Engagement in care among adolescents and young adults living with HIV in Canada

by

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Abstract

Background: More than thirty years after the beginning of the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic, HIV continues to be a problem among adolescents and young adults (AYA).. The benefits of combination antiretroviral therapy (cART), including lower morbidity and improved survival, are realized through timely uptake of treatment, virological suppression, and retention in care; however, compared with their adult counterparts, AYA living with HIV tend to have poorer treatment and clinical outcomes. In the current context of UNAIDS' ambitious 90-90-90 campaign, there is a push to expand cART to all those in need in order to reduce morbidity/mortality and to curb transmission of HIV. We will not achieve the 90-90-90 goals without addressing HIV treatment and outcomes among AYA; however this population remains under-researched; to date there is very little research describing AYA living with HIV in Canada. The overall aim of this dissertation is to examine key cART treatment outcomes among Canadian AYA (ages 18-29 years) living with HIV and compare outcomes with those of older adults (30 years and older).

Methods: The quantitative studies in this dissertation utilize clinical and laboratory data from the Canadian Observational Cohort Collaboration (CANOC)*,* Canada's largest HIV cohort study, which includes data from the year 2000 onward on a total of 10,044 people living in three of Canada's largest provinces—British Columbia, Ontario, and Quebec. All participants in CANOC are HIV-positive and were cART-naive prior to initiating antiretroviral treatment on or after January 1, 2000.

Findings: There are 1168 (13.7%) AYA (ages 18-29 years) in CANOC. Significant differences in treatment outcomes were found between AYA and older adults. AYA were more likely than older adults to initiate cART before their CD4 counts were <200 cells/mm^3 and/or they had an AIDS-defining illness (ADI) (51.7% vs 40.2% $p<0.001$). When looking at virological suppression, fewer AYA experienced virological suppression than older adults (86% vs. 91%, $p<0.001$) and of these, only 73% (compared with 80% of older adults) suppressed within the first year of cART inititation ($p<0.001$). Additionally, a greater proportion of AYA who achieved virological suppression experienced viral rebound than older adults (26% vs. 22%, $p=0.009$).

Discussion: When comparing AYA with older adults, AYA are more likely to initiate treatment when recommended but once on treatment, they are less likely to virologically suppress and remain suppressed. The importance of supporting AYA to achieve optimal health is a long-term investment with benefits over the life course. In order to meet ambitious public health goals such as those that the UNIADS 90-90-90 campaign has set, AYA will require tailored health care services and programming to assist them to access and remain in care.

Keywords: HIV and AIDS; Adolescents and Young Adults; cART; Late Initiation; Virological Suppression; Retention; Canada

Dedication

To all of the young people living with HIV/AIDS across the globe. Your courage and strength continues to inspire and motivate change.

"Sometimes it falls on a generation to be great. You can be that great generation. Let your greatness blossom." – Nelson Mandela

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I would like to give a special shout-out to my Uncle Rick for keeping me humble and for always reminding me of the early days of the HIV pandemic when fear was abundant and hope was scarce – look how far we have come!

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List of Acronyms

AIDS	Acquired Immunodeficiency Syndrome
ADI	AIDS-defining illness
aOR	Adjusted Odds Ratio
ART	Antiretroviral therapy
AYA	Adolescents and Young Adults
BC	British Columbia
BC-CfE	British Columbia Centre For Excellence in HIV/AIDS
BCCDC	British Columbia Centre for Disease Control
CAAN	Canadian Aboriginal AIDS Network
CANOC	Canadian Observation Cohort collaboration
cART	Combination antiretroviral therapy
CAS	Canadian AIDS Society
CATIE	Canadian AIDS Treatment Information and Exchange
CDC	Center for Disease Control
CIHR	Canadian Institutes for Health Research
CVL	Community viral load
CWQHR	Canadian Working Group on HIV and Rehabilitation
DTP	Drug Treatment Program
EARTH	Electronic Antiretroviral therapy cohort
HAART	Highly active antiretroviral therapy
HCV	Hepatitis C Virus
HEPB	Hepatitis B
HIV	Human Immunodeficiency Virus
HPV	Human papilloma virus
IAS	International AIDS Society
ICES	Institute for Clinical Evaluative Sciences
IDU	Injection Drug Users
IQR	Inter-quartile Range
IRIS	Immune reconstitution inflammatory syndrome

MLMC	Maple Leaf Medical Clinic
MSM	Men who have sex with men
MTCT	Mother-to-child-transmission
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
OCS	Ontario Cohort Study
ON	Ontario
OHTN	Ontario HIV Treatment Network
OR	Odds Ratio
PI	Protease Inhibitor
PHAC	Public Health Agency of Canada
PLWH	People living with HIV
PQ	Quebec
RAMQ	Régie de l'assurance maladie du Québec
RCT	Randomized Control Trial
RNA	Ribonucleic acid
STOP HIV/AIDS	Seek and Treat for Optimal Prevention of HIV/AIDS
STI	Sexually Transmitted Infection
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TasP	Treatment as Prevention
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Preface

This manuscript-based thesis is comprised of seven chapters, several of which are in various stages of publication. As of June 2015, two of the chapters (Chapters 3 and 4) have been published in peer-reviewed journals and an additional two manuscripts (Chapters 5 and 6) are being developed for publication with content from this dissertation. Please note that the methods sections are repetitive as they are published, or will be published, and must reflect the STROBE guidelines (1).

