Predictors of virologic suppression and rebound among HIV-positive men who have sex with men in a large multi-site Canadian cohort

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Abstract

Objectives: Men who have sex with men (MSM) represent the largest HIV transmission category in Canada, but there are limited pan-provincial data regarding combination antiretroviral therapy (cART) treatment outcomes. We sought to identify socio-demographic and clinical correlates of virologic suppression and rebound in this population.

Methods: Our analysis included MSM participants in the Canadian Observational Cohort (CANOC) collaboration ≥ 18 years old who initiated ART naïvely between 2000 and 2011. We used accelerated failure time models to identify factors predicting time to suppression and time to subsequent rebound.

Results: 3,180 participants were eligible for inclusion, of whom 2,616 (82.3%) achieved virologic suppression in a median time of 4 months. Our analysis identified more recent era of ART initiation, no history of injection drug use, older age, lower baseline viral load, higher viral load testing rate, and being on an initial regimen consisting of nonnucleoside reverse transcriptase inhibitors as significant predictors of virologic suppression. Subsequent virologic rebound was experienced by 298 participants (11.4%) in a median time of 22 months. Significant factors predicting rebound were more recent era of ART initiation, IDU history, younger age, higher baseline CD4 cell count, > 6 annual viral load tests, and living in British Columbia.

Conclusion: The majority of HIV-positive MSM on ART are successfully achieving virologic suppression, which marks significant improvements in the health of HIV-positive MSM in Canada since the emergence of ART. A minority of MSM experience an increased risk of virologic rebound. Priority target groups include younger MSM and those with a history of IDU.

Key Words: Canada, HIV, MSM, suppression, rebound, ART

INTRODUCTION

Gay, bisexual, and other men who have sex with men (MSM) represent the population most affected by the human immunodeficiency virus (HIV) in Canada (Public Health Agency of Canada, 2013a). Between 1985 and 2011, over half (54.7%) of the 69,856 diagnosed HIV cases with known exposure status were attributable to MSM, despite self-identified gay and bisexual men only compromising an estimated 2.1% of the Canadian population (Public Health Agency of Canada, 2013b; Statistics Canada, 2011). In the 1980s and 1990s, this disproportionate burden was characterized by premature mortality across gay urban communities (Strathdee et al., 2000). At the height of the epidemic, acquired immune deficiency syndrome (AIDS) was identified as a leading cause of death among middle-aged men living in urban areas (Hogg et al., 1997). In some urban environments, the life expectancy for gay and bisexual men was estimated to be between 8-20 years shorter than that of the general male population (Hogg et al., 1994; Hogg et al., 1997).

Since the discovery of combination antiretroviral therapy (cART) in the 1990s, people living with HIV/AIDS (PHAs) have experienced significant improvements in health outcomes and life expectancy (Druyts, Rachlis et al., 2009; Hogg et al., 1998; Lima et al., 2007; Samji et al., 2013). Between 2001 and 2011, new AIDS diagnoses in Canada decreased by over 56.4% (Public Health Agency of Canada, 2013b). High levels of adherence to cART, usually defined as taking > 95% of prescribed medication (O'Neil et al., 2012), can lower HIV RNA to levels of virological suppression and reduce the risk of both horizontal and vertical HIV transmission (M. S. Cohen et al., 2011; Montaner et al., 2010). Patients who are adherent to their antiretroviral regimen can usually achieve viral suppression between 8 and 24 weeks after initiating treatment (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015). Expanded antiretroviral

treatment availability and its use in pre-exposure prophylaxis (PrEP) also serves as an HIV prevention strategy. Previous research analyzing HIV-positive gay and bisexual men has found that expanded ART uptake among this at-risk population coincided with a significant reduction in community/population viral load and the number of new HIV diagnoses (Das et al., 2010; Grant et al., 2010).

Despite the proven clinical benefits of cART, MSM in Canada continue to experience a sustained rate of HIV incidence (British Columbia. Provincial Health Officer, 2014; Public Health Agency of Canada, 2013b). In 2011, MSM accounted for an estimated 49.1% of new HIV infections (Public Health Agency of Canada, 2013b). The rate of diagnosis for this transmission pathway is over twice as high at those attributable to injection drug use and heterosexual transmission (Public Health Agency of Canada, 2013b). This higher incidence is linked to increased risk of infection via anal sex compared with vaginal sex (Jaffe, Valdiserri, & De Cock, 2007). The ongoing, disproportionate burden of HIV among MSM also results from behavioural factors, such as unsafe sexual practices, having multiple sexual partners, substance use, and mental health issues, as well as social factors, including homophobia, stigma, social exclusion, race, and ethnicity (British Columbia. Provincial Health Officer, 2014; Brooks, Etzel, Hinojos, Henry, & Perez, 2005; Jaffe et al., 2007; Jeffries, Marks, Lauby, Murrill, & Millett, 2013; Public Health Agency of Canada, 2013b). Additionally, structural barriers within the healthcare system, such as insufficient access to gay-friendly health services and distrust of available health care providers, may deter some MSM from seeking testing and ongoing treatment (McNairy & El-Sadr, 2012; Nelson et al., 2010)

Accessible health services staffed by professionals who are well-informed and sensitive to MSM-related health issues can improve provider-patient communication. If health care providers are aware and accepting of their patient's MSM status, they are more likely to offer appropriate counselling (Petroll & Mosack, 2011). Unfortunately, many services lack this cultural sensitivity, which restricts their capacity to provide appropriately tailored care and support to gay, bisexual, and other MSM. It is estimated that in some Canadian regions, fewer than 50% of gay and bisexual men have disclosed their sexual orientation to their health care provider (Holtzman & Drabot, 2011). Some MSM are reluctant to share their sexual practices with physicians for fear of judgment and discrimination (Arnold, Rebchook, & Kegeles, 2014; O'Byrne, MacPherson, Ember, Grayson, & Bourgault, 2014). Previous research in BC found that 14% of gay and bisexual survey respondents at one point stopped seeing a health care professional because of a perceived homophobic attitude (British Columbia. Provincial Health Officer, 2014). This has troubling implications for HIV-related health, as continued engagement in care is a core component of the HIV care continuum (Gardner, McLees, Steiner, Del Rio, & Burman, 2011). Disrupted health service engagement can compromise treatment adherence. Continuation of treatment is crucial for ongoing clinical success and HIV prevention, as incomplete ART adherence promotes episodes of viral rebound, in which measured plasma viral loads surpass detectable limits (Raboud et al., 2002). Failure to retain virologic suppression increases the risk of onward HIV transmission, can promote drug resistance, lower CD4 cell count, and result in treatment failure and future AIDS diagnosis (Castilla et al., 2005; de Mendoza et al., 1999).

While there is a substantial amount of literature exploring risk factors for HIV seroconversion among MSM, there is a sizable gap regarding modern-day cART treatment response among MSM. Both virologic suppression and any subsequent experience of viral rebound are important

clinical outcomes and have meaningful implications for prevention and long-term health. Determining factors associated with suppression is essential for identifying MSM at higher risk of treatment failure, preventing future HIV incidence, and promoting better care for MSM living with HIV. Furthermore, identifying common elements shared by MSM who experience viral rebound following suppression is needed to tailor more specific intervention strategies focused on adherence and continued engagement in care. This will help minimize the likelihood of future rebound episodes and treatment failure.

