TRENDS, PREDICTORS AND OUTCOMES ASSOCIATED WITH UNSTRUCTURED TREATMENT INTERRUPTIONS AMONG HIV-POSITIVE INDIVIDUALS ON ANTIRETROVIRAL THERAPY IN CANADA

by

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Dissertation Abstract

Background

The expanded use of combination antiretroviral therapy (cART) has dramatically enhanced the quality of care and life expectancy of HIV-positive individuals. However, incomplete adherence and treatment interruptions (TIs) due to treatment fatigue, side effects and cART toxicities have emerged as major challenges to the full realization of the therapeutic promise of cART. Despite the relatively high frequency of TIs, their determinants and outcomes are still not well-characterized.

Methods

Trends, predictors and consequences of treatment interruption (TI) and resumption in two study populations were estimated. First, the Longitudinal Investigations into Supportive and Ancillary health services (LISA) is a cross-sectional study of hard-to-reach individuals on cART in British Columbia. Between 2007 and 2010, 1000 participants were interviewed about sociodemographic and clinical factors. Using pharmacy recording, TIs were defined as a patient-initiated interruption in treatment of at least 90 days during the 12 months preceding or following the study interview. Multivariable logistic regression was used to identify factors associated with treatment interruption. The second study, the Canadian Observational Cohort (CANOC) collaboration, is composed of treatment-naïve HIV-positive individuals who initiated cART between 2000-2011. TIs were defined as interruptions in cART for a period of at least 90 days. Cox proportional hazards regression was used to identify determinants and consequences of cART interruption and resumption.

Results

Of 768 participants included in the LISA study, 15% had a TI recorded during the study window. In multivariable analysis, TIs were significantly associated with current illicit drug use (adjusted odds ratio (aOR): 1.68, 95% confidence interval (CI): 1.05-2.68); <95% adherence in the first year of treatment (aOR: 2.68, 95% CI: 1.67-4.12); living with more than one person (aOR: 1.95; 95% CI: 1.22-3.14) or on the street (aOR: 5.08, 95% CI: 1.72-14.99) compared to living alone; poor perception of overall health (aOR: 1.64 95% CI: 1.05-2.55); being unemployed (aOR: 2.22, 95% CI: 1.16-4.23); and younger age at interview (aOR: 0.57, 95% CI: 0.44-0.75, per 10 year increment).

A total of 7,633 CANOC participants initiating cART between 2000 and 2011, of whom 1,860 (24.5%) had at least one TI ≥90 days. The prevalence of TI in the first calendar year of cART decreased by half over the study period. Predictors of a first TI were female sex (adjusted hazard ratio (aHR): 1.59, 95% CI: 1.33-1.92), Aboriginal ancestry (aHR: 1.67, 1.27-2.20), a history of injecting drug use (aHR: 1.43, CI: 1.09-1.89), hepatitis C antibody seropositivity (aHR: 2.17, CI: 1.68-2.79), a baseline CD4 cell count above 350 cells/mm^3 versus less than 200 cells/mm^3 (aHR: 1.46, CI: 1.17-1.81) and use of zidovudine versus tenofovir in the initial cART regimen (aHR: 2.47, CI: 1.92-3.20). Factors protective against TI were older age (aHR: 0.79, CI: 0.73-0.87), higher HIV plasma viral load (log10) (aHR: 0.87, CI: 0.78-0.97) and residence in Ontario (aHR: 0.55, CI: 0.43-0.70) or Quebec (aHR: 0.42, CI: 0.31-0.57) versus British Columbia (BC). Factors predicting resumption of treatment after a first TI included male sex, residence in BC, older age, more recent cART initiation and a CD4 cell count <200 cells/mm^3 at

cART initiation (all $p<0.05$). TIs were associated with increased risk of mortality (aHR: 1.79, CI: (1.49-2.16)) after adjusting for socio-demographic and clinical factors.

Conclusions

Despite significant improvements in cART since its advent and the decreasing prevalence of TIs, gaps in treatment remain relatively common. As cART is propagated at increasing levels globally, and the impetus to provide treatment earlier in the course of HIV infection for individual and public health benefits gains momentum, ensuring continuity of treatment becomes even more vital. Strategies to support continuous HIV treatment are needed to maximize the benefits of cART.

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Chapter 1

INTRODUCTION

1.1 Specific Aims

There are 71,300 people currently living with HIV/AIDS in Canada. As individuals with HIV live longer, thereby spending more time on treatment, it is important to emphasize and facilitate continuity of treatment. Moreover, characteristics of individuals with poor engagement in care and the effect of interruptions on HIV disease progression should be ascertained. As the paradigm of "treatment as prevention" gains traction and treatment earlier in the course of disease is being encouraged, it is particularly timely that we seek to understand how to keep individuals engaged in treatment. Furthermore, new recommendations from the World Health Organization expand the eligibility of HIV-positive individuals initiating cART from 350 to 500 cells/mm^3, rendering the facilitation of continuous, lifelong therapy even more essential. The overall objective of this study is to identify the determinants and consequences of interrupted access to treatment ≥ three months in order to design strategies to optimize the benefits of long-term, continuous treatment in a setting of universal access to care in Canada. Two studies will be used to assess this objective: the Canadian Observational Cohort (CANOC) collaboration, the largest HIV treatment cohort in Canada, composed of antiretroviral naïve HIV-positive individuals who have initiated cART since 2000, and the Longitudinal Investigation into Supportive and Ancillary Health Services (LISA) study, a provincial study of 1,000 participants that will be used to explore socio-behavioral and clinical factors associated with TIs. The aims are as follows:

Aim 1: Identify socio-behavioral and clinical correlates of treatment interruption.

Hypothesis: Individuals dealing with concurrent health issues, lack of access to care and competing life demands (addictions, substandard housing and depression) will be more likely to interrupt treatment.

Aim 2: Identify demographic, clinical and laboratory factors that predict time to first treatment interruption following ART initiation, as well as factors associated with time to resumption of ART following first interruption.

Hypothesis: The prevalence of TIs will decrease over time.

Aim 3: Investigate the impact of unstructured treatment interruption on mortality.

Hypothesis: Individuals who interrupt treatment will have higher mortality than those who do not.

Aim 1 will be evaluated in the LISA study, while Aims 2 and 3 will be investigated in CANOC. The new knowledge generated by this research will serve to identify modifiable factors related to treatment interruption that may be used to inform interventions aimed at improving the lives of individuals on antiretroviral therapy.

1.2 Overview

In the 30 years since HIV was discovered as the virus causing AIDS, our capacity to fight the scourge that has claimed 36 million lives globally [1] since its advent has been revolutionized. While a cure for HIV remains out of reach, combination antiretroviral therapy, or cART, has improved treatment to the degree that a young adult on cART without pre-existing conditions has the potential to live as long as his HIV-negative peers [2]. However, while excellent drugs exist for treatment and allow HIV-

positive individuals to live relatively unmarred by the once-unavoidable ravages of HIV, their viability in controlling viremia and in achieving the best possible patient outcomes is predicated on daily, lifelong use. As one patient eloquently framed the issue, "HIV is not a death sentence, but it's a life sentence. You'll be taking pills forever, going to the doctor and fighting for insurance forever [3]."

The dissertation has three aims related to trends in the continuity of HIV treatment and the gaps in treatment that have the potential to derail the gains achieved in life expectancy and quality of life. The first aim is to identify predictors of TIs in the era of modern cART, often characterized as the period beginning in 2000. Secondly, the dissertation aims to determine what factors predict resumption of treatment after a first TI. The final aim is to characterize the effect of treatment interruptions (TIs) on all-cause mortality. To address these aims I will use data from the aforementioned Canadian studies undertaken in the era of modern cART.

1.3 HIV in Canada

At the end of 2011, there were an estimated 71,300 (58,600-84,000) individuals living with HIV in Canada (including those with AIDS), an increase of about 11% from 2008 [4]. Men who have sex with men (MSM) constitute the largest group of individuals, with 47% of the total proportion, while heterosexual individuals from non-endemic countries represent 18% and injection drug users represent 17%. HIV prevalence has continued to increase and there are approximately 3,000 new infections a year. Individuals of Aboriginal descent (including Métis, First Nations and Inuit) are disproportionately affected by the HIV epidemic in Canada. Since 2011, despite

composing only 4% of the Canadian population, Aboriginal people represented 12% of new HIV infections in Canada in 2011 (of those cases with reported ethnicity) [4]. As in many parts of the world, HIV in Canada targets society's most vulnerable groups; those who are victims of structural inequalities that put them at higher risk of infection. The same factors that make these groups vulnerable to infection with HIV can also prevent them from both accessing care and treatment in a timely manner and consistently engaging in care, causing worse outcomes in both morbidity and mortality [5-7].

Canadians have had relatively good access to HIV/AIDS medication since they were introduced in 1986. A national health insurance program provides affordable access to hospital and physician services and subsidizes cART [8]. All antiretroviral drugs must go through clinical trials and prove their safety and effectiveness to Health Canada before being licensed. Provincial and territorial programs for HIV/AIDS medications differ, ranging from complete coverage as in British Columbia, to special coverage categories, or coverage through programs with income-based deductibles.

1.4 History of treatment interruptions

Until 2006, structured treatment interruptions or "drug holidays" were occasionally prescribed by physicians in order to minimize treatment-related side effects, improve patient quality of life and decrease the costs of HIV treatment and care [9]. While the life-saving and life-extending benefits of antiretroviral therapy are manifest, treatment fatigue is a common phenomenon and can lead to interrupted therapy. Prior to 2006, clinicians and researchers investigated the option of physician-directed TIs, on the basis that if interruptions in treatment occur regardless of whether or not they are

prescribed, physicians should prescribe the interruptions based on medical criteria and monitor patients. However, following the results of the Strategies for Management of Antiretroviral Therapy (SMART) trial in which intermittent therapy of HIV (versus continuous therapy) led to statistically significantly increased risk of HIV disease progression, severe complications and death, the use of treatment interruptions in the management of HIV-positive individuals were no longer recommended [10-12].

Two types of periodic structured, or supervised, treatment interruptions have been evaluated: a) CD4 cell count-guided and b) time-defined. The former strategy, used in the SMART trial, uses intermittent therapy in which CD4 cell counts determine the thresholds for starting and stopping treatment. The latter strategy sets predetermined interruptions in treatment, such as stopping treatment on weekends or alternating months on treatment. This dissertation will focus primarily on unstructured interruptions as those most relevant in a period of modern cART; however, evidence gleaned from both types of interruptions will be described in the following sections to provide a comprehensive illustration of research related to TIs.

1.5 Prevalence of unstructured antiretroviral treatment interruption

Studies vary in their definitions of treatment interruption – some consider a stoppage in treatment intake of a single day to be an interruption, while others use longer periods to denote an interruption. Thus, considerable variability among studies exists in the recording of interruptions, making comparisons challenging. Moreover, studies that occurred before 2006 often include individuals who interrupted treatment based on their physician's recommendation (a supervised or structured interruption).

Considering studies examining longer unstructured treatment interruptions, a Swiss cohort found that 28% of individuals interrupted therapy between one and three months [13]. A large European study determined that after three years, 16% of patients had interrupted treatment for three months or longer [14], while 23% of participants interrupted for at least three months in an Italian study [15]. Research from the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) has also identified that almost 40% of patients, followed for a median of 3.3 years, had experienced at least one TI of at least three months [16], while a study of injecting drug users in Baltimore reported that 78% of participants had at least one TI of six months or longer, and 20% never resumed cART [17].

Assessing studies with shorter defined TIs, a multi-centre study in the United States found that 30% of participants had interrupted treatment for more than seven days [18] while a Spanish cohort study observed that 43% of participants had TI longer than 3 days [19]. A study examining cohorts in Europe, Israel and Argentina reported an incidence rate of 6.0 per 100 person years of follow up [14]. Lastly, a systematic review of TIs in both developed and developing countries and cognizant of the many definitions of TIs ascribed by different studies, reported a median proportion of patients interrupting cART of 23% (Interquartile range: 15-48) [20].

1.6 Risk factors predicting unstructured interruptions in treatment

A number of studies have elucidated predictors of treatment interruption in a developed world context. Demographically, interrupters are more likely to be female patients [14, 16, 21]; younger [13, 14, 16]; and of black ethnicity [18]. Behaviorally, they

are more likely to have suboptimal adherence [18]; and have a history of injection drug use [13, 16, 21]. In terms of clinically relevant predictors, treatment interrupters are more likely to be depressed [18]; have a shorter duration of cART use [14, 18]; higher baseline CD4 cell counts [13, 14, 16]; higher HIV plasma viral loads [13, 14, 18, 21]; and hepatitis C co-infection [16]. They are also more likely to be taking certain antiretroviral regimens [14, 16]. A study of injection drug users in British Columbia found that recent incarceration, lack of faith in the benefits of cART, and poor efficacy expectations (ability to manage treatment schedules and side effects) were independently associated with cART discontinuation [22].

As yet, there is limited research examining treatment interruption in antiretroviral-naïve cART initiators and patients initiating treatment in the modern cART era, which is characterized by more tolerable and convenient cART regimens. Moreover, few studies investigate the frequency and impact of interruptions in the period occurring after interruptions were no longer recommended (2006 onwards). Similarly, the epidemiology of treatment interruption in a Canadian context has not been well elucidated.

1.7 Factors association with resumption of treatment

Structured TI

A randomized trial by the Swiss-Thai-Australia Treatment Interruption Trial (Staccato) group described factors associated with re-starting cART in the scheduled interruption trial arm. These were lower CD4 cell count before cART initiation, lower CD4 cell count at study screening and higher viral load before starting cART [23]. Also

of note, 50% of individuals in the interrupted arm restarted cART within 18 weeks of randomization and after 100 weeks, 75% of individuals had been re-engaged in treatment.

Unstructured TI

A South African study found that women, older individuals, and shorter duration of interruption predicted resumption of treatment [24]. A study in BC observed that 71% (488) of patients who interrupted therapy restarted, with males and individuals with a history of AIDS-defining illness more likely to restart. Those less likely to re-engage in therapy had higher CD4 cell counts at the time of interruption [16]; this is especially problematic in light of the fact that lifelong cART is now being advocated for individuals with CD4 counts $\leq$ 500 cells/mm^3 [25]. Another study defining TIs as a gap of three months or greater reported that 76% of patients restarted treatment; however, in this study, 50% of individuals were on a structured interruption [26].

1.8 Detrimental effects of treatment interruptions

Structured

As the SMART study demonstrated, there are severe and detrimental sequelae for individual as well as public health outcomes associated with interruptions in antiretroviral treatment. TIs result in significantly heightened risk of opportunistic infection and death from any cause compared to continuous antiretroviral therapy [27]. They also lead to plasma viral load rebound [28, 29], potentially increased risk of transmitting virus to others [30], risk of acute viral infection [26, 29], which was found in 6% of participants who interrupted treatment in the Staccato trial [23], and the development of new resistance to antiretroviral agents [31-35]. Results of the SMART trial showed that there

was an increased risk of cardiovascular, hepatic and renal disease in the intermittent treatment group compared to the group receiving continuous treatment [11]. Furthermore, a similar large-scale study showed that the increased risk did not abate once treatment was re-initiated [36].

A Cochrane review of structured treatment interruptions in chronically unsuppressed HIV-positive adults indicated that interruptions are harmful [37]. A similar Cochrane review examining virologically suppressed adults found that time-defined interruption strategies led to the development of drug resistance while CD4 cell count-guided approaches reduced costs and improved tolerability of regimens but led to concerns about long-term safety related to immunological, virological and clinical outcomes [33]. Although interruptions in treatment are considered by some to enhance health-related quality of life, a randomized controlled trial refuted this observation [38].

Unstructured

In studies specifically examining the effects of unstructured treatment interruptions, similar detrimental effects have been found. For example, a large cohort collaboration studying patients in Europe, Israel and Argentina observed a risk of AIDS and death more than two-fold greater in individuals who interrupted treatment relative to those who did not [14]. There is little consensus determining what length of interruption leads to clinically significant consequences. Some studies have found that rebound in viral load before 7 days after stopping cART is uncommon [39, 40]; however, other findings examining viral uncovered that HIV plasma viral load levels returned to > 500 copies/mL within 6 to 15 days (median 10 days) and approached or exceeded pre-therapy levels in all patients within 21 days of stopping therapy [28]. Examining mortality as a

consequence of TI, Moore et al. found that individuals who interrupted treatment more than 230 days were at higher risk of mortality than those who interrupted less than 230 days [16].

However, some studies found no detrimental effect of TIs. Results from the Swiss Cohort Study examining short TIs of one to three months found that TIs did not statistically significantly raise the risk of HIV-related morbidity and mortality [13]; similarly, a factorial randomized trial evaluating two types of treatment (standard versus intensified cART) as well as immediate retreatment or a 12-week structured TI for patients with cART failure did not find significant differences in clinical outcomes between the groups [41]. A small Thai trial also did not observe statistically significant differences in clinical outcomes between structured TI arms and continuous treatment, though the study had a short follow-up period [42].

1.9 Relevance of the current research

This dissertation first seeks to establish whether TIs are detrimental in the Canadian population in the context of modern cART. Second, in this era of modern cART, with ostensibly fewer barriers to treatment as drug-related side effects and pill burden decrease, do individuals on HIV treatment continue to interrupt treatment? If so, who is most likely to interrupt, and why? Which individuals are more likely to resume cART after a TI? Lastly, does resumption of cART after TI confer any survival benefits, and if yes, to what degree? Drawing on several available datasets, we will determine whether it is possible to construct an accurate depiction of TIs in the modern cART era.

