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Methadone Maintenance Therapy Decreases the Rate of Antiretroviral Therapy Discontinuation Among HIV-Positive Illicit Drug Users

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Abstract

We sought to examine whether methadone maintenance therapy (MMT) decreased rates of antiretroviral therapy (ART) discontinuation and was associated with plasma HIV RNA responses among a cohort of illicit drug users. Cumulative ART discontinuation rates were estimated using Kaplan–Meier methods and factors independently associated with ART discontinuation were identified using Cox proportional hazards regression. Engagement in MMT was negatively and independently associated with ART discontinuation [Adjusted Relative Hazard = 0.67 (95 % CI 0.54–0.83); $p < 0.001$]. Among participants receiving ART and MMT, 81.6 % of plasma HIV-1 RNA assessments were <500 copies/mL, while 65.81 % of HIV-1 RNA assessments among those prescribed ART without MMT were <500 copies/mL ($p < 0.001$). These results demonstrate that engagement in MMT conferred a protective benefit against ART discontinuation and was associated with a significant increase in plasma HIV RNA suppression among HIV-infected opioid-dependent drug users.

Keywords

HIV; Drug use; Antiretroviral therapy; Methadone; Discontinuation

INTRODUCTION

Since the mid-1990s, the advent of antiretroviral therapy (ART) has led to substantial reductions in morbidity and mortality among illicit drug users living with HIV/AIDS [1, 2]. Treatment effectiveness relies, however, upon high and sustained levels of medication adherence, which can present challenges for patients [3, 4]. Many treatment regimens are complex, with varying dosing protocols, dietary restrictions and potential adverse side

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effects [5]. While some recent treatments have alleviated these issues by decreasing pill burden, sustained adherence is required for durable viral suppression, as well as the prevention of antiretroviral resistance and disease progression [6–8].

Despite the documented benefits of ART, several previous studies have demonstrated that HIV-infected drug users face barriers to healthcare and optimal treatment outcomes as a result of social instability related to illicit drug addiction, as well as the pervasive stigma experienced by this population [9–13]. ART use may be complicated due to the high prevalence of homelessness, incarceration, and untreated psychiatric illness among people who use illicit drugs [13–15]. As such, drug users are known to have lower uptake of ART compared to other HIV-positive individuals and are more likely to die without ever having received treatment [16]. In addition to challenges related to ART access, drug users also face barriers that preclude adherence to HIV treatment. These barriers have been observed even in those settings where HIV care is delivered free of charge and where drug users do not face financial barriers to treatment. In Vancouver, Canada, where ART is provided free of charge, up to 50 % of drug users discontinue ART prematurely, and among those drug users who remain engaged in treatment, 60 % have suboptimal levels of adherence [17–19]. Accordingly, disparities in HIV-related mortality have been observed due to problems with access to ART and/or poor retention in HIV-related treatment among illicit drug users [20].

Several recent studies have indicated improved access and adherence to treatment among drug users when ART is delivered in conjunction with methadone maintenance therapy (MMT) [21–23]. However, we know of no prospective studies examining the effect of engagement in MMT on the risk of discontinuation of ART. Given the ongoing problem of ART discontinuation and the associated clinical sequelae potentiated by ART discontinuation, we undertook the present study to evaluate the impact of MMT use on ART discontinuation among a cohort of HIV-positive drug users in a setting of universal access to HIV care and treatment.

METHODS

Study Participants

The data for this investigation were collected through a prospective cohort of HIV-positive illicit drug users, which has been described in detail previously [23]. Briefly, the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) is an open prospective cohort of HIV-seropositive illicit drug users in Vancouver, Canada. The cohort was populated through snowball sampling and extensive street outreach methods in the city's Downtown Eastside, the local epicenter of injection drug use and drug-related HIV infection [24]. Individuals are eligible for ACCESS if they are aged ≥18 years, are HIV seropositive, have a history of illicit drug use and provide written informed consent. Participants answer a standardized interviewer-administered questionnaire and provide blood samples for disease monitoring at baseline and at every 6-month follow-up visit. The questionnaire elicits detailed demographic data, as well as information pertaining to drug use patterns and related exposures, and blood sampling provides a prospective clinical profile, including plasma HIV-1 RNA viral load and CD4+ cell counts for every participant. All participants provide informed consent and are remunerated $20 (CAD) for each study visit and, when

appropriate, are referred to additional healthcare services, including addiction treatment. Ethical approval is provided annually by the University of British Columbia/Providence Health Care Research Ethics Board.