There has yet to be a pan-provincial assessment of treatment response or a more thorough examination of the clinical and social circumstances associated with virologic suppression and rebound among MSM in Canada. It is important to explore how these conditions, as well as interprovincial differences in MSM demographic and social profiles, influence ART access and adherence. The Public Health Agency of Canada identified this knowledge gap and has advocated for more research regarding long-term cART use among MSM in Canada (Public Health Agency of Canada, 2013b). Available provincial-level research suggests that in Ontario and British Columbia (BC), MSM have a higher likelihood of achieving virologic suppression than non-MSM males and females living with HIV in these provinces (BC Centre for Excellence in HIV/AIDS, 2015; Light et al., 2013). However, no research has yet examined how these types of health outcomes may vary between gay, bisexual, and other MSM living in different regions of Canada. Furthermore, UN AIDS has recently announced a new plan to end the spread of HIV. This solution, known as 90-90-90, advocates for expanded uptake of HIV testing, linkage to care, and cART adherence so that 90% of PHA are diagnosed, 90% of diagnosed individuals are on treatment, and 90% are virally suppressed (UNAIDS, 2014). Mathematical modeling suggests that achieving these targets by 2020 will enable the world to end the AIDS epidemic by 2030

(UNAIDS, 2014). This new objective for viral suppression provides a timely and pertinent framework for assessing where Canadian MSM on cART stand with regard to this ambitious HIV treatment and prevention target.

Obtaining a better understanding of regional, demographic, and clinical factors associated with HIV virologic suppression and rebound among MSM will help inform cART initiation and retention strategies that meet the unique health needs of MSM. Moreover, this research will help guide interventions to improve treatment outcomes and reduce HIV transmission risk. The purpose of this study is to identify socio-demographic and clinical correlates of treatment response among MSM in Canada, as measured by virologic suppression and subsequent rebound.

METHODS

Study Population

The Canadian Observational Cohort (CANOC) collaboration is an observational cohort study of antiretroviral-naïve HIV-positive individuals initiating cART after 1 January 2000 (Palmer et al., 2011). This dynamic, multi-site study is comprised of eight cohorts located in three Canadian provinces (BC, Quebec, and Ontario). Approximately one quarter of Canadians on cART are represented within CANOC (Ndumbi et al., 2014). This collaboration provides researchers with an opportunity to longitudinally examine treatment access, patient management, and health outcomes across Canada (Palmer et al., 2011).

Patient eligibility criteria for inclusion in CANOC are: documented HIV infection, residence in Canada, age 18 years or older, initiation of a first antiretroviral regimen comprised of at least three individual agents, and at least one measurement of HIV plasma viral load and CD4 T-cell

count within 6 months of initiating cART. Patient selection and data extraction are performed locally at the data centres 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. The study was established in March 2008 with funding from the Canadian Institutes of Health Research (grant #711098) and the CIHR Canadian HIV Trials Network (CTN242) and includes cohorts and investigators from across the country.

CANOC currently includes HIV-positive MSM from British Columbia (BC), Ontario, and Quebec, and provides a unique opportunity to assess HIV treatment response among a sizable proportion of MSM on ART. These three provinces accounted for 85% of all HIV diagnoses between 1985 and 2011 (Public Health Agency of Canada, 2014). For this analysis, we focused exclusively on males within the cohort and excluded any males with missing or unknown data regarding MSM status. We also excluded individuals who did not have at least 2 viral load measurements within 6 months prior to the start of ART, as well as those with a baseline viral load of 200 copies/mL or less because it was assumed that they were not actually ARV-naive. The last date of follow-up in the cohort was 31 December 2012.

Outcomes

The first outcome, initial viral suppression, was defined as the time to the first of at least 2 consecutive plasma HIV RNA measurements below 50 copies/mL, at least 30 days apart in a 1-year period. The second outcome of interest, virologic rebound, was only measured among

participants who achieved suppression within 1 year. Rebound was defined as the time to the first of at least 2 consecutive VL measures above 200 copies/mL, at least 30 days apart.

Variables of Interest

Individual-level covariates of interest, evaluated prior to treatment initiation, included province of residence, race/ethnicity, age, baseline CD4 cell count, baseline viral load, history of injection drug use (IDU), hepatitis C co-infection, baseline diagnosis of AIDS defining illness (ADI), and era of ART initiation (2000-2003, 2004-2007, 2008-2012). Other variables of interest included composition of initial antiretroviral regimen, as well as the number of viral load measurements taken per year following treatment initiation.

Statistical Methods

Demographic and clinical characteristics at treatment initiation (baseline) were summarized using frequencies and proportions for categorical variables and medians and interquartile ranges (Q1-Q3) for continuous variables. In preliminary analysis, demographic and clinical covariates of participants were compared by whether or not they ever achieved virological suppression and rebound. P-values for categorical variables were calculated using the Chisquare test and p-values for continuous variables were calculated using the Wilcoxon Rank Sum test.

Next, univariate accelerated failure time models were used to explore the association between covariates and each outcome. Then an exploratory model selection process based on the Akaike Information Criterion (AIC) and Type III p-values was pursued to construct the multivariable accelerated failure time model and determine independent predictors for each outcome (time to suppression and rebound). The two criteria balance the model choice on finding the best

exploratory model (Type III p-values indicate more significance) and at the same time a model with the best goodness-of-fit statistic (AIC: lower values reflect a better fit). All analyses were performed using SAS software version 9.3.

Ethical Consideration

The human subjects activities of CANOC were approved by the Simon Fraser University Research Ethics Board, the University of British Columbia Research Ethics Board and the following local institutional review boards of the participating cohorts: Providence Health Care Research Institute Office of Research Services, The Ottawa Hospital Research Ethics Board, University Health Network (UHN) Research Ethics Board, Véritas Institutional Review Board (IRB), Biomedical C (BMC) Research Ethics Board of the McGill University Heath Centre (MUHC), University of Toronto HIV Research Ethics Board (HIV REB), and Women's College Hospital Research Ethics Board.

As a research assistant and co-investigator for CANOC, I received ethical approval to conduct analyses using the collaboration's data from both the University of British Columbia and Simon Fraser University. Participant data was de-identified, and I had no access to individual level participant information at any point during this research endeavor. I was added to CANOC ethics as a co-investigator in December 2014. The SFU Office of Research Ethics' study number assigned to CANOC is 2013s003.

RESULTS

Study Population

Drawing on CANOC data from 2000-2012, a total of 3,180 individuals met the eligibility criteria and were included in subsequent analyses. 935 (29%) participants were from BC, 1,138 (36 %) from Ontario, and 1,107 (35%) from Quebec. Demographic and clinical characteristics of the study participants are listed in Table 1, along with bivariate comparisons with regard to achieving suppression. Bivariate comparisons by subsequent rebound status are listed in Table 2. The median follow-up time for the MSM cohort was 4.7 years (Q1-Q3: 2.4-7.7 years). A total of 239 (8%) participants were lost to follow-up for more than 18 months during the study period. At baseline, the median age of all participants was 40 years (Q1-Q3: 33-46 years). 1,407 (44%) MSM participants identified as Caucasian, 59 (2%) as Black, 76 (2%) as Aboriginal, and 399 (13%) as other. Race/ethnicity was unknown for 1,239 (39%) MSM in the cohort. The median baseline CD4 count was 237 cells/mm^3 (Q1-Q3: 130-340 cells/mm^3) and the median baseline viral load was 4.95 $\log_{10}$ copies/mL (Q1-Q3: 4.48-5.00 $\log_{10}$ copies/mL). Of the 3,046 participants with available hepatitis C testing data, 352 (12%) tested positive. Additionally, 259 (8%) participants had a history of IDU. At baseline, 489 (15%) participants had been diagnosed with an AIDS-defining illness. The median rate of viral load testing was 4 tests per year (Q1-Q3: 3-5). Supplemental to two nucleoside reverse transcriptase inhibitors (NRTIs), third initial ARVs included Nevirapine (8%), Efavirenz (36%), Lopinavir (14%), Atazanavir (20%), or other non-specified/grouped drug (22%).