One motivation for the study is to reproduce the results of randomized trials examining TIs in actuality rather than in controlled environment. David Savitz describes how certain phenomena are impossible to simulate in the laboratory [43]; similarly, randomized controlled trials, such as the SMART trial, while the gold standard of research, provide better information about the efficacy (effect of periodic scheduled interruptions) than effectiveness (actual patterns and effects of interruptions for a patient outside of a trial). Although the SMART trial demonstrated that treatment interruptions resulted in adverse outcomes for study participants, a randomized trial does not reflect the real world, in which HIV-positive participants on cART have diverse reasons for interrupting and resuming treatment. Furthermore, a randomized trial may not produce the heterogeneity found outside of the "laboratory." For instance, inclusion in the SMART trial required an individual to have a CD4 cell count greater than 350 cells/mm^3 within 45 days of study entry, have good health at the time of study entry and be able, in the clinician's opinion, to comply with the protocol, which does not mimic the population in treatment [11]. There is a clear impetus for non-clinical trial observations as to the frequency, predictors and consequences of interruptions in treatment.

In "The Nature of Epidemiologic Evidence," Savitz describes how the causal impact of an exposure on disease (such as treatment interruption on adverse HIV outcomes), even when established by a reputable and well-executed study, needs to be assessed more than once, and in different populations, to ascertain the generalizability of the association and further support decision-making in public health practice and policy [44]. While one can have confidence that measures of association found in the SMART trial will be similar in other contexts – a Canadian population of individuals initiated on

modern cART regimens, for example – this confidence does not preclude the implementation of a similar study. In effect, the basis for the scientific method is repeatability and reproducibility.

Now that the benefits of antiretroviral treatment in improving survival have been established, the focus of HIV research in the developed world has shifted from a mindset of not only saving lives but also ensuring the quality of life of HIV-positive individuals. Until a veritable cure for the disease can be developed, antiretroviral treatment represents the optimal approach for managing HIV care. Thus, establishing how to maximize the effect of this treatment is a necessary and vital area of epidemiologic research addressing HIV.

1.10 Conceptual framework and directed acyclic graph (DAG)

Gardner et al. created a model examining the continuum of HIV engagement in care in the United States. He suggests that HIV treatment and care can be conceptualized as a continuum, from initial acquisition of HIV to successful engagement in care, characterized by a high level of adherence and an undetectable HIV plasma viral load [45]. Each step in the aptly named "cascade" must be monitored since individuals exit the cascade at each step. For instance, only 75% of individuals who were diagnosed in the United States as HIV-positive remained linked to HIV care, and less than 20% of HIV-positive individuals were adherent with undetectable HIV plasma viral load [45]. Thus, there are numerous points at which to intervene in the cascade, and efforts at each stage are needed to best ensure that individuals living with HIV have the best possible treatment and care. Lack of retention in care, one step in the cascade, can be assessed by

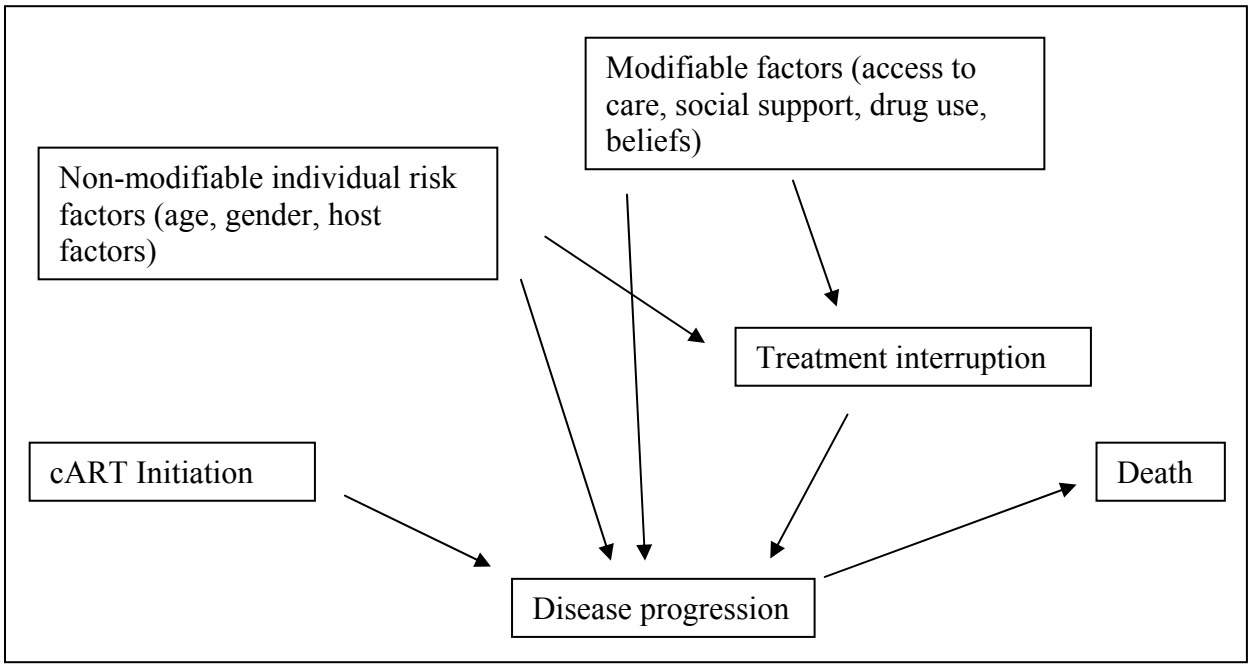
examining interruptions in treatment, since individuals who interrupt treatment are not retained. Gardner's review estimates that as high as 50% of known HIV-positive individuals are not engaged in regular HIV care, whether that is sustained access to antiretroviral therapy, prophylactic medications or other medical services [45].

Individuals who are intermittent or episodic users (defined in this study as those with gaps greater than or equal to three months) are hypothesized to be different from continuous users (those who do not have gaps, although who may not have perfect adherence). That is, those who take their pills inconsistently (poor adherence) are different from those who discontinue all antiretroviral therapy for sustained periods of time. This latter concept has been described as medication persistence, defined as "the duration of time from initiation to discontinuation of treatment" [46] or "the duration during which a patient remains on a prescribed therapy" in contrast to adherence, which is the "percentage of patient behavior to a prescribed therapy" [47]. However, medication persistence differs from TI because the concept of persistence precludes modifications of a regimen, while individuals can simplify their regimen and not be categorized as a TI.

The social ecological framework has been applied by a number of researchers to explore health-seeking behavior in the context of both discontinuations of antiretroviral therapy as well as adherence [48, 49]. This framework describes human behavior as a function of personal and environmental (social, economic, political, health system) factors [49]. Using facets from this framework, the Gardner model and knowledge of the literature on TIs, a directed acyclic graph (DAG) was developed that summarizes assumptions about how the variables in the analysis are causally related, as shown in Figure 1 below. Variations in factors such as social support, gender, age, and beliefs

about HIV treatment may lead to differential rates of treatment interruption and differences in disease progression and mortality. In particular, injection drug users may be most at risk for interrupting treatment due to concurrent health issues and competing life demands, such as poor housing.

Figure 1. Directed Acyclic Graph depicting the relationship of factors with treatment interruption



1.11 Study Population

1.11.1 Longitudinal Investigation into Supportive and Ancillary Health Services (LISA)

The recruitment period for the LISA cohort occurred from July 2007 to January 2010. Participants were recruited through letters distributed by their physicians, which were received when patients filled their cART prescription at their pharmacy, through word-of-mouth and advertisements at HIV/AIDS service organizations in BC. To be eligible for LISA, participants had to be at least 19 years of age and antiretroviral naïve prior to initiating highly active antiretroviral therapy. Once screened, eligible participants provided informed consent in writing. Cross-sectional interviews were confidential and took approximately 45 minutes to complete. A $20 honorarium was provided to all participants as compensation for their time. Interviews occurred at various HIV/AIDS organizations across British Columbia such as AIDS Vancouver Island and Vancouver Native Health.

Cross-sectional questionnaire data was linked with clinical data (e.g. CD4 cell count, HIV viral load and treatment adherence) obtained through longitudinal linkages with the Drug Treatment Program at the BC-CfE, which is mandated to distribute antiretroviral medications free of charge to all eligible HIV-positive individuals in the province. Two years of enrollment for the LISA study yielded a total of 1000 participants, of whom 83 (9%) were excluded due to problems in linking to clinical variables, leaving 917 as the final study sample. Ethical approval for the LISA study was obtained from the University of British Columbia/ Providence Health Care, Vancouver Coastal Health, University of Victoria, and Simon Fraser University Research Ethics Boards.

1.11.2 Canadian Observational Cohort Study (CANOC)

The CANOC collaboration provides important insights into the care and treatment of HIV-positive individuals on antiretroviral therapy in Canada. Of the estimated 24,000 people on HIV treatment in the provinces of British Columbia, Ontario and Quebec, nearly a third are currently captured in cohorts that constitute CANOC. As of October 2011, there are 7,473 men and women in CANOC. In comparison to the Canadian population in 2011, CANOC participants are older (median age 41 vs. 40 years) and more likely to be male (81.0% vs. 49.6%), which reflects the HIV population on therapy. Contributing cohorts must have at least 100 active HIV-positive participants who meet the following eligibility criteria: documented HIV infection, residence in Canada, aged 18 years and over, initiation of three or more antiretroviral drugs for the first time (i.e. ART-naïve cART start) after January 1, 2000, and a viral load measurement and CD4 cell count within six months of the start of therapy. All participating cohorts have received approval from their institutional ethics boards to contribute non-nominal (a study identity number is assigned to replace patient name) patient-specific data to CANOC.

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Chapter 2

CORRELATES OF HIV TREATMENT INTERRUPTION AMONG HIV-POSITIVE INDIVIDUALS IN BRITISH COLUMBIA

ABSTRACT

Objectives: In British Columbia (BC), persistent gaps exist in the care and treatment of HIV-positive individuals. Treatment interruptions (TIs) limit the therapeutic success of combination antiretroviral therapy (cART) and are associated with higher morbidity and mortality. HIV-positive individuals dealing with concurrent health issues, access challenges and competing life demands are hypothesized to be more likely to interrupt treatment.

Methods: The Longitudinal Investigations into Supportive and Ancillary health services (LISA) Project is a cross-sectional study of hard-to-reach individuals on cART in BC. Between 2007 and 2010, information was collected from 1000 participants on behavioral, psychosocial, health services utilization and other clinically relevant factors. Using pharmacy recording, TIs were defined as a patient-initiated interruption in treatment of at least 90 consecutive days during the 12 months preceding or following the study interview. Multivariable logistic regression was used to identify factors associated with TI.

Results: Of 768 participants included in the study, 15% had a TI recorded in the 24 month study window. In the multivariable model, TIs were significantly associated with current illicit drug use (adjusted odds ratio (aOR): 1.68, 95% confidence interval [CI]: 1.05-2.68); less than 95% adherence in the first year of treatment (aOR: 2.68, 95% CI: 1.67-4.12); living with more than one person (aOR: 1.95; 95% CI: 1.22-3.14) or living on the street (aOR: 5.08, 95% CI: 1.72-14.99) compared to living alone; poor perception of

overall health (aOR: 1.64 95% CI: 1.05-2.55); being unemployed (aOR: 2.22, 95% CI: 1.16-4.23); and younger age at interview (aOR: 0.57, 95% CI: 0.44-0.75, per 10 year increment).

Discussion: Individuals with social vulnerabilities such as poor housing stability, younger age, unemployment and drug use were more likely to report TIs. In addition, poor adherence after treatment initiation was associated with TIs, suggesting that early inconsistencies in medication persistence may represent a warning sign of future TIs. Addressing socioeconomic barriers to treatment retention is vital for supporting the continuous engagement of patients in care.

INTRODUCTION

Once engaged in HIV care, it is imperative for HIV-positive individuals to strictly adhere to their prescribed medication protocol in order to maximize the life-extending benefits of combination antiretroviral therapy (cART). One stage of the "cascade," as expounded by Gardner and colleagues [1], continuity of treatment is a vital component of care and the best predictor of an HIV-positive individual's successful management of HIV. Treatment continuity can be examined on a continuum from measures of daily adherence to measures of long-term medication persistence. This distinction represents the difference between asking "how often" and "for how long," respectively, with respect to a patient's medication-taking practices [2]. As cART is propagated at increasing levels globally, and the impetus to provide treatment earlier in the course of HIV infection for individual and public health benefits gains momentum [3-5], ensuring continuity of treatment becomes even more of a pressing issue.

Until 2006, structured treatment interruptions (TIs) or "drug holidays" were prescribed by physicians in order to minimize treatment-related side effects, improve patient quality of life and decrease the costs of HIV treatment and care [6]. These interruption strategies were characterized as either time-defined gaps in treatment, as in the STACCATO trial, or gaps based on CD4 cell count, as demonstrated in the largest trial examining TIs, the SMART trial [7, 8]. As evidence accumulated that these drug holidays led to a statistically significantly increased risk of HIV disease progression, severe complications and death, the use of structured TIs in the management of HIV-positive individuals were no longer recommended [9, 10].

Whether planned or otherwise, TIs result in a heightened risk of opportunistic infection [9, 11, 12], plasma viral load rebound [13, 14], increased risk of person-to-person transmission [15, 16], risk of acute viral infection [14], found in 5.9% of participants with TIs in the Staccato trial [7], and the development of new resistance to antiretroviral agents [17-19]. Results of the SMART trial showed that there was an increased risk of cardiovascular, hepatic and renal disease in the intermittent treatment group compared to the group receiving continuous treatment [8]. Furthermore, a similar large-scale study showed that the increased risk did not abate once treatment was re-initiated [20].

Despite recognition of the detrimental effects of TIs, many studies continue to report on the high prevalence of TIs in their patient populations, which can range anywhere from 6% to 51% [21-26]. Research from British Columbia (BC) has identified that almost 40% of patients, followed for a median of 3.3 years, had experienced a TI [21]. Despite the frequency of TIs, determinants of unstructured or self-elected TIs are still not well-characterized [27]. This study purported to examine gaps in care of 90 consecutive days or longer in antiretroviral treatment and factors associated with these gaps.

METHODS

Study design and participant recruitment

The Drug Treatment Program (DTP) at the BC Centre for Excellence in HIV/AIDS is mandated by the government of BC to distribute cART free of charge to eligible HIV-positive individuals. The DTP distributes cART according to standards

developed by the BC Therapeutic Guideline Committee, which are consistent with guidelines proposed by the International AIDS Society [28], described previously at length [29].

Briefly, HIV-positive individuals are enrolled in the DTP when they are first prescribed cART by their physicians, and are followed prospectively for clinical and laboratory measurements thereafter. HIV-positive individuals enrolled in the DTP between July 2007 and January 2010 were eligible to participate in the Longitudinal Investigations into Supportive and Ancillary health services (LISA) study. The LISA study enrolled 1,000 HIV-positive individuals over the age of 19 residing in British Columbia who had ever accessed cART. Study participants were actively recruited non-randomly through letters distributed via HIV physicians and pharmacists, by word-of-mouth and via advertisements at HIV/AIDS service organizations located throughout the province. Informed consent was obtained from patients prior to conducting the survey. The LISA study oversampled particular sub-populations in order to sufficiently power sub-analyses on women, people who inject drugs and people identifying as Aboriginal.

Study instrument and ethical approval

Cross-sectional socio-demographic data on LISA study participants were collected through a comprehensive interviewer-administered survey which captured a range of variables including: basic demographic data, information about housing, income, social support networks, mental health disorders, drug and alcohol use and quality of life measures. Clinical variables were obtained through longitudinal linkages with the DTP administrative database and integrated with interview data. Ethical approval for the LISA

study was obtained from the University of British Columbia/ Providence Health Care, Simon Fraser University, the University of Victoria, and Vancouver Coastal Health Research Ethics Boards.

Inclusion criteria

In order to be included in this analysis, participants were required to have initiated cART at least one year prior to their interview date, which was necessary in order to obtain a complete measure of treatment adherence in the year prior to enrollment. Patients were excluded if they moved out of the province during the study period, entered a randomized trial, or if they had already interrupted treatment 12 months prior to the interview, as determined by clinical linkages to the DTP, which excluded 149 individuals. 83 individuals who initiated treatment outside of BC and did not have a CD4 cell count or initial regimen recorded at initiation were also excluded, leaving a sample size for this analysis of 768 individuals.

Outcome variable

The outcome variable, treatment interruption, was defined as a non-medically supervised interruption in antiretroviral treatment of at least 90 consecutive days during the 12 months preceding or following the study interview. Instances of medically supervised TIs were recorded in the provincial database and could therefore be excluded. Pharmacy prescription refill of cART was used to identify TIs of 90 days; that is, when individuals did not retrieve their prescription, they were recorded in the database as interrupted until they picked up their medication. While there is considerable variability

among studies in defining the length of a TI, a period of 90 days or longer was chosen to help decrease misclassification of TIs due to reporting delays or stockpiled medication.

Explanatory variables

A number of covariates were identified as possible factors that might influence TI occurrence. Socio-demographic variables included: age, gender, sexual orientation, Aboriginal ancestry, education (<high school vs. ≥high school), current employment status, current income (dichotomized at $15,000) and provincial income assistance. The survey also asked about lifetime diagnosis of a mental health disorder, lifetime experience of violence and abuse, and incarceration and drug use, both lifetime and current. Lifetime drug use was defined as having ever used cocaine, crack cocaine, heroin, speedball (cocaine and heroin) and methamphetamine; current was defined as drug use in the three months preceding the interview date. Housing was assessed by asking how many other people participants resided with (alone, with more than one person or live on the street) and the type of residence (hotel, treatment centre, shelter or hostel, no fixed address, prison vs. house or apartment). Depressive symptoms were measured using the validated 10-item Center for Epidemiological Studies Depression (CES-D 10) scale [30, 31] and food insecurity was measured using a modified version of the Radimer and Cornell questionnaire [32, 33]. Participants were also asked to report on their perception of their overall health (dichotomized as excellent and very good and good vs., poor and fair) and were asked about a series of non-mutually exclusive possible options for not taking cART medications, "are any of these explanations a reason you have EVER missed taking your HIV meds."

