DOI: 10.1111/hiv.12493
HIV Medicine (2017)

ORIGINAL RESEARCH

The effect of engagement in an HIV/AIDS integrated health programme on plasma HIV-1 RNA suppression among HIV-positive people who use illicit drugs: a marginal structural modelling analysis

L Ti,[1,2] H Dong,[1] T Kerr,[1,2] RB Turje,[3] S Parashar,[1] JE Min,[1] J Montaner,[1,2] E Wood[1,2] and M-J Milloy[1,2]

[1]St. Paul's Hospital, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada, [2]Department of Medicine, University of British Columbia, Vancouver, BC, Canada and [3]Dr. Peter AIDS Foundation, Vancouver, BC, Canada

Objectives

HIV treatment-as-prevention campaigns emphasize early diagnosis and immediate access to care and antiretroviral therapy for HIV-positive individuals in order to increase levels of plasma HIV RNA viral load (VL) suppression. However, the possible role of harm reduction-based programmes in this objective has not yet been well evaluated. The objective of the study was to examine the relationship between being a client of the Dr. Peter Centre (DPC; an HIV/AIDS-focused adult integrated health programme) and VL suppression among highly active antiretroviral therapy (HAART)-exposed HIV-positive people who use illicit drugs (PWUD) in Vancouver, Canada.

Methods

Data were derived from the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS) study, a study of a community-recruited cohort of HIV-positive PWUD. A marginal structural model using inverse probability of treatment weights was used to estimate the longitudinal relationship between being a DPC client and exhibiting a VL < 50 HIV-1 RNA copies/mL plasma.

Results

Between 2005 and 2014, 746 HAART-exposed participants were included in the study, of whom 269 (36.1%) reported being a DPC client at some time during the study period. A marginal structural model estimated a 1.54 greater odds of achieving VL suppression (95% confidence interval 1.20–1.99) among DPC clients.

Conclusions

Our findings demonstrate that participating in an innovative HIV/AIDS-focused adult integrated health programme that provides a broad range of clinical, harm reduction, and support services may contribute to optimizing the benefits of HAART in terms of morbidity, mortality and viral transmission among PWUD, and as a result help to fulfill the goals of the treatment-as-prevention strategy.

Keywords: Canada, harm reduction, HIV/AIDS, people who use illicit drugs, viral load suppression

Accepted 27 November 2016

Introduction

The advent of highly active antiretroviral therapy (HAART) has been associated with dramatic declines in HIV-related morbidity and mortality [1,2]. Moreover, recent advances in our understanding of HIV/AIDS transmission dynamics have revealed the beneficial impact of HIV treatment on the prevention of onward viral transmission. Specifically, experimental and observational studies have highlighted the important role of HAART in lowering community-level plasma HIV-1 RNA viral load (VL), which in turn reduces the incidence of new HIV infections [3,4]. The treatment-as-prevention (TasP) strategy [5] has been endorsed by a number of major

Correspondence: Dr M-J Milloy, Urban Health Research Initiative, BC Centre for Excellence in HIV/AIDS, 608–1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada. Tel: 604 806 8473; fax: 604 806 9044; e-mail: uhri-mjsm@cfenet.ubc.ca

international organizations, including the Joint United Nations Programme on HIV/AIDS and the World Health Organization [6], and has been widely adopted in various jurisdictions around the world [7,8]. Despite these advances, rates of access and adherence to HAART among people who use illicit drugs (PWUD) remain low compared with other risk groups [9,10], and structural barriers to optimal antiretroviral use among this population, such as the criminalization of illicit drug use, continue to limit efforts to scale up TasP-based programming [11] to reach the 90-90-90 target to end the HIV/AIDS pandemic by 2020 [12].