A version of **Chapter 3** has been published in the *International Journal of Epidemiology* as a cohort profile of the Canadian Observational Cohort Collaboration (CANOC) study. The manuscript outlines the HIV epidemic in Canada, describes participants enrolled in CANOC, and provides an overview of the data sources used for all of the subsequent analyses in this dissertation. The manuscript details the methods of data collection and synthesis used to harmonize clinical and HIV treatment data across different provinces and databases. As well, I outline the objectives of the CANOC collaboration and describe the knowledge dissemination plan. I designed and wrote the first draft of the paper. Co-authors MBK, CC, SH, ML, NM, JSM, SBR, MA, CT, and RSH provided guidance and in-depth knowledge of the various cohorts. RSH provided mentorship and is the Principal Investigator of CANOC. Co-authors BY and DM managed the data and linked CANOC data with census data. All authors approved the final version of the manuscript prior to publication.

Palmer AK, Klein MB, Raboud J, Cooper C, Hosein S, Loutfy M, Machouf N, Montaner JSG, Rourke SB, Smieja M, Tsoukas C, Yip B, Milan D, Hogg RS; CANOC Collaboration. Cohort Profile: The Canadian Observational Cohort Collaboration. *International Journal of Epidemiology*. 2011;40(1):25-32.

A modified version of **Chapter 4** has been published in *The Journal of the International Association of AIDS Care Providers*. The manuscript examines factors associated with late cART initiation among young HIV-positive Canadians (18-29 years), who have access to a publicly funded universal health care system. AP designed and

wrote the first draft. AMC provided extensive feedback and review. MRL provided mentorship and guidance. KC provided statistical support. Co-authors CC, JMR, CLM, ANB, MBK, NM, JSM, CT, and RSH provided in-depth knowledge of the cohorts and the participant population. RSH provided strategic guidance and is the Principal Investigator of the CANOC study. All authors approved the final version of the manuscript prior to publication.

> Factors Associated with Late Initiation of Highly Active Antiretroviral Therapy among Young HIV-Positive Men and Women Aged 18 to 29 Years in Canada. Palmer AK, Cescon AM, Chan K, Cooper C, Raboud JM, Miller CL, Burchell AN, Klein MB, Machouf N, Montaner JSG, Tsoukas C, Hogg RS, Loutfy MR and the CANOC Collaboration. *Journal of the International Association of Providers of AIDS Care*. 2014; 13:56-62.

A version of **Chapter 5** is in development for submission to the *Journal of Adolescent Health.* The manuscript aims to assess time to virological suppression among AYA taking cART and to explore factors associated with virological suppression. AP designed and wrote the first draft. ED provided statistical support. AMC, AK, CLM and WS provided feedback and review. RSH provided mentorship and strategic guidance and is the Principal Investigator of the CANOC study. The formal author list is yet to be determined.

Chapter 1.

Background, Rationale, and Objectives

1.1. Abstract

Chapter 1 presents an overview and an outline of this dissertation. In Chapter 1 I describe: 1) the burden of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) among adolescents and young adults (AYA); 2) recent advances in and success with antiretroviral treatment of AYA living with HIV; and 3) ongoing treatment challenges for AYA living with HIV. I also present and discuss the frameworks used in my dissertation: (a) *Treatment as Prevention* is used to explain the importance of engaging youth in care in terms of both the importance of addressing the clinical health of AYA living with HIV as well as opportunities to reduce risks of onward HIV transmission(2); (b) *Cascade of Care* is used to identify the stages of HIV care (from HIV testing and diagnosis through to linkages and retention in care) where AYA are succeeding or meeting challenges (3); and (c) an adapted *Seek, Test, Treat, and Retain* framework situates this research within a larger context of contemporary HIV treatment and prevention programming (4). Finally, in this first chapter I list the study objectives and hypotheses and describe the study setting, sample, and design that form the basis of the subsequent analyses included in this dissertation.

1.2. HIV among Adolescents and Young Adults

Despite recent significant scientific advances in prevention and treatment, HIV continues to affect young people at an alarming rate (5). Globally, 15- to 24-year-olds comprise 41% of all new infections in people older than 15 years, with young women disproportionately affected (6). From 2005 to 2012 deaths among adolescents aged 10

to 19 living with HIV increased by 50% while rates decreased over this time period for older adults (6). AIDS remains the leading cause of death among adolescents in sub-Saharan Africa and is the second leading cause of death among adolescents globally (7,8).

In Canada, of 78,511 HIV positive tests, 25% were among adolescents and young adults aged 15-29 (9). The Public Health Agency of Canada (PHAC) began reporting data about HIV incidence and prevalence in 1985. From 1985 to 2013, there were 19,783 confirmed HIV diagnoses among AYA in Canada.