HIV/AIDS Drug Treatment Program

In our setting, antiretroviral therapy and HIV clinical monitoring are available free of cost to all HIV-infected residents of British Columbia. Participants can fill their initial 4-week prescription and subsequent 3-to 4-month prescriptions for ART at any pharmacy in the province. Furthermore, there is a province-wide centralized antiretroviral dispensation program and a HIV/AIDS laboratory, which enables a complete prospective profile of all patient CD4 cell count determinations, plasma HIV-1 RNA levels (as measured by Amplicor Monitor assay, Roche Molecular Systems, Mississauga, Canada), and antiretroviral therapy use among cohort participants. This consists of the specific antiretroviral agents prescribed, as well as a previously validated measure of patient adherence derived from prescription refill compliance [14, 25]. In addition to antiretroviral therapy, methadone is provided free of charge under the provincial healthcare program and offered primarily through pharmacies, doctor offices, and clinics. Within BC and throughout Canada, standard pharmacotherapy for opioid dependence involves oral solution methadone, a long lasting synthetic opioid agonist that is prescribed by licensed physicians, while pharmacists witness daily ingestion [26]. Given that sustained adherence to methadone has been shown to decrease the risk of relapse and mortality, a treatment philosophy emphasizing indefinite maintenance of MMT has become widely accepted in Canadian settings [27]. Similar to antiretrovirals, the centralized provincial drug dispensation database permits analysis of dosing patterns among all patients [26]. The universal healthcare system enables the examination of HIV-related outcomes in a setting where financial barriers to health care and HIV treatment are largely eliminated.

Outcome Variables

For the current analysis, individuals were eligible if they reported being on ART at the time of recruitment or if they subsequently initiated ART during the study period. Since we were interested in the effect of MMT, individuals also had to be on MMT at baseline or opioid-using at baseline or during follow-up. In previous studies involving drug users in our setting, adherence to ART has been defined as the number of days ART was dispensed over the number of days an individual was eligible for ART. Non-adherence refers to less than 95 % adherence to ART during this period. In the present study, we looked at discontinuation of ART, which is defined as a ≥90 day period without receiving any antiretrovirals [17]. If a patient died within 3 months of treatment discontinuation, they were censored out of the analysis at the date of death and defined as a non-event. Since we were interested in the impact of MMT, the primary independent variable of interest was MMT in the past 6 months. Any self-report of MMT treatment (a single dose to 100 % adherence) in the last 6 months was classified as MMT participation. The reference category for this variable was no report of enrollment in MMT in the past 6 months. Within Cox regression analyses, individuals could move from being on MMT in one 6 month period and then off in the next 6 month period. This method allowed for the identification of factors associated with the outcome over the entire study period adjusted by multiple observations for each individual.

As each individual could report MMT use or not during different study visits, the analyses identified factors correlated with periods of MMT use both within and between individuals.

Statistical Analyses

As a first step, cumulative ART discontinuation rates, stratified by MMT enrolment, were estimated using Kaplan–Meier methods. Survival curves were compared using the log-rank test. We then generated bivariate Cox regression analyses to identify predictors of ART discontinuation. We were aware that confounding may have persisted if the rate of discontinuation differed between participants enrolled in ART at varying stages of disease progression, or among those who engaged in higher risk behaviors or who were potentially at higher risk of ART discontinuation as a result of other individual-level differences. Therefore, we considered secondary explanatory variables that may be related to methadone engagement or antiretroviral treatment patterns. These included age (per year older); gender (female vs. male); Aboriginal ancestry (yes vs. no); engagement in MMT (yes vs. no); homelessness (yes vs. no); binge drug use (yes vs. no); sex work involvement (yes vs. no); at least daily heroin injection (yes vs. less) and at least daily cocaine injection (yes vs. less). All drug-related and behavioral variables refer to behaviors in the past 6 months, and were time-updated based on data from the semi-annual follow-up visits. Further, all behavioral variables were lagged in our analyses in order to protect against reverse causality. Specifically, we employed measures of our time-updated independent variables of interest in our model from interviews that occurred prior to ART discontinuation. We also considered the following clinical variables: baseline CD4 cell count (cells/μL, per 100-cell increase), baseline plasma HIV-1 RNA ($\log_{10}$/μL, per $\log_{10}$ increase), date of initiating MMT (per years later) and physician experience. In line with a previous analysis in this setting, an HIV-experienced physician was defined as one who had previously enrolled six or more individuals into the HIV treatment registry at the time the participant initiated treatment [7]. Inclusion of this variable is warranted given that physician experience with HIV-infected patients is associated with improved survival [28]. Since participants were continuously enrolled in the treatment program during the study period, a physician could become ‘experienced’ over time. However, the experience level assigned to each participant was determined based on their physician’s HIV-related experience at the time of the participant’s first interview.