Integrated harm reduction-based models of care have been implemented in numerous settings with the aim of improving HIV prevention and treatment outcomes for people living with HIV/AIDS (PLWHA), including HIV-positive PWUD [13,14]. In Vancouver, Canada, the Dr. Peter Centre (DPC) is a low-threshold HIV/AIDS-focused adult integrated health programme that provides support to PLWHA who experience multiple barriers to achieving optimal health outcomes, including poverty, homelessness, mental health and addiction issues [15]. Established in 1997, the DPC is a nonprofit organization that provides three core programmes to clients, including a day health programme, a 24-h specialized nursing care residence, and an enhanced supported housing programme. The DPC offers a wide array of therapeutic and harm reduction services, such as addictions counselling, provision of food and nutrition services, art and music therapy, and a supervised injection facility [16].

There is a large body of evidence supporting the provision of HAART to increase levels of VL nondetectability to prevent morbidity and mortality, and secondarily to decrease the risk of HIV transmission. However, there are several competing hypotheses regarding the possible impact of a harm reduction-based integrated health programme on VL suppression. Specifically, access to these types of programme have been shown to be associated with improved health and HIV treatment outcomes [14,17]; however, a hypothesis can also be made for the impact of improved HIV treatment outcomes on further engagement with integrated HIV/AIDS programmes.

Although conventional methods used in observational studies [e.g. generalized linear mixed effects modelling (GLMM)] can largely adjust for baseline and time-dependent confounding in longitudinal cohort studies, these methods may be biased in the case that some variables may be acting as confounders of the main effect and may be predicted by previous treatment/outcome [18]. Alternatively, marginal structural modelling is an innovative analytic approach that aims to estimate the causal relationship between two variables using observational data. This type of statistical model is designed to address time-varying confounding effects and selection bias associated with nonrandom exposure, allowing for causal interpretations as to the true extent to which accessing an HIV/AIDS integrated health programme may influence VL suppression [19]. Marginal structural models have previously been used in the HIV/AIDS context to understand the effects of various exposures, such as the use of antidepressants and pillbox organizers, on VL suppression [20,21]. Following the methodological approaches of these studies, the objective of the present study was to estimate the effect of being a DPC client on VL suppression among HIV-positive PWUD in Vancouver, Canada using a marginal structural model applied to observational data with comprehensive information on VL determinants.

Methods

Study design

Data for these analyses were derived from the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS) study, a community-recruited open prospective cohort study of HIV-positive people who use illicit drugs. The study has been described in detail previously [22]. In brief, beginning in 1996, participants have been recruited through extensive street-based outreach and word of mouth from Vancouver's Downtown Eastside, a postindustrial area with a large open drug market and high levels of illicit drug use, poverty, and HIV infection. Individuals are eligible to participate in ACCESS if they are ≥ 18 years old, reside in the greater Vancouver region, are HIV-positive upon entry, used illicit drugs other than or in addition to cannabis in the month prior to enrolment, and provide written informed consent.

At baseline and semi-annually, participants complete a comprehensive interviewer-administered questionnaire that elicits information on sociodemographic characteristics, drug use patterns, involvement in drug treatment, and other relevant exposures and outcomes. Additionally, participants provide blood samples to monitor disease progression. Participants are compensated for each study visit. In June 2013, the remuneration amount increased from $20 CDN to $30 CDN. Interview data are augmented by comprehensive information on HIV care and treatment from the local centralized HIV/AIDS registry. Specifically, through a confidential linkage, we obtained a complete clinical profiles of participants' CD4 T-cell counts, VL observations, and exposure to specific antiretroviral

agents. In British Columbia, all provision of HAART is centralized through a province-wide HAART dispensation programme, where HAART and related care are provided at no cost through the province's universal health care system. The ACCESS study has been approved by the University of British Columbia/Providence Health Care Research Ethics Board.

Study sample

The study sample included all participants who had received at least 1 day of HAART prior to the end of the study period. Individuals who were HAART-naïve at baseline but who initiated treatment during follow-up were included from the next follow-up interview forward. Also, to be included in these analyses, participants had to have at least one observation of CD4 cell count and VL within $\pm$ 180 days of the day they entered the study.

