MMT) على معدل الوفيات لدى الأشخاص الذين يتعاطون المواد الأفيونية المفعول عن طريق الحقن الذين يتلقون العلاج بمضادات الفيروسات القهقرية (ART) لعلاج عدوى فيروس العوز المناعي البشري (HIV) في الصين.

الطريقة تضمنت الدراسة فئة من الأتراب، على الصعيد الوطني عددها 23813 شخصاً إيجابياً لفيروس العوز المناعي البشري، ويتعاطون المواد الأفيونية المفعول عن طريق الحقن وتلقوا العلاج بمضادات الفيروسات القهقرية في الفترة من 31 كانون الأول/ ديسمبر 2002 إلى 31 كانون الأول/ ديسمبر 2011. وتم إجراء مقارنة لمعدلات الوفيات والخصائص الديمغرافية والمرضية والعلاجية لدى المرضى الذين تلقوا إما العلاج بمضادات الفيروسات القهقرية والعلاج الصياني بالميثادون أو العلاج بمضادات الفيروسات القهقرية فقط. وتم تحديد العوامل المرتبطة بمعدل الوفيات من خلال تحليل أحادي المتغيرات ومتعدد المتغيرات.

النتائج بشكل عام، وقعت 3057 حالة وفاة خلال 41959 شخص-سنوات متابعة (معدل الوفيات: 7.3 لكل 100 شخص-سنوات؛ فاصل الثقة 95 ٪، فاصل الثقة: من 7.0 إلى 7.5) وانخفض معدل الوفيات بعد بدء العلاج بمضادات الفيروسات القهقرية بستة أشهر إلى حد كبير عند استخدام العلاج بمضادات الفيروسات القهقرية والعلاج الصياني بالميثادون عنه عند استخدام مضادات الفيروسات القهقرية فقط (6.6 مقابل 16.9 لكل 100 شخص-سنوات، على التوالي؛ الاحتمال < 0.001). وبعد 12 شهراً، كان معدل الوفيات 3.7 و7.4 لكل 100 شخص-سنوات في الفئتين، على التوالي (الاحتمال < 0.001). وكان عدم تلقي العلاج الصياني بالميثادون عاملاً مستقلاً من عوامل التكهن بالمرض (نسبة المخاطر المصححة: 1.4؛ فاصل الثقة 95 ٪: من 1.3 إلى 1.6) وكانت عوامل التكهن الأخرى هي انخفاض مستوى الهيموغلوبين وانخفاض إحصاء الخلايا اللمفاوية التائية المساعدة (CD4+) عند بدء العلاج بمضادات الفيروسات القهقرية والعلاج في المرافق بخلاف مستشفيات الأمراض المعدية.

الاستنتاج ستزداد استفادة المرضى من برامج العلاج الصياني بالميثادون وعلاج فيروس العوز المناعي البشري جميعها وسيواجهون عدداً أقل من العقبات التي تحول بينهم وبين الرعاية في حالة تعزيز الإحالات المتبادلة بين البرامج وجعل العلاج بمضادات الفيروسات القهقرية في نفس مواقع العلاج الصياني بالميثادون.

摘要

中国注射阿片类药物的艾滋病阳性人群美沙酮维持治疗和死亡率

目的 调查美沙酮维持治疗（MMT）对中国接受治疗艾滋病毒（HIV）感染的抗逆转录病毒疗法（ART）的注射阿片类药物人群死亡率的影响。

方法 研究涉及2002 年12 月31 日至2011 年12 月31 日之间在全国范围内接受ART治疗的23813 名艾滋病阳性（HIV +）注射阿片类药物人者。比较接受ART和MMT治疗或仅接受ART治疗的患者的死亡率和人口学、疾病和治疗特点。使用单因素和多因素分析确定与死亡率相关的因素。

结果 总体而言，在随访的41959 人年中发生3057 例死亡（死亡率：每百人年7.3 例；95%置信区间：7.0-7.5）。在开始ART治疗6 个月之后，接受ART和MMT治疗的死亡率显著低于仅接受ART治疗的死亡率（两者每百人年分别为6.6 和16.9；P < 0.001）。12 个月后，这两组中的死亡率分别是每百人年3.7 和 7.4（P < 0.001）。没有接受MMT治疗是一个独立的死亡预测因素（调整后的风险比：1.4；95%置信区间：1.3-1.6）。其他的预测因素是开始ART治疗时的低血红蛋白水平和低CD4 +淋巴细胞计数以及在非传染病医院之外的设施治疗。

结论 如果MMT和HIV治疗计划之间的转诊有所改善，将ART和MMT服务设在一起，患者就会从MMT和HIV治疗计划中都得到更大好处，护理障碍也会更少。

Résumé

Thérapie de maintien à la méthadone et mortalité chez les personnes séropositives qui s'injectent des opioïdes en Chine

Objectif Examiner l'effet du traitement de maintien à la méthadone (TMM) sur la mortalité des usagers d'opioïdes par injection, qui reçoivent des antirétroviraux (ARV) pour le traitement de l'infection par le virus de l'immunodéficience humaine (VIH) en Chine.

Méthodes L'étude a porté sur une cohorte nationale de 23 813 participants séropositifs (VIH+) s'injectant des opioïdes et ayant reçu des ARV entre le 31 décembre 2002 et le 31 décembre 2011. Les taux de mortalité et les caractéristiques démographiques, pathologiques et thérapeutiques ont été comparés chez les patients ayant reçu des ARV et un TMM ou uniquement des ARV. Les facteurs associés à la mortalité ont été identifiés à l'aide d'une analyse univariée et multivariée.

