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METHADONE MAINTENANCE THERAPY PROMOTES INITIATION OF ANTIRETROVIRAL THERAPY AMONG INJECTION DRUG USERS

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Abstract

Aims—Despite proven benefits of antiretroviral therapy (ART), many HIV-infected injection drug users (IDU) do not access treatment even in settings with free health care. We examined whether methadone maintenance therapy (MMT) increased initiation and adherence to ART among an IDU population with free health care.

Design—We prospectively examined a cohort of opioid-using antiretroviral-naïve HIV-infected IDU and investigated factors associated with initiation of antiretroviral therapy as well as subsequent adherence. Factors independently associated with time to first initiation of antiretroviral therapy were modelled using Cox proportional hazards regression.

Findings—Between May 1996 and April 2008, 231 antiretroviral-naïve HIV-infected opioid using IDU were enrolled, among whom 152 (65.8%) initiated ART, for an incidence density of 30.5 (95% confidence interval [CI]: 25.9–35.6) per 100 person-years. After adjustment for time-updated clinical characteristics and other potential confounders, use of MMT was independently associated with more rapid uptake of antiretroviral therapy (relative hazard = 1.62 [95% CI: 1.15–2.28]; $p = 0.006$). Those prescribed methadone also had higher rates of ART adherence after first antiretroviral initiation (odds ratio = 1.49 [95% CI: 1.07–2.08]; $p = 0.019$).

Conclusion—These results demonstrate that MMT contributes to more rapid initiation and subsequent adherence to ART among opioid-using HIV-infected IDU. Addressing international barriers to the use and availability of methadone may dramatically increase uptake of HIV treatment among this population.

Keywords

HIV; AIDS; methadone; ART; Vancouver; Canada

INTRODUCTION

Since the mid-1990s, there have been major advances in the medical management of HIV disease [1]. In particular, antiretroviral therapies have been shown to suppress plasma HIV

RNA to undetectable levels, and in turn substantial reductions in HIV-related morbidity and mortality have been documented among persons receiving antiretroviral therapy (ART) [2,3]. More recently, the Strategies for Management of Antiretroviral Therapy (SMART) trial demonstrated that earlier ART initiation was associated with significantly decreased AIDS-related opportunistic infections and death [4]. This prompted a revision of international therapeutic guidelines to recommend treating all asymptomatic HIV-infected individuals before CD4+ cell counts fall below 350/ μ L, which highlights the need for strategies that can promote earlier use of ART [5]. Despite these benefits, the clinical management of HIV disease continues to present major challenges. High levels of adherence are required to durably suppress viral replication [6], and incomplete adherence has been associated with virological failure and the rapid emergence of antiretroviral resistance [7].

In this context, the epidemiology of HIV infection among injection drug users (IDU) continues to be a global public health concern [8]. The Joint United Nations Programme on HIV/AIDS estimates that one-third of new HIV infections outside of sub-Saharan Africa are attributable to injection drug use [9]. In North America, injection drug use accounts for approximately one in four cases of HIV [8], and in some areas where HIV is spreading most rapidly, such as Eastern Europe and Central Asia, more than 80% of all HIV cases occur among IDU [9]. In turn, as the HIV epidemic has matured among this population, large and growing numbers of HIV-infected injection drug users are in need of ART [10–12].

At present, the provision of optimal care to HIV-infected IDU is a major challenge [13] since injection drug use has been associated with both non-adherence to ART and more rapid HIV disease progression [14,15]. Difficulties also stem from the fact that IDU often exhibit several characteristics, such as homelessness, incarceration, and untreated psychiatric illness, which may severely complicate ART delivery [16–18]. One potential avenue for improving access to ART is methadone maintenance therapy (MMT), which has been shown to improve adherence to ART in earlier studies [19,20]. However, methadone remains illegal in some settings, including Russia, despite being on the World Health Organization's (WHO) list of essential medicines [21]. Despite the known association between methadone and antiretroviral adherence, we know of no prospective studies involving antiretroviral-naïve IDU to assess the potential role of methadone in improving initiation of ART. This remains an important clinical question, given the large proportion of IDU who die without ever receiving HIV treatment [22]. Therefore, we conducted the present study using a cohort of antiretroviral-naïve HIV-infected IDU to investigate whether exposure to methadone maintenance therapy increased initiation and subsequent adherence to ART.

METHODS

Data for these analyses were collected through a prospective cohort study of HIV-positive illicit drug users, which has been described in detail previously [20]. In brief, the AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS) was created to study issues related to access to HIV/AIDS care among HIV-infected IDU [23,24]. Beginning in May 1996, participants were recruited through self-referral and street outreach from Vancouver's Downtown Eastside. At baseline and semi-annually, all participants complete an interviewer-administered questionnaire. The questionnaire elicits demographic data as well as information about participants' drug use, including information about type of drug, frequency of drug use, involvement in drug treatment, and periods of abstinence. All participants provide informed consent and are remunerated \$20 (CAD) for each study visit. Ethical approval has been provided annually by the University of British Columbia's Research Ethics Board.