Variable selection

The primary outcome of interest was nondetectable VL in the previous 6 months, defined as having achieved a VL of < 50 HIV-1 RNA copies/mL plasma (yes *vs.* no). In the event that more than one VL observation was collected within a 6-month follow-up period, we used the median of all the observations. Being a client of the DPC, defined by participant self-report during each 6-month study visit, was the key independent variable considered.

We also considered a selection of other time-invariant and time-varying confounders hypothesized to be associated with the main independent and outcome variables, including: age (per year increase); gender (male *vs.* female); indigenous ancestry (yes *vs.* no); hepatitis C virus (HCV) antibody positivity (yes *vs.* no); homelessness, defined as living on the street or having no fixed address (yes *vs.* no); mental health diagnosis ever (yes *vs.* no); at least daily heroin injection (yes *vs.* no); at least daily cocaine injection (yes *vs.* no); at least daily crack noninjection (yes *vs.* no); enrolment in methadone maintenance therapy (yes *vs.* no); HAART adherence, defined as the quotient of the number of days that HAART was dispensed divided by the total number of days since an individual had initiated HAART, capped at 180 days ($\geq$ 95% *vs.* < 95%); and CD4 cell count (per 1 cell/mL increase). As with VL, we used the median of all CD4 cell count observations if more than one was collected in any 6-month period, or the most recent in the event that none were collected. All time-varying variables were time-updated and refer to the 6-month period prior to the follow-up interview unless otherwise indicated.

Statistical analyses

To estimate the effect of being a DPC client on VL suppression, we used marginal structural models with inverse probability of treatment weights (IPTWs). This statistical approach can handle time-dependent variables that are simultaneously confounders of the effect of interest and are also predicted by previous treatment (i.e. being a DPC client), and can also adjust for selection bias. This approach has been successfully applied in the field of HIV/AIDS and models the relationship between the explanatory and outcome variables by correcting for the nonrandom assignment of the treatment [18,20,21,23].

Prior to calculating the weights, missing time-varying confounder information was imputed using the most recent observation carried forward. This method has been successfully used in previously published HIV-related analyses [20,24]. Given that there was only a small proportion of missing time-varying confounder information (< 2% of observations with missing data), we do not believe this will have had significant impacts on the study results. Additionally, time-lagged confounder variables were used to ensure that confounders occurred before being a DPC client. We then computed the stabilized IPTWs using pooled logistic regression. We chose to use stable weights given that unstable weights can potentially lead to estimators with large variance [19,25]. Factors considered for calculating the weights included the confounding variables listed above. To calculate stabilized IPTWs, we first calculated the denominator, which was the probability that the participant received the observed treatment (i.e. being a DPC client), given their past DPC exposure history and prognostic factor history (i.e. confounding variables listed above). Then, we calculated the numerator, which was the probability that the participant received the observed treatment conditional on their past DPC exposure history and baseline covariates. Finally, unconditional logistic regression was used to estimate the effect of being a DPC client on VL suppression after adjusting for the stabilized weights calculated.

As a comparison, we constructed adjusted and unadjusted unweighted estimates of the effect of being a DPC client on VL suppression using GLMM and a confounding model approach [26] using a backwards-selection procedure based on observing the relative change in the value for the coefficient for the primary explanatory variable of interest (being a DPC client). Specifically, we started with a full multivariable GLMM model including all secondary variables that were statistically significantly associated with VL suppression ($P < 0.05$) in bivariable analyses, which included gender, HCV serostatus, homelessness,

mental health diagnosis, daily heroin injection, daily crack noninjection, enrolment in methadone maintenance therapy, and CD4 cell count. Then, in a stepwise manner, we removed the secondary explanatory variable corresponding to the smallest relative change in the effect of being a DPC client on VL suppression from further consideration. We continued this iterative process until the minimum change of the value of the coefficient for calendar year from the full model exceeded 5%. Remaining variables were considered confounders in multivariable analysis. We also conducted a mediation analysis using the Baron and Kenny approach [27] and the Sobel test statistic [28] to determine whether adherence to HAART mediated the relationship between being a DPC client and VL suppression. All statistical analyses were executed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of study cohort