Résultats Au cours des 41 959 personnes-années de suivi, un total de 3 057 décès a été enregistré (mortalité: 7,3 par 100 personnes-années; intervalle de confiance de 95 %, IC:7,0-7,5). La mortalité constatée 6 mois après le début des ARV était significativement plus faible avec ARV et TMM qu'avec ARV uniquement (6,6 contre 16,9 par 100 personnes-années, respectivement; P < 0,001). Après 12 mois, la mortalité était de 3,7 et 7,4 par 100 personnes-années dans les deux groupes, respectivement (P < 0,001). Le fait de n'avoir pas reçu de TMM était un prédicteur indépendant de décès (rapport de risques ajusté: 1,4, IC de 95 %: 1.3-1,6). Les autres prédicteurs étaient un faible niveau d'hémoglobine et une numération basse des lymphocytes CD4+ T en début d'ARV, ainsi qu'un traitement dans des installations autres que des hôpitaux spécialisés dans les maladies infectieuses.

Conclusion Les patients tireraient meilleur profit des programmes de traitement TMM et VIH et rencontreraient moins d'obstacles aux soins si des aiguillages croisés interprogrammes étaient encouragés et si les services ARV et TMM étaient disponibles au même endroit.

Резюме

Метадоновая поддерживающая терапия и смертность среди потребителей инъекционных опиоидных препаратов в Китае

Цель Исследовать влияние метадоновой поддерживающей терапии (МПТ) на смертность среди потребителей инъекционных опиоидных препаратов, получающих антиретровирусную терапию (АРТ) для лечения инфекции вируса иммунодефицита человека (ВИЧ) в Китае.

Методы Исследование включало общенациональную группу из 23 813 ВИЧ-инфицированных (ВИЧ-положительных) потребителей инъекционных опиоидных препаратов, которые получали АРТ в период между 31 декабря 2002 г. и 31 декабря 2011 г. Уровни смертности и демографические данные, характеристики заболевания и лечения сопоставлялись с данными пациентов, получавших либо АРТ и МПТ, либо только АРТ. Факторы, связанные со смертностью, определялись однофакторным и многофакторным анализом.

Результаты В целом, в течении 41 959 человеко-лет наблюдений зарегистрировано 3 057 смертельных исходов (смертность: 7,3 на 100 человеко-лет; 95% доверительный интервал, ДИ: 7,0-7,5). Смертность спустя шесть месяцев после начала АРТ значительно снизилась при получении АРТ и МПТ по сравнению только с АРТ (6,6 против 16,9 на 100 человеко-лет соответственно; P < 0,001). Спустя 12 месяцев уровень смертности составлял 3,7 и 7,4 на 100 человеко-лет в двух группах соответственно (P < 0,001). Неполучение МПТ являлось независимым предиктором смерти (скорректированное соотношение рисков: 1,4; 95% ДИ: 1,3-1,6). Другими предикторами являлись низкий уровень гемоглобина и низкое количество CD4+ Т-лимфоцитов при проведении АРТ и лечении в учреждениях, отличных от инфекционных больниц.

Вывод Для пациентов более благоприятны программы, сочетающие МПТ и ВИЧ-терапию, и при наличии перекрестного направления пациентов на программы и расположения служб АРТ и МПТ в одном помещении они сталкивались бы с меньшими препятствиями для лечения.

Resumen

El tratamiento de mantenimiento con metadona en seropositivos que se inyectan opiáceos en China

Objetivo Examinar el efecto del tratamiento de mantenimiento con metadona (TMM) sobre la mortalidad de personas que se inyectan opiáceos y reciben una terapia antirretroviral (TAR) para tratar la infección del virus de la inmunodeficiencia humana (VIH) en China.

Métodos El estudio incluyó una cohorte a nivel nacional de 23 813 personas seropositivas (VIH+) que se inyectaban opiáceos y que recibieron TAR entre el 31 de diciembre de 2002 y el 31 de diciembre de 2012. Se compararon las tasas de mortalidad y demografía, las características de las enfermedades y de los tratamientos con pacientes que recibieron TAR y TMM o sólo TAR y, por medio de análisis univariantes y multivariantes, se identificaron los factores asociados con la mortalidad.

Resultados En total se produjeron 3057 fallecimientos durante los 41 959 años-persona de seguimiento (mortalidad: 7,3 por cada 100 años-persona; intervalo de confianza del 95%, CI: 7,0 - 7,5). La mortalidad una vez transcurridos 6 meses después de iniciar la TAR fue notablemente inferior con TAR y TMM que sólo con TAR (6,6 frente a 16,9 por cada 100 años-persona, respectivamente; P < 0,001). Tras 12 meses, la mortalidad en los dos grupos fue de 3,7 y 7,4 por cada 100 años-persona, respectivamente (P < 0,001). No haber recibido TMM fue un factor predictivo de muerte independiente (índice de riesgo ajustado: 1,4; IC del 95%: 1,3–1,6). Otros factores predictivos fueron un nivel bajo de hemoglobina y un recuento bajo de linfocitos CD4+ al comenzar la TAR, así como llevar a cabo el tratamiento en centros que no fueran hospitales de enfermedades infecciosas.

Conclusión Los pacientes podrían aprovechar mejor los programas de TMM y de tratamiento del VIH y no tendrían que hacer frente a tantas barreras para obtener el tratamiento si se promovieran las referencias cruzadas entre ambos programas y se ubicaran los servicios de TAR y TMM en el mismo lugar.

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