Overall, 2,616 (82.3%) MSM participants achieved viral suppression within 12 months of cART initiation. The median time to suppression was 4 months (Q1-Q3: 3-6 months). Of these individuals, 298 (11.4%) experienced subsequent rebound to HIV RNA levels above 200 copies/mL in a median time of 22 months (Q1-Q3: 11-39 months).

Predictors of Viral Suppression

As noted in Table 1, MSM participants who suppressed their virus within one year of treatment initiation were more likely to be from Ontario and Quebec (p=0.036), to be older (p=0.002) and Caucasian (p=0.029), to have no previous history of IDU (p <0.001) or hepatitis C co-infection (p=0.002), and to have initiated more recently (p<0.001), 3-4 viral load tests per year (p<0.001), a boosted or NNRTI containing regimen (p<0.001), and a lower baseline viral load (p<0.001) than those who did not suppress.

Univariate analysis identified IDU history ($p < 0.001$), era of ART initiation ($p < 0.001$), province of residence ($p = 0.004$), ethnicity ($p = 0.001$), class of third initial ARV ($p < 0.001$), number of annual viral load tests ($p < 0.001$), baseline ADI ($p = 0.046$), baseline viral load ($p < 0.001$), and baseline CD4 cell count ($p < 0.001$), as significant correlates of virologic suppression. These are further detailed in Table 3. Because of variable collinearity, history of IDU was used in place of hepatitis C status in the final models. A Chi squared test assessing collinearity between hepatitis C status and IDU history was significant at $p < 0.001$

Adjusted multivariable analysis found that participants who initiated ART from 2004-2007 [HR 1.27, 95% CI 1.14-1.42] and 2008-2012 [HR 1.26, 95% CI 1.14-1.40] compared with 2000-2003 were more likely to experience virologic suppression within one year of treatment initiation. Other significant predictors of suppression include older age [HR 1.05, 95% CI 1.01-1.09] and receiving 3-4 annual viral load tests [HR 1.19, 95% CI 1.07-1.31] compared to < 3. Individuals with IDU history [HR 0.75, 95% CI 0.65-0.87], higher baseline viral load [HR 0.65, 95% CI 0.60-0.70], and on an initial 3rd ARV class consisting of an unboosted PI [HR 0.65, 95% CI 0.53-

0.81] or boosted PI [HR 0.81, 95% CI 0.74-0.88] compared to NNRTI were less likely to achieve suppression.

Predictors of Viral Rebound

As highlighted in Table 2, MSM participants who experienced viral rebound were more likely to be from BC ($p<0.001$), to be younger ($p=0.009$), to be black or Aboriginal ($p<0.001$), to have a history of IDU ($p<0.001$) or hepatitis C co-infection ($p<0.001$), and to have initiated treatment in an earlier ART era ($p<0.001$), an unboosted PI containing regimen ($p=0.012$), a higher baseline viral load ($p=0.011$), and a lower baseline CD4 cell count ($p=0.002$) than those who did not rebound.

Unadjusted and adjusted results from the accelerated failure time model for virologic rebound are shown in Table 4. Univariate analysis identified IDU history ($p < 0.001$), era of ART initiation ($p < 0.001$), province of residence ($p < 0.001$), ethnicity ($p = 0.007$), baseline age ($p < 0.001$), and number of annual viral load tests ($p < 0.001$) as significant predictors of viral rebound.

In adjusted multivariable analysis, significant predictors of rebound included having a history of IDU [HR 2.28, 95% CI 1.64-3.17], being on an initial ART regimen other than NNRTI or PI [HR 1.62, 95% CI 1.07-2.45], and having more than 6 annual viral load tests [HR 2.54, 95% CI 1.62-3.97]. Older age [HR 0.70, 95% CI 0.61-0.80], initiating ART from 2004-2007 [HR 0.60, 95% CI 0.46-0.79], 2008-2012 [HR 0.29, 95% CI 0.20-0.43], and living in Ontario [HR 0.63, 95% CI 0.46-0.86] or Quebec [HR 0.59, 95% CI 0.43-0.82] compared to BC predicted a lower likelihood of rebound.

DISCUSSION

This study represents the first longitudinal, pan-provincial analysis of HIV treatment response among MSM in Canada. In summary, we found that 2,616 (82.3%) MSM living in BC, Ontario, and Quebec achieved virologic suppression within a one-year timeframe, and 298 (11.4%) of these suppressed individuals subsequently experienced viral rebound within a median time of 22 months. The median time to suppression was 4 months, well within documented timeframes reflecting stable treatment adherence (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015). Moreover, only 4% of suppressed MSM participants who started treatment since 2008 experienced an episode of viral rebound, demonstrating near comprehensive sustained suppression among MSM initiating cART in more recent years. This conveys that the large majority of ART-naïve, HIV-positive MSM on cART and living in Canada are quickly and successfully achieving virologic suppression following treatment initiation, and that most of these individuals retain suppressed viral loads. The MSM participants who eventually rebounded initially maintained suppressed HIV RNA levels for almost two years, on average. Overall, these results mark significant improvements in HIV health outcomes among MSM in Canada since the emergence of antiretroviral therapy, and signify that the population most affected by HIV/AIDS is within reach of the UNAIDS proposed target that 90% of individuals on ART reach viral suppression (UNAIDS, 2014).

However, the finding that approximately one in six HIV-positive MSM failed to achieve virologic suppression within one year of treatment initiation indicates that despite universal access to healthcare in Canada, other significant social and clinical factors are preventing more optimal treatment responses among a minority of MSM on ART. The proportion of participants

reaching suppressed HIV RNA levels falls in line with findings from other longitudinal, MSM-focused treatment response research conducted in Canada and the United States (Axelrad, Mimiaga, Grasso, & Mayer, 2013; Light et al., 2013). The Ontario HIV Treatment Network Cohort Study estimates that for 2011, 86% of MSM participants living in Ontario and engaged in HIV care were virologically suppressed (Light et al., 2013). In BC, for the year 2014, it is estimated that 84% of MSM on antiretroviral therapy achieved suppression (BC Centre for Excellence in HIV/AIDS, 2015). Unfortunately, the availability of additional, similarly MSM-oriented cohort treatment response research is quite limited (Public Health Agency of Canada, 2013b). Cross-sectional, surveillance-based estimates from the U.S. Centers for Disease Control calculate that 82% of ART-prescribed MSM from in 14 U.S. jurisdictions are virally suppressed (Hall et al., 2013). Broader U.S. estimates of suppressed MSM place this proportion at 42% (Singh et al., 2014). However, this statistic considers all HIV-positive MSM, and not just individuals engaged in care or on ART.