Between December 2005 and May 2014, there were a total of 847 participants in the ACCESS study. Of those, 756 (89.3%) received at least 1 day of HAART prior to the end of the study period. Among those on HAART, 746 (98.7%) HIV-positive PWUD met the inclusion criteria for the analyses, including 246 (33.0%) women. The individuals had a median age of 43.5 [interquartile range (IQR) 36.9–48.6] years (Table 1). Over the study period, the participants contributed 3337 total person-years of follow-up. Individuals in the cohort were followed for a median duration of 53.3 (IQR 29.2–84.0) months. In total, 269 (36.1%) reported being a DPC client at some point during the study period; of these, 161 (21.6%) reported being a DPC client at baseline. The median number of study visits was nine visits (IQR 6–12 visits) among participants who reported being a DPC client during the study period and eight visits (IQR 4–12 visits) among participants who did not report being a DPC client. At baseline, VL suppression was observed in 289 (38.7%) participants and, in total, 627 (84.0%) participants achieved at least one period of VL suppression at some time during the study period.

Effect of being a DPC client on VL suppression

Presented in Table 2 are the results of the unweighted and weighted estimates of the effect of being a DPC client on VL suppression. The marginal structural model using IPTWs to adjust for the time-updated weights yielded an adjusted odds ratio (AOR) of 1.54 [95% confidence interval (CI) 1.20–1.99]. Stabilized weights had a mean of 0.995 (standard deviation = 0.14), indicating correct specification. Using GLMM methods, the unadjusted odds of VL suppression among DPC clients were 2.06 times higher (95% CI 1.58–2.69) compared with non-DPC clients. Adjusting for HAART adherence, gender, HCV serostatus, homelessness, mental health diagnosis, daily crack noninjection, enrolment in methadone maintenance therapy, and CD4 cell count, a GLMM model yielded an AOR of 1.51 (95% CI 1.13–2.02). To assess a mediation effect, a second multivariable model, where HAART adherence was excluded, was constructed. In this model,

Table 1 Baseline characteristics of 746 HIV-positive people who use illicit drugs in Vancouver, Canada, stratified by being a Dr. Peter Centre (DPC) client

		A DPC client		
Characteristic	**Total (%) (*n* = 746)**	**Yes (%) (*n* = 161)**	**No (%) (*n* = 585)**	***P*-value**
Age (years) [median (IQR)]	43.5 (36.9–48.6)	45.6 (40.4–50.3)	42.8 (36.2–48.2)	< 0.001
Male gender	500 (67.0)	134 (83.2)	366 (62.6)	< 0.001
Indigenous ancestry	302 (40.5)	54 (33.5)	248 (42.4)	0.043
HCV-positive serostatus	653 (87.5)	135 (83.9)	518 (88.5)	0.098
Homelessness*	222 (29.8)	37 (23.0)	185 (31.6)	0.038
Diagnosed mental illness	372 (49.9)	102 (63.4)	270 (46.2)	< 0.001
At least daily heroin injection*	109 (14.6)	8 (5.0)	101 (17.3)	< 0.001
At least daily cocaine injection*	61 (8.2)	7 (4.3)	54 (9.2)	0.044
At least daily crack noninjection*	258 (34.6)	36 (22.4)	222 (37.9)	< 0.001
Enrolment in MMT*	303 (40.6)	51 (31.7)	252 (43.1)	0.007
≥ 95% HAART adherence*	322 (43.2)	89 (55.3)	233 (39.8)	< 0.001
CD4 count (cells/mL) [median (IQR)]*	320 (200–465)	310 (175–455)	320 (200–467)	0.579
Achieved VL suppression*	289 (38.7)	83 (51.6)	206 (35.2)	< 0.001

Data are *n* (%), unless otherwise stated.
DPC, Dr. Peter Centre; IQR, interquartile range; HCV, hepatitis C virus; MMT, methadone maintenance therapy; HAART, highly active antiretroviral therapy; VL, viral load.
*Refers to the 6-month period prior to the interview.