Clinical variables included in the analysis were CD4 cell count (cells/mm^3), HIV viral load at time of treatment interruption (log_{10} copies/mL), AIDS at treatment initiation (yes or no), adherence in the first year of treatment (defined as taking ≥95% of prescribed cART in the one-year period following initiation of therapy based on pharmacy refill compliance) and cART regimen. A complete list of variables is included in Appendix 1.

Statistical Analysis

Bivariate analyses to compare differences between treatment interrupters and non-interrupters were undertaken using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Correlates that were statistically significantly associated at the univariate level ($p<0.1$) were candidates for inclusion in the multivariable logistic regression model to evaluate the independent association of variables with treatment interruptions. Variables that had been shown to be related to TIs, such as age and gender, were included in this analysis regardless of statistical significance, which was defined as $p<0.05$. A selection procedure based on the Akaike Information Criterion (AIC) was used to select the variables in the final model. All analyses were conducted using the STATA statistical package version 12.1 [34]. A sensitivity analysis was performed to determine whether results changed if the TI observation period was limited to the period 12 months following the study interview.

RESULTS

Of 768 participants included in the study, 117 (15%) had a recorded TI 90 days or longer within the 24 month window surrounding their interview date (37 prior to the interview and 80 subsequently), as determined by clinical linkage to the DTP. Demographic and clinical differences between those with and without experiences of TIs are presented in Table 1. Individuals with TIs were more likely to be female versus male (42% vs. 21%), younger (median age, interquartile range (IQR): 42 (37-41) vs. 46 (41-52), of Aboriginal ancestry (61% vs.75%), unemployed (87% vs. 73%) and report an income of less than $15,000 CDN annually (74% vs. 55%). They were also significantly more likely to have ever been incarcerated (65% vs. 49%), to have ever injected drugs (78% vs. 55%) and to be using illicit drugs at the time of interview (66% vs. 50%), to have completed less than a high school education (50% vs. 36%) and to rate their overall health poorer than their counterparts who did not interrupt (48% vs. 30%). Importantly, those who interrupted were much more likely to report unstable housing (46% vs. 28%) and to cohabitate with other people (44% vs. 39%) or live on the street (7% vs. 1%) versus living alone. Moreover, individuals who interrupted were more likely to report adherence ≤95% in the first year of treatment (68% vs. 40%) or no cART at study interview (34% vs. 2%) (though for an interruption period less than three months) (all $p<0.05$).

Several factors were shown to be associated with TI in multivariable analysis, as shown in Table 2. These included younger age at interview (per 10 year increment) (aOR: 0.57, 95% CI: 0.44-0.75); imperfect adherence in the first year of treatment (aOR: 2.68, 95% CI: 1.67-4.12); unemployment (aOR: 2.22, 95% CI: 1.16-4.23); illicit drug use (aOR:1.68, 95% CI: 1.05-2.68); living with many people (aOR: 1.95; 95% CI: 1.22-3.14)

or on the street (aOR: 5.08, 95% CI: 1.72-14.99) versus alone; and having a poor impression of one's overall health (aOR: 1.64 95% CI: 1.05-2.55). Female gender was included in the final model as a variable deemed clinically important but did not achieve statistical significance in the multivariable analysis. Results of the sensitivity analysis showed that there was no difference in the model limiting inclusion of TI events to solely after the interview date.

When asked about possible reasons for missing doses of cART, participants reported a number of barriers and obstacles to consistent medication persistence, which are summarized in Figure 1. Of 768 participants, 168 (22%) responded that the question was not applicable to them because they always take their pills, a group that did however include 20 treatment interrupters. Of the remaining 600 individuals, 89% of those who did interrupt cited "to avoid side effects" as a reason for missing doses versus 68% of those who did not interrupt ($p<0.001$). Equal proportions of each group (66%) reported that the second most common reason for missing doses was that they "simply forgot." Traveling or being away from home was reported by 34% of individuals who did not interrupt and 44% of those who did. Significantly more individuals who interrupted missed doses due to nausea and diarrhea (39% vs. 24%, $p=0.002$), running out of pills (32% vs. 22%, $p=0.035$), losing or misplacing pills (29% vs. 15%, $p=0.001$), and not having the right foods or liquids to take with the pills (28% vs. 11%, $p<0.001$). More than a quarter of those who interrupted stated that they missed doses because they "didn't feel like the meds really work sometimes" (28% vs. 7%, $p<0.001$) and because they were "feeling well so they didn't bother" (26% vs. 10%, $p<0.001$). Those experiencing TIs

were more likely to miss doses because they didn't want anyone to see or notice them taking HIV meds (18% vs. 7%, p=0.001).

DISCUSSION

In a population of HIV-positive individuals on treatment in British Columbia, patient-initiated TIs continue to occur; the prevalence of TI was 15% (117/768) in the sample. The TI prevalence in this study is comparable to other studies examining unstructured TIs of similar lengths of three months or longer. For instance, a Swiss cohort found that 27.5% of individuals interrupted therapy between one and three months [35], while a large European study determined that after three years, 16% of patients had interrupted treatment for at least three months [36]. Results of this study are a conservative estimate of TIs since those who had not accessed cART at all in the 24-month study window (possibly due to prior interruption) were excluded.

A number of demographic and socio-behavioral factors were independently associated with interrupting treatment such as younger age, illicit drug use, overcrowding or living on the street, unemployment and a poor perception of overall health. Individuals dealing with concurrent issues such as a lack of stable housing or employment, as well as challenges related to addiction, may be unable to prioritize adherence to an HIV treatment regimen, resulting in periods of interruptions of cART that may compromise long term prognosis. Individuals with a poor perception of their overall health were more likely to interrupt, indicating that they may be pessimistic about the efficacy of cART in improving their health, leading them to discount the importance of sustained treatment.

Similarly, a study of injecting drug users in BC found that lack of faith in the benefits of cART, and poor efficacy expectations (ability to manage treatment schedules and side effects) were independently associated with cART discontinuation [22].

Corroborating previous literature, this study also found that suboptimal adherence in the first year of ART was strongly associated with future interruptions in treatment [37]. This may signify that individuals who are more likely to embark on lengthy interruptions may effectively be identified and targeted for assistance early on in their course of therapy.

With respect to factors associated with TIs, a number of findings were largely consistent with studies in other settings examining TIs; in particular, younger age was correlated with TIs in this and many other studies [21, 35, 36], which suggests that younger individuals may be more prone to more chaotic and dynamic lifestyles. Similarly, illicit drug use and hepatitis C co-infection were also associated with TIs in this study and in the literature [21, 35, 36]. However, this study did not find that higher baseline CD4 cell counts were correlated with TIs during the study period as did a number of other studies [21, 35, 36]; in fact, CD4 cell count at treatment initiation was exceedingly low for both groups. It is likely, due to our sampling strategy, that the population under analysis here represents a more marginalized population with lower variability in CD4 count than that examined in other studies. Policy-makers and clinicians should be especially vigilant in preventing TIs in groups of late initiators to prevent significantly compromised patient outcomes.

While female gender was significantly associated with TIs in a number of studies [21, 26, 36], gender was not significantly associated with TI in this study's final model.

In BC, a higher proportion of women acquire HIV through injecting drug use than men (23% vs. 10% of new diagnoses in 2011 were attributable to IDU in women vs. men [38]) and have demonstrated poorer adherence [39], which may result in less stability in their lives overall and a higher preponderance of TIs. In this study, it is likely that a higher proportion of men were injecting drug users than found in the general HIV-population in the province, leading to higher vulnerability to TIs than found for men in other studies.

Housing status and unemployment have not been described in many studies examining TIs though numerous studies have found associations between unstable housing and suboptimal adherence [40-44] as well as treatment discontinuation [37]. It is conceivable that a substandard living situation or lack of income from not having a job could exercise a degree of stress on an individual that would preclude attention to a regimen of daily pills. Establishing safe and stable housing for HIV-positive individuals and access to employment is paramount for maintaining engagement in treatment.

In reporting reasons for missing doses, participants cited various physical, social and interpersonal concerns that may act as barriers to treatment continuity, some of which have been described in a meta-analysis of studies in developing and developed countries examining poor adherence [45]. Of note, this study found that a number of individuals reported missing doses because they felt well. A study investigating reasons for loss to follow-up in a population of HIV-positive individuals in New York City similarly concluded that 41% left care because they "felt well" [46]. Likewise, literature on antibiotic compliance shows similar findings [47]. Clinicians should include information about the importance of continuity of treatment and provide strategies and support for

patients in order to prevent resistance and to ensure that patients experience the long-term benefits of cART.

Limitations of the study

Appreciating that many studies solely collect clinical data, LISA provides critical insight into complex socio-economic and demographic characteristics of HIV-positive individuals who have accessed treatment in BC. However, readers should be cautious when interpreting our results. Firstly, the study is a non-probability sample, which limits the generalizability of our results. Specifically, this study is subject to selection bias, as the modest honorarium offered to participants might have led to over-sampling of individuals in need of financial gain. A range of recruitment strategies were employed in an effort to attenuate the effect of this bias.

Additionally, as in many studies that ask for self-reported information collected by interviewers, this study is vulnerable to social desirability and recall biases. As the study design is cross-sectional, temporal and causal relationships cannot be inferred. Further, by design the LISA study only includes individuals who have accessed cART, and thus is not representative of HIV-positive individuals who have yet to access therapy, who may be the most marginalized. Similar studies including all HIV-positive individuals in the province would be beneficial.

This study included TIs both preceding and following the study interview in order to maximize the study sample. Since it is association and not causation (which presupposes a temporal relationship in which the exposure precedes the outcome) that is being investigated in this cross-sectional analysis, including TIs that occur prior to the

interview is consistent with our goal of determining correlates of interruption. Results from a sensitivity analysis in which only TIs recorded in the period following the interview date were included in the analysis were consistent with the original analysis.

Conclusions and future directions

Despite universal access to treatment across the province of British Columbia, interruptions in treatment among HIV-positive individuals on cART continue to be pervasive. Future research that includes a qualitative perspective would lead to a deeper understanding of the reasons that people interrupt treatment. In addition, longitudinal research would be able to illustrate how changes in circumstances affect treatment interruptions; for instance, how the loss of housing or a job might create an environment where the risk of an interruption is higher. Following individuals who interrupt treatment over time may also elucidate the long-term effects of interrupting treatment.

In order to ensure the continuity of treatment and the best possible health outcomes for HIV-positive individuals, the barriers to secure, enduring, and accessible treatment must be addressed. Programs to assist individuals adhere to treatment should be developed; simultaneously, researchers, policy-makers, and clinicians alike must work to improve overall quality of life for individuals living with HIV so that lack of adequate housing, employment and addictions do not impede access to life-saving and life-extending treatment for HIV. Only by ensuring that basic life needs are met for individuals living with HIV can there be an expectation of improved retention and the continuous engagement of patients in care.

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Table 1. Characteristics of HIV-positive individuals who did and did not interrupt treatment in the 12 month period before or after LISA interview date (N=768)

Characteristic	N	No treatment Interruption n (%) n = 651	Treatment Interruption n (%) n = 117	*p* - value
Gender	768			
Male		516 (79.2)	68 (58.1)	<0.001
Female		135 (20.7)	49 (41.9)	
Median age (IQR)*	768	46 (41-52)	42 (37-41)	0.001
History of IDU†	766			
yes		358 (55.1)	90 (77.6)	<0.001
no		292 (44.9)	26 (22.4)	
Current illicit drug use	766			
yes		325 (50.0)	76 (65.5)	0.002
no		325 (50.0)	40 (34.5)	
Aboriginal	768			
yes		165 (25.4)	46 (39.3)	0.002
no		486 (74.7)	71 (60.7)	
Completed High School	767			
yes		418 (64.3)	58 (49.6)	0.002
no		232 (35.7)	59 (50.4)	
Earn ≥$15,000	762			
yes		288 (44.6)	30 (25.9)	<0.001
no		358 (55.4)	86 (74.1)	
Ever Incarcerated	767			
yes		315 (48.5)	76 (65.0)	0.001
no		335 (51.4)	41 (35.0)	
Currently Employed	768			
yes		177 (27.2)	15 (12.8)	0.001
no		474 (72.8)	102 (87.2)	
Unstable Housing**	767			
yes		182 (28.0)	54 (46.1)	<0.001
no		468 (72.0)	63 (53.9)	
Who do you live with?	766			
Live alone		391 (60.1)	57 (49.1)	<0.001
With ≥ 1 person		250 (38.5)	51 (44.0)	
Homeless		9 (1.4)	8 (6.9)	
Adherence ≥95%‡	761			
yes		384 (59.6)	38 (32.5)	<0.001
no		260 (40.4)	79 (67.5)	

* IQR= interquartile range
†IDU= injecting drug user
**Not living in a house or apartment
‡ In first year of treatment

Table 1. Characteristics of HIV-positive individuals who did and did not interrupt treatment in the 12 month period before or after LISA interview date (N=768) (continued)

Characteristic	N	No treatment Interruption n (%) n = 651	Treatment Interruption n (%) n = 117	p - value
Median CD4 cell count at treatment initiation*	763	210 (120-330)	215 (120-330)	0.294
AIDS at Baseline	768			
yes		94 (14.4)	17 (14.5)	0.980
no		557 (85.6)	100 (85.5)	
Overall Health	768			
Exc., very good, good		453 (69.6)	61 (52.1)	<0.001
vs. poor, fair		198 (30.4)	56 (47.9)	
NRTI combo in cART regimen at interview	768			
Tenofovir/Emtricitabine		303 (46.5)	46 (39.3)	<0.001
Abacavir/Lamivudine		151 (23.2)	11 (9.4)	
Tenofovir/Lamivudine		59 (9.1)	6 (5.1)	
Zidovudine/Lamivudine		20 (3.1)	3 (2.6)	
Other		104 (16.0)	11 (9.4)	
Not on cART		14 (2.2)	40 (34.2)	
Third drug in cART regimen at interview	768			
Nevirapine		69 (10.6)	2 (1.7)	<0.001
Efavirenz		152 (23.4)	16 (13.7)	
Lopinavir		103 (15.8)	12 (10.3)	
Atazanavir		249 (38.3)	42 (35.9)	
Other		64 (9.8)	5 (4.3)	
Not on cART		14 (2.2)	40 (34.2)	

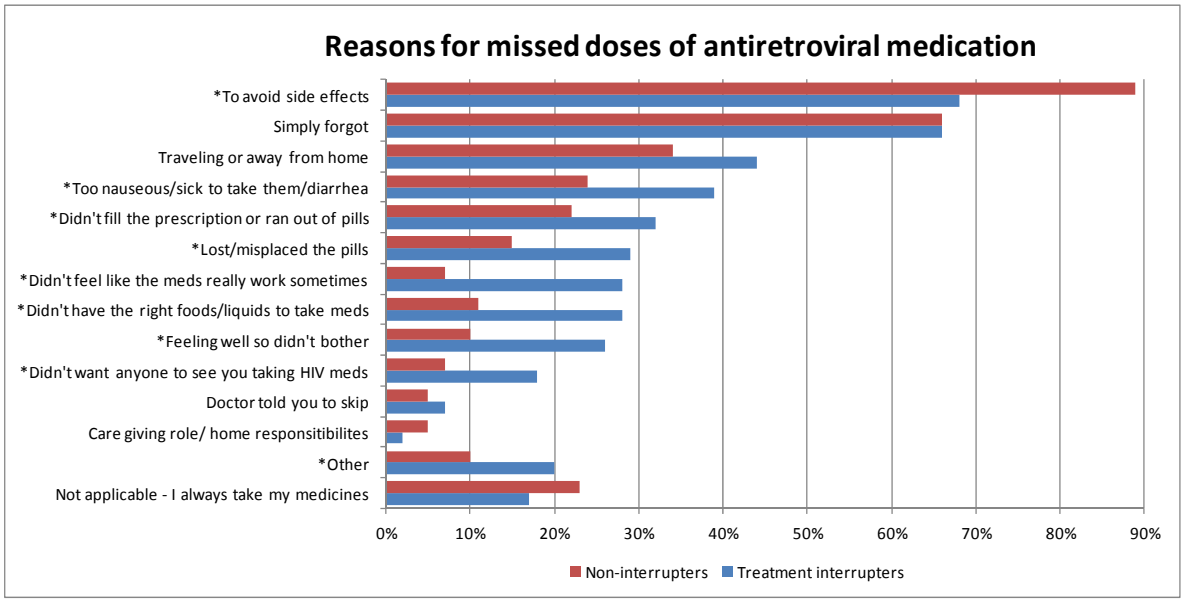
* IQR= interquartile range
†IDU= injecting drug user
**Not living in a house or apartment
‡ In first year of treatment

Table 2. Factors associated with treatment interruption of ≥90 days among 757 LISA participants in British Columbia, Canada

	Unadjusted odds ratio (95% confidence interval)	p-value	Adjusted odds ratio (95% confidence interval)	p-value
Female vs. Male	2.75 (1.82-4.16)	<0.001	1.58 (0.99-2.52)	0.054
Age (per 10 year increment)	0.54 (0.43-0.68)	<0.001	0.57 (0.44-0.75)	<0.001
Current illicit drug use	1.90 (1.26-2.87)	0.002	1.68 (1.05-2.68)	0.030
Aboriginal ancestry	1.91 (1.27-2.88)	0.002		
Unemployed	2.54 (1.44-4.49)	0.001	2.22 (1.16-4.23)	0.016
Completed high school	1.83 (1.23-2.72)	0.003		
Unstable housing*	2.20 (1.47-3.29)	<0.001		
Living situation				
Alone	1.00		1.00	
With many others	1.40 (0.93-2.11)	0.108	1.95 (1.22-3.14)	0.005
On the street	6.10 (2.26-16.44)	<0.001	5.08 (1.72-14.99)	0.003
Overall health self-rated (poor, fair and neutral) vs. excellent and good)	2.10 (1.41-3.13)	<0.001	1.64 (1.05-2.55)	0.030
Ever incarcerated	1.97 (1.31-2.97)	0.001		
Currently earn <$15,000	2.31 (1.48-3.59)	<0.001		
Ever depressed	1.29 (0.87-1.92)	0.199		
Ever diagnosed with Hepatitis C	2.58 (1.66-4.01)	<0.001		
CD4 cell count/mm^3 (per 100 cell increase) at treatment initiation	1.30 (0.76-2.25)	0.336		
< 95% adherence in 1st year of treatment	3.07 (2.02-4.66)	<0.001	2.68 (1.67-4.12)	<0.001
AIDS at treatment initiation	1.01 (0.58-1.76)	0.980		

*Not living in a house or apartment

Figure 1. Reasons for missed doses of antiretroviral medication in LISA treatment interrupters (N=651) and non-interrupters (N=117)



*Significant at the p<0.05 level

**Denominator was 600 individuals for all responses except not applicable category, which included the whole sample (N=768)

Chapter 3

PREDICTORS AND OUTCOMES ASSOCIATED WITH UNSTRUCTURED TREATMENT INTERRUPTIONS AMONG HIV-POSITIVE INDIVIDUALS ON ANTIRETROVIRAL THERAPY IN CANADA

ABSTRACT

Objectives: To better understand trends, determinants and consequences of combination antiretroviral treatment (cART) interruption and resumption.