The use of different denominators when estimating the proportion of different populations reaching virologic suppression is an ongoing challenge in population level HIV treatment response research. When similar research uses different steps of the HIV care cascade to estimate suppression volumes, direct comparisons become more difficult. Moreover, the inconsistency of how treatment responses like viral suppression and rebound are operationalized in different studies also complicate the process of compiling a more cohesive knowledge base on this subject. In the literature, virologically suppressed HIV-positive individuals are frequently defined by either a point estimate obtained from a single viral load measurement or more ideally, by two consecutive viral load measurements gathered through patient follow-up. To complicate matters further, previously established thresholds for quantifying suppression are inconsistent.

Recent advancements in polymerase chain reaction (PCR) testing have enabled assays to discern previously undetectable levels of HIV RNA in the bloodstream (Cobb, Vaks, Do, & Vilchez, 2011). But more precise PCR-based technologies with improved sensitivity are not available in all HIV testing settings. As such, studies drawing on viral load data frequently define virologic suppression as plasma HIV RNA concentrations below 500 copies/mL, 400 copies/mL, 200 copies/mL, or 50 copies/mL (Nosyk et al., 2014; Singh et al., 2014). Our analysis was able to use the latter threshold, which has improved sensitivity relative to the other cut points. As such, our analysis had a lower likelihood of falsely classifying non-suppressed individuals.

Though these varied definitions of suppression complicate the analysis of treatment response across different studies, these comparisons remain important for establishing our results within a broader context of HIV-positive MSM health outcomes. Our findings are also comparable to similarly oriented HIV cohort research that includes women and non-MSM men. In their analysis of the multi-site North-American-based NA ACCORD cohort, Hanna et al. (2013) discovered that between 2001 and 2009, the cumulative incidence of 1-year virologic suppression was 84%, although a more sensitive threshold was used to define suppressed RNA levels in this study (a single viral load measurement < 500 copies/ML within 1 year). In the analysis by Hanna et al., MSM participants had an increased likelihood of achieving suppression compared to male injection drug users and non-MSM male participants. With regard to viral rebound, Mocroft et al. (2003) found that 14.6% of their treatment naïve sample had a rebound episode within a median follow-up time of 23 months. By contrast, a literature review found that smaller U.S. and European-based clinical and cohort studies reported higher instances of rebound among individuals initially achieving virologic suppression, ranging from 27-32% of study participants (Le Moing et al., 2002; Parienti et al., 2004; Robbins et al., 2007).

As expected (Sozio et al., 2008), participants who initiated antiretroviral therapy in more recent ART eras had a higher likelihood of reaching suppression within one year, as the development of improved ARV regimens in more recent years has improved drug efficacy and reduced side effects. It is also notable that more recent era of ART initiation also predicted a lower likelihood of virologic rebound in the multivariable accelerated failure time model. This second finding may also be attributable to the fact that persons who initiated ART in earlier years have had more time to both experience an episode of rebound and/or develop drug resistance. Another time-related factor that had no bearing on rebound likelihood was the time it took to reach suppression after starting treatment, which stands in contrast with similar research (Jose et al., 2013). Rebound and non-rebound MSM participants both achieved suppression within a median time of 4 months.

Our analysis did not identify ethnicity as a significant predictor of either outcome, at least in part due to the small number of black and Aboriginal MSM participants in our study population. Similar research has uncovered stark racial and ethnic disparities in HIV health outcomes in North America. In the United States, an estimated 37.0% of HIV-positive black MSM were virologically suppressed in 2010, compared to 43.9% of HIV-positive Caucasian MSM (Singh et al., 2014). Clinic-based cohort studies in the U.S. have also identified black MSM as having a lower chance of achieving suppression (Axelrad et al., 2013; Viswanathan et al., 2015). Treatment response analyses not restricted to MSM populations have identified black racial identity as a significant correlate of viral rebound and treatment failure (Frater et al., 2002; Robertson, Laraque, Mavronicolas, Braunstein, & Torian, 2015; Smith et al., 2005). Similarly, previous HIV research in Canada has demonstrated that Aboriginal people living with HIV have

poorer treatment outcomes (Lefebvre, Hughes, Yasui, Saunders, & Houston, 2014; Martin, Houston, Yasui, Wild, & Saunders, 2010) and are less likely to receive optimal antiretroviral therapy compared with the general population (Miller et al., 2006). Our findings address a gap in treatment response research specifically focusing on Aboriginal MSM. This should be pursued as a priority area, as heightened HIV risk factors and broader health disparities among this subpopulation of MSM have been documented (Heath et al., 1999). More complete data on ethnicity among CANOC participants may allow for a more comprehensive determination of whether this demographic factor is related to HIV RNA suppression or subsequent rebound among MSM on antiretroviral treatment in Canada.

The finding that participants with a history of IDU were less likely to achieve suppression and more likely to experience subsequent rebound is consistent with previous research (Hadland et al., 2012; Kerr et al., 2012; Viswanathan et al., 2015). People who inject drugs (PWID) face complex barriers to ongoing care that can compromise treatment outcomes. Hadland et al. (2012) found that younger PWIDs in particular face a disproportionate burden of poor treatment adherence and failure to achieve suppressed viral levels. HIV treatment research with MSM who inject drugs is scarcer, and it is important to reiterate that individuals who fall into this category remain at the nexus of two at-risk HIV exposure categories. Intervention strategies targeting MSM-IDU must recognize this added vulnerability. There is a discrepancy in that the proportion of HIV-positive MSM in our study population identified as having a history of IDU (8%) is considerably higher than the Canadian estimate (3%) (Public Health Agency of Canada, 2014). This may be explained by several factors. Among all MSM included from BC, 174 (18.6%) had a history of IDU. This IDU subset also comprises 67.2% of all MSM-IDU included in this analysis. This study population characteristic, along with the large representation of BC

participants from Vancouver's Downtown Eastside neighbourhood, one of Canada's most socially and economically disadvantaged communities (McInnes et al., 2009), may account for the disproportionate representation of MSM-IDU in this analysis.

In our study, increasing baseline age heightened the likelihood of suppression and also demonstrated a protective effect against subsequent viral rebound, which is congruent with other studies on MSM and broader HIV-positive populations (Hanna et al., 2013; Singh et al., 2014; Viswanathan et al., 2015). Each decade of younger age was associated with a 5% reduced likelihood of achieving suppression within 1 year and a 43% increased chance of experiencing rebound. Young MSM can face a wide array of challenges, including sexual identity issues, substance abuse, precarious employment, and housing instability (Eastwood & Birnbaum, 2007). Understandably, these circumstances can interfere with ongoing retention in HIV care. Youth-focused case management interventions and other outreach services have demonstrated effectiveness in helping younger MSM manage their HIV infection and achieve better treatment responses (Harris et al., 2003; Tenner, Trevithicka, Wagnera, & Burch, 1998; Wohl et al., 2011) and should be pursued as a strategy to promote treatment adherence and retention in care among younger MSM on ART in Canada.