Table 2 Regression analyses on the effect of being a Dr. Peter Centre client on plasma viral load suppression among HIV-positive people who use illicit drugs (n = 746)

Model specification	Measure of effect [OR (95% CI)]	Mean of IPTWs
Unweighted estimates		
Unadjusted, generalized linear mixed effect model	2.06 (1.58–2.69)	–
Adjusted, generalized linear mixed effect model [excluding adherence (mediator) variable]*	1.63 (1.22–2.18)	–
Adjusted, generalized linear mixed effect model [including adherence (mediator) variable]*	1.51 (1.13–2.02)	–
Weighted estimates		
Marginal structural model with IPTWs	1.54 (1.20–1.99)	0.995

OR, odds ratio; CI, confidence interval; IPTW, inverse probability of treatment weights.
*Adjusting for gender, hepatitis C virus (HCV) serostatus, homelessness, mental health diagnosis, daily crack noninjection, and enrolment in methadone maintenance therapy.

the effect of being a DPC client on VL suppression increased (AOR 1.63; 95% CI 1.22–2.18), suggesting that a partial mediation effect was observed. A second test of mediation confirmed the role of HAART adherence as a mediating variable in the relationship between being a DPC client and VL suppression (Sobel test statistic = 2.77; P = 0.006).

Discussion

Using a marginal structural model to adjust for time-varying confounding and selection bias, in the present study it was observed that being a DPC client was associated with a dramatically increased likelihood of VL suppression among HAART-exposed PWUD. These results suggest a potentially important contribution of a harm reduction model-based HIV/AIDS integrated health programme to producing optimal virologic responses in a setting where there are no financial barriers to HIV treatment and care. This association may be attributable, in large part, to the comprehensive set of programmes offered by the DPC, resulting in the provision of appropriate housing, treatment, and care for this vulnerable population. Specifically, the DPC incorporates a wide range of harm reduction strategies and services to meet the needs of clients, including the distribution of drug use paraphernalia as well as a supervised injection facility [14,29]. Other services offered through the DPC, such as nursing care, art therapy, nutrition services, and counselling, may also be contributing to the observed association [16]. While we hypothesize that the continuum of care provided by the DPC alleviates the health and social inequities experienced by this vulnerable population, thereby improving HIV treatment outcomes, future in-depth qualitative research should seek to explore this area further.

Our findings have several public health implications. Importantly, these findings highlight the potential for harm reduction-based HIV/AIDS integrated health programmes to complement existing TasP efforts by serving vulnerable individuals with complex comorbidities. The increased availability of integrated services that facilitate the uptake of, and adherence to, HAART, including various harm reduction strategies and directly observed and assisted therapy, has previously been shown to improve virological outcomes among vulnerable individuals living with HIV [30–33]. The present study adds to this existing literature by being the first to utilize causal inference techniques for observational data to mimic randomized experiments in an effort to gain a better understanding of the effect of an HIV/AIDS integrated health programme on VL suppression. With the expansion of HAART and further scale-up of TasP-based efforts, our findings support calls for harm reduction programmes and services to be incorporated into treatment strategies in order to provide HIV-positive PWUD with the necessary care to ensure VL suppression and limit disease progression and premature death, as well as HIV transmission in this population [10].