Methods: We estimated frequency, determinants and outcomes of treatment interruption (TI) and resumption among treatment-naïve HIV-positive individuals in the Canadian Observational Cohort (CANOC) collaboration from 2000-2011. Participants resided in Canada, were at least 18 years of age, initiated a first antiretroviral regimen comprised of at least three agents, had at least 90 days of follow-up and at least one measurement of HIV plasma viral load and CD4 cell count within six months of initiating cART. TIs were defined as interruptions in cART for a period of at least 90 days and the time to TI analysis was limited to patients initiating cART from 2006-2011 to exclude structured TIs which were prescribed prior to 2006.

Results: A total of 7,633 CANOC participants initiating cART between 2000 and 2011 were included in the analyses, of whom 1,860 (24.5%) had at least one TI ≥ 90 days. The prevalence of TI in the first calendar year of cART decreased by half over the study period. Predictors of a first TI were female sex (adjusted hazard ratio (aHR): 1.59, 95% CI: 1.33-1.92), Aboriginal ancestry (aHR: 1.67, 1.27-2.20), a history of injecting drug use (aHR: 1.43, CI: 1.09-1.89), hepatitis C antibody seropositivity (aHR: 2.17, CI: 1.68-2.79), a baseline CD4 cell count above 350 cells/mm^3 versus less than 200 cells/mm^3 (aHR: 1.46, CI: 1.17-1.81) and use of zidovudine versus tenofovir in the initial cART regimen (aHR: 2.47, CI: 1.92-3.20). Factors protective against TI were older age (aHR:

0.79, CI: 0.73-0.87), higher HIV plasma viral load (log_{10}) (aHR: 0.87, CI: 0.78-0.97) and residence in Ontario (aHR: 0.55, CI: 0.43-0.70) or Quebec (aHR: 0.42, CI: 0.31-0.57) versus British Columbia (BC). Factors predicting resumption of treatment after a first TI included male sex, residence in BC, older age, more recent cART initiation and a CD4 cell count <200 cells/mm^3 at cART initiation (all $p<0.05$). TIs were associated with increased risk of mortality for individuals who subsequently resumed treatment (aHR: 1.30, CI: (1.06-1.59)) and those who did not resume treatment (aHR: 7.41, CI: (5.73-9.60)) after adjusting for socio-demographic and clinical factors.

Discussion: Despite significant improvements in cART since its advent, TIs remain relatively common. Strategies to support continuous HIV treatment are needed to maximize the benefits of cART.

INTRODUCTION

The expanded use of combination antiretroviral therapy (cART) since 1996 has dramatically enhanced the quality of care and the life expectancy of HIV-positive individuals [1]. However, sustained optimal use of cART is necessary to ensure maximum therapeutic benefits. Incomplete adherence and treatment interruptions (TIs) due to treatment fatigue, side effects and cART toxicities [2-4] have therefore emerged as major challenges to the full realization of the therapeutic promise of cART.

Explored as a strategy to reduce cost and cART-related toxicities and improve patient quality of life, TIs, whether physician-directed (structured) or patient-initiated (unstructured), have been found to promote viral rebound and CD4 cell loss, and more importantly, to increase the risk of opportunistic infections and death in observational studies and prospective clinical trials [5-14]. As evidence accumulated demonstrating the adverse effects of TIs, culminating in the publication of results from the seminal SMART trial in 2006, [15] TIs were no longer recommended. However, results from several studies indicate that unstructured, patient-elected TIs continue to occur [5, 16, 17]. Despite the relatively high frequency of TIs, their determinants and outcomes from 2000 onwards, a time period often characterized as the era of modern cART [16, 18], and since 2006 when treatment recommendations were developed that precluded physician-directed TIs, are still not well-characterized [16].

As the paradigm of "treatment as prevention" and earlier treatment become entrenched in contemporary treatment guidelines in North America [19-22] and globally [23], it is vital that we minimize the occurrence of TIs. In particular, the World Health

Organization's revised guidelines effectively increase the number of individuals eligible for treatment globally by 50% [23], providing urgent impetus to better understand and address TIs.

Thus, we conducted the present study to characterize trends, determinants and consequences of treatment interruption and resumption in a setting of universal free access to HIV care, including medical and laboratory monitoring as well as cART, in Canada. We hypothesized that individuals who are intermittent or episodic users of cART (defined here as those with gaps in cART of at least 90 days [5, 10, 24]) are different from continuous users. Moreover, we hypothesized that TIs should be less common than in previous studies due to improvements in cART profiles over time. We also sought to identify which individuals are more likely to reinitiate cART once interrupted, and whether individuals who have interrupted cART have a higher risk of mortality.

METHODS

Study Population

The Canadian Observational Cohort (CANOC) collaboration is a national collaboration of eight cohorts situated in three provinces (British Columbia (BC), Quebec and Ontario) of antiretroviral-naive HIV-positive individuals initiating cART after January 1, 2000. The cohort has been described in more detail elsewhere [25]. Briefly, patient eligibility criteria for inclusion into CANOC consists of the following points: documented HIV infection, residence in Canada, at least 18 years of age, initiation of a first antiretroviral regimen comprised of at least three agents, and at least one measurement of HIV plasma viral load and CD4 cell count within six months of initiating

cART. Patient selection and data extraction are performed locally at the data centers of the participating cohort studies. Non-nominal data from each cohort on a predefined set of demographic, laboratory, and clinical variables are then pooled and analyzed at the Project Data Centre in Vancouver, BC. All participating cohorts have received approval from their institutional ethics boards to contribute non-nominal patient-specific data to CANOC. In this analysis we excluded individuals with less than 90 days of follow-up to account for immortal person-time since these individuals were never at risk for the outcome of interest (a TI ≥90 days). The cohort was administratively censored on September 1st, 2011.

Outcomes

The primary outcome in this study was time to first TI, which was defined as an interruption in all antiretroviral drugs for a period of at least 90 consecutive days, treated as time-varying into an absorbent state (once interrupted always interrupted). However, we also separated TIs into two groups for the time to death analysis: those who restarted cART after a first TI and those who did not. TIs were identified through prescription refill information in BC and through a mixture of clinician reports and pharmacy information for sites in Ontario and Quebec. We performed a sensitivity analysis to assess the impact of differences in ascertainment of TI on mortality. Time origin for this aim was cART initiation and the time axis used was time since cART initiation. A secondary outcome was time to resumption of cART, defined as the time from initiation of first TI (time origin) to time of treatment resumption for participants who had at least one interruption. TI was subsequently examined as the primary covariate of interest in an

analysis identifying factors associated with time to death, which was defined as all-cause mortality with time origin at cART initiation.

Exposures

Additional potential covariates in the models included age at treatment initiation (per 10 year increase), sex, Aboriginal ancestry, province, risk category (men who have sex with men (MSM), injecting drug use (IDU), heterosexual contact, country of origin where HIV is endemic, blood transfusion), and clinical variables such as composition of initial cART regimen (nucleoside reverse transcriptase inhibitor (NRTI) backbone and third drug in the regimen), hepatitis C antibody seropositivity, and AIDS, HIV plasma viral load ($\log_{10}$) and CD4 cell count at cART initiation.

Statistical Analyses

The chi-squared test was used to determine whether there were significant trends over time in the frequency of TIs within one year of cART initiation, among individuals with at least 12 months of follow-up from 2000 to 2011. We also examined the proportion of CANOC participants with at least 12 months of follow-up who initiated and interrupted cART in the same calendar year to demonstrate temporal trends. Patient demographical and clinical characteristics at cART initiation were tabulated by treatment interruption status and examined for differences using chi-square statistics for categorical data and Wilcoxon's rank sum test for continuous variables.

Descriptive analyses included Kaplan-Meier curves of time to event by categorical variables of interest and continuous variables based on predetermined cut-off

points. The log-rank and likelihood ratio tests were used to assess whether the survival curves differed by strata of covariates of interest. Univariate Cox proportional hazards models were used to examine the relationship of each covariate with the outcome. Covariates with p-values less than <0.05 and those deemed to be requisite based on a priori information were considered candidates for the multivariable model. Multivariable Cox proportional hazards models were constructed to examine factors associated with time to first TI. In this analysis, we limited the sample to individuals who initiated treatment after January 1st, 2006, to assess only the effect of unstructured TIs and not structured TIs, which ceased being prescribed in 2006.

Cox regression was then used to examine factors associated with time to resumption of cART after a first interruption. We also used Cox proportional hazards modeling to identify factors associated with time to death from all causes. As the assumption of proportional hazards was not met in the time to death analysis, a flexible parametric survival model using restricted cubic splines to model the baseline cumulative hazard was considered [26]. The proportional hazards assumption was met for the remaining two endpoints. Akaike Information Criteria, which balances model goodness of fit with the number of parameters, was used to select the models which best fit the data for all analyses (lower AIC indicates better fit). Analyses were performed using Stata statistical software, version 12.1 [27].

RESULTS

Data were available on 7,633 individuals with at least 90 days of follow-up, of whom 577 (8%) died during 34,921 person-years of follow-up. 1,860 participants

(24.5%) interrupted cART over the study period from 2000-2011. Overall, 81% of the sample was male, 22% IDU, 67% MSM, and 45% resided in BC. Figure 1 shows the decrease in TIs in the first calendar year of treatment among CANOC participants over the study period. TIs declined every year from 14% in the year 2000 until 2006, at which point the proportion of new initiators interrupting treatment in their first calendar year of cART leveled off to approximately 7%. Similarly, TIs in the first year of treatment (based on the first 365 days of treatment, data not shown) declined from 11% in 2000 to 8% in 2009. Of all first TIs, 681 (37%) occurred within the first 6 months after cART initiation; 290 (16%) occurred between 6-12 months; 351 (19%) between 1-2 years and 538 (29%) occurred ≥2 years after cART initiation. In terms of duration of TIs, 604 (33%) individuals interrupted for less than six months, 418 (23%) interrupted between six months and a year, 285 (15%) of individuals interrupted for one to two years, and 553 (30%) had TIs longer than two years. Of the 1,860 individuals who interrupted, 1,221 (16%) interrupted once, 371 (5%) had two interruptions, 158 (2%) had three interruptions and 110 (6%) had between four and nine interruptions (Appendix 2).

Table 1 shows patient demographic and clinical characteristics at cART initiation by treatment interruption status. Compared to non-interrupters, treatment interrupters were more likely to be female (31% vs. 15%), younger (median age, interquartile range (IQR): 38 (32-44) vs. 41 (34-47)), report Aboriginal ancestry (13% vs. 3%), and live in BC (64% vs. 39%) (all $p<0.001$). Behavioral and clinical factors more commonly reported by interrupters were a history of IDU (43% vs. 16%), heterosexual transmission (33% vs. 25%), hepatitis C antibody seropositivity (46% vs. 18%), use of zidovudine/lamivudine (33% vs. 21%) and stavudine/lamivudine (16% vs. 7%) as initial

NRTI combinations and use of nevirapine (20 vs. 9%) and an "other" third drug in the cART regimen at initiation (all p<0.001). Interrupters were less likely to be men who have sex with men (MSM) (25% vs. 38%, p<0.001), originate from a country in which HIV is endemic (7% vs. 9%, p<0.001), report AIDS prior to cART (13% vs. 14%, p=0.005), use abacavir/lamivudine (10% vs. 16%, p<0.001) or tenofovir/emtricitabine (20% vs. 41%, p<0.001) and efavirenz (25% vs. 38%, p<0.001), or atazanivir (16% vs. 23%) as NRTI combinations and third drugs in the initial cART regimen, respectively.

Time to first TI

The Cox regression model evaluating factors predicting time to first TI was restricted to individuals initiating cART from 2006 onwards and is presented in Table 2. Data were available on 4,134 individuals, of whom 626 (15%) had at least one TI over 9,833 person-years. Mean follow up in this analysis was 2.4 years and median time to first TI was 0.60 years (7.2 months). Predictors of a first TI were female sex (adjusted hazard ratio (aHR): 1.59, 95% CI: 1.33-1.92), Aboriginal ancestry (aHR: 1.67, CI: 1.27-2.20), a history of injecting drug use (aHR: 1.43, CI: 1.09-1.89), a hepatitis C antibody seropositivity (aHR: 2.17, CI: 1.68-2.79), a baseline CD4 cell count above 350 cells/mm^3 versus less than 200 cells/mm^3 (aHR: 1.46, CI: 1.17-1.81) and use of zidovudine versus tenofovir in the initial cART regimen (aHR: 2.47, CI: 1.92-3.20). Factors protective against TI were older age (aHR: 0.79 per 10 year increase, CI: 0.73-0.87), higher HIV plasma viral load (log_{10}) (aHR: 0.87, CI: 0.78-0.97) and residence in Ontario (aHR: 0.55, CI: 0.43-0.70) or Quebec (aHR: 0.42, CI: 0.31-0.57) versus BC. There was some collinearity demonstrated in the model between IDU and hepatitis C variables as well as

plasma viral load and CD4 cell count that attenuated both HRs. Figure 2 shows that the cumulative probability of interrupting treatment over the study period, which was 0.10 (CI: 0.09-0.11) after one year on cART.

Time to cART resumption

Of 1,860 individuals who interrupted therapy, 1,566 (84%) eventually restarted cART. Median time to cART resumption was 9.6 months. The Cox regression model examining factors predicting resumption of treatment after a first TI, presented in Table 3, shows that male sex (aHR: 1.22, CI: 1.09-1.37), older age (aHR: 1.10 per 10 year increase, CI: 1.04-1.17) and initiation of cART in 2004-2006 (aHR: 1.27, CI: 1.11-1.45) or 2007-2011 (aHR: 1.45, CI: 1.24-1.70) versus 2000-2003 were significantly association with treatment resumption, while a CD4 cell count 200-349 cells/mm^3 (aHR: 0.76, CI: 0.68-0.85) and greater than 350 cells/mm^3 (aHR: 0.43, CI: 0.37-0.50) at cART initiation compared to a CD4 cell count less than 200 cells/mm^3 and residence in Ontario (aHR: 0.81, CI: 0.71-0.92) versus BC were associated with less likely resumption of treatment.

Time to death

Figure 3 shows that cumulative mortality was higher in treatment interrupters who did not resume cART in addition to those who did compared to non-interrupters ($p<0.001$, log-rank test). Individuals who did not resume cART were at the highest risk of death. The cumulative probability of death at 5 years for non-interrupters was 0.06 (CI: 0.05-0.07), 0.10 (95% CI: 0.08-0.11) for individuals who interrupted and restarted treatment and 0.35 (95%CI: 0.29-0.42) for those who interrupted and never resumed

treatment. Table 4 shows unadjusted and adjusted factors predicting time to death. Predictors of poorer survival were TI with treatment resumption (aHR: 1.30, CI: 1.06-2.59), TI with no treatment resumption (aHR: 7.41, CI: 5.73-9.60), female sex (aHR: 1.32, CI: 1.07-1.62), older age (aHR: 1.56 per 10 year increase, CI: 1.43-1.70), Aboriginal ancestry (aHR: 2.25, CI: 1.67-3.03), and a history of IDU (aHR: 2.44, CI: 1.91-3.12) or unknown IDU history (aHR: 1.83, CI: 1.30-2.58). Clinical factors predicting mortality were a baseline diagnosis of AIDS (aHR: 1.54, CI: 1.25-1.91), and a NRTI combination in the initial cART regimen of zidovudine/lamiduvine (aHR: 1.64, CI: 1.21-2.22), stavudine/lamiduvine (aHR: 1.91, CI: 1.37-2.66) or "other" (aHR: 2.05, CI: 1.48-2.85). Lopinavir as the third drug in the initial cART regimen was also associated with higher mortality (aHR: 1.41, CI: 1.09-1.84). Protective factors included residence in Ontario (aHR: 0.034, CI: 0.25-0.45) or Quebec (aHR: 0.53, CI: 0.37-0.75) versus BC, heterosexual transmission (aHR: 0.54, CI: 0.43-0.67) and a CD4 cell count at cART initiation of 200-349 cells/mm^3 (aHR: 0.74, CI: 0.60-0.90) or greater than 350 cells/mm^3 (aHR: 0.50, 0.38-0.67) versus less than 200 cells/mm^3.