This analysis identified baseline viral load as a significant predictor of one-year suppression over baseline CD4 cell count. Other studies have similarly recognized the former as a better predictor of time to virological suppression, contending that baseline CD4 cell count may serve as a better indicator for long-term cART outcomes (Cescon et al., 2011; O. J. Cohen & Fauci, 2000; Hogg et al., 2001; Phillips et al., 2001). The low median baseline CD4 cell count among participants (237 cells/mm^3) is concerning. Previous research suggests that PHA who initiate cART with

similarly low CD4 measures are at higher risk of AIDS and death (Kitahata et al., 2009; Sterne et al., 2009). This finding may reflect both late diagnosis and older ART treatment guidelines. Although older treatment guidelines stipulated that ARV treatment should begin at CD4 levels below 250 cells/mm^3, these have since been revised to recommend earlier initiation (World Health Organization, 2015). Future CANOC analyses should pursue whether there is a corresponding increase in median CD4 cell count at baseline as treatment initiation guidelines are updated. Our finding that higher baseline CD4 cell count was a significant predictor of viral rebound was surprising (Street et al., 2009). However, it is important to note that this analysis did not track treatment response beyond the first virologic rebound episode, so this finding should be interpreted with caution. It is possible that ART adherent MSM with high baseline CD4 cell counts did not experience adverse medical complications and retained comparatively better health throughout the study timeline than MSM with a lower baseline CD4. This may have influenced healthier patients to "take a break" from their ART regimens, thus increasing risk for viral rebound. Indeed, improved health has been previously cited by patients on ART as a reason for interrupting treatment (Chesney et al., 2010). Another CANOC study recognized an association between higher baseline CD4 cell count and subsequent treatment interruptions (Samji et al., 2015).

There were significant differences between provinces regarding rebound likelihood. This may be partially attributable to differences in patient selection between regions. There is a clinic-based selection bias in Ontario and Quebec, whereas the participants from BC represent the entire sample of HIV-positive patients on ART in the province. It should also be noted that there were considerable provincial distinctions in viral load testing frequency. A previous CANOC analysis found that rates of viral load testing were significantly higher in BC compared with Ontario and

Quebec (Raboud et al., 2010). In our analysis, 50% of BC participants received 5 or more annual viral load tests, whereas only 17% and 19% of participants from Ontario and Quebec, respectively, received this volume of testing. Official guidelines concerning viral load testing do not differ between these 3 provinces (Raboud et al., 2010). Our study identified increased frequency of viral load testing as a predictor for both virologic suppression and subsequent rebound, estimating that participants with more than 6 annual tests were 2.54 times as likely to experience viral rebound than those who had fewer than 3 annual tests.

Our finding regarding viral load testing has several implications. It likely represents a case of censored interval data, in which some participants who do not get tested as frequently may be experiencing comparable rebound episodes within the timeframe when they are not getting tested, but by the time they receive another viral load test, they may be suppressed once again. Because of less frequent testing, some participants may experience undetected spikes in HIV viral load that are not addressed clinically, which could have repercussions on longer-term treatment outcomes. Additionally, recently suppressed participants who receive more frequent viral load tests will be classified as suppressed more quickly relative to recently suppressed participants who test less often, which may also explain viral load testing rate as a strong predictor of suppression.

Viral load testing frequency also provides an indirect indicator of patient treatment response and engagement in care (Irvine et al., 2015). MSM participants with comparatively worse health may utilize health services more frequently and have their HIV RNA levels tested more often. This would lead to more timely detections of rebound episodes. For example, a BC analysis of HIV-positive individuals on ART found that participants with the lowest CD4 cell counts and highest

HIV RNA levels accessed viral load testing more frequently than those with better health indicators (Druyts, Yip et al., 2009). This may explain the lower likelihood of suppression and the substantially greater risk of rebound among MSM participants who receive more than 6 annual viral load tests.

In summary, these potential scenarios help convey that our findings are sensitive to the frequency of viral load testing. We are not advocating for reduced viral load testing. In fact, quite the opposite, as these findings also highlight the point that recurrent testing is necessary to accurately describe ongoing patient response to ART. It is concerning that nearly a quarter of MSM participants who failed to suppress within the first year of treatment received an average of 2 annual viral load tests. Current guidelines recommend that in the first year following ART initiation, patients should receive testing from every 3 months (Günthard et al., 2014) to as frequently as every 4 weeks (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015). It is important to increase access to and uptake of this essential HIV health service by MSM who have recently initiated antiretroviral therapy in Canada. This will help provide a more timely and precise assessment of HIV treatment response as well as better inform HIV care providers how to respond to clinical changes in HIV infection.

This analysis originally considered two additional covariates of interest: loss to follow-up and treatment interruptions experienced by participants. We had suppression and rebound data for a subset of these participants before they were lost to follow-up, and we compared their treatment responses to the rest of the CANOC MSM sample. In the original multivariable analysis, MSM who were lost to follow-up for more than 18 months had a significantly ($p = 0.006$) lower likelihood of experiencing suppression [HR 0.79, 95% CI 0.67-0.93]. However, because we were

examining predictors of virologic suppression and rebound, and loss to follow-up in this case was an outcome that occurred after our two outcomes of interest, it was difficult to rationalize loss to follow-up as a predictor variable. As a result, it was ultimately removed from consideration. However, this finding still underscores that patients who are not retained in care are at higher risk of experiencing adverse health outcomes. Regarding patients who experienced a treatment interruption at some point during follow-up, multivariable analysis originally found that they were significantly ($p < 0.001$) less likely to suppress [HR 0.49, 95% CI 0.43-0.55] and more likely to rebound [HR 17.59, 95% CI 13.88-22.29]. The hazard ratio for the rebound model was particularly extreme. After discussions with statisticians and CANOC principal investigators, we came to the decision that treatment interruptions were on the causal pathway to both viral rebound and suppression. In light of this, we decided to remove this variable from our analysis.

Strengths

Strengths of our analysis include its large sample size. CANOC represents the largest cohort of PHA in Canada, and is comprised of an estimated 25% of HIV-positive individuals on antiretroviral therapy. This improves the generalizability of study findings to the remaining PHA on antiretroviral therapy in Canada. This study also had a long clinical follow-up period, spanning 12 years. The longitudinal nature of this study allowed us to examine temporal trends in HIV viral load suppression and subsequent rebound. As previously mentioned, a considerable amount of HIV treatment response research is limited to surveillance data and cross-sectional analyses, and is more restricted in its capacity to make inferences over time. Use of CANOC data allows for a comparatively precise definition for viral load suppression, and an ability to track treatment response in MSM.

Limitations

We aggregated data from only 3 of 10 provinces in Canada and no territories although it is estimated that 85% of PHA in Canada live in BC, Ontario, and Quebec. But since our study population is limited to 3 provinces, the generalizability of our findings across the entire Canadian HIV-positive population on cART is more limited. There is also a clinic-based selection bias in Ontario and Quebec, whereas the participants from BC represent the entire sample of HIV-positive patients on ART in the province. A further limitation is missing data, especially with regard to MSM status. There were 2,547 male CANOC participants with missing or unknown MSM status, and were subsequently excluded from this analysis. However, male participants with unknown MSM status did not differ from the MSM sample significantly with regard to baseline CD4 cell count, achieving suppression, or experiencing rebound, so excluding them from the analysis likely did not bias our results to be more favourable. Additionally, the unknown/missing MSM sample experienced a slightly lower percentage of viral rebound episodes (8% compared to 11% in the MSM sample), so it is possible that including data from the unknown/missing MSM group would have yielded treatment response outcomes closer to the UNAIDS suppression target. Missing data and small sample sizes also limited our ability to identify significant correlations between race/ethnicity and treatment response.