Our study has several noteworthy limitations. First, it is difficult to truly assess causality given the observational nature of cohort studies and nonrandom assignment of participants to the exposure of interest, particularly when standard approaches for adjusting for confounders are usually biased as a consequence of time-dependent factors. However, we attempted to address this by constructing a marginal structural model to adjust for time-dependent confounding to estimate the causal effect of being a DPC client on VL suppression [25]. Similarly, there may be remaining unmeasured confounding (e.g. undiagnosed mental illness or other chronic comorbidities) given that we were only able to control for known confounders. Another limitation of our study relates to the generalizability of the study findings. As we included HIV-positive PWUD who were engaged in some level of care (e.g. on HAART), the study sample may not be representative of all HIV-positive PWUD and therefore the findings may not be widely generalizable. In addition, our main explanatory measure, being a DPC client, does not account for the frequency and type of service(s) used; thus, it is unclear whether there is a dose-dependent relationship between the main explanatory and outcome variables. Lastly, the study included some data derived from self-report and thus may be subject to reporting biases. However, it is noteworthy that the outcome of

interest, VL suppression, and other clinical measures were obtained from comprehensive administrative records.

In summary, we analysed the effect of being a DPC client on VL suppression using data derived from a long-standing prospective cohort study of HIV-positive PWUD. Our results demonstrate that DPC clients had a significantly increased odds of VL suppression compared with their non-DPC client counterparts. These findings highlight the importance of, and need for, harm reduction-based strategies to be integrated into the scale-up of TasP-based efforts to improve HIV care and treatment outcomes among HIV-positive PWUD.

Acknowledgements

The authors thank the study participants for their contribution to the research, as well as current and past researchers and staff. The study was supported by the US National Institutes of Health (R01DA021525). This research was undertaken, in part, thanks to funding from the Canada Research Chairs programme through a Tier 1 Canada Research Chair in Inner City Medicine which supports EW. M-JM is supported, in part, by the National Institutes of Health (R01-DA021525). His institution has received an unstructured gift from NG Biomed, Ltd, to support his research.

References

1 INSIGHT START Study Group, Lundgren JD, Babiker AG *et al.* Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795–807.

2 TEMPRANO ANRS 12136 Study Group, Danel C, Moh R *et al.* A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373**: 808–822.

3 Cohen MS, Chen YQ, McCauley M *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365**: 493–505.

4 Montaner JSG, Lima VD, Barrios R *et al.* Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet Lond Engl* 2010; **376**: 532–539.

5 Montaner JSG, Hogg R, Wood E *et al.* The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet Lond Engl* 2006; **368**: 531–536.

6 World Health Organization. *Guideline on When to Start Antiretroviral Therapy and on Pre-exposure Prophylaxis for HIV*. Geneva, World Health Organization, 2015. Available from: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/.

7 British Columbia Centre for Excellence in HIV/AIDS. *Brazil adopts BC Treatment as Prevention HIV strategy*. Vancouver, Canada, British Columbia Centre for Excellence in HIV/AIDS: Vancouver, 2013. Available from: http://www.cfenet.ubc.ca/news/releases/brazil-adopt-bc%E2%80%99s-treatment-prevention-strategy-country%E2%80%99s-national-hivaids-policy.

8 Jia Z, Mao Y, Zhang F *et al.* Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003–11): a national observational cohort study. *Lancet* 2013; **382**: 1195–1203.

9 Nolan S, Milloy M-J, Zhang R *et al.* Adherence and plasma HIV RNA response to antiretroviral therapy among HIV-seropositive injection drug users in a Canadian setting. *AIDS Care* 2011; **23**: 980–987.

10 Wolfe D, Carrieri M, Shepard D. Treatment and care for injecting drug users with HIV infection: a review of barriers and ways forward. *Lancet* 2010; **376**: 355–366.

11 Milloy M-J, Kerr T, Buxton J *et al.* Dose-response effect of incarceration events on nonadherence to HIV antiretroviral therapy among injection drug users. *J Infect Dis* 2011; **203**: 1215–1221.

12 Joint United Nations Programme on HIV/AIDS. *90–90-90: An Ambitious Treatment Target to Help End the AIDS Epidemic*. Geneva, Joint United Nations Programme on HIV/AIDS, 2014. Available from: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf.