DISCUSSION

Our results demonstrate that the frequency of TI remains relatively high in a setting of universal free access to HIV care. TIs continue to be pervasive, with 25% of CANOC participants reporting at least one interruption of at least 90 days over the study period. However, it is reassuring that the proportion of individuals interrupting cART within the first calendar year of treatment decreased over time and stabilized over the last

five years. TIs were a significant predictor of all-cause mortality, despite the fact that a sizeable majority of individuals who interrupted treatment went on to resume cART. While individuals who resumed cART had a lower risk of mortality than those who did not resume, even one TI led to a statistically significantly increased risk of death. Collectively, these data suggest that there is an urgent need to strengthen communication about the need to embrace sustained, lifelong therapy with health providers and patients, as a means to optimize the morbidity, mortality and transmission benefits associated with the use of cART.

Improvements in ease of delivery and the side effect profile of cART over time appear to have improved the acceptability of these medications for patients. Of note, we have documented a marked decline in the proportion of individuals interrupting treatment in their first year of treatment over the study period. These results are complementary to data from BC which reported a reduction in the prevalence of TIs over the period from 2000-2006 [5]. While medication side effects were the primary reason for TIs at one time [28-31], decreased toxicity associated with cART component drugs has improved the tolerability of these medications considerably [31-34]. Consistent with this information, we demonstrated that patients who initiate on certain older drugs such as zidovudine have a higher risk of interrupting treatment. Additionally, the preponderant use of compact once daily fixed dose formulations as preferred first line regimens may have contributed to the observed reduction in the proportion of TIs in the first year of treatment in more recent years [35], as are 2006 guidelines discontinuing physician-directed TIs.

Nonetheless, it is concerning that our analysis highlighted a higher risk of TI among individuals who initiate treatment earlier in the course of their disease, as

demonstrated by higher CD4 cell counts and lower plasma viral load pre-cART, as has been observed in previous studies [16, 24, 36-39]. Additionally, we found that individuals with higher CD4 cell counts are less likely to reinitiate therapy after interruption. In this context, it is important to emphasize that the current analyses were undertaken using data from 2000-2011, during which time cART guidelines were evolving. It is only now, in 2013, that consensus has been reached regarding the use of cART at CD4 counts ≤500 cells/mm^3 and in selected additional populations regardless of CD4 count (such as serodiscordant couples, pregnant women and individuals with co-existing tuberculosis) [19-23]. Therefore, it will be important to closely prospectively monitor the incidence and determinants of TIs for the foreseeable future, as the number of HIV-positive individuals initiating treatment with higher cell counts and lower viral load is likely to increase. Assuring that these relatively less immunosuppressed patients are provided with the support to maintain continuity of treatment will be imperative to avoid the development of drug resistance and worsened prognosis due to TIs as the HIV "treatment as prevention" strategy is more widely implemented [32]. Moreover, as many of these newly eligible individuals will continue treatment for an extended period of time, strategies to counter treatment fatigue are urgently needed.

Our results suggest that women are at increased risk of interrupting treatment and less likely to resume cART following TI. However, this has not been a consistent finding across studies [5, 24, 40-43]. Higher risk in women is a phenomenon that may partly be due to initiation of cART during pregnancy and subsequent discontinuation of treatment. Other possible explanations are that women may report more cART side-effects and toxicities [41, 44], that they may have greater drug intolerance during pregnancy [45] and

that women may be unwilling to engage consistently with or prioritize cART if doing so may lead to negative perceptions or neglect from others [46]. Consistent with previous studies, we found that younger individuals [5, 36, 43, 47], those initiating cART with a regimen containing zidovudine [5], and those with hepatitis C co-infection [5, 24] and a history of IDU [5, 24, 36] were more likely to interrupt cART. Regional differences were also observed, with less risk of TI in Ontario and Quebec compared to BC, a finding likely explained by inherent cohort differences. For instance, BC data represents all HIV-positive individuals on cART across the province while Ontario and Quebec data are derived from a selection of specialized clinics; in addition, there are differences in the proportion of women, Aboriginal individuals and IDU.

Lastly, individuals self-reported as having Aboriginal ancestry were at higher risk of interrupting treatment. Aboriginal peoples are over-represented in the HIV epidemic in Canada, constituting 4% of the population according to the 2011 Canadian census and 12% of new HIV infections in 2011 [48, 49]. Additional knowledge should be generated to understand the reasons for interruption for each of these specific sub-populations and specialized services should be designed to support continuous engagement of treatment accordingly.

Resumption of treatment, observed in more than three quarters of individuals who interrupted, was more likely in individuals who were males, resided in BC, were older, initiated cART more recently and had a CD4 cell count <200 cells/mm^3 at treatment initiation. Thus, certain predictors of TI were the opposite of predictors of resumption, with women and those with higher CD4 cell counts more likely to interrupt and men and those with lower CD4 cell counts more likely to resume cART. Other studies have found

similar rates of resumption [5, 42, 50]. While the probability of restarting cART is relatively high, it is important to note that 15% of individuals never reinitiated treatment while under observation. This remains a substantial concern, as these individuals are at increased risk of disease progression and premature death, as well as at increased risk of transmitting HIV infection. There was some survival benefit conferred to individuals resuming cART after TI compared to those who did not reinitiate cART; however, even those who resumed cART had a statistically significantly greater risk of mortality. As with risk of TI, younger, female individuals initiating cART with higher CD4 cell counts should be targeted for additional support to increase the likelihood of resumption after TI.

Retention in treatment represents a crucial indicator of long-term success for people living with HIV. Risk factors for TI identified in this study will aid in identifying populations in need of increased support. A number of useful guidelines for managing patient retention in care have been developed specifically addressing adherence [51] and may also be useful in the context of TIs. The findings presented here may be useful in the development of interventions specific to interruptions in treatment; this is an opportune area for future research. In particular, more than half of first TIs occurred in the first year of treatment, which suggests that new initiators are particularly vulnerable to prolonged gaps in engagement and could be targeted for increased monitoring and support.

Strengths and limitations

Using data from the largest collaboration of HIV cohorts in Canada to inform analyses lent considerable power to analyses. CANOC represents about a quarter of all HIV-positive individuals in the country who are currently on cART and approximately

half of those who have initiated on more modern regimens since 2000 [52]. This improves the ability to generalize study results to the remainder of the HIV-positive population in Canada currently accessing treatment. Unlike many other studies examining interruptions in treatment, this study focused on the modern cART period and restricted analyses pertaining to predictors of TIs to the period following the recommendation not to prescribe TIs, from 2006 onwards. CANOC also enrolled cART-naïve individuals, which helps isolate the effect of the latest treatment regimens on risk of TI.

This study has several limitations. Ascertainment of TI differs among CANOC sites, with some sites recording TIs from medical charts (data from physician, nurses and pharmacists), and others using cART prescription refill information as well as information from medical charts to identify TIs. We sought to mitigate this potential bias by examining differences in time to mortality and time to first TI comparing sites using medical charts versus those that used pharmacy and medical charts. No differences were observed (data not shown); however, residual confounding may be present that may also help explain regional differences in risk of TI. In addition, only the BC cohort recorded Aboriginal ancestry, a strong predictor of TI and mortality that may also help account for regional difference. We were not able to measure some factors which have been associated in other studies with TIs, such as pregnancy, co-morbidities, depression [47, 53], mental disorders [38], incarceration [54-56], and socioeconomic factors such as unstable housing and lack of social supports; these were not captured in the CANOC database. As data become available, it will be interesting to observe the impact of these latter factors. Future research studying TIs should seek to examine these factors and their

contribution to the incidence and prevalence of TIs. Lastly, CANOC includes data from only three provinces, and a clinic-based selection bias exists, as included data from BC includes the entire sample of people on cART province-wide while data from Ontario and Quebec come from a selection of clinics that are mainly HIV-specific.

In conclusion, our results demonstrate that TIs remain relatively prevalent. This is of particular concern given that within our study, TIs continue to be associated with increased mortality. Specific strategies may be warranted to decreased the incidence of TIs, particularly targeting the most affected groups, such as those who are women, younger, of Aboriginal ancestry, IDU, less immunosuppressed at treatment initiation, initiate cART with zidovudine/lamivudine, HCV co-infected and have lower HIV plasma viral load at cART initiation. Our results uncovered the use of zidovudine versus tenofovir in the initial cART regimen as a potentially amenable factor associated with TIs. Full implementation of current guidelines, which clearly favor the use of tenofovir over zidovudine as a first line agent for cART, should help address this issue. On the other hand, the finding that earlier initiation of cART was associated with higher rates of TIs is concerning, and merits close prospective monitoring as new guidelines are widely and fully implemented. Finally, while it is reassuring to see that over three quarters of the observed TIs were time-limited, in view of the serious individual and societal consequences of TIs, further targeted efforts are required to maximize resumption of sustained cART as soon as possible following TIs.

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Table 1. Baseline characteristics of 7,633 CANOC participants from 2000-2011 by treatment interruption status

Characteristic	N	No treatment Interruption n (%) n = 5,773	Treatment Interruption n (%) n = 1,860	p-value
Sex	7,633			
Male		4,904 (85.0)	1,287 (69.2)	<0.001
Female		869 (15.1)	573 (30.8)	
Median age (IQR)*	7,633	41 (34-47)	38 (32-44)	<0.001
History of IDU†	7,633			
Yes		906 (15.7)	790 (42.5)	<0.001
No		3,477 (60.2)	780 (41.9)	
Unknown		1,390 (24.1)	290 (15.6)	
Province	7,633			
British Columbia		2,276 (39.4)	1,183 (63.6)	<0.001
Ontario		2,135 (37.0)	422 (22.7)	
Quebec		1,362 (23.6)	255 (13.7)	
Aboriginal	7,633			
Yes		172 (3.0)	242 (13.0)	<0.001
No		836 (14.5)	441 (23.7)	
Unknown		4,765 (82.5)	1,177 (63.3)	
Transmission Category				
Men who have sex with men	7,633			
Yes		2,217 (38.4)	457 (24.6)	<0.001
No		1,666 (28.9)	961 (51.7)	
Unknown		1,890 (32.7)	442 (23.8)	
Heterosexual	7,633			
Yes		1,415 (24.5)	607 (32.6)	<0.001
No		2,461 (42.6)	822 (44.2)	
Unknown		1,897 (32.9)	431 (23.2)	
Endemic country of origin	7,633			
Yes		524 (9.1)	128 (6.9)	<0.001
No		3,380 (58.6)	1,302 (70.0)	
Unknown		1,869 (32.4)	430 (23.1)	
Blood transfusion	7,633			
Yes		97 (1.7)	36 (1.9)	<0.001
No		3,731 (64.6)	1,372 (73.8)	
Unknown		1,945 (33.7)	452 (24.3)	

* IQR= interquartile range
†IDU= injecting drug use
^pVL=HIV plasma viral load
**NRTI=nucleoside reverse transcriptase inhibitor
‡ cART: combination antiretroviral therapy

Table 1 (continued). Characteristics of 7,633 CANOC participants from 2000-2011 by treatment interruption status

Characteristic	N	No treatment Interruption n (%) n = 5,773	Treatment Interruption n (%) n = 1,860	p-value
AIDS prior to cART‡	7,633			
Yes		791 (13.7)	237 (12.7)	0.005
No		4,521 (78.3)	1,513 (81.3)	
Unknown		461 (8.0)	110 (5.9)	
Hepatitis C	7,633			
Yes		1,024 (17.7)	851 (45.8)	<0.001
No		4,338 (75.1)	902 (48.5)	
Unknown		411 (7.1)	107 (5.8)	
Median CD4 cell count (IQR)	7,633	210 (120-300)	210 (110-310)	0.004
Median pVL^ (log10) (IQR)	7,633	4.87 (4.33-	4.84 (4.29-5.00)	<0.001
Year initiated cART	7,633			
2000-2003		1,309 (22.7)	878 (47.2)	<0.001
2004-2006		1,520 (26.3)	526 (28.3)	
2007-2011		2,944 (51.0)	456 (24.5)	
NRTI combo in baseline cART‡ regimen**	7,633			<0.001
Tenofovir/Emtricitabine		2,375 (41.1)	363 (19.5)	
Zidovudine/Lamivudine		1,223 (21.2)	619 (33.3)	
Tenofovir/Lamivudine		458 (7.9)	157 (8.4)	
Abacavir/Lamivudine		905 (15.7)	177 (9.5)	
Stavudine/Lamivudine		395 (6.8)	292 (15.7)	
Other		417 (7.2)	252 (13.6)	
Third drug in baseline cART‡ regimen	7,633			<0.001
Nevirapine		507 (8.8)	371 (20.0)	
Efavirenz		2,193 (38.0)	470 (25.3)	
Lopinavir		1,118 (19.4)	351 (18.9)	
Atazanavir		1,347 (23.3)	296 (15.9)	
Other		608 (10.5)	372 (20.0)	

* IQR= interquartile range
†IDU= injecting drug use
^pVL=HIV plasma viral load
**NRTI=nucleoside reverse transcriptase inhibitor
‡ cART: combination antiretroviral therapy

Table 2. Factors predicting time to first TI among CANOC participants who initiated treatment from 2006 to 2011 (N=4,134)

	Unadjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
Female vs. Male	2.78 (2.34-3.13)	<0.001	1.59 (1.33-1.92)	<0.001
Age (per 10 year increment)	0.78 (0.71-0.85)	<0.001	0.79 (0.73-0.87)	<0.001
Province				
British Columbia	1.00		1.00	
Ontario	0.46 (0.38-0.57)	<0.001	0.55 (0.43-0.70)	<0.001
Quebec	0.29 (0.22-0.39)	<0.001	0.42 (0.31-0.57)	<0.001
Aboriginal ancestry				
No	1.00		1.00	
Yes	3.12 (2.37-4.11)	<0.001	1.69 (1.27-2.20)	<0.001
Unknown	0.59 (0.47-0.73)	<0.001	1.01 (0.90-1.28)	0.932
Transmission group				
History of injecting drug use				
No	1.00		1.00	
Yes	3.92 (3.27-4.70)	<0.001	1.43 (1.08-1.89)	0.010
Unknown	1.14 (0.90-1.45)	0.285	1.02 (0.79-1.31)	0.874
Men who have sex with men				
No	1.00			
Yes	0.33 (0.27-0.41)	<0.001		
Unknown	0.45 (0.37-0.55)	<0.001		
Heterosexual				
No	1.00			
Yes	1.38 (1.15-1.68)	0.001		
Unknown	0.79 (0.64-0.98)	0.030		
Endemic country				
No	1.00			
Yes	0.63 (0.44-0.90)	0.011		
Unknown	0.66 (0.54-0.80)	<0.001		
Blood transfusion				
No	1.00			
Yes	1.16 (0.64-2.10)	0.636		
Unknown	0.68 (0.56-0.82)	<0.001		

**cART: combination antiretroviral therapy
**NRTI=nucleoside reverse transcriptase inhibitor

Table 2 (continued). Factors predicting time to first TI among CANOC participants who initiated treatment from 2006 to 2011 (N=4,134)

	Unadjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
AIDS prior to cART*				
No	1.00			
Yes	0.93 (0.71-1.21)	0.597		
Unknown	0.60 (0.39-0.93)	0.023		
Ever diagnosed with Hepatitis C				
No	1.00			
Yes	3.81 (3.22-4.51)	<0.001	2.17 (1.68-2.79)	<0.001
Unknown	0.99 (0.66-1.48)	0.958	0.75 (0.50-1.12)	0.160
CD4 cell count at treatment initiation				
<200 cells/mm^3	1.00		1.00	
200-349 cells/mm^3	0.76 (0.63-0.92)	0.004	0.96 (0.80-1.16)	0.688
350+ cells/mm^3	1.27 (1.02-1.57)	0.030	1.46 (1.17-1.81)	<0.001
Plasma viral load at initiation (log10)	0.84 (0.77-0.93)	0.001	0.87 (0.78-0.97)	0.015
Year initiated cART*				
2006	1.00			
2007	0.84 (0.68-1.04)	0.110		
2008	0.67 (0.53-0.85)	0.001		
2009	0.67 (0.52-0.87)	0.002		
NRTI** combo in baseline cART* regimen				
Tenofovir/Emtricitabine	1.00		1.00	
Zidovudine/Lamivudine	2.41 (1.89-3.08)	<0.001	2.47 (1.92-3.20)	<0.001
Tenofovir/Lamivudine	1.26 (0.95-1.67)	0.110	1.32 (1.00-1.75)	0.052
Abacavir/Lamivudine	0.85 (0.68-1.08)	0.189	1.22 (0.97-1.53)	0.089
Stavudine/Lamivudine	1.17 (0.48-2.83)	0.729	1.63 (0.67-3.99)	0.282
Other	1.20 (0.72-2.02)	0.481	1.64 (0.97-2.80)	0.066
Third drug in baseline cART* regimen				
Nevirapine	1.00			
Efavirenz	1.63 (0.97-2.71)	0.061		
Lopinavir	2.08 (1.23-3.50)	0.006		
Atazanavir	1.72 (1.03-2.87)	0.037		
Other	3.47 (1.93-6.22)	<0.001		