To account for possible confounding, we constructed a multivariate Cox regression model using a priori-defined modelling strategy proposed by Maldonado and Greenland [29]. As a first step, we fit a model that included the primary explanatory variable and all secondary explanatory variables. In a manual stepwise manner, we removed one secondary variable at a time to construct reduced models. The value of the coefficient for the primary explanatory in the full model was compared to each of the reduced models. We removed the secondary explanatory that corresponded to the smallest relative change. This process was continued until the maximum change from the full model exceeded 5 %. The objective of this procedure is to retain secondary covariates with a greater relative influence on the relationship between the outcome and the explanatory variable of interest in the final model. Several studies have successfully used this technique to estimate the relationship between an outcome of interest and a selected explanatory variable [29–31].

As a sub-analysis, we conducted an attributable risks analysis to examine the incidence of ART discontinuation for those on and off MMT and we compared the proportion of HIV-1 RNA observations <500 copies/mL for those on and off MMT. All statistical analyses were performed using SAS software version 9.2 (SAS, Cary, NC, USA). All tests of significance were two-sided, with a *p* value of less than 0.05 indicating that an association was statistically significant.

RESULTS

Between May 1996 and April 2008, we recruited 574 HIV-positive illicit drug users, of whom 408 (71.0 %) were ART-exposed at baseline or initiated treatment during follow-up and were included in this study. Of these, 164 (40.2 %) were women and 150 (36.8 %) individuals reported Aboriginal ancestry. The median age of participants at baseline was 39 years (Interquartile range: 33–45) and those engaged in MMT were similar to those not engaged in MMT with respect to gender ($p = 0.080$) and Aboriginal ancestry ($p = 0.202$). Participants contributed 940 observations over the study period, and 526 ART discontinuations were observed among 257 (63 %) participants for a cumulative incidence of 70.6 % (95 % CI 65.8–75.3 %). Among those engaged in ART, the average duration of enrolment was 15.34 months (IQR 3.70–19.73). There were 91 deaths for an incidence rate estimate of 17 per 100 person years (95 % CI 13.81–21.03).

Figure 1 shows the Kaplan–Meier estimates of the cumulative therapy discontinuation rate for the overall cohort stratified by engagement in MMT. As shown here, the cumulative incidence rate was significantly elevated among those not engaged in MMT (log-rank $p < 0.001$). By 24 months after ART initiation, the cumulative incidence rate of ART discontinuation was 42.62 per 100 person-years (95 % CI 33.10–52.14) among those engaged in MMT and 71.42 per 100 person-years (95 % CI 59.42–83.43) for those not engaged in MMT. Additionally, the proportion of participants on MMT to never discontinue their ART was 53 % compared to 67 % among those not on MMT.