Among AYA living with HIV, approximately 75% are men (10), a proportion that has remained relatively consistent since the early/mid- 1990s (10). The age distribution among young women and men from 1985 to 2013 differs with young women more likely to be diagnosed at a young age (15-19 years) than their male counterparts (30 years and older); however, young men still made up the majority of new infections (77%) among adolescents and young adults in 2013. In terms of perinatally infected AYA, no data are available on the exact number, but from 1985 to 2013, there were 642 reported cases of HIV among children (<15 years), representing 0.9% of the HIV-positive population. People from HIV-endemic countries represent an important proportion of people living with HIV in Canada. Countries where HIV is endemic are defined as those where the prevalence of HIV among people ages 15 to 49 years is 1.0% or greater and one of the following: (1) 50% or more of HIV cases are attributed to heterosexual transmission; (2) a male to female ratio of 2:1 or less among prevalent infections; (3) or HIV prevalence greater than or equal to 2% among women receiving prenatal care (9). Between January 1, 2005 and December 31, 2012, 1,058 applicants screened overseas who landed in Canada were diagnosed with HIV, with 26.1% of them between the ages of 20 and 29 years.

Cumulatively from 1985 to 2013, the majority of people living with HIV have been concentrated in three provinces: Ontario (43.8%), Quebec (22.4%), and British Columbia (18.8%). Although data specifically for AYA is not available as PHAC doesn't give provincial breakdowns, we can assume that youth represent about 25% of these cases (11). Recently the Prairie provinces (Alberta, Saskatchewan, and Manitoba) have seen

the greatest increase in new HIV cases. In the Prairie region, there was a 12% increase per year in new HIV cases between 2003 and 2007 (12). The age distribution differs between men and women with women being diagnosed at a younger age(10).

Sexual minority youth (gay, bisexual, and transgender), young people who inject drugs, and Aboriginal youth are disproportionately represented among AYA living with HIV (5). Using the HIV risk exposure categories employed by PHAC, of 504 incident HIV cases among AYA in 2013, more than half (59%) of incident HIV infections were attributable to men who have sex with men (MSM), one-quarter (24%) to heterosexual sex (11), 10% to injection drug use (IDU), and 4% to a combined category of IDU and MSM.

The HIV incidence rate among MSM 15 years and over is 71 times higher than the rate for heterosexual men in the same age range (9,11). Recent data from the United States shows that young MSM aged 13 to 24 years had the greatest percentage increase in HIV incidence (26%) from 2008 to 2011 compared with older age groups of MSM (13). Research from British Columbia shows that sexual minority street youth are more likely to engage in HIV risk behaviours such as injection drug use and unprotected sex than other street youth, increasing their vulnerability to HIV acquisition (14). Based on the above data, young MSM have an increased chance for HIV acquisition when compared to both older MSM and young heterosexual men.

The HIV incidence rate for people who inject drugs in Canada in 2011 was 46 times higher than the rate among people who had never injected drugs (9). AYA who use injection drugs, particularly those who are entrenched in street-based drug scenes, are especially vulnerable to acquiring HIV. A study from Montreal shows injection drug use to be the biggest predictor of HIV seroconversion among street youth (15). In Vancouver, unstable housing environments among young people who inject drugs have been found to be associated with elevated risk of HIV- infection. This association was related to an independent association between unstable housing and increased HIV risk behaviours such as syringe sharing and not enrolling in a substance support program (16) showing that unstably housed young people are not engaged well with HIV prevention services.

Another key population affected by HIV is Aboriginal youth, including First Nations, Metis, and Inuit youth. In Canada, Aboriginal people are overrepresented in the HIV epidemic, comprising 3.8% of the Canadian population yet representing 8.9% of all people living with HIV in 2011 (9). They are more likely to be diagnosed with HIV at a younger age with approximately one-third of HIV-positive Aboriginal people diagnosed between the ages of 15 and 29 years compared with 20.5% among non-Aboriginal people (17).

Aboriginal people are disproportionately represented in the three Prairie provinces where they make up 36% of all new HIV cases (12). In Saskatchewan, among HIV incident cases of 20 to 29 year-olds, 92% self-reported as Aboriginal (18). Consistent with earlier findings, women tend to be younger than men when diagnosed; in 2009, 38% of HIV diagnoses among Aboriginal women were among those 25 years and younger whereas only 14% of Aboriginal male HIV diagnoses were among men in the same age group (18). The average age of HIV diagnosis among Aboriginal women is 29.4 years; among Aboriginal men is 36 years; and among non-Aboriginal people in Saskatchewan is 41.4 years (18). As with other youth populations in Canada, a high prevalence of HIV infection has been reported among homeless and street-involved Aboriginal youth (19).