Adherence to antiretroviral therapy is another important determinant of treatment response, but due to variable data collection and availability across provinces, we were unable to include and assess the predictive value of this variable. However, the suppression and subsequent rebound outcomes measured in this analysis may serve as proxies for ARV adherence, as disparities in these two outcomes are downstream outcomes of poor adherence. Potential changes from initial

patient drug regimens during the study timeline were also not incorporated into this study. It should also be noted that information pertaining to current injection drug use practices is not available. Similarly, hepatitis C status only indicates whether a participant has ever tested positive for HCV through antibody tests or polymerase chain reaction tests, and does not account for all cases that may have eliminated this infection spontaneously or through treatment. Finally, there are likely other uncaptured social and demographic characteristics that influence treatment response among MSM participants.

Recommendations

Intervention strategies should prioritize improving continued engagement in health care services among HIV-positive MSM, seeing as one in five study participants received 2 or fewer annual viral load tests, and that these individuals were significantly less likely to show suppressed HIV RNA levels. Recurrent testing is necessary to accurately describe ongoing patient response to cART, and assess whether drug resistance testing or regimen switches are required. Mainstreaming HIV care services throughout primary care demonstrates promise in expanding the reach and efficacy of HIV care (Wong, Kidd, & Tucker, 2013), and could improve uptake of viral load monitoring. At a broader provincial and municipal legislative level, developing organizational policies and practice standards that curtail sexual orientation-based discrimination (British Columbia. Provincial Health Officer, 2014) are needed to combat the stigma that some gay, bisexual, and other MSM experience or anticipate when accessing health care services. Disseminating pertinent educational materials and imagery showcasing same sex couples throughout practice settings (e.g. posters in waiting rooms) could help MSM patients feel more welcomed across health service environments (Makadon, Mayer, & Garofolo, 2006). Moreover, updating patient intake forms to use gender-neural language and having GPs confirm their

commitment to non-discrimination during initial patient visit may encourage more MSM to share their sexual identity and behaviours (Wong et al., 2013), which is important for receiving appropriately tailored health advice and services.

A shorter-term solution could entail anonymizing HIV treatment initiation. As opposed to HIV ART initiation, HIV testing can be accessed anonymously. Treatment is usually linked to individuals' names, but revising access-to-care HIV treatment provisions so that HIV-positive patients can initiate antiretroviral therapy more discretely for a limited time immediately following diagnosis could encourage more MSM who fear revealing their identity and encountering systemic discrimination to be linked to care (O'Byrne et al., 2014). Other policy-level solutions could include collaborating with academic institutions and exploring potential curriculum changes, online learning modules, and continuing education for health care professionals (British Columbia. Provincial Health Officer, 2014). This could increase the knowledge, cultural competency, and capacity for health services to deliver appropriate care to MSM living in Canada.

Improving HIV health service utilization among MSM also requires community level interventions. Several community-level initiatives in BC have demonstrated positive results on the health of gay and bisexual men living with HIV. For instance, the Vancouver-based STOP Outreach Team component of the broader provincial STOP HIV/AIDS provides training to MSM-oriented healthcare services to normalize HIV testing, educate clients, and promote continued engagement in care (Johnston, 2013). This specialized clinical outreach group of doctors, nurses, social workers, and peer navigators also collaborate with other Vancouver area family practices and acute care facilities to promote organizational capacity for handling HIV-

related health issues (CATIE, 2013). This is essential for linking MSM living with HIV to appropriate treatment and care. Similar initiatives that expand cultural sensitivity training should be pursued in other settings, as they will help foster a clinical environment that is more receptive to the health needs of HIV-positive MSM.

This analysis specifically identified younger MSM and MSM with a history of injection drug use as being at increased risk of both failing to suppress and experiencing virologic rebound. There is a scarcity of research and evaluation work specific to MSM-youth, but available evidence suggests that the most encouraging interventions for improving retention in care and ART adherence among the broader population of HIV-positive youths involve self-monitoring, peer support, telephone follow-up, and caregiver education (Reisner et al., 2009). Health care providers with younger HIV-positive MSM patients should become more knowledgeable about local LGBT-focused hotlines, agencies, and media so that they can better connect them to these social opportunities (Beyrer et al., 2012), Furthermore, HIV case management services could accommodate more flexible hours to promote continued engagement in care. Young HIV-positive MSM are more likely to miss scheduled appointment times, and providing more flexible scheduling has previously demonstrated improved clinical care attendance and HIV treatment response among this population (Wohl et al., 2011)

For PWID and other vulnerable PHA subpopulations, more intensive case management and outreach services have a strong record of improving health outcomes among MSM, non-MSM males, and women. The Manitoba HIV program provides follow-up and uniquely tailored case management to boost retention in care among more complex HIV cases (Wilton & Broeckaert, 2013). BC's Maximally Assisted Therapy Program and STOP Outreach Team have intensive

case management services for PWID, unstably housed individuals, and other vulnerable PHA, and these have significantly improved ongoing treatment adherence and retention in care (Johnston, 2013; Parashar et al., 2011). Focusing on psychosocial supports is also a necessary strategy for reducing treatment disparities within this priority group. Collaboration with housing and food security programs in BC and Quebec have shown promise in addressing some of the structural barriers that undermine HIV care engagement (Johnston, 2013; Wilton & Broeckaert, 2013). Incorporating harm reduction services such as supervised injection facilities into HIV care settings and increasing the availability of methadone maintenance therapy for HIV-positive MSM who inject drugs are other potential options for addressing substance use problems and improving HIV treatment self-efficacy, and have already been shown to improve ARV adherence (Krusi, Small, Wood, & Kerr, 2009; Spire, Lucas, & Carrieri, 2007). It should be noted that MSM on both cART and methadone therapy may require additional monitoring from care providers, as this substance use treatment has been shown to interact with the following ARV drugs - zidovudine, efavirenz, nevirapine, and lopinavir (BC Centre for Excellence in HIV/AIDS, 2011). When planning treatment engagement strategies for HIV-positive MSM-IDU, it is important to bear in mind that this vulnerable population faces stigma over 3 circumstances: their sexual orientation, drug use, and their HIV status.

Reflection

Upon undertaking this project, I was made increasingly aware of the fact that my knowledge regarding the social and structural factors of HIV infection was considerably stronger than my understanding of the biomedical and clinical side of this disease. As it currently stands, the CANOC data dictionary has more information pertaining to drug regimens, biological markers of treatment response, and comorbidities than it does for the social and demographic factors that

can influence health outcomes. But exploring these data provided an opportunity to familiarize myself with the clinical side of the HIV epidemic among MSM in Canada. I feel privileged to have had the opportunity to work with data from this collaboration, and have gained a broader understanding of HIV treatment response as a result.

Another important experience I gained through this retrospective cohort study was learning how to refine research questions and operationalize HIV-related health indicators in order to generate a more meaningful and informative analysis. When I originally submitted my data request for the MSM CANOC analysis, my suppression definition was not restricted to a specific time interval. After extensive discussion with other CANOC co-investigators and BC Centre for Excellence (CfE) researchers, I saw the value in incorporating a more time-sensitive unit into may analysis. Going forward, this will facilitate treatment outcome comparisons between other CANOC subpopulations from analyses using the same outcome definitions. Treatment response research similar to mine concerning women and youth from the CANOC dataset are currently under review for publication or have been accepted as abstracts at the Canadian Association for HIV Research (CAHR) and International AIDS Society (IAS) conferences. I look forward to comparing my analysis to these other CANOC studies, which will provide a new perspective for how HIV-positive MSM in BC, Ontario, and Quebec are responding to ART relative to other at-risk populations.