Table 1 shows the crude and adjusted relative hazards (RH) of treatment discontinuation. As indicated here, in bivariate analyses, homelessness (RH = 1.72, 95 % CI 1.26–2.35; $p < 0.001$), binge drug use (RH = 1.34, 95 % CI 1.03–1.74; $p = 0.031$), sex work involvement (RH = 1.51, 95 % CI 1.10–2.07; $p = 0.011$), daily heroin injection (RH = 2.00, 95 % CI 1.48–2.70; $p < 0.001$), daily cocaine injection (RH = 1.69, 95 % CI 1.29–2.22; $p < 0.001$) and a higher viral load (RH = 1.18, 95 % CI 1.11–1.24; $p < 0.001$) were associated with shorter time to ART discontinuation. Conversely, participation in MMT (RH = 0.60, 95 % CI 0.43–0.72; $p < 0.001$) date of therapy initiation (RH = 0.89, 95 % CI 0.85–0.92; $p < 0.001$) and age (RH = 0.95, 95 % CI 0.94–0.97; $p < 0.001$) were negatively associated with ART discontinuation in bivariate analyses. The multivariate analysis is also shown in Table 1 and reveals that engagement in MMT (RH = 0.58, 95 % CI 0.44–0.76; $p < 0.001$) was independently and negatively associated with ART discontinuation after adjustment for year of initiation, CD4+ cell count, viral load and gender. The attributable risk analyses revealed that non-use of MMT increased the incidence rate of ART discontinuation by 28.80 cases per 100 person-years.

In a sub-analysis, among 1076 viral load assessments of 198 participants receiving ART and MMT, 878 (81.6 %) of plasma HIV-1 RNA assessments were <500 copies/mL compared to 718 (65.81 %) of 1091 plasma HIV-1 RNA assessments <500 copies/mL among those prescribed ART without MMT ($p < 0.001$).

DISCUSSION

In the present analyses, we observed a high rate of ART discontinuation among HIV-positive drug users. However, participants engaged in MMT had significantly lower rates of ART discontinuation compared to those not engaged in MMT. MMT enrollment remained independently and negatively associated with treatment discontinuation in multivariate analyses that adjusted for a range of potential confounders. These findings translated into higher rates of plasma HIV RNA undetectability among those patients prescribed MMT.

Although MMT has previously been shown to enhance access and adherence to ART, to our knowledge this is the first study to report a positive effect of MMT in preventing ART discontinuation and subsequent plasma HIV RNA responses. These findings are encouraging given that antiretroviral non-adherence has been associated with elevated mortality [7, 32]. While the mechanisms that explain the association between MMT and ART discontinuation are likely to be multifaceted, it seems likely that MMT is having a direct effect in terms of reducing discontinuation of ART in this setting [21]. First, being enrolled in MMT allows more regular contact with the health care system and related programs including the co-administration of ARVs with daily dispensed MMT [33]. Second, the stabilizing effect of MMT may facilitate supportive counseling and other interventions to address barriers to adherence, such as co-occurring mental illness and other psychosocial concerns [34]. Third, enrollment in MMT may provide opportunities for monitoring and adjustment of ART [21]. Fourth, engagement in MMT has been shown to reduce the risk of incarceration, which has been shown to be strongly associated with premature discontinuation of ART, as well as non-adherence [35, 36]. Prior analyses of treatment interventions that address the common psychological and medical co-morbidities of drug use highlight the need for multifaceted and interdisciplinary treatment delivery systems to HIV-infected drug users [37]. Given that MMT may provide a means of enhancing uptake and adherence to ART while reducing rates of discontinuation, concurrent delivery of MMT and antiretrovirals should be an essential component of prospective treatment interventions to optimize health outcomes among drug users who are eligible for this therapy. Given the relationship between MMT and higher rates of plasma HIV RNA undetectability, these findings have implications for the recently identified role of ART as a HIV prevention strategy [38].

The beneficial effect of MMT for HIV-positive opioid users observed in this study also highlights unaddressed HIV-related treatment challenges faced by illicit stimulant users [39, 40]. Although this study examined the impact of cocaine use, recent reports have shown that participants using other stimulants are likely to have sub-optimal levels of adherence, and a growing proportion of HIV infections are attributable to stimulants [41, 42]. This issue is of particular concern since no analogous substitution therapy is available to stimulant users. Given the success of MMT as a treatment for opioid dependence [43], and its role in

improving adherence to ART, the search for effective addiction treatments for stimulant users is an urgent priority, as is removing other barriers to optimal HIV treatment outcomes.