Aboriginal peoples' disproportionate representation in the HIV epidemic stems from Canada's history of colonization, specifically the dispossession and dislocation of Aboriginal communities through the reserve, residential school and child welfare systems; as well as the social- structural marginalization of First Nations, Inuit and Metis peoples(20–22). Since colonization, Aboriginal people have been denied access to the resources necessary to maximize economic and social opportunities (16,17). Poverty is a well-documented driver of HIV (18,19) resulting in lack of access to education systems, health care and employment, which can all lead to risk of HIV. Historical trauma (as a result of the residential school programs and other oppressive programs) is a reality for many young Aboriginal people in Canada, making trust in authorities difficult(23–25). Consequently, testing positive for HIV and being linked into care can be a difficult and frightening activity for Aboriginal youth (20–22). The lack of culturally

appropriate health services can hinder their willingness to seek care, therefore limiting opportunities for HIV prevention and education (22).

More than thirty years into the HIV/AIDS epidemic, HIV continues to affect adolescents and young adults. Improvements in HIV education, prevention, and treatment have led to an overall decrease in the number of people acquiring HIV; however, young people are still disproportionally overrepresented (5,26–28).

1.2.1. Antiretroviral therapy

Combination antiretroviral therapy (cART) has transformed HIV into a chronic, manageable illness for those with access to medication, appropriate social support, and the ability to adhere to cART regimens (29,30). People living with HIV derive the benefits of cART, including lower morbidity and improved survival (30–32), through timely initiation of treatment, optimal adherence to prescribed cART medication, and retention in care (33–35). In addition, By suppressing plasma HIV viral load, use of cART drastically reduces risk of vertical and sexual HIV transmission (36,37), and is associated with population-level reductions in HIV incidence in what is referred to as the scientific breakthrough of 'Treatment as Prevention (TasP)' (30,38).

While adherence to cART is the determining factor of treatment success and a key component in the TasP paradigm, achieving and maintaining optimal adherence to cART remains a critical challenge (31,32,39–41). Poor adherence or non-adherence, including treatment interruptions (interruptions of 90 days or more in the treatment course), results in loss of virological suppression (plasma viral load rebound) and represents a form of treatment failure (31,42). Treatment failure can have negative consequences for individual clinical health; as well, it increases the potential for HIV transmission, which undermines TasP strategies (2,43). In addition, poor adherence to cART threatens the preservation of future drug regimens by raising the potential of drug resistance (43).

1.2.2. cART use among AYA

Adolescence can be a confusing, emotionally-charged phase of life and complicated for AYA to negotiate. A diagnosis of a highly stigmatized illness such as HIV can only compound the complications (44,45). Navigating the transition from adolescence to adulthood, while simultaneously navigating a serious illness, is a reality for an estimated five million AYA across the globe (5). This critical transition period of biological and social development presents an optimal opportunity to promote healthy living and influence health decision-making among youth living with HIV/AIDS. According to the World Health Organization (WHO), approximately 70% of premature deaths in adults are the result of patterns and behaviours developed in adolescence (46). AYA who initiate cART need to remain on treatment for the rest of their lives, making the development of positive health practices and adherence behaviours very important. These behaviours will follow AYA across the course of their lives and help to enable good health and well-being (47).

The importance of supporting AYA to achieve optimal health is a long-term investment with benefits over time, as people living with HIV have life expectancies nearing those of HIV-negative individuals (29,48). According to a recent multi-site cohort study, a 20-year-old person living with HIV in Canada or the United States can now expect to live into their 70s as long as they take their prescribed cART as directed (49). Early initiation of cART, retaining AYA in care, and optimal adherence to achieve sustained virological suppression are critical priorities for minimizing the HIV-related health burden and lowering HIV transmission risks over the life course (35,41,50,51). For HIV-positive young people who are initiating and navigating new sexual relationships, adhering to cART and maintaining virological suppression has the enormous potential to normalize sexual relationships and promote healthy sexuality (6,47,52–54).

However, many AYA are not successfully engaged in care. For instance, rates of cARTadherence among youth living with HIV are significantly poorer than adults (55–57), with studies reporting that 50 to 60% of adolescents (ages 13-21) are sub-optimally adherent (defined as taking less than 95% of their prescribed dose of cART) (39,41–43). A recent study from the USA estimated that less than 6% of young people living with HIV

successfully reach virological suppression and remain virologically suppressed, proving them to be a population in need of intervention (60).

In a previous analysis using Canadian data for people of all ages, time to virological suppression was approximately 4.5 months and was associated with older age (61). Although Canadian data is limited, in a number of American studies, AYA tend to report slower time to suppression than older adults (60,62–65). As well, once they are in treatment, they experience poorer retention in care, greater loss-to-follow-up, are more likely to experience treatment interruptions, and are more likely to experience virological rebound compared with older adults (60,62–70).

Compared with their adult counterparts, young people living with HIV have poorer treatment and clinical outcomes overall, largely owing to social and structural factors that intersect to compromise their agency and access to care (6,28,55,71,72). Youth living with HIV are especially vulnerable and experience increased rates of social isolation, mental health issues, sexual and physical abuse, unstable housing, and addiction, all of which impact adherence to HIV care and to cART (73–75).