Going forward, I am hoping to update this MSM analysis with more recent data. Follow-up is currently limited to 2012, but the CANOC data cut for participant information through 2014 is scheduled for Spring 2016. I am curious as to whether incorporating these two more recent years of data into the analysis will improve the standing of treatment outcomes among BC MSM

relative to MSM in Ontario and Quebec. The BC Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) initiative expanded to encompass the entire province in 2013, and it will be interesting to see if its enhanced testing, treatment initiation, and retention strategies are associated with improved virologic suppression and rebound prevention in BC for 2013 and 2014. Connected to this hypothesis is another research question I want to explore using CANOC data. Specifically, I want to assess whether median CD4 cell count at treatment initiation has increased over time among MSM since 2000. The median baseline CD4 cell counts among all study participants was only 237 cells/mm^3. Previous HIV treatment research involving large cohorts have established that similarly low CD4 cell counts at treatment initiation are associated with an increased risk of AIDS diagnosis and premature mortality compared to PHA who begin ART at higher CD4 levels (Kitahata et al., 2009; Sterne et al., 2009). Considering the emphasis that the STOP initiative places on earlier HIV testing, especially among MSM populations, I think it is important to discern whether or not there is an association between rising baseline CD4 count among MSM in BC and the timeline corresponding to the expansion of the STOP program. As previously mentioned, there is a clinic-based selection bias for the Ontario and Quebec CANOC cohorts, and I'm curious as to whether the expansion of BC HIV testing and treatment initiatives will help overcome this limitation and demonstrate improvement in BC compared to the other two provinces.

The abstract based on this CANOC analysis was accepted as a poster for the upcoming IAS conference in Vancouver. I feel very fortunate to have the opportunity to share this research at such a venue. This will mark my first experience at a scientific conference, and I anticipate discovering other MSM-focused HIV research that can both help inform the results I obtained, as well as guide me towards exploring new research themes. I also hope to find more of an

emphasis on MSM research at IAS this summer. Reviews of HIV conference abstracts indicate that recently, only a small proportion of scientific conferences have focused on the unique health needs of MSM. Out of the accepted abstracts at the 2010 IAS conference, only 6.6% focused on gay and bisexual men, while at CAHR conferences between 2007 and 2011, only 7% of annually accepted abstracts focused on this at-risk population (Ayala, Beck, Hebert, Padua, & Sundararaj, 2011; Tooley, 2011).

Working on this analysis also made me reflect on my potential future role in HIV research. I am thankful to have had the opportunity to work with CANOC, but am also enthusiastic at the prospect of contributing to other BC CfE projects. Although CANOC data represents the largest cohort of HIV-positive Canadians, working with such a vast source of health-related data requires that some of the more unique experiences of HIV infection, which often cannot be reduced to numbers or dichotomized measures, be sacrificed. Because of its vast scope and huge study population, CANOC is unable to explore narrative data and discover some of the lived experiences of HIV among its participants. While conducting my analysis, I often felt like I was dealing with a set of numbers and disembodied measurements, rather than individuals who were living with HIV infection. I hope to have the opportunity to explore this qualitative and more social side of HIV infection through the CfE Momentum and At Home studies in the coming months.

Conclusion

In conclusion, this analysis discerned critical information regarding predictors of one-year virologic suppression and subsequent rebound among gay, bisexual, and other MSM in BC, Ontario, and Quebec. This represents an important step towards informing and improving HIV

treatment and retention programs for this population across Canada. The identification of younger MSM and those with a history of IDU as being at greater risk of virologic rebound reinforces the importance of prioritizing appropriately tailored case management interventions to avoid future treatment failure. However, the finding that 82% of HIV-positive MSM achieved virologic suppression within a year of cART initiation demonstrates that a sizable majority of the population most affected by HIV is responding to treatment successfully. Adding onto this favorable outcome is the fact that an even greater percentage of MSM who achieve suppression within this timeframe retain suppressed HIV RNA levels throughout this study's time horizon. Improved treatment regimens, HIV prevention, and care-engagement strategies have dramatically improved the epidemiologic profile of HIV-positive MSM since the 1980s, transforming this infection from a leading cause of death into a manageable, chronic condition.

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Tables/Figures

Table 1

Baseline characteristics of participants in total and by suppression status (n = 3180)

		Suppressed, n (%)		
	Total (%)	**No (n = 564)**	**Yes (n = 2616)**	**P-value**
Province				
British Columbia	935 (29)	191 (34)	744 (28)	0.036
Ontario	1138 (36)	191 (34)	947 (36)	
Quebec	1107 (35)	182 (32)	925 (35)	
Age (years)	40 (33-46)	38 (33-44)	40 (34-46)	0.002
Ethnicity				0.029
Caucasian	1407 (44)	262 (46)	1145 (44)	
Black	59 (2)	10 (2)	49 (2)	
Aboriginal	76 (2)	21 (4)	55 (2)	
Other	399 (13)	54 (10)	34 (13)	
Unknown	1239 (39)	21 (38)	1022 (39)	
History of IDU				< 0.001
No	2854 (90)	475 (84)	2379 (91)	
Yes	259 (8)	70(12)	189 (7)	
Unknown	67 (2)	19 (3)	48 (2)	
Hepatitis C status				0.009
No	2694 (85)	455 (81)	2239 (86)	
Yes	352 (11)	82 (15)	270 (10)	
Unknown	134 (4)	27 (5)	107 (4)	
Era of ART initiation				0.002
2000-2003	746 (23)	161 (29)	585 (22)	
2004-2007	966 (30)	145 (26)	821 (31)	
2008-2012	1468 (46)	258 (46)	1210 (46)	
Number of viral load tests per year				< 0.001
Less than 3	643 (20)	129 (23)	514 (20)	
3-4	1666 (52)	213 (38)	1453 (56)	
5-6	394 (12)	66 (12)	328 (13)	
More than 6	477 (15)	156 (28)	321 (12)	
Initial 3rd ARV class				< 0.001
NNRTI	1422 (45)	200 (35)	1222 (47)	
Unboosted PI	135 (4)	40 (7)	95 (4)	
Boosted PI	1347 (42)	261 (46)	1086 (42)	
Other	276 (9)	63 (11)	213 (8)	
Initial 3rd ARV				< 0.001
Nevirapine	261(8)	44 (8)	217 (8)	
Efavirenz	1147(36)	150 (27)	997 (38)	
Lopinavir	440(14)	82 (15)	358 (14)	
Atazanavir	647(20)	121 (21)	526 (20)	
Other	685(22)	167 (30)	518 (20)	
NRTI combination				0.060
Tenofovir/emtricitabine	1445(45)	240 (43)	1205 (46)	
Zidovudine/lamivudine	612(19)	123 (22)	489 (19)	
Tenofovir/lamivudine	213(7)	31 (5)	182 (7)	
Abacavir/lamivudine	526(17)	86 (15)	440 (17)	
Stavudine/lamivudine	215(7)	45 (8)	170 (6)	
Other	169(5)	39 (7)	130 (5)	
AIDS-defining illness				0.159
No	2565 (81)	439 (78)	2126 (81)	
Yes	489 (15)	101 (18)	388 (15)	
Unknown	126 (4)	24 (4)	102 (4)	
Viral load (log_{10} copies/mL)	4.95(4.48-5.00)	5.00 (4.69-5.00)	4.91 (4.44-5.00)	< 0.001
CD4 count (cells/uL)	237 (130-340)	220 (110-347)	240 (140-340)	0.085