The primary endpoint of interest in the present analysis was time to first antiretroviral therapy (ART) use among participants who were HIV-positive opioid users. The setting is somewhat unusual in that there is a centralized province-wide antiretroviral dispensation program, and a confidential record linkage allows for accurate ascertainment of HIV-related outcomes, including the exact date of ART initiation as well as subsequent adherence [25,26]. Therefore, participants could be followed even if they missed a follow-up appointment at the study's research office. In order to restrict the analyses to individuals who were medically eligible for methadone, participants were eligible for the present study if they reported use of heroin at baseline or during follow-up. Since we were interested in the role of methadone in promoting use of ART, individuals were further eligible if they were antiretroviral-naïve at baseline and had a CD4+ cell count measure within one year of recruitment to allow for control of ART eligibility.

To present the sample characteristics, baseline characteristics of study participants stratified by enrolment in MMT at baseline were analyzed using Pearson's Chi-square test (or Fisher's exact test if at least one of the cells had expected counts less than five). Explanatory variables considered included: age (≤ 24 years vs. > 24 years); gender (female vs. male); ethnicity (Aboriginal vs. non-Aboriginal); involvement in the sex trade in the past six months (yes vs. no); daily cocaine use (yes vs. no); daily heroin use (yes vs. no); any injection drug use in the past six months (yes vs. no); plasma HIV-1 viral load ($< 100\,000$ copies/mL vs. $\geq 100\,000$ copies/mL); and CD4+ cell count (< 200 cells/mm³ vs. ≥ 200 cells/mm³). The cut-off age of twenty-four was used in our analysis as this is the upper age limit of "youth" conventionally used in United Nations publications [27], and all other variable definitions were identical to earlier studies [28,29]. The baseline characteristics of study participants are shown in Table 1.

As an initial analysis, the time to the initiation of ART among those participants receiving or not receiving MMT at baseline was examined using Kaplan-Meier analyses. In addition, Cox regression was used to model the time to first ART use. Unless otherwise noted, all variables refer to the six-month period prior to the interview and the multivariate model treated all behavioural variables, including MMT enrolment, as time-updated based on each semiannual follow-up visit.

Finally, we investigated if methadone treatment was associated with antiretroviral adherence levels after ART initiation. Here, we used the same model building protocol as above, and used generalized estimating equation (GEE) logistic regression to determine factors associated with $\geq 95\%$ antiretroviral adherence during each semi-annual follow-up period based on prescription refill compliance [30]. We have previously shown how adherence defined in this way predicts HIV-RNA suppression and patient survival [25,31]. All statistical analyses were performed using SAS 9.1 (SAS, Cary, NC). All *p*-values are two-sided. The final models were fit using an *a priori* defined model-building approach in which we adjusted for all variables that were statistically significant at the $p < 0.05$ level in the univariate analyses.

RESULTS

Between May 1996 and April 2008, 709 HIV-infected participants were recruited for this study, among whom 457 (64.5%) had never been on ART at baseline. Of these 457, 231 (50.5%) participants reported heroin injection and had at least one CD4+ count within 12 months of recruitment, and were therefore eligible for the present study.

The characteristics of the overall study population stratified by MMT enrolment at baseline are shown in Table 1. As shown here, 55 (23.8%) of study participants were receiving MMT

at baseline, and statistical comparisons demonstrated that age ($p = 0.999$), ethnicity ($p = 0.135$), sex-trade involvement ($p = 0.654$), daily cocaine use ($p = 0.066$), daily heroin use ($p = 0.115$), plasma HIV-1 RNA viral load ($p = 0.237$), and CD4+ cell count ($p = 0.312$) did not differ significantly between the two groups. Women, however, were more likely to be receiving MMT at baseline compared to men ($p = 0.009$). Among the 153 non-Aboriginal participants, 11 were Asian, 3 were black, 136 were white, and 3 were other.

Initiation Rate of ART (Kaplan-Meier Analyses)

As of April 2008, 152 (65.8%) of 231 participants had initiated ART, for an incidence density of 30.5 (95% confidence interval [CI]: 25.9–35.6) per 100 person-years. As shown in Figure 1, at 24 months after recruitment, the Kaplan-Meier cumulative incidence rate was 64.2% among those who were on MMT at baseline and 44.8% among those who were not on MMT at baseline (log-rank $p = 0.004$).