The present study has limitations. First, like most other cohort studies involving high-risk drug users, ACCESS is not a random sample. Therefore, our study findings may not generalize well to the larger population of HIV-positive drug users in Vancouver. Second, we relied on self-reported measures, which may have introduced response biases into our results, such as socially desirable reporting. Although the reliability of self-reporting drug related behaviours has been validated previously [44], socially desirable reporting of high-risk and stigmatized behaviors and problems with recall remain concerns [45, 46]. However, we note that engagement in ART was measured based on prescription refill compliance rather than self-report. Third, ART was co-administered with MMT in some cases while other patients received each medication from separate facilities. It is possible that the co-administration of these treatments could impact ART discontinuation and confound the results. Additional analyses that measure the proportion of patients who receive these treatments in conjunction would provide insight into this matter. Fourth, the data regarding length of enrolment in MMT was not available but this did not prevent us from assessing the impact of current MMT enrolment on ART discontinuation, which was the primary objective of the analysis. Lastly, since this is an observational study the results presented must be interpreted with caution. For instance, the negative association between MMT and ART discontinuation may have resulted from unmeasured differences between those who used MMT and those who did not, rather than the effect of MMT itself. Yet, as prior investigations have indicated, there is reason to suggest that this relationship is causal: [1] the study was conducted in a setting where MMT is often dispensed daily with antiretroviral drugs as a means of improving adherence; [2] dispensing MMT facilitates routine contact with the health care system; and [3] the accessibility of MMT decreases the time and money necessary to procure other opioids, which allows more time for individuals to focus on personal health [21, 43].

In summary, we found that engagement in MMT confers a protective benefit against ART discontinuation among HIV-infected opioid-dependent drug users and that these results translated into higher rates of plasma HIV RNA undetectability. These results underscore the importance of providing MMT to opioid-dependent HIV-infected drug users as a strategy to address sub-optimal HIV treatment outcomes. Concurrent delivery of MMT and ART should be a fundamental component of efforts to reduce HIV-related morbidity and mortality among opioid-dependent drug users.

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REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investig N Engl J Med. 1998; 338(13):853.
2. Hogg RS, Yip B, Kully C, Craib KJ, O'Shaughnessy MV, Schechter MT, et al. Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. CMAJ. 1999; 160(5):659–665. [PubMed: 10102000]
3. Mannheimer SB, Matts J, Telzak E, Chesney M, Child C, Wu AW, et al. Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. AIDS Care. 2005; 17(1):10–22. [PubMed: 15832830]
4. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. J Acquir Immune Defic Syndr. 2001; 28(1):47. [PubMed: 11579277]
5. Ferguson TF, Stewart KE, Funkhouser E, Tolson J, Westfall AO, Saag MS. Patient-perceived barriers to antiretroviral adherence: associations with race. AIDS Care. 2002; 14(5):607–617. [PubMed: 12419110]
6. Deeks SG. Treatment of antiretroviral-drug-resistant HIV-1 infection. Lancet. 2003; 362(9400): 2002–2011. [PubMed: 14683662]
7. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? AIDS. 2003; 17(5): 711. [PubMed: 12646794]
8. Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, Sheiner L, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS. 2000; 14(4):357. [PubMed: 10770537]
9. Wood E, Kerr T, Montaner JSG. HIV treatment, injection drug use, and illicit drug policies. Lancet. 2007; 370(9581):8–10. [PubMed: 17617253]
10. Lert F, Kazatchkine MD. Antiretroviral HIV treatment and care for injecting drug users: an evidence-based overview. Int J Drug Policy. 2007; 18(4):255–261. [PubMed: 17689373]
11. Aceijas C, Oppenheimer E, Stimson GV, Ashcroft RE, Matic S, Hickman M. Antiretroviral treatment for injecting drug users in developing and transitional countries 1 year before the end of the "Treating 3 million by 2005. making it happen The WHO strategy" ("3 by 5"). Addiction. 2006; 101(9):1246–1253. [PubMed: 16911723]
12. Poundstone KE, Chaisson RE, Moore RD. Differences in HIV disease progression by injection drug use and by sex in the era of highly active antiretroviral therapy. AIDS. 2001; 15(9):1115–1123. [PubMed: 11416713]
13. Ding L, Landon BE, Wilson IB, Wong MD, Shapiro MF, Cleary PD. Predictors and consequences of negative physician attitudes toward HIV-infected injection drug users. Arch Intern Med. 2005; 165(6):618–623. [PubMed: 15795336]
14. Wood E, Montaner JS, Yip B, Tyndall MW, Schechter MT, O'Shaughnessy MV, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. CMAJ. 2003; 169(7):656–661. [PubMed: 14517122]
15. Treisman GJ, Angelino AF, Hutton HE. Psychiatric issues in the management of patients with HIV infection. JAMA. 2001; 286(22):2857–2864. [PubMed: 11735762]
16. Wood E, Montaner JS, Tyndall MW, Schechter MT, O'Shaughnessy MV, Hogg RS. Prevalence and correlates of untreated human immunodeficiency virus type 1 infection among persons who have died in the era of modern antiretroviral therapy. J Infect Dis. 2003; 188(8):1164–1170. [PubMed: 14551887]
17. Wood E, Montaner JS, Braitstein P, Yip B, Schechter MT, O'Shaughnessy MV, et al. Elevated rates of antiretroviral treatment discontinuation among HIV-infected injection drug users: implications for drug policy and public health. Int J Drug Pol. 2003; 15(2):133–138.
18. Kerr T, Marshall A, Walsh J, Palepu A, Tyndall M, Montaner J, et al. Determinants of HAART discontinuation among injection drug users. AIDS Care. 2005; 17(5):539. [PubMed: 16036240]