1.2.3. Factors compromising sustained cART use among AYA

Several leading studies have highlighted the urgent need to prioritize young people in the HIV treatment response (28,56,71,76,77) owing to observed worse treatment outcomes and compromised access to HIV care among AYA compared with adults. Increased risk-taking behaviour and greater emotional reactivity in adolescents are associated with different developmental trajectories (78). This often results in heightened pleasure-seeking and risky behaviours such as a unprotected sex, multiple sexual partners and drug and alcohol use (78–80) making tailored sexual health and HIV prevention programs extremely important.

Advancing pubertal stage often carries with it a change in peer group and greater vulnerability to peer influence (81). Adherence has been shown to be affected by peer-behaviour and fear of being stigmatized by peer groups (44), highlighting the different layers of stigma experienced.In a phase of their lives where socializing and acceptance is a priority, AYA may not view taking medication, something that differentiates them

from their peers, as important as taking part in “normal” experiences (82). It is when navigating these new peer groups that AYA may start to experiment with substance use (83). Due to maturing and developing identity and breaking away from parental/caregiver figures, many adolescents can feel invincible and, therefore, think that they don’t need medications (84).

Fear of HIV status disclosure and the need to maintain a sense of normalcy may be a large driving factor for sub-optimal cART adherence and poor retention in care for AYA. Over 50% of respondents in one study reported that they skipped a dose of medication because they were worried about family or friends discovering their HIV-positive status (85). In situations where family members or caregivers other than a biological parent are involved in medical care, AYA are more likely to be adherent to their medication (86), suggesting that the presence of guardians or adult role models in AYA’s lives may have a mediating effect on adherence levels.

AYA living with other chronic illnesses such as diabetes or epilepsy also tend to struggle with their medical care and treatment while transitioning into adulthood (82,87). However, AYA living with HIV often face internalized and social stigma and discrimination, which may complicate coping mechanisms. This stigma might exist outside as well as inside the home. However, some AYA report being, or being afraid of being, discriminated against by family members when they disclose their status (85).

1.2.4. Health-seeking behaviours among AYA

There are significant barriers to engaging AYA in HIV-related care, which greatly predicts clinical success including treatment adherence and virological suppression (31). Many young people do not access health services because of perceived barriers related to the availability, accessibility, appropriateness, and relevance of health services (88).

For AYA who live in rural areas, accessing sexual health information, testing, and medication can be challenging (89–91). In other instances, health care centres may not offer the necessary services (e.g., family planning options). In under-serviced areas, health care centres may not offer comprehensive or more specialized services required by AYA(92). They may have to travel to neighbouring towns or cities to access the

appropriate care, which can be time-consuming, expensive, and can threaten disclosure and confidentiality (93). Confidentiality in rural areas and on First Nations reserves may be a concern for those seeking care for taboo or stigmatized health issues as anonymity is less likely (89,90). Parental consent for sexual health-related procedures and medications is be an important limitation as mandatory parental consent for sexual health tends to reduce adolescents' willingness to access them (94,95).

Talking with AYA about their sexual health can be difficult, and compassion and patience is required from health care providers to ensure the individual that they are in a safe, secure, and accepting environment. Unfortunately, many AYA experience judgmental health care environments and hostile health care workers (96). AYA have long voiced their frustration with the lack of youth-friendly messaging and language that would enable them to feel more comfortable and accepted (97). Experiences of health care workers being critical and disapproving of their lifestyle may inhibit the likelihood for an individual to discuss sensitive topics such as STI testing in the future (98). AYA who are street-involved or involved in drug use report feeling stigmatized and discriminated against by health providers, which often prevents them from asking questions about their health or returning for follow-up care (88,93,96,99,100). Given that youth represent one of the fastest-growing HIV-affected populations, it is imperative that health care and prevention services meet the needs of this unique population. The analyses in this dissertation will provide evidence to support the demand for improved health services for AYA.

1.3. Frameworks

1.3.1. Treatment as Prevention (TasP)

Treatment as Prevention (TasP) is based on the understanding that viral load is the chief predictor of HIV transmission and when the viral load is suppressed, an individual has a greatly reduced chance of transmitting the virus (101). Based on ecological and observational studies and the landmark HPTN052 randomized control trial, it has been shown that the spread of HIV can be reduced by 96% by early and sustained treatment of people living with HIV with cART (37,38,102–105). The effectiveness of TasP was

shown in Taiwan where by following free widespread delivery of cART, the population-level transmission of HIV was reduced by 53% (102). As well, over the past decade, vertical transmission (also known as mother-to-child-transmission) of HIV was greatly reduced with the use of cart, creating a compelling argument for the increased use of cART as a prevention tool (106).

Community viral load (CVL) is an indicator of how much virus is in a population, or how "infectious" a population is (37,38,103,104). For instance, in a population with limited access to cART, the CVL, and hence HIV incidence, would be expected to be elevated unless other risk reduction behaviours were implemented including high rates of condom use, needle exchange, and other harm reduction activities (103). With widespread access to and use of cART, a higher proportion of HIV-infected people will be virologically suppressed and, therefore, the community as a whole will be less infectious and HIV incidence will be lower.(101–103) A CVL is an indicator of population level health rather than of individual health. This may also serve as a marker of equitable access and uptake.