13 Grau LE, Arevalo S, Catchpool C, Heimer R. Expanding harm reduction services through a wound and abscess clinic. *Am J Public Health* 2002; **92**: 1915–1917.

14 Krüsi A, Small W, Wood E, Kerr T. An integrated supervised injecting program within a care facility for HIV-positive individuals: a qualitative evaluation. *AIDS Care* 2009; **21**: 638–644.

15 Dr. Peter AIDS Foundation. Dr. Peter AIDS Foundation. 2015 [cited 2014 Jun 19]. Available from: http://www.drpeter.org/.

16 Baltzer-Turje R, McDougall P, Payne M. The Dr. Peter Centre residence: integrated harm reduction health services (including supervised injection services) in a licensed 24-hour specialized nursing care facility for adults with HIV/AIDS and complex health issues including mental illness and active addiction. 2013.

17 Lambers FAE, Stolte IG, van den Berg CHSB, Coutinho RA, Prins M. Harm reduction intensity-Its role in HAART adherence amongst drug users in Amsterdam. *Int J Drug Policy* 2011; **22**: 210–218.

18 Hernán M, Brumback B, Robins J. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med* 2002; **21**: 1689–1709.

19 Robins J, Hernán M, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiol Camb Mass* 2000; **11**: 550–560.
20 Petersen ML, Wang Y, van der Laan MJ, Guzman D, Riley E, Bangsberg DR. Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2007; **45**: 908–915.
21 Tsai AC, Weiser SD, Petersen ML, Ragland K, Kushel MB, Bangsberg DR. A marginal structural model to estimate the causal effect of antidepressant medication treatment on viral suppression among homeless and marginally housed persons with HIV. *Arch Gen Psychiatry* 2010; **67**: 1282–1290.
22 Wood E, Hogg RS, Lima VD *et al*. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. *J Am Med Assoc* 2008; **300**: 550–554.
23 Nosyk B, Min JE, Colley G *et al*. The causal effect of opioid substitution treatment on HAART medication refill adherence. *AIDS Lond Engl* 2015; **29**: 965–973.
24 Cole SR, Jacobson LP, Tien PC, Kingsley L, Chmiel JS, Anastos K. Using marginal structural measurement-error models to estimate the long-term effect of antiretroviral therapy on incident AIDS or death. *Am J Epidemiol* 2010; **171**: 113–122.
25 Hernán M, Brumback B, Robins J. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiol Camb Mass* 2000; **11**: 561–570.
26 Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol* 1993; **138**: 923–936.
27 Baron R, Kenny D. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51**: 1173–1182.
28 Sobel ME. Effect analysis and causation in linear structural equation models. *Psychometrika* 1990; **55**: 495–515.
29 Wood R, Zettel P, Stewart W. Dr. Peter Centre: harm reduction nursing. *Can Nurse* 2003; **99**: 20–24. Available from: http://www.drpeter.org/media/canadiannurse-may03.pdf.
30 Parashar S, Palmer AK, O'Brien N *et al*. Sticking to it: the effect of maximally assisted therapy on antiretroviral treatment adherence among individuals living with HIV who are unstably housed. *AIDS Behav* 2011; **15**: 1612–1622.
31 Small W, Van Borek N, Fairbairn N, Wood E, Kerr T. Access to health and social services for IDU: the impact of a medically supervised injection facility. *Drug Alcohol Rev* 2009; **28**: 341–346.
32 Tyndall MW, Wood E, Zhang R, Lai C, Montaner JSG, Kerr T. HIV seroprevalence among participants at a Supervised Injection Facility in Vancouver, Canada: implications for prevention, care and treatment. *Harm Reduct J* 2006; **3**: e1–e5.
33 Tyndall MW, McNally M, Lai C *et al*. Directly observed therapy programmes for anti-retroviral treatment amongst injection drug users in Vancouver: access, adherence and outcomes. *Int J Drug Policy* 2007; **18**: 281–287.