19. Kerr T, Palepu A, Barness G, Walsh J, Hogg R, Montaner J, et al. Psychosocial determinants of adherence to highly active antiretroviral therapy among injection drug users in vancouver. Antivir Ther. 2004; 9(3):407. [PubMed: 15259903]
20. Wood E, Montaner JS, Bangsberg DR, Tyndall MW, Strathdee SA, O'Shaughnessy MV, et al. Expanding access to HIV antiretroviral therapy among marginalized populations in the developed world. AIDS. 2003; 17(17):2419–2427. [PubMed: 14600512]
21. Uhlmann S, Milloy MJ, Kerr T, Zhang R, Guillemi S, Marsh D, et al. Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users. Addiction. 2010; 105(5):907–913. [PubMed: 20331553]
22. Roux P, Carrieri MP, Villes V, Dellamonica P, Poizot-Martin I, Ravaux I, et al. The impact of methadone or buprenorphine treatment and ongoing injection on highly active antiretroviral therapy(HAART) adherence: evidence from the MANIF 2000 cohort study. Addiction. 2008; 103(11):1828–1836. [PubMed: 18778390]
23. Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. Drug Alcohol Depend. 2006; 84(2):188–194. [PubMed: 16542797]
24. Strathdee SA, van Ameijden EJ, Mesquita F, Wodak A, Rana S, Vlahov D. Can HIV epidemics among injection drug users be prevented? AIDS. 1998; 12(Suppl A):S71. [PubMed: 9632987]
25. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4(+) cell count is 0.200 to 0.350 × 10(9) cells/L. Ann Intern Med. 2003; 139(10):810–816. [PubMed: 14623618]
26. Nosyk B, Marsh DC, Sun H, Schechter MT, Anis AH. Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996–2006. J Subst Abuse Treat. 2010; 39(1):22–31. [PubMed: 20418051]
27. Caplehorn JR, Dalton MS, Cluff MC, Petrenas AM. Retention in methadone maintenance and heroin addicts' risk of death. Addiction. 1994; 89(2):203–209. [PubMed: 8173486]
28. Kitahata MM, Koepsell TD, Deyo RA, Maxwell CL, Dodge WT, Wagner EH. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. N Engl J Med. 1996; 334(11):701–706. [PubMed: 8594430]
29. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993; 138(11):923–936. [PubMed: 8256780]
30. Lima V, Fernandes K, Rachlis B, Druyts E, Montaner J, Hogg R. Migration adversely affects antiretroviral adherence in a population-based cohort of HIV/AIDS patients. Soc Sci Med. 2009; 68(6):1044–1049. [PubMed: 19157668]
31. Marshall BD, Kerr T, Shoveller JA, Patterson TL, Buxton JA, Wood E. Homelessness and unstable housing associated with an increased risk of HIV and STI transmission among street-involved youth. Health Place. 2009; 15(3):753–760. [PubMed: 19201642]
32. Hogg RS, Heath KV, Bangsberg D, Yip BPN, O'Shaughnessy MVMJS. Intermittent use of triple combination therapy is predictive of mortality at baseline and after one year of follow-up. AIDS. 2002; 16(7):1051. [PubMed: 11953472]
33. Berg KM, Mouriz J, Li X, Duggan E, Goldberg U, Arnsten JH. Rationale, design, and sample characteristics of a randomized controlled trial of directly observed antiretroviral therapy delivered in methadone clinics. Contemp Clin Trials. 2009; 30(5):481–489. [PubMed: 19505589]
34. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). Int J Drug Policy. 2007; 18(4):262–270. [PubMed: 17689374]
35. Werb D, Kerr T, Marsh D, Li K, Montaner J, Wood E. Effect of methadone treatment on incarceration rates among injection drug users. Eur Addict Res. 2008; 14(3):143. [PubMed: 18552490]
36. Milloy MJ, Kerr T, Buxton J, Rhodes T, Guillemi S, Hogg R, et al. Dose-response effect of incarceration events on nonadherence to HIV antiretroviral therapy among injection drug users. J Infect Dis. 2011; 203(9):1215–1221. [PubMed: 21459814]

37. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet. 2010; 376(9738):367–387. [PubMed: 20650518]
38. Novitsky V, Essex M. Using HIV viral load to guide treatment-for-prevention interventions. Curr Opin HIV Aids. 2012; 7(2):117–124. [PubMed: 22258501]
39. Arnsten JH, Demas PA, Grant RW, Gourevitch MN, Farzadegan H, Howard AA, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. J Gen Intern Med. 2002; 17(5):377–381. [PubMed: 12047736]
40. Sharpe TT, Lee LM, Nakashima AK, Elam-Evans LD, Fleming PL. Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women. J Community Health. 2004; 29(2):117–127. [PubMed: 15065731]
41. DeBeck K, Kerr T, Li K, Fischer B, Buxton J, Montaner J, et al. Smoking of crack cocaine as a risk factor for HIV infection among people who use injection drugs. Can Med Assoc J. 2009; 181(9):5.
42. Hinkin CH, Barclay TR, Castellon SA, Levine AJ, Durvasula RS, Marion SD, et al. Drug use and medication adherence among HIV-1 infected individuals. AIDS Behav. 2007; 11(2):185–194. [PubMed: 16897351]
43. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009; (2):CD002209. [PubMed: 19588333]
44. Darke S. Self-report among injecting drug users: a review. Drug Alcohol Depend. 1998; 51(3): 253–263. [PubMed: 9787998]
45. Johnson T, Fendrich M. Modeling sources of self-report bias in a survey of drug use epidemiology. Ann Epidemiol. 2005; 15(5):381–389. [PubMed: 15840552]
46. Latkin CA, Vlahov D. Socially desirable response tendency as a correlate of accuracy of self-reported HIV serostatus for HIV seropositive injection drug users. Addiction. 1998; 93(8):1191–1197. [PubMed: 9813900]