Predictors of ART Initiation (Cox Regression Analyses)

Table 2 shows the unadjusted and adjusted relative hazards (RH) for factors associated with initiation of ART. In the univariate analysis, plasma viral load $\geq 100\,000$ copies/mL (RH = 2.34 [95% CI: 1.63–3.36]; $p < 0.001$), CD4+ cell count < 200 cells/mm³ (RH = 2.30 [95% CI: 1.53–3.47]; $p < 0.001$), and methadone use (RH = 1.75 [95% CI: 1.26–2.43]; $p < 0.001$) were each significantly associated with more rapid uptake of ART. After adjusting for plasma viral load and CD4+ cell count, those participants on MMT initiated ART at a significantly elevated rate (RH = 1.62 [95% CI: 1.15–2.28]; $p = 0.006$).

When we examined factors associated with 95% adherence among the 152 (65.8%) individuals who initiated ART during the study period, MMT was independently associated with antiretroviral adherence in GEE logistic regression (odds ratio [OR] = 1.49 [95% CI: 1.07–2.08]; $p = 0.019$) after adjustment for age (OR = 1.04 [95% CI: 1.01–1.07]; $p = 0.008$), gender (OR = 0.63 [95% CI: 0.40–1.00]; $p = 0.051$), daily cocaine use (OR = 0.80 [95% CI: 0.58–1.10]; $p = 0.176$) and daily heroin use (OR = 0.60 [95% CI: 0.44–0.82]; $p = 0.002$). In post-hoc analyses that adjusted for additional potential confounders, we found that adjustment for methamphetamine use, age as continuous variable, and homelessness did not significantly affect our estimates.

DISCUSSION

The present study demonstrates that, among a community-recruited sample of antiretroviral-naïve opioid-using HIV-infected IDU, those who used MMT initiated ART at an elevated rate compared to those not receiving MMT. Additionally, those individuals on MMT had increased subsequent adherence to antiretroviral therapy. To our knowledge, this is the first study of antiretroviral-naïve HIV-infected IDU to examine the possible role of MMT on time to initiation of ART and subsequent antiretroviral adherence. Given the many barriers these individuals face in accessing appropriate HIV treatment [32], MMT appears to be an effective and under-utilized strategy for increasing access to care.

MMT is increasingly recognized as the standard of care for opioid-addicted HIV-infected IDU and has previously been associated with improved adherence to ART [33,34], as well as with decreased viral loads and increased CD4+ cell counts [20]. Importantly, use of methadone has also been associated with more regular monitoring of CD4+ cell counts, an important factor in timing ART initiation [35]. While the mechanisms that explain these findings are likely multifactorial and involve both physician and patient characteristics, having patients enrolled in MMT allows regular contact with the health care system and allows for programs such as directly observed administration of ART [36]. Enrolment in

MMT may also address previous negative experiences with health care providers and can allow monitoring and adjustment of ART treatment. Finally, the stabilizing effect of methadone may allow for counselling and intervention to address traditional barriers, such as mental health concerns and psychosocial factors such as homelessness and poverty [37]. Importantly, active drug use should not be a contraindication to receiving ART, as MMT can still offer improved adherence in this setting [19].

The well established benefits of MMT have led the World Health Organization to recommend the integration of opioid substitution therapies in its HIV treatment guidelines for IDU, even in resource-limited settings [38]. As well, methadone is currently on the WHO's list of essential medicines [21]. Despite these recommendations, methadone and other opioid substitution therapies, such as buprenorphine, are often not offered, provided in a suboptimal fashion, or are illegal in several of the countries where injection-related HIV epidemics are currently occurring [39,40]. The limited availability of methadone in many areas in Eastern Europe and south-east Asia (where IDU make up a large proportion of new HIV infections) is of particular concern [39]. Because the Asian HIV epidemic is concentrated in identifiable subgroups such as IDU, and given that MMT may improve uptake of ART, these regions' efforts to control the epidemic could be furthered by increasing access to MMT to opioid injectors [41]. However, it is important to stress that issues with methadone access are also relevant to North America. A paper by Friedman et al. estimated that treatment coverage for IDU in 96 metropolitan areas of the United States ranged from 1% to 39%, with a median of only 9% [42]. Importantly, the US has the highest rates of HIV of any industrialized country, and more than half of the incident infections in the United States occur among IDU or their sexual partners [43].

It is also noteworthy that a growing proportion of HIV infections among IDU are attributable to stimulant rather than opioid injection [44]. This trend is of notable concern given that there remains no gold standard substitution therapy for stimulant users [45]. Obviously, given the success of methadone as a treatment for opioid dependence [46] as well as its apparent role in improving uptake and adherence to ART, the search for a suitable substitution therapy candidate for stimulant users is an urgent ongoing priority.