Reducing the CVL is one of the goals behind TasP. Through 'Seek and Treat for Optimal Prevention of HIV/AIDS' (STOP-AIDS), British Columbia is working to grant access to cART for every person living with HIV (107). Preliminary results from British Columbia have shown that the rapid expansion of cART in that province has contributed to a decrease in HIV incidence, a trend in contrast to other Canadian provinces that have not seen a reduction in HIV incidence over time (108). TasP demonstrates that treating the individual has a secondary benefit of reducing HIV transmission risk to HIV sero-discordant sexual partners. For these reasons it is imperative that AYA have access to, and sustained use of cART, both for their own clinical health as well as for HIV prevention goals. The importance of supporting AYA living with HIV to remain on cART is extremely important as people living with HIV can expect life expectancies nearing those of HIV-negative individuals as long as they are retained in care and have maintain virological suppression (49).

Analyses in this dissertation will refer to TaSP to situate the findings in real-world applications. This will help to strengthen the argument for individual as well as

population effects of retaining AYA in the HIV Cascade of Care and supporting them to achieve and maintain virological suppression. Although to date TasP has only been formally adopted in British Columbia, it can be used as a framework for action for the whole country.

1.3.2. The HIV Cascade of Care

In order for TasP to be successful and for AYA to experience improved population health status, AYA must be engaged in a spectrum of care known as the HIV Cascade of Care. The seven stages involved in the Cascade of Care as designed by Gardner et al. (109) are: HIV Infected; HIV Diagnosed; Linked to HIV Care; Retained in HIV Care; Need Antiretroviral Therapy; On Antiretroviral Therapy; Adherent/Undetectable. For the purpose of this study, I will be using the Cascade of Care as adjusted previously by researchers (110), which recognizes Adherent and Undetectable (Virologically Suppressed) as distinct and separate stages (**Figure 1.1**).

Figure 1.1 The HIV Cascade of Care (based on Gardner et al., 2011)

This spectrum of engagement in care represents an important framework for surveillance and evaluation for HIV treatment. Further, as part of the TasP initiative, this Cascade of Care lays out the roadmap to achieving virological suppression and well-being for people living with HIV. Each step in the Cascade represents numerous opportunities to engage with clients and to assist them in successfully transitioning through the continuum of care. A better understanding of the barriers facing AYA living with HIV will help to ensure that the final pieces of the Cascade of Care are completed and that AYA are experiencing the full benefits of cART. This study concentrates on comparing clinical outcomes of AYA and adults on the latter stages of the Cascade of Care, namely initiation of cART, retention in HIV care (measured by viral rebound), and achieving virological suppression where many AYA drop out of the Cascade (**Figure 1.1**). As demonstrated in **Figure 1.2**, AYA in Canada are much less likely to be retained at each level in the Cascade compared with older people. Of all HIV-positive AYA who initiated treatment in 2012, only 54% of them reached virological suppression within a

year compared with 65% of people aged 30 to 39 and 78% of people over the age of 50 (111).

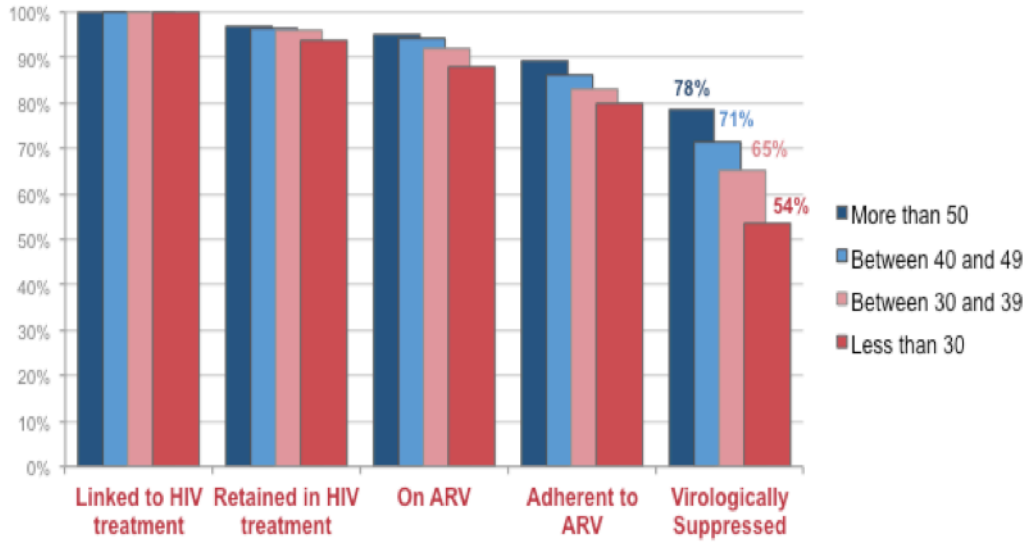

Figure 1.2. Engagement in the HIV Cascade of Care among Canadians in 2012, by age category (40)

Hull and Montaner (4) adapted the HIV Cascade of Care to incorporate potential barriers, actions, and interactions that may occur at each step in the Cascade. This continuum of care is known as *Seek, Test, Treat, and Retain* and seeks to evaluate individual components of health care engagement necessary to promote virological suppression (**Figure 1.3**). In order to improve the health and well-being of young people living with HIV, it is important to identify youth-focused factors associated with initiation, retention, adherence, and suppression. The Cascade of Care is an ideal framework for examining how AYA are accessing and engaging in care as it lays out the different steps in the continuum of HIV care. We hope to learn how AYA differ from older adults in terms of clinical outcomes, as this knowledge will help to highlight the importance of developing youth-specific services and programming.