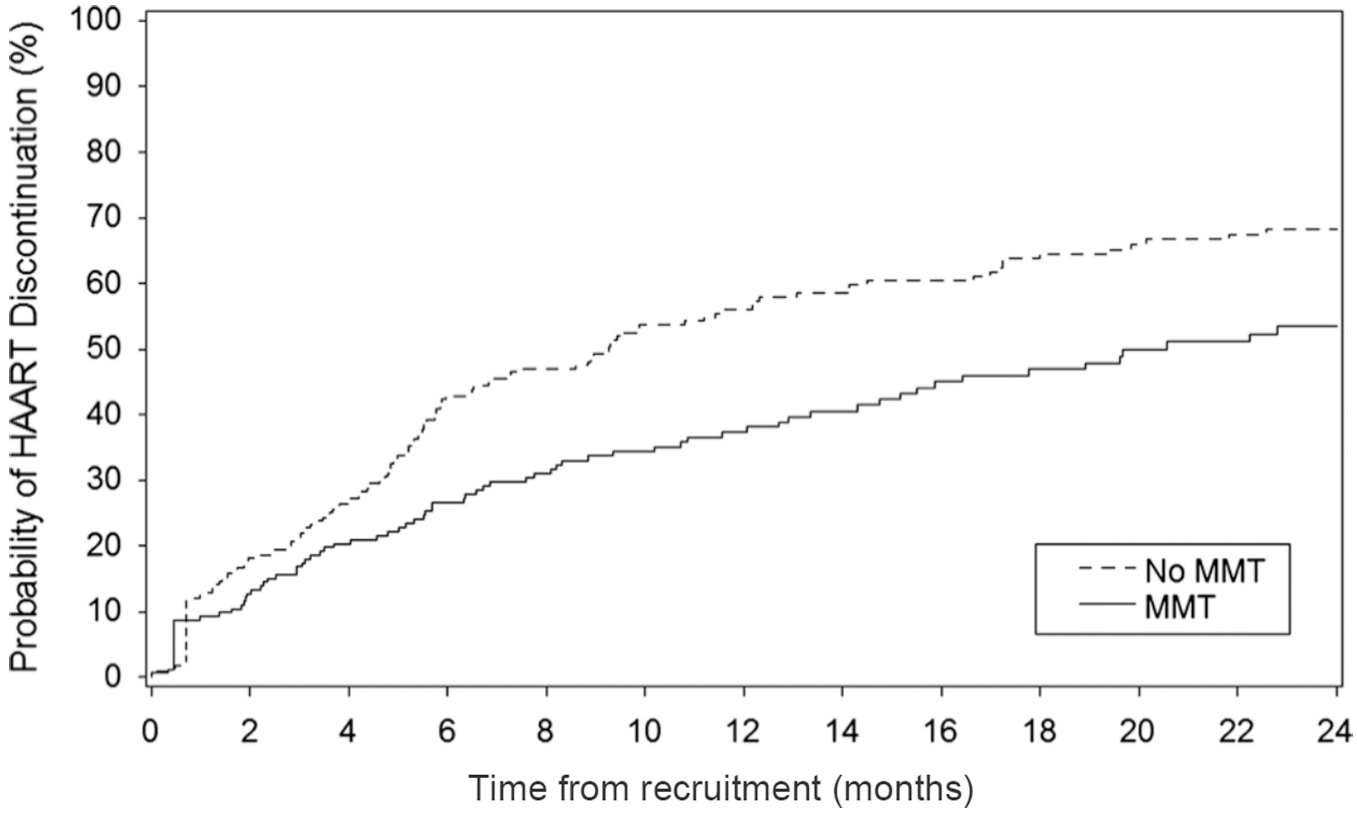

Fig. 1.

Time to antiretroviral therapy (*ART*) discontinuation among a prospective cohort of HIV-infected illicit drug users, stratified by baseline enrollment in methadone maintenance therapy (*MMT*) Time from recruitment (months)

Table 1

Bivariate and multivariate Cox proportional hazard analyses of antiretroviral discontinuation among illicit drug users (n = 408)

Characteristic	Unadjusted relative hazard (RH)		Adjusted relative hazard (RH)	
	RH (95 % CI)	*p*-value	RH (95 % CI)	*p*-value
Age (per years older)	0.95 (0.94–0.97)	<0.001		
Gender (female vs. male)	1.25 (0.97–1.60)	0.080	1.43 (1.11–1.85)	0.006
Aboriginal ancestry (yes vs. no)	1.18 (0.92–1.52)	0.202		
Homelessness[a] (yes vs. no)	1.72 (1.26–2.35)	<0.001		
Binge drug use[a] (yes vs. no)	1.34 (1.03–1.74)	0.031		
Sex trade involvement[a] (yes vs. no)	1.51 (1.10–2.07)	0.011		
Daily heroin injection[a] (yes vs. less)	2.00 (1.48–2.70)	<0.001		
Daily cocaine injection[a] (yes vs. less)	1.69 (1.29–2.22)	<0.001		
Physician experience (yes vs. no)	1.06 (0.78–1.46)	0.704		
CD4 cell count (cells/μL) (per 100 cells increase)	1.04 (0.99–1.10)	0.128	1.08 (1.03–1.15)	<0.001
Viral load (cells/mL) (per $\log_{10}$ increase)	1.18 (1.11–1.24)	<0.001	1.42 (1.07–1.22)	<0.001
Methadone use[a] (yes vs. no)	0.60 (0.43–0.72)	<0.001	0.58 (0.44–0.76)	<0.001
Date of therapy initiation (per years later)	0.89 (0.85–0.92)	<0.001	0.94 (0.90–0.98)	0.004

[a] Behaviours refer to activities in the 6 months prior to the interview, and variables are time updated