**cART: combination antiretroviral therapy
**NRTI=nucleoside reverse transcriptase inhibitor

Table 3. Factors predicting time to resumption of cART after a first TI among 1,860 participants who initiated and interrupted treatment from 2001-2011

	Unadjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
Female vs. Male	0.72 (0.65-0.81)	<0.001	0.82 (0.73-0.92)	0.001
Age (per 10 year increment)	1.19 (1.13-1.26)	<0.001	1.10 (1.04-1.17)	0.001
Province				
British Columbia	1.00		1.00	
Ontario	0.70 (0.62-0.80)	<0.001	0.81 (0.71-0.92)	0.002
Quebec	0.77 (0.66-0.89)	0.001	0.88 (0.75-1.03)	0.112
Aboriginal ancestry				
No	1.00			
Yes	0.92 (0.78-1.09)	0.350		
Unknown	0.78 (0.69-0.87)	<0.001		
Transmission group				
History of injecting drug use				
No	1.00			
Yes	1.19 (1.07-1.33)	0.001		
Unknown	0.96 (0.83-1.12)	0.634		
Men who have sex with men				
No	1.00			
Yes	0.96 (0.85-1.09)	0.557		
Unknown	0.97 (0.86-1.09)	0.595		
Heterosexual				
No	1.00			
Yes	0.97 (0.87-1.09)	0.660		
Unknown	0.97 (0.86-1.11)	0.679		
Endemic country				
No	1.00			
Yes	0.66 (0.53-0.81)	<0.001		
Unknown	0.95 (0.84-1.07)	0.412		
Blood transfusion				
No	1.00			
Yes	0.90 (0.62-1.29)	0.557		
Unknown	0.95 (0.85-1.07)	0.438		

*cART: combination antiretroviral therapy
**NRTI=nucleoside reverse transcriptase inhibitor

Table 3 (continued). Factors predicting time to resumption of cART after a first TI among 1,860 participants who initiated and interrupted treatment from 2001-2011

	Unadjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
AIDS prior to cART*				
No	1.00			
Yes	1.45 (1.25-1.67)	<0.001		
Unknown	0.87 (0.70-1.08)	0.218		
Ever diagnosed with Hepatitis C				
No	1.00			
Yes	1.12 (1.01-1.24)	0.025		
Unknown	0.76 (0.60-0.97)	0.028		
CD4 cell count at treatment initiation				
<200 cells/mm^3	1.00		1.00	
200-349 cells/mm^3	0.75 (0.67-0.84)	<0.001	0.76 (0.68-0.85)	<0.001
350+ cells/mm^3	0.40 (0.35-0.46)	<0.001	0.43 (0.37-0.50)	<0.001
Year initiated cART*				
2000-2003	1.00		1.00	
2004-2006	1.25 (1.11-1.40)	<0.001	1.27 (1.11-1.45)	0.001
2007-2011	1.42 (1.25-1.62)	<0.001	1.45 (1.24-1.70)	<0.001
NRTI** combo in baseline cART* regimen				
Tenofovir/Emtricitabine	1.00			
Zidovudine/Lamivudine	0.55 (0.47-0.64)	<0.001		
Tenofovir/Lamivudine	0.93 (0.76-1.13)	0.457		
Abacavir/Lamivudine	0.89 (0.73-1.10)	0.267		
Stavudine/Lamivudine	0.74 (0.62-0.88)	<0.001		
Other	0.59 (0.49-0.70)	<0.001		
Third drug in baseline cART* regimen				
Nevirapine	1.00		1.00	
Efavirenz	1.22 (1.05-1.41)	0.011	0.96 (0.81-1.14)	0.640
Lopinavir	1.27 (1.08-1.49)	0.003	1.16 (0.97-1.38)	0.095
Atazanavir	1.59 (1.35-1.88)	<0.001	1.02 (0.84-1.25)	0.838
Other	0.83 (0.71-0.97)	0.017	0.88 (0.75-1.04)	0.124

*cART: combination antiretroviral therapy
**NRTI=nucleoside reverse transcriptase inhibitor

Table 4. Factors predicting time to death from cART initiation among 7,633 CANOC participants from 2000-2011

	Unadjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
Interruption type				
No interruption	1.00		1.00	
Interrupted and resumed treatment	1.74 (1.45-2.08)	<0.001	1.30 (1.06-1.59)	0.011
Interrupted and did not resume treatment	7.81 (6.16-9.90)	<0.001	7.41 (5.73-9.60)	<0.001
Female vs. Male	1.42 (1.18-1.72)	<0.001	1.32 (1.07-1.62)	0.009
Age (per 10 year increment)	1.44 (1.33-1.56)	<0.001	1.56 (1.43-1.70)	<0.001
Province				
British Columbia	1.00		1.00	
Ontario	0.27 (0.21-0.35)	<0.001	0.34 (0.25-0.45)	<0.001
Quebec	0.40 (0.31-0.52)	<0.001	0.53 (0.37-0.75)	<0.001
Aboriginal ancestry				
No	1.00		1.00	
Yes	2.71 (2.06-3.57)	<0.001	2.25 (1.67-3.03)	<0.001
Unknown	0.92 (0.74-1.14)	0.446	1.72 (1.34-2.22)	<0.001
Transmission group				
History of injecting drug use				
No	1.00		1.00	
Yes	3.68 (3.05-4.44)	<0.001	2.44 (1.91-3.12)	<0.001
Unknown	2.04 (1.62-2.56)	<0.001	1.83 (1.30-2.58)	0.001
Men who have sex with men				
No	1.00			
Yes	0.42 (0.34-0.52)	<0.001		
Unknown	1.00 (0.82-1.21)	0.966		
Heterosexual				
No	1.00		1.00	
Yes	0.56 (0.45-0.70)	<0.001	0.54 (0.43-0.67)	<0.001
Unknown	0.89 (0.74-1.07)	0.217	0.94 (0.66-1.36)	0.854
Endemic country				
No	1.00			
Yes	0.28 (0.17-0.48)	<0.001		
Unknown	1.01 (0.84-1.21)	0.936		
Blood transfusion				
No	1.00			
Yes	1.00 (0.55-1.82)	0.994		
Unknown	1.08 (0.91-1.29)	0.382		

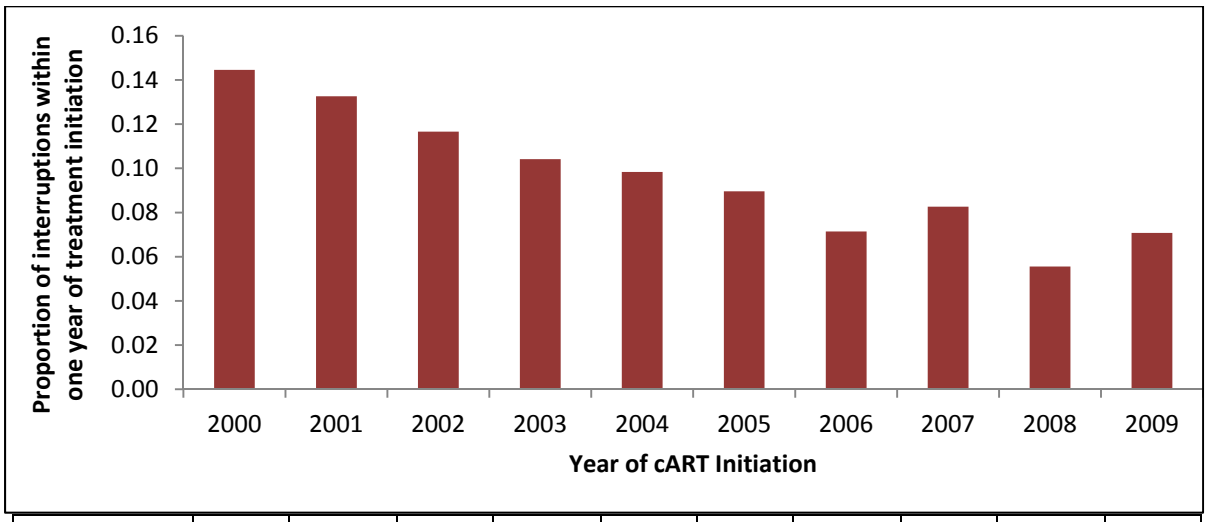
*cART: combination antiretroviral therapy
**NRTI=nucleoside reverse transcriptase inhibitor

Table 4 (continued). Factors predicting time to death from cART initiation among 7,633 CANOC participants from 2000-2011

	Unadjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
AIDS prior to cART*				
No	1.00		1.00	
Yes	1.59 (1.30-1.94)	<0.001	1.54 (1.25-1.91)	<0.001
Unknown	0.83 (0.58-1.20)	0.325	1.26 (0.83-1.92)	0.280
Ever diagnosed with Hepatitis C				
No	1.00			
Yes	4.28 (3.58-5.11)	<0.001		
Unknown	4.17 (3.15-5.51)	<0.001		
CD4 cell count at treatment initiation				
<200 cells/mm^3	1.00		1.00	
200-349 cells/mm^3	0.61 (0.51-0.74)	<0.001	0.74 (0.60-0.90)	0.003
350+ cells/mm^3	0.53 (0.40-0.69)	<0.001	0.50 (0.38-0.67)	<0.001
Baseline plasma viral load (log_{10})	1.33 (1.15-1.54)	<0.001		
Year initiated cART*				
2000-2003	1.00			
2004-2006	0.74 (0.61-0.90)	0.003		
2007-2011	0.54 (0.42-0.70)	<0.001		
NRTI** combo in baseline cART* regimen				
Tenofovir/Emtricitabine	1.00		1.00	
Zidovudine/Lamivudine	1.22 (0.93-1.61)	0.152	1.64 (1.21-2.22)	0.002
Tenofovir/Lamivudine	1.21 (0.84-1.74)	0.314	0.99 (0.68-1.45)	0.978
Abacavir/Lamivudine	0.97 (0.69-1.40)	0.915	1.16 (0.80-1.67)	0.431
Stavudine/Lamivudine	2.09 (1.56-2.80)	<0.001	1.91 (1.37-2.66)	<0.001
Other	2.23 (1.66-3.00)	<0.001	2.05 (1.48-2.85)	<0.001
Third drug in baseline cART* regimen				
Nevirapine	1.00		1.00	
Efavirenz	0.53 (0.41-0.68)	<0.001	0.96 (0.73-1.26)	0.786
Lopinavir	0.90 (0.71-1.51)	0.415	1.41 (1.09-1.84)	0.010
Atazanavir	0.63 (0.47-0.83)	0.001	1.16 (0.83-1.62)	0.387
Other	0.67 (0.52-0.88)	0.003	0.94 (0.72-1.25)	0.688

*cART: combination antiretroviral therapy
**NRTI: nucleoside reverse transcriptase inhibitor

Figure 1. Proportion of CANOC participants with at least 12 months of follow-up who interrupted combination antiretroviral therapy (cART) for at least 3 months within one year of initiation (by calendar year) (N=6,463)



# initiating therapy	498	475	506	557	610	625	686	847	882	777
# (%) interrupted therapy	72 (14)	63 (13)	59 (12)	58 (10)	60 (10)	56 (9)	49 (7)	70 (8)	49 (6)	55 (7)

Figure 2. Cumulative proportion of CANOC participants interrupting treatment after cART initiation (2006-2011)

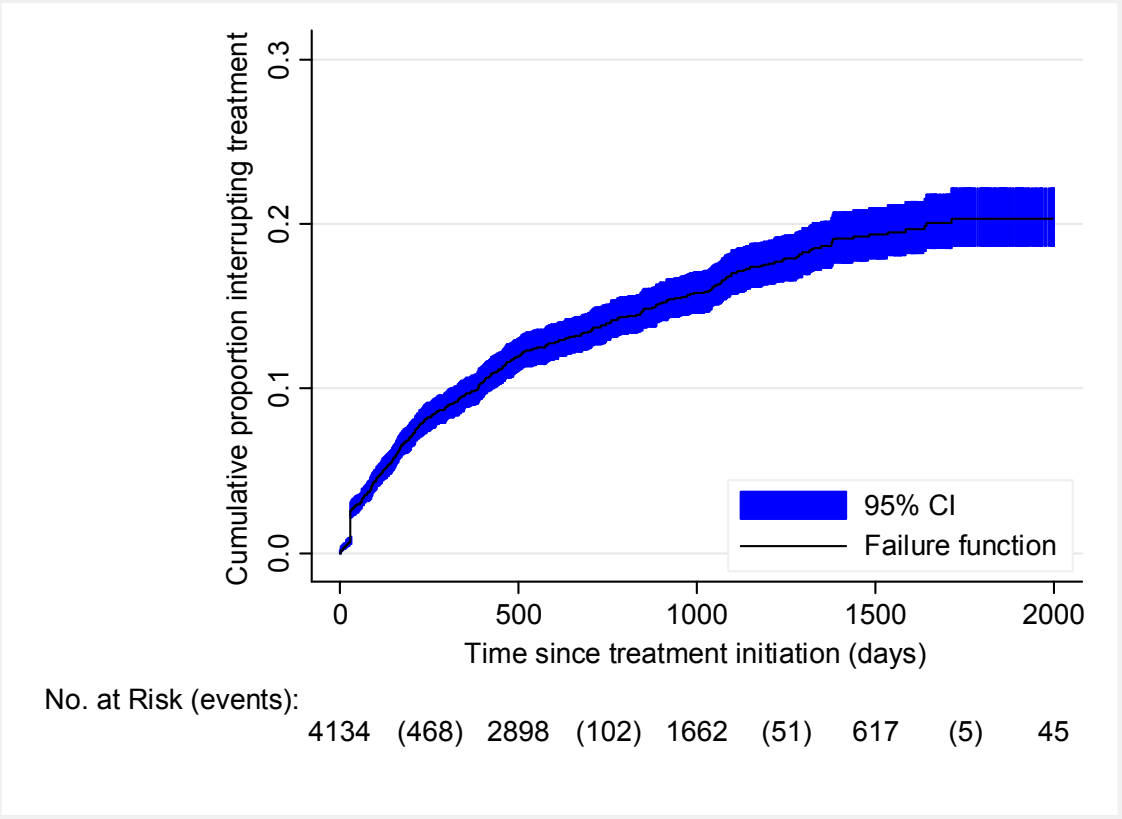
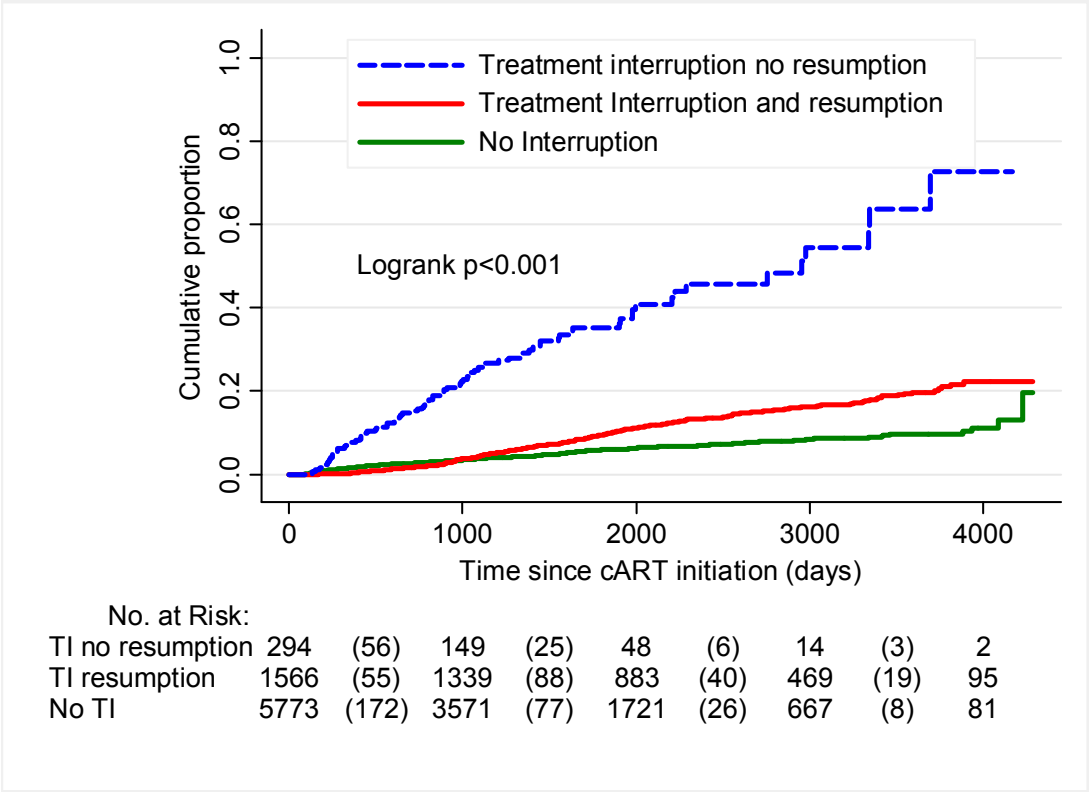


Figure 3. Cumulative mortality of CANOC participants who interrupt and do not resume treatment, those who interrupt but do resume treatment and those who do not interrupt (2000-2011)



*Curves comparing only treatment interrupters who resumed cART to non-interrupters were also statistically significantly different (Logrank p<0.001)

Chapter 4

DISSERTATION SYNTHESIS

4.1. Overview

The purpose of this dissertation was to evaluate the impact of selected demographic, clinical and socio-behavioral characteristics on treatment interruption for HIV-positive individuals on combination antiretroviral therapy (cART). The primary aims of the research were: a) to assess underlying socio-behavioral factors that are associated with treatment interruptions (i.e. distal factors beyond clinical and laboratory predictors); b) to identify demographic, laboratory and clinical predictors of a first treatment interruption and resumption; and c) assess the impact of treatment interruption on HIV disease progression. The first aim (Chapter 2) was completed in the Longitudinal Investigations into Supportive and Ancillary health services (LISA) study, using data from the province of British Columbia (BC) and the second and third aims (Chapter 3) were undertaken using data from the Canadian Observational Cohort (CANOC) collaboration, which is the largest HIV treatment cohort in Canada. Chapter 1 described the background of the HIV epidemic in Canada and the general literature pertaining to unstructured (patient-initiated) and structured (physician-directed) TIs.