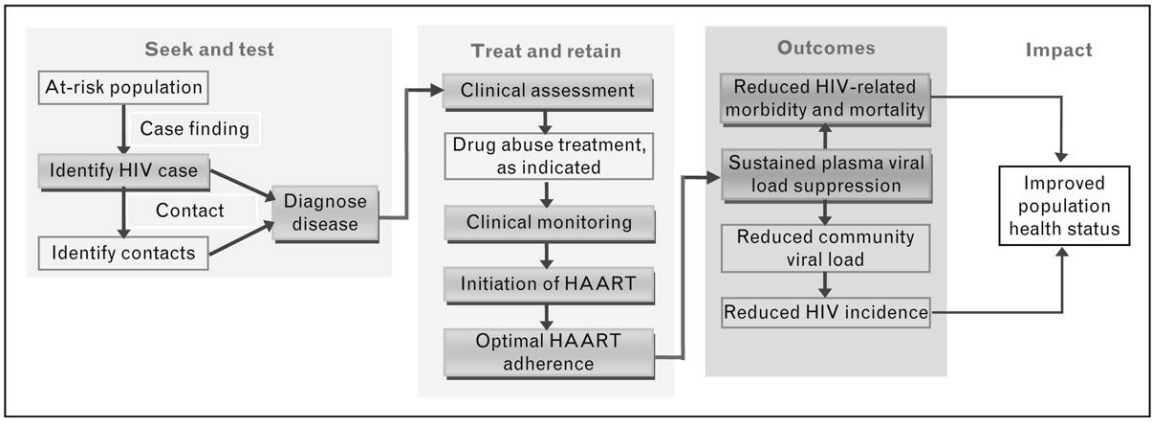

Figure 1.3. Montaner and Hull's *Seek, Test, Treat, and Retain* framework

1.3.3. Adapted approach

This dissertation draws on an adapted *Seek, Test, Treat, and Retain* framework to explore young people's engagement in care. Depicted in **Figure 1.4**, this framework suggests that steps in the HIV Cascade of Care are influenced by an interplay of factors. It situates the Cascade in relation to a variety of social and structural factors—some modifiable and others non-modifiable—that affect various stages of the Cascade and that may influence each other. We know from previous research that factors such as younger age, female gender, minority status, and Aboriginal ethnicity are associated with poorer engagement in care (52,56–58,60,62,65,112,113). As well, we know that other factors such as drug use, access to health services, and stigma affect an individual's engagement in care (65,74,85,114–121). Many of these factors are outside the scope of this dissertation as the CANOC data is limited; however, it is important to recognize the power that these factors hold.

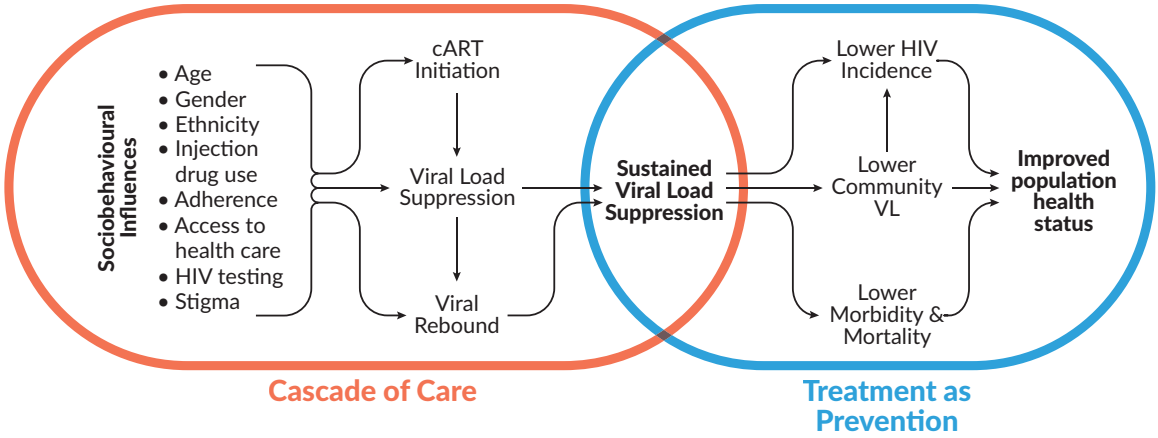

Figure 1.4. Adapted *Seek, Test, Treat, and Retain* framework

In this adapted *Seek, Test, Treat, and Retain* framework, it is assumed that the impact of these different factors will have a cumulative effect on an individual's clinical outcomes. In **Figure 1.4**, relationships (represented by arrows) between the different layers of influence and their clinical outcomes illustrate the various ways in which HIV-positive AYA's circumstances may influence their decision to begin treatment, remain in treatment, and their success with treatment. The clinical outcomes (cART Initiation, Viral Load Suppression, and Viral Rebound) affect the clinical endpoint, which is an individual's ability to maintain sustained virological suppression. As the TasP framework explains, sustained virological suppression can lead to lower morbidity and mortality, lower community viral load, and lower HIV incidence—in turn leading to an overall improved population health status, which in this instance would be an improved health status among AYA. This framework will allow us to conceptualize how any one type of influence or combination of influences may affect single and multiple clinical outcomes among AYA living with HIV.