The present study has limitations. Since this is an observational study, the association of MMT and more rapid initiation of ART must be interpreted with caution. For instance, the effect of methadone on uptake of ART may be as a result of inherent differences between those who used methadone and those who did not rather than the effect of methadone. However, there are several reasons why we believe this relationship to be causal. First, in Vancouver, Canada, where the study was conducted, methadone is often daily dispensed with antiretroviral drugs as a strategy to achieve high rates of adherence. Second, dispensing methadone affords more regular contact with the healthcare system. Third, ready access to methadone decreases the time-consuming routine of obtaining opioids, and the money to pay for them, which allows more time for individuals to focus on personal health [46]. In this regard, we should note that a randomized trial to assess the impact of MMT use on subsequent antiretroviral initiation would not be ethical, given the known benefits of MMT in reducing drug-related harms. Nevertheless, an area for future research should be to examine how the quality of MMT programmes affects access and adherence to ART.

In summary, MMT leads to greater initiation of ART among HIV-infected opioid-dependent IDU as well as higher subsequent antiretroviral adherence. These results underscore the importance of providing MMT to opioid-dependent HIV-infected IDU as a strategy to address the ongoing HIV epidemic among this population. MMT should be an essential component of any campaign to curb HIV infection in this population, and policies and

regulations restricting access to MMT should be repealed in favour of more evidence-based strategies.

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Figure 1. Time to antiretroviral therapy (ART) initiation among a prospective cohort of HIV-infected injection drug users, stratified by baseline enrolment in methadone maintenance therapy (MMT).

Table 1

Baseline demographic characteristics of IDU stratified by methadone use.

Characteristic	No methadone <i>n</i> = 176 (%)	Methadone <i>n</i> = 55 (%)	Odds Ratio (95% CI)	<i>p</i> value
Age				
≤ 24 years	14 (8)	4 (7)		
> 24 years	162 (92)	51 (93)	1.1 (0.4–3.5)	0.999
Gender				
Male	112 (64)	24 (44)		
Female	64 (36)	31 (56)	2.3 (1.2–4.2)	0.009
Ethnicity				
Non-Aboriginal	112 (64)	41 (75)		
Aboriginal	64 (36)	14 (25)	0.6 (0.3–1.2)	0.135
Sex trade involved*				
No	124 (70)	37 (67)		
Yes	52 (30)	18 (33)	1.2 (0.6–2.2)	0.654
Cocaine use*				
Daily use	89 (51)	20 (36)	0.6 (0.3–1.0)	0.066
Less than daily	87 (49)	35 (64)		
Heroin use*				
Daily use	95 (54)	23 (42)	0.6 (0.3–1.1)	0.115
Less than daily	81 (46)	32 (58)		
Viral load (copies/mL)				
< 100 000	122 (69)	35 (64)		
≥ 100 000	42 (24)	18 (33)	1.5 (0.8–2.9)	0.237
CD4 count (cells/mm³)				
< 200	28 (16)	12 (22)	1.5 (0.7–3.1)	0.312
≥ 200	148 (84)	43 (78)		

Note:

* Indicates behaviour during the six-month period prior to the baseline interview.

Univariate and multivariate Cox proportional hazard analyses of antiretroviral therapy initiation among 231 opioid injection drug users.

Table 2

Variable	Unadjusted Relative Hazard (RH)			Adjusted ^{**} Relative Hazard (RH)		
	RH	(95% CI)	p-value	RH	(95% CI)	p-value
Age						
(> 24 yrs. vs. ≤ 24 yrs.)	0.99	(0.50–1.95)	0.972			
Gender						
(Female vs. Male)	1.08	(0.78–1.49)	0.629			
Ethnicity						
(Aboriginal vs. other)	0.85	(0.60–1.20)	0.350			
Sex trade involved[*]						
(Yes vs. no)	1.18	(0.81–1.72)	0.390			
Cocaine use[†]						
(Daily vs. not daily)	1.10	(0.79–1.53)	0.569			
Heroin use[†]						
(Daily vs. not daily)	0.94	(0.67–1.30)	0.692			
IV drug use[*]						
(Yes vs. no)	0.99	(0.54–1.82)	0.967			
Viral load (copies/mL)						
(≥ 100 000 vs. < 100 000)	2.34	(1.63–3.36)	<0.001	1.87	(1.26–2.78)	0.002
CD4+ count (cells/mm³)						
(< 200 vs. ≥ 200)	2.30	(1.53–3.47)	<0.001	1.93	(1.22–3.04)	0.005
Methadone Use						
(Yes vs. no)	1.75	(1.26–2.43)	<0.001	1.62	(1.15–2.28)	0.006
Other addiction treatment[‡]						
(Yes vs. no)	1.32	(0.90–1.93)	0.159			

* Behaviours refer to activities in the last six months.

[†] Indicates current use.

^{**} Model was fitted adjusting for all variables significant in unadjusted analyses.

[‡] Defined as drug treatment other than methadone in the past six months.