4.2. Findings from the Longitudinal Investigations into Supportive and Ancillary health services (LISA) study (Chapter 2)

The dissertation used the LISA study, a cross-sectional study of hard-to-reach individuals on cART in BC, to examine the association of TIs with factors such as housing, drug use, health services utilization and clinical indicators. The LISA study enrolled 1,000 HIV-positive individuals over the age of 19 residing in BC between July 2007 and January 2010 who had ever accessed cART. Using pharmacy records, a TI was defined as a patient-initiated interruption in treatment of at least 90 days during the 12

months preceding or following the study interview. Multivariable logistic regression was used to identify factors associated with treatment interruption.

Results of the LISA study showed that individuals with social vulnerabilities such as poor housing stability, unemployment and drug use were more likely to interrupt treatment. Individuals dealing with concurrent issues such as a lack of stable housing or employment, as well as challenges related to addiction may be unable to prioritize maintenance of an HIV treatment regimen, resulting in periods of interruptions of cART that may compromise long term prognosis. Thus, establishing safe and stable housing for HIV-positive individuals and access to employment is a vital component of the constellation of support for patients needed to maintain engagement in treatment. In addition, poor adherence in the first year after treatment initiation was associated with TIs, suggesting that early inconsistencies in adherence may represent a warning sign of future TIs. Individuals who are more likely to embark on lengthy interruptions may effectively be identified and targeted for assistance early on in their course of therapy.

Another valuable set of findings from the LISA study concerned reasons for missing cART doses. As the most frequent reason cited, side effects continue to be evident in this population; similarly, being too nauseous or sick were commonly reported reasons. Logistical issues such as simply forgetting to take pills or to fill a prescription, travel, and not having appropriate food or drink were also frequently reported. Individuals who interrupted treatment also reported that they did not believe in the efficacy of cART or felt well enough that they felt continuing cART was unnecessary, at least for the time being. Improved understanding of the reasons for interrupting treatment and missing doses is helpful for designing interventions to better support patients in

continuing their treatment as prescribed. In addition, these results show that addressing socioeconomic barriers to treatment retention is vital for supporting the continuous engagement of patients in care.

4.3. Findings from the Canadian Observation Cohort (CANOC) study (Chapter 3)

In Chapter 3 of the dissertation, results from the CANOC study addressing two main aims were presented. Firstly, survival models examining factors predicting a first TI of at least 90 days and resumption of cART subsequent to TI were evaluated. Secondly, survival models were constructed to identify factors associated with mortality. Socio-demographic covariates in the models included age, sex, Aboriginal ancestry, province and risk category (men who have sex with men (MSM), injecting drug use (IDU), heterosexual contact, HIV endemic country of origin, blood transfusion). Clinical variables such as composition of initial cART regimen (nucleoside (NRTI) backbone and third drug in the regimen), hepatitis C antibody seropositivity and HIV plasma viral load ($\log_{10}$), AIDS and CD4 cell count at cART initiation were considered.

Overall, we found that the proportion of individuals interrupting in their first calendar year of treatment decreased from 14% to 7% over the study period. Fewer pills and the predominance of one pill, once daily fixed dose regimens may be responsible for reducing the proportion of TIs in the first year of treatment, as are guidelines discontinuing physician-directed TIs from 2006 onwards. Findings from Cox proportional hazards regressions models showed that particular groups are at increased risk of TIs; specifically, women (aHR: 1.59, 95% CI: 1.33-1.92), younger individuals (aHR: 1.27 per 10 years, CI: 1.15-1.37), those with Aboriginal ancestry (aHR: 1.67, 1.27-

2.20), and IDU (aHR: 1.43, CI: 1.09-1.89). Clinical factors were also predictive of higher risk of TI such as: higher CD4 cell count at treatment initiation (aHR: 1.46, CI: 1.17-1.81), lower HIV plasma viral load (log_{10}) (aHR: 1.15, CI: 1.03-1.28), cART initiation with zidovudine/lamivudine (aHR: 2.47, CI: 1.92-3.20) and hepatitis C antibody seropositivity (aHR: 2.17, CI: 1.68-2.79).

The fact that Aboriginal peoples demonstrated higher risk of TIs is of particular concern as they are the fastest growing populations in Canada, and also one of the youngest. While treatment responses for Aboriginal peoples on cART are on par with non-Aboriginal individuals, individuals reporting Aboriginal ancestry have poorer survival [1] and increased vulnerability to other risk factors that may exacerbate their risk of TIs in the future [2]. For instance, many Aboriginal people live in small on-reserve communities, where seeking access to healthcare can be problematic due to issues related to stigma, lack of confidentiality and availability.

Older cART drugs were associated with TIs, suggesting that certain regimens may have higher risk profiles for treatment interruption. This information may be useful for physicians identifying an initial regimen for a patient who has been identified as having a higher risk of TIs. Moreover, as cART delivery expands globally, that older drugs such as zidovudine lead to increased risk of interruption is especially relevant to discussions of regimen selection. Results from this study have demonstrated that the first year of treatment is of particular importance, with more than half of first interruptions occurring within the first year after cART initiation. This is an opportune area to target interventions and additional patient support. As cART regimens continue to reduce the number of side-effects and toxicities associated with them, the rate of individuals

interrupting treatment may also concomitantly decrease. However, as individuals initiating cART with regimens containing relatively tolerable drugs continue to report TIs, efforts to reduce TIs must be multi-pronged, addressing both clinical and socio-behavioral factors that lead to higher risk of interruption.

Resumption of treatment was observed in more than three quarters of individuals who interrupted treatment in CANOC. Individuals more likely to reinitiate cART after a first interruption were male, resided in BC, older, initiated cART more recently and had a CD4 cell count <200 cells/mm^3. Our results indicated that while a majority of participants resumed cART, 15% of individuals never reinitiated treatment. These patients are unlikely to maintain suppressed pVL during their interruption of cART, increasing their own risk of HIV-related morbidity and mortality as well as the likelihood of transmission of HIV to others.

There was some survival benefit conferred by resuming cART after TI compared to individuals who did not reinitiate cART; however, even those who resumed cART had a statistically significantly greater risk of mortality, suggesting that even one TI may compromise an individual's long-term outcomes. While this study did not have access to information on co-morbidities, a possible mechanism leading to increased risk of mortality associated with TIs may be due to increased risk of HIV-related complications such as cardiovascular and renal disease which are non-reversible.

4.4. Limitations of the study

Participants in the LISA study were high risk and unstable in their lifestyle, which could lead to missing data. Fortunately, since all HIV plasma viral load testing is

undertaken at the British Columbia Centre for Excellence in HIV/AIDS, patients lost to the study could be passively followed up through laboratory data. Many of the variables being reported in the LISA study were based on self-report. Thus, study data may be subject to recall and social desirability biases. In order to mitigate the influence of social desirability bias, LISA interviewers who have extensive experience in working with injection drug users, MSM and Aboriginal populations in a sensitive manner were chosen.

Ascertainment of TI differs among CANOC sites, with some sites recording TIs from medical charts (data from physician, nurses and pharmacists), and others using cART prescription refill information as well as information from medical charts to identify TIs. We sought to mitigate this potential bias by examining differences in time to mortality and time to first TI comparing sites using medical charts versus those that used pharmacy and medical records. No differences were observed; however, residual confounding may be present that may also help explain regional differences in risk of TI. We were not able to measure some factors which have been associated in other studies with TIs, such as pregnancy, co-morbidities, depression, mental disorders, incarceration, and socioeconomic factors such as unstable housing and lack of social supports; these were not captured in the CANOC database. As data become available through linkages and other sources, it will be interesting to observe the impact of these latter predictors.

Future research studying TIs should seek to examine these factors and their contribution to the incidence and prevalence of TIs. Lastly, CANOC includes data from only three provinces and a clinic-based selection bias also exists, as data from BC includes the entire sample of people on cART province-wide while data from Ontario and

Quebec come from a selection of clinics that are mainly HIV-specific with highly experienced physicians.

4.5. Strengths of the study

The prospective nature of this study has elucidated how the frequency of interruptions in treatment changes over time for people living with HIV on cART. We have determined what factors predict TIs, to what extent TIs lead to mortality, and what factors predict resumption of cART. Using data from the largest collaboration of HIV cohorts in Canada to inform analyses lent considerable power to analyses. CANOC represents about a quarter of all HIV-positive individuals in the country who are currently on cART and approximately half of those who have initiated on more modern regimens since 2000, which improves the generalizability of the study results to the remainder of the HIV-positive population in Canada currently accessing treatment. Unlike many other studies examining interruptions in treatment, this study focused on the modern cART period and restricted analyses pertaining to predictors of TIs to the period following the recommendation not to prescribe TIs, from 2006 onwards. CANOC also enrolled cART-naïve individuals, which helps isolate the effect of the latest treatment regimens on risk of TI.

In addition, LISA is one of very few Canadian studies that collect socio-demographic information such as housing status and availability of social support on HIV-positive individuals on treatment; thus, though it is a cross-sectional study, using the LISA dataset provides a more complete picture of the social and structural factors that impact interruptions in treatment. Close community involvement and collaboration

through a Community Advisory Board (CAB) composed of members located across BC will ensure that results from the study are shared with study participants and policy-makers, allowing the study to have real-world implications and also giving voice to the lived experiences of HIV-positive individuals in Canada.

4.6. Comparative strengths and weaknesses of the two studies

LISA was chosen to undertake an examination of TIs due to the uncommon breadth of social and behavioral data collected by the study. A major strength of CANOC, meanwhile, is its large sample size derived from cohorts across the country, improving the generalizability of results to a greater population; in fact, the HIV epidemic in Canada is not dissimilar in scope to epidemics in other North American and European contexts, in that it is driven by MSM with rising rates of HIV stemming from heterosexual transmission in women. Thus, results from the CANOC cohort may have more than simply national relevance. Both LISA and CANOC have unique characteristics that combined, offer a diversity of perspectives on the occurrence of TIs in HIV-positive individuals on treatment in the modern cART era.

4.7. Directions for future research

There is sparse literature available on interventions designed to address TIs; however characteristics of successful interventions designed to improve cART adherence may also be applicable in the context of TI reduction. A review by Tuldra and Wu found evidence suggesting that interventions to improve adherence are most successful when

they are comprehensive, longitudinal, and tailored to the person [3]. A systematic review by Sandelowski and colleagues examined studies that describe facilitators and barriers to antiretroviral adherence as well as interventions designed to address these factors [4]. The review found that of the 47 interventions reviewed, 20 targeted one specific problem related to non-adherence, such as depression, forgetting to take medication, drug use, risky behavior, or poor health literacy. Cognitive-behavioral interventions were the most common interventions. The authors concluded that interventions in general were too focused on the individual without enough emphasis on targeting larger issues such as negative effects on adherence due to societal norms or the health care system [4].

Recently published guidelines on improving entry, retention and adherence to cART [5] offer a comprehensive review of interventions to improve adherence and make recommendations based on the evidence reviewed. Examples of recommendations include those relating to cART strategies (once-daily, fixed dose regimens); adherence tools for patients (reminder devices, education and counseling); education and counseling interventions (one-on-one education and adherence support, group education and counseling, multidisciplinary education and counseling, and peer support); and health system and service delivery interventions (using nurses and community care, case management services and resources to address food insecurity, housing, and transportation needs, integration of medication management services into pharmacy systems) [5]. Specific recommendations are also made for select groups such as pregnant women, those with mental health issues, homeless individuals, youth, incarcerated populations and drug users. These interventions should be evaluated in the context of TIs.

On the other end of the spectrum of adherence, medication persistence represents the duration from cART initiation to first instance of TI or substitution of another regimen. Interventions from the medication persistence field may also be applicable in the context of TIs. However, few interventions have been designed to-date to address persistence [6]. Another source for guidance on creating interventions to prevent TIs is the literature developed to improve compliance to antibiotic therapy. Counseling and patient education were traditionally less successful in this context, though success improved when the counseling and patient education were combined with written instruction, which could also aid in the context of TIs [7].

Caveats in adapting recommendations not specifically designed for TIs are that, while related, the concepts of adherence, medication persistence and TI are not indistinguishable; efforts should be made to understand the differences and implement this understanding in the development of interventions for TIs. Measures to address TIs and interventions that are developed need to focus not simply on the individual level but address structural factors that impede persistence such as unstable living conditions and poverty. Lastly, qualitative work will also be useful in deriving reasons for TIs.

4.8. Dissertation Synthesis and Final Reflections

There are 71,300 people currently living with HIV/AIDS in Canada. As individuals with HIV live longer, thereby spending more time on treatment, it is important to emphasize and facilitate the continuity of engagement in treatment once begun. Continuity of treatment is the best approach to maximize the life-extending benefits of cART and the best predictor of an HIV-positive individual's successful

management of HIV. As the paradigm of "treatment as prevention" becomes established and treatment earlier in the course of disease is being encouraged, it is important to understand how to keep individuals consistently engaged in treatment.

Moreover, considerably more people will initiate cART after the World Health Organization and the International AIDS Society recently expanded the definition of patients medically eligible for treatment to include those at any level of CD4 cell count, thereby increasing the potential number of individuals who may now initiate cART by 50% [8, 9]. These recommendations will improve individual outcomes of individuals living with HIV and also prevent a number of secondary HIV transmissions. As cART is propagated at increasing levels globally, and the impetus to provide treatment earlier in the course of HIV infection for individual and public health benefits gains momentum, ensuring continuity of treatment becomes even more vital.

TIs will become increasingly numerous if the frequency of TIs observed in this study and others is evident in this group of newly treatment eligible individuals. Gaps in treatment will reduce the effectiveness of the newly established guidelines. The dangers associated with TIs, such as increased risk of mortality, the development of resistant strains of virus as well as increased risk of HIV transmission will need to be closely monitored as treatment is scaled up.

Results from this dissertation showed that despite universal access to treatment, interruptions in treatment among HIV-positive individuals on cART continue to be pervasive. Despite the risks associated with TIs, a quarter of individuals in CANOC interrupted treatment in the era of modern cART, and 15% of LISA participants interrupted treatment in a two year window. Our results demonstrate negative outcomes

associated with interruptions in treatment, which caused a pronounced increase in mortality in those who interrupted treatment compared to those who maintain continuous therapy, even for those who resumed cART. Key findings from this dissertation are that a number of clinical factors such as higher CD4 cell count and lower HIV plasma viral load at treatment initiation, a history of hepatitis C virus co-infection, and older regimens predict TIs. In addition, poor adherence in the first year of treatment was associated with TIs, suggesting that early inconsistencies in medication persistence may lead to later interruptions in treatment.

Beyond these clinical findings, results showed that individuals with social vulnerabilities such as poor housing stability, unemployment and drug use were more likely to report TIs. Addressing both clinical predictors and socioeconomic barriers to treatment retention is vital for supporting the continuous engagement of patients in care. A finding across both studies that deserves to be highlighted is that individuals who "felt well" and those who were less immunosuppressed were more likely to interrupt treatment; this result has serious implications in an era of cART expansion. Other factors associated with TIs in both LISA and CANOC were injecting drug use and younger age; these groups merit special attention in future research investigating interruption.

Examining resumption of treatment after interruption, results from this dissertation show that a large proportion of individuals are likely to reinitiate treatment, decreasing but not eliminating their heightened risk of mortality due to interruption. Re-engaging individuals who have interrupted treatment is another opportune area for further research. While interventions specific to prevention of TIs are not yet available, policy-makers and clinicians can build on interventions designed to promote treatment

adherence among HIV-positive individuals. Risk factors identified by this dissertation can also be used to inform interventions. The continual improvements in tolerability of cART will help reduce the incidence of TIs among the HIV-positive population on treatment.

Collectively, the results presented here support improving patient support and education about the harms of interrupting treatment. Moreover, strategies to support continuous HIV treatment are needed to maximize the benefits of cART. In 2002, Diane Havlir asked, "one is left wondering whether advocating less therapy for this virus represents a cutting-edge strategy, a necessary concession, or a shortsighted, premature compromise" [10]. This dissertation concludes that TIs are, indeed, a compromise both for individual and public health.