Table 2

Baseline characteristics of participants by rebound status (n = 2616)

		Rebound, n (%)	
	No (n = 2318)	**Yes (n = 298)**	**P-value**
Province			
British Columbia	613 (26)	131 (44)	< 0.001
Ontario	852 (37)	95 (32)	
Quebec	853 (37)	72 (24)	
Age (years)	40 (33-47)	39 (34-44)	0.009
Ethnicity			< 0.001
Caucasian	986 (43)	159 (53)	
Black	42 (2)	7 (2)	
Aboriginal	43 (2)	12 (4)	
Other	303 (13)	42 (14)	
Unknown	944 (41)	78 (26)	
History of IDU			< 0.001
No	2138 (92)	241 (81)	
Yes	141 (6)	48 (16)	
Unknown	39 (2)	9 (3)	
Hepatitis C status			< 0.001
No	2009 (87)	230 (77)	
Yes	208 (9)	62 (21)	
Unknown	101 (4)	6 (2)	
Era of ART initiation			< 0.001
2000-2003	438 (19)	147 (49)	
2004-2007	715 (31)	106 (36)	
2008-2012	1165 (50)	45 (15)	
Number of viral load tests per year			0.219
Less than 3	459 (20)	55 (18)	
3-4	1297 (56)	156 (52)	
5-6	288 (12)	40 (13)	
More than 6	274 (12)	47 (16)	
Initial 3rd ARV class			0.012
NNRTI	1101 (47)	121 (41)	
Unboosted PI	76 (3)	19 (6)	
Boosted PI	957 (41)	129 (43)	
Other	184 (8)	29 (10)	
Initial 3rd ARV			< 0.001
Nevirapine	174 (8)	43 (14)	
Efavirenz	917 (40)	80 (27)	
Lopinavir	310 (13)	48 (16)	
Atazanavir	475 (20)	51 (17)	
Other	442 (19)	76 (26)	
NRTI combination			< 0.001
Tenofovir/emtricitabine	1150 (50)	55 (18)	
Zidovudine/lamivudine	399 (17)	90 (30)	
Tenofovir/lamivudine	158 (7)	24 (8)	
Abacavir/lamivudine	391 (17)	49 (16)	
Stavudine/lamivudine	124 (5)	46 (15)	
Other	96 (4)	34 (11)	
AIDS-defining illness			0.346
No	1893 (82)	233 (78)	
Yes	337 (15)	51 (17)	
Unknown	88 (4)	14 (5)	
Viral load (log_{10} copies/mL)	4.91 (4.42-5.00)	4.99 (4.62-5.00)	0.011
CD4 count (cells/uL)	240 (143-340)	211 (99-315)	0.002
Time to suppression (months)	4 (3-5)	4 (3-5)	0.257

Table 3 Factors predicting time to viral suppression among MSM in CANOC

	Unadjusted hazard ratio (95% confidence interval)	**P-value**	**Adjusted hazard ratio (95% confidence interval)**	**P-value**
Era of ART initiation				
2000-03	1.00	< 0.001	1.00	< 0.001
2004-07	1.20 (1.08-1.34)		1.27 (1.14-1.42)	
2008-12	1.33 (1.21-1.47)		1.26 (1.14-1.40)	
Province				
British Columbia	1.00	0.004		
Ontario	1.08 (0.98-1.19)			
Quebec	1.18 (1.07-1.30)			
Ethnicity				
Caucasian	1.00	0.001		
Black	1.17 (0.88-1.56)			
Aboriginal	0.81 (0.62-1.06)			
Other	1.21 (1.07-1.36)			
Unknown/Missing	1.13 (1.04-1.23)			
Baseline age (per 10 year increment)	1.03 (0.99-1.07)	0.138	1.05(1.01-1.09)	0.017
IDU History (yes vs. no)	0.75 (0.65-0.87)	< 0.001	0.75 (0.65-0.87)	< 0.001
Number of viral load tests per year				
Less than 3	1.00	< 0.001	1.00	< 0.001
3-4	1.17 (1.06-1.30)		1.19 (1.07-1.31)	
5-6	1.11 (0.96-1.27)		1.14 (0.99-1.31)	
More than 6	0.91 (0.79-1.04)		0.91 (0.79-1.05)	
Initial 3rd ARV class				
NNRTI	1.00	< 0.001	1.00	< 0.001
Unboosted PI	0.59 (0.48-0.73)		0.65 (0.53-0.81)	
Boosted PI	0.79 (0.73-0.86)		0.81 (0.74-0.88)	
Other	0.94 (0.81-1.09)		0.98 (0.84-1.13)	
Baseline CD4 count (per 100 cells/mm^3)	1.05 (1.03-1.08)	< 0.001		
Baseline viral load (per log10 copies/mL)	0.63 (0.59-0.68)	< 0.001	0.65 (0.60-0.70)	< 0.001
Baseline AIDS defining illness (yes vs. no)	0.87 (0.78-0.97)	0.046		

Table 4 Factors predicting time to viral rebound among MSM in CANOC

	Unadjusted hazard ratio (95% confidence interval)	**P-value**	**Adjusted hazard ratio (95% confidence interval)**	**P-value**
Era of ART initiation				< 0.001
2000-03	1.00	< 0.001	1.00	
2004-07	0.67 (0.52-0.86)		0.60 (0.46-0.79)	
2008-12	0.38 (0.27-0.54)		0.29 (0.20-0.43)	
Province				
British Columbia	1.00	< 0.001	1.00	0.003
Ontario	0.55 (0.42-0.71)		0.63 (0.46-0.86)	
Quebec	0.47 (0.35-0.63)		0.59 (0.43-0.82)	
Ethnicity				
Caucasian	1.00	0.007		
Black	1.46 (0.68-3.11)			
Aboriginal	1.68 (0.93-3.01)			
Other	0.98 (0.70-1.38)			
Unknown/Missing	0.67 (0.51-0.88)			
Baseline age (per 10 year increment)	0.77 (0.68-0.87)	< 0.001	0.70 (0.61-0.80)	< 0.001
IDU History (yes vs. no)	2.65 (1.94-3.61)	< 0.001	2.28 (1.64-3.17)	< 0.001
Number of viral load tests per year				
Less than 3	1.00	< 0.001	1.00	< 0.001
3-4	1.03 (0.75-1.39)		0.97 (0.70-1.33)	
5-6	1.46 (0.97-2.20)		1.26 (0.80-1.98)	
More than 6	2.66 (1.79-3.93)		2.54 (1.62-3.97)	
Initial 3rd ARV class				
NNRTI	1.00	0.064	1.00	0.090
Unboosted PI	1.63 (1.01-2.65)		1.46 (0.89-2.39)	
Boosted PI	1.17 (0.91-1.50)		1.12 (0.85-1.46)	
Other	1.56 (1.04-2.35)		1.62 (1.07-2.45)	
Baseline CD4 count (per 100 cells/mm^3)	1.03 (0.96-1.12)	0.415	1.13 (1.04-1.22)	0.002
Baseline viral load (per log10 copies/mL)	1.13 (0.87-1.48)	0.364		
Baseline AIDS defining illness (yes vs. no)	1.01 (0.75-1.37)	0.994		
Time to suppression (months)	1.04 (0.99-1.08)	0.140		