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Appendices

Appendix 1

Variables investigated in the LISA study for possible inclusion in analyses

*Age
*Sex
*Aboriginal ancestry
*Unstable housing
*Education
*Income
*Employment
Smoking (current, ever)
*Illicit drug use (current, ever)
Stimulant use (current, ever)
*Injection drug use (current, ever)
*Adherence
Foster home (ever)
Food security
*Number of people living with (alone, with many others, on the street)
Incarceration (ever, last 6 months)
*Hepatitis C
*Regimen at interview
*CD4 count at initiation
*AIDS at treatment initiation
HIV plasma viral load at initiation
Duration of cART use
*Depression
Social Support
Experience of violence (ever, before age 16)
*Overall health rating
HIV limits activities
Stigma
Alcohol use (ever, ever binged, binged last 6 months)
Methadone treatment
Diabetes
Heart disease
Cancer
Men who have sex with men
Sex trade
Reasons for missing cART doses
HIV diagnosis year

*Used in analysis

Appendix 2

Table A.2 Number of treatment interruptions in CANOC participants from 2000-2011

Number of Treatment Interruptions	Frequency	Percent
0	5,7330	75.63
1	1,221	16.00
2	371	4.86
3	158	2.07
4	64	0.84
5	21	0.28
6	14	0.18
7	5	0.07
8	3	0.04
9	3	0.04

Chapter 5

CURRICULUM VITAE

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EDUCATION

Ph.D. in Infectious Disease Epidemiology Expected 2013

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Dissertation: Trends, predictors and outcomes associated with unstructured treatment interruptions and resumption among HIV-positive individuals on antiretroviral therapy in Canada

Master of Science in Infectious Disease Epidemiology June 2009

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Thesis: Breaking the cycle: risk profile of injection drug users who inject in front of non-injection drug users and circumstances surrounding initiation of injection drug use

Bachelor of Arts in Human Biology Class of 2005

Brown University, Providence, RI

Concentration: Human Health and Disease

Relevant coursework: AIDS in the International Perspective, Statistics, Burden of Disease in Developing Countries, Emerging Microbial Disease, Emergency Medical Systems, Medical Anthropology

Semester Abroad Spring 2004

American University in Cairo, Egypt

Coursework: Anthropology, Politics in the Middle East and Arabic

RESEARCH EXPERIENCE

Epidemiologist 2010 – Present

British Columbia Centre for Excellence for HIV/AIDS: Vancouver, BC

- Research examines social and structural barriers to the initiation and continuation of HIV treatment and the impact of each on HIV disease progression. Manage the BC-CfE's participation in two international cohort collaborations, the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) and the Antiretroviral Cohort Collaboration (ART-CC). Member of the Interdisciplinary Modeling for the Prevention, Care and Treatment of HIV (IMPACT-HIV) team.

Research Assistant 2010 – 2010

British Columbia Centre for Excellence for HIV/AIDS: Vancouver, BC

- Provided research assistance for the creation of guidelines for primary care physicians treating HIV/AIDS in British Columbia

Consultant 2008 – 2010

First Nations Inuit Health Branch, Health Canada: Vancouver, BC

- Conducted a qualitative study involving interviews with TB experts across Canada and co-wrote a report entitled "Perceptions of Tuberculosis Outbreak Definitions in a First Nations Community Context"
- Completed a literature review report on Tuberculosis in First Nations and Inuit in Canada to inform the TB renewal strategy for FNIHB

- Provided guidance on a variety of FNIBH research initiatives such as an evaluation of the Residential Schools Healing Program Conference

Research Associate Summer 2009

Canadian Aboriginal AIDS Network (CAAN)

- Assisted in organizing the organization's annual general meeting in Winnipeg and evaluated workshops held over the two-day event
- Created and analyzed results of a survey of healthy sexuality services available for Aboriginal youth
- Attended community-based participatory research conferences and trained staff in these methods

Research Assistant 2006 - 2007

Centre for Health Evaluation and Outcome Sciences: Vancouver, BC

- Provided qualitative and quantitative research assistance on projects being undertaken at the Centre. Current research examines Aboriginal youth in foster care and Crystal Meth use in the Aboriginal community.

Overseas Intern (9 months) 2005 – 2006

Department of Community Health Sciences, Aga Khan University: Karachi, Pakistan

- Initiated a survey of HIV/AIDS services available at hospitals in Karachi**,** organized a nationally recognized community intervention in an urban slum involving government, school children and community leaders to raise awareness about health and hygiene

TEACHING EXPERIENCE

Sessional Instructor Fall 2013

Faculty of Health Sciences, Simon Fraser University

- Infectious Disease Epidemiology. HSCI 432 (upper-level undergraduate seminar)

Guest Lecturer 2012-2013

Faculty of Health Sciences, Simon Fraser University

- Global Epidemiology of HIV/AIDS. HSCI 212. March 26, 2013.
- Global Epidemiology of HIV/AIDS. HSCI 212. October 31, 2012.
- Natural History of HIV. HCSI 212. March 13, 2012.
- Natural History of HIV. HSCI 431. January 26, 2012.

Teaching Assistant 2008 - 2010

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

- Coordinated classes, created and graded exams, and led bi-weekly sessions for the Epidemiology and Natural History of Human Immunodeficiency Virus and Advanced Topics On Control and Prevention Of HIV/AIDS (online and in-class)

Trainer Summer 2008

Healing Our Spirit – Aboriginal HIV/AIDS NGO

- Taught different groups such as jail inmates and youth about transmission and prevention of HIV/AIDS and other sexually transmitted and blood-borne infections.

PUBLIC HEALTH LEADERSHIP

Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS) 2011 - Present

- Coordinated the development of the incarceration survey section as a survey team lead and member of the Community Advisory Board

CIHR Centre for Research Evidence in Action for Community Health in HIV/AIDS (REACH) 2010 - Present

- Aboriginal and Youth Programs of research member

American Public Health Association Representative on the Student Assembly 2009-2010

- Liaised between APHA and JHSPH students about events and opportunities and promoted American Public Health Week
- Served on Finance and Student Groups sub-committees
- Attended APHA conference and the APHA Student Leadership Institute

Epidemiology Departmental Representative to the JHSPH Student Assembly 2008 - 2009

- Liaised between the Epidemiology Department and Student Assembly
- Served on Finance and Student Groups sub-committees

International Health Promotion Conference 2007 Summer 2007

- Served as team leader for volunteers organizing the poster sessions

Karachi HIV Working Group 2005 – 2006

- Facilitated the re-establishment of the KHWG, which is composed of the city's leaders in HIV/AIDS treatment, advocacy and control

PUBLICATIONS

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CONFERENCE POSTERS AND ORAL PRESENTATIONS

1. Puskas CM, Zhang W, Yip B, **Samji H**, Salters KA, Kaida A, Miller KL, Hogg RS, Montaner, JSG. Women, ART, and Adherence: A Longitudinal Comparison of Antiretroviral Adherence by Gender in British Columbia. Canadian Public Health Association. Montreal, June 2013 (oral).
2. Salters KA, Cui Z, **Samji H**, Small W, Chen Y, Montaner JSG, Hogg RS. Complex health challenges facing HIV-positive individuals with a history of incarceration in British Columbia, Canada. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2013). Kuala Lumpur, Malaysia, 30 June - 3 July 2013. Abstract #A-581-0070-02451 (poster presentation).

3. Hogg RS, Chan K, Cescon A, **Samji H**, Yip B, Colley G, Lima VD, Montaner JSG. Considerable gaps in life expectancy among HIV-positive individuals initiating HAART in British Columbia, Canada. 7th IAS Conference on HIV Pathogenessis, Treatment and Prevention. Kuala Lumpur, Malaysia. 30 June - 3 July 2013. Abstract TUPE256 (poster).
4. Lima VD, Nosyk B, Colley G, Heath K, Yip B, **Samji H**, Hogg R, Montaner J. The Cascade of Care: A Promising Tool in HIV Surveillance. 7th IAS Conference on HIV Pathogenessis, Treatment and Prevention. Kuala Lumpur, Malaysia. 30 June - 3 July 2013. Abstract TUPE338 (poster).
5. Hogg RS, Althoff KN, **Samji H**, Cescon A, Modur S, Buchacz K, Burchell AN, Cohen M, Gebo KA, Gill MJ, Justice A, Kirk G, Klein MB, Korthuis PT, Martin J, Napravnik S, Rourke SB, Sterling TR, Silverberg MJ, Deeks S, Jacobson LP, Bosch RJ, Kitahata MM, Goedert JJ, Moore R, Gange SJ, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Increases in life expectancy among treated HIV-positive individuals in the United States and Canada, 2000-2007. 7th IAS Conference on HIV Pathogenessis, Treatment and Prevention. Kuala Lumpur, Malaysia. 30 June - 3 July 2013. Abstract TUPE260 (poster).
6. Milloy MJ, Kerr T, Salters K, **Samji H**, Guillemi S, Montaner J, Wood E. Incarceration is associated with use syringe lending among active injection drug users with detectable plasma HIV-1 RNA. 3rd Treatment as Prevention Workshop (TASP). Vancouver, Canada. April 22-25, 2013 (poster).
7. Salters KA, Cui Z, **Samji H**, Small W, Chen Y, Montaner JSG, Hogg RS. History of incarceration among harder-to-reach people living with HIV and the impact on viral

suppression. 22nd Canadian Conference on HIV/AIDS Research (CAHR). Vancouver, April 11-14, 2013 (poster).

8. Gurm J, Zhu J, Zhang W, Parashar S, **Samji H**, McNeil R, Strike C, Pauly B, Salters K, Worthington C, Milloy MJ, Kirkland S, Guillemi S, Skinner S, Panessa C, McDougall P, Turje Baltzer R, Barrios R, Hogg RS. Getting in the way: intangible barriers that are creating treatment and care inequities, and compromising the health outcomes of vulnerable PHAs. 22nd Canadian Conference on HIV/AIDS Research (CAHR). Vancouver, April 11-14, 2013 (poster).
9. Lourenco L, Ding E, Shurgold S, Colley G, Yip B, Lima V, **Samji H**, Barrios R, Montaner JSG, Hogg RS, Moore D. Factors Associated with Varying Levels of HAART Prescription Refill Adherence. 22nd Canadian Conference on HIV/AIDS Research (CAHR). Vancouver, April 11-14, 2013 (poster).
10. Hogg RS, Chan K, Cescon A, **Samji H**, Colley G, Yip B, Lima VD, Montaner JSG. Inequities in life expectancy among people initiating HAART in British Columbia. 22nd Canadian Conference on HIV/AIDS Research (CAHR). Vancouver, April 11-14, 2013 (**presenting author, oral**).
11. Cescon A, Min J, Colley G, Hosein SR, Machouf N, **Samji H**, Burchell AN, Cooper C, Klein MB, Loutfy MR, Montaner JS, Raboud JM, Rachlis A, Tsoukas C, Hogg RS, Lima VD, CANOC Collaboration. Compliance to treatment guidelines at the programmatic level in Canada: Extension of a composite assessment metric for HIV therapy. 22nd Canadian Conference on HIV/AIDS Research (CAHR). Vancouver, April 11-14, 2013 (oral presentation).

12. Buchacz K, Lau B, Jing Y, Bosch R, Gandhi N, Gill MJ, Abraham A, Napravnik S, Goedert J, Eron J, Martin JN, Patel P, Rourke S, **Samji H**, Mayor A, Saag M, Silverberg MJ, Gange SJ, Moore RD, Brooks JT, for the NA-ACCORD. Incidence of AIDS-defining opportunistic illnesses (ADOIs) among patients with no prior clinical AIDS: the NA-ACCORD, 2000-2010. International Workshop on Observational HIV Databases in Cavtat, Croatia, April 11-13, 2013. Abstract #CSN1205 (poster).
13. Nosyk B, Montaner JSG, Colley G, Chan K, Heath K, Yip B, Samji H, Gilbert M, Barrios R, Gustafson R, Lima VD, Hogg RS, on behalf of the STOP HIV/AIDS Study Group. The Evolution of the Cascade of HIV Care in British Columbia, Canada: 1996-2009. 20th Conference on Retroviruses and Opportunistic Infections (CROI). Atlanta, 2013 (poster presentation).
14. **Samji H**, Wang H, Chau W, Colley G, Lepik K, Barrios R, Lima V, Lourenco L, Hogg RS, Montaner JSG, Moore D. Trends in late initiation of antiretroviral therapy (ART) in British Columbia, Canada and the contribution of late diagnosis. XIX International AIDS Conference (AIDS 2012). Washington, D.C., 22-27 July 2012. Abstract # A-452-0146-08163 (poster).
15. D'Souza G, Strickler H, Jing Y, Sterling T, Silverberg M, **Samji H**, Napravnik S, Moore R, Mathews WC, Klein M, Kitahata M, Kirk G, Gill J, Dubrow R, Burchell A, Brooks JT, Beachler DC and Abraham A, on behalf of the North American AIDS Cohort on Collaboration and Design NA-ACCORD. Incidence and Risk Factors for Head and Neck Cancer and Cervical Cancer Among HIV-Infected Individuals in North America. EUROGIN 2012, International Multidisciplinary Congress. July 2012.

16. **Samji H**, Cescon A, Kanters S, Milan D, Lepik K, Hull M, Zhang W, Forrest JI, Moore D, Hogg RS, Montaner JS. HIV Treatment as Prevention: A Comparison of Four Groups of Virologically Unsuppressed HIV-Positive Individuals in British Columbia, Canada. 21st Canadian Conference on HIV/AIDS Research. Montreal, 19-22 April 2012. Abstract # 162 (poster).
17. Hogg R, **Samji H**, Cescon A, Modur SP, Napravnik S, Martin JN, Gill MJ, Klein MB, Kirk GD, Gange SJ. Temporal Changes in Life Expectancy of HIV-Positive Individuals in North America. Oral presentation accepted at the 19th Conference on Retroviruses and Opportunistic Infections, March 2012.
18. Lourenco L, Chan K, **Samji H**, Hogg R, Montaner JS, Lima V, Milan D, Gustafson R, Yip B, Moore D. Declines in Community Viral Load are Uniformly Distributed Across Geographic Areas in British Columbia, Canada. Poster presentation accepted at the 19th Conference on Retroviruses and Opportunistic Infections, March 2012.
19. Cescon A, Kanters S, **Samji H**, Milan D, Lepik K, Hull M, Forrest J, Moore D, Hogg R, Montaner JS. Epidemiological and Clinical Characteristics of Virologically Detectable HIV-Positive Individuals and Temporal Trends in HIV-RNA Suppression: A Population-Based Study in British Columbia (BC), Canada. Poster presentation accepted at the 19th Conference on Retroviruses and Opportunistic Infections, March 2012.
20. **Samji H**, O'Brien N, Palmer AK, Chen A, Wang H, Montaner JSG, Hogg RS. Factors associated with late initiation of HIV treatment in a cohort of HIV-positive individuals in British Columbia, Canada. Poster presentation accepted at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, July 2011.

21. Rutherford AR, Vasarhelyi, K, Kok S, Lourenco L, Michelow W, **Samji H**, Wittenberg RW, Montaner JSG. Evaluating the impact of "Treatment as Prevention" on reducing HIV transmission, using surveillance data. Oral presentation accepted at the 6th International Workshop on HIV Transmission, July 2011.
22. Parashar S, Palmer A, O'Brien N, Chan K, Milan D, **Samji H**, Montaner JSG, Hogg RS. Sex, drugs and structural interventions: unstable housing associated with increased HIV risk behaviour in a cohort of people on treatment in British Columbia. Poster presentation accepted at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, July 2011.
23. **Samji H**, O'Brien N, Palmer AK, Chen A, Wang H, Montaner JSG, Hogg RS. Correlates of HIV treatment interruption in a cohort of HIV-positive individuals in British Columbia, Canada. Oral presentation accepted to the 20th Annual Canadian Conference on HIV/AIDS Research, April 2011.
24. **Samji H**, O'Brien N, Palmer AK, Chen A, Wang H, Montaner JSG, Hogg RS. Factors associated with late initiation of HIV treatment in a cohort of HIV-positive individuals in British Columbia, Canada. Poster presentation accepted to the 20th Annual Canadian Conference on HIV/AIDS Research, April 2011.
25. Parashar S, Chan K; **Samji H**; O'Brien N; Palmer AK; Montaner JSG; Hogg RS. Sex, drugs and structural interventions: unstable housing associated with increased HIV risk behaviour in a cohort of people on treatment in British Columbia. Poster presentation accepted to the 20th Annual Canadian Conference on HIV/AIDS Research, April 2011.

26. Pappas G, Chaudhry S, Memon Y, **Samji H**, Khattak M, Bana A. Community Partnerships to Improve Public Health: A case study of a slum in the megacity of Karachi, Pakistan. Oral presentation accepted to the 136th Annual APHA Annual Meeting & Exposition, October 2008.

RESEARCH GRANT PARTICIPATION

Title: A mixed method evaluation of the impact of the Dr. Peter Centre on health care access and outcomes for persons living with HIV/AIDS who use illicit drugs

Duration: 2012-2015

Funding Source: Canadian Institutes of Health Research (CIHR)

Principal Applicant: Robert S. Hogg

Title: Family Matters: Informing a family-based model of care with Aboriginal families affected by HIV

Duration: 2012-2015

Funding Source: Canadian Institutes of Health Research (CIHR)

Principal Applicant: Renee Masching

Title: Determinants of late initiation and treatment interruption in a context of the

Duration: 2012-2015

Funding Source: Canadian Institutes of Health Research (CIHR)

Principal Applicant: Robert S. Hogg

Title: Assessing the impact of HIV on aging: A Canadian pan-provincial HIV-treatment cohort

Duration: 2012-2013

Funding Source: Canadian Institutes of Health Research (CIHR)

Principal Applicant: Robert S. Hogg

AWARDS AND SCHORLARSHIPS

- Young Investigator Scholarship to represent NA-ACCORD at IeDEA meetings in Rome, Italy (2011)
- New Investigator Award, Canadian Association for HIV Research (2011)
- Doctoral Student Entrance Merit Scholarship, Johns Hopkins School of PH (2009-2013)
- Duke of Edinburgh Young Canadians Challenge Gold Recipient (2010)

PROFESSIONAL DEVELOPMENT

Computer and Data Management Skills: Microsoft Office Suite, STATA, SAS, SPSS, Arc GIS

Languages: Fluent in English and French, knowledgeable in Gujarati, Urdu and Arabic

Certificates: Working Effectively in Post-Conflict Reconstruction and Humanitarian Situations for Public Health Professionals - United States Institute for Peace, 2008; Royal Conservatory of Music level 8 (piano)