1.4. Gaps in the Literature

Initiation of cART is an important component of the HIV Cascade of Care, especially in light of the ambitious 90-90-90 targets laid out by UNAIDS to have 90% of all people living with HIV to know their HIV status, 90% of all people with diagnosed HIV infection to receive cART, and 90% of all people receiving cART to achieve virological suppression by 2020 (7,109). Before these goals can be realized, barriers and

facilitators to reaching these targets must be addressed. Research from the USA regarding young people living with HIV shows them to be less likely to initiate cART when medically eligible compared with adults for a myriad of reasons including: homelessness; lack of family support; and high rates of substance use (55,75,122). However, little research has focused on Canadian AYA living with HIV who are seeking HIV care and treatment in the context of a publicly funded health care system (where presumably financial barriers to accessing care would be lower), with the purpose of assessing the prevalence and correlates of late initiation. **As timely cART initiation is a critical component in the Cascade of Care, it is imperative that we have a better understanding of timely treatment initiation in order to help AYA experience the full benefits of cART.**

Once on cART, AYA living with HIV are less likely to achieve virological suppression compared with their older counterparts (57,60,65,123). It is important to note that the majority of studies conducted are specific to AYA who use drugs and AYA living in British Columbia. To date, no studies have looked at virological suppression among a pan-Canadian cohort of AYA. This study will use a larger sample size to investigate independent covariates of virological suppression and to explore geographic and other differences in suppression rates. **Critical gaps remain regarding assessment of rates and covariates of virological suppression among AYA in Canada.** There is a need for comprehensive data on the treatment experiences of young people related to HIV care and the likelihood that they will reach virological suppression.

While adherence is a determining factor of treatment success, achieving and maintaining optimal adherence to cART remains a critical challenge. As viral rebound can indicate a departure from the prescribed course of treatment, viral load will be used as a proxy for retention in care as retention data is not available in CANOC. Previous research suggests that AYA living with HIV struggle to access appropriate services, stay in care, and continue taking their prescibed medications (74,111). Helping young people remain in treatment must be a priority; however, **there is little information available regarding viral load rebound among young people in Canada.** This dissertation will add much-needed information about Canadian adolescents and young adults to the literature and will set the stage for further engagement with this population.

1.5. Relevance

In light of the evidence from the TasP initiative, WHO and the United Nations have now adopted TasP as a primary strategy to reduce HIV incidence worldwide (7). The 90-90-90 initiative carries with it ambitious goals that risk failure if barriers to engagement in care are not addressed in a multi-faceted, holistic manner (7).

In order for the ambitious targets to be reached, AYA must be well-informed and engaged in care. AYA are one of the fastest growing populations and are key to the success of 90-90-90 in Canada. By measuring and comparing rates of initiation of cART; virological suppression; and viral load rebound among AYA and older adults, including assessment of correlates of treatment outcomes, this information will help health care practitioners and policy makers to better meet the HIV care priorities of AYA and support them in reaching optimal health.

1.6. Study Objectives and Hypotheses

The overall aim of this dissertation is to examine key cART treatment outcomes along the HIV Cascade of Care among AYA living with HIV in Canada. The study aim is supported by three primary study objectives and hypotheses:

1. **To compare the prevalence of late cART initiation among HIV-infected AYA (18-29 years) and older adults (30+ years) in Canada and to identify factors associated with late initiation.**

   Previous research in the United States has shown that young people living with HIV are less likely than adults to initiate cART when medically eligible (55,122). Given that young people in Canada share similar attributes with young people in the USA, this study assumes the following hypothesis:

   Hypothesis 1: AYA living with HIV in Canada will be more likely to initiate cART late compared with adults.

2. **To assess and compare time to, and factors associate with, virological suppression between HIV-infected AYA (18-29 years) and older adults (30+**

years) in Canada and to explore factors associated with time to virological suppression.

In light of the high rates of poor adherence and retention reported among young people living with HIV and taking cART (74,124) and the vulnerability of this group to poor clinical outcomes (65), this study assumes the following hypothesis:

Hypothesis 2: AYA living with HIV in Canada will take longer than older people to achieve virological suppression and will be less likely to achieve suppression.

3. **To assess and compare the prevalence of viral rebound among HIV-positive AYA (18-29 years) and older adults (30+ years) in Canada and to characterize trends and determinants of viral load rebound.**

   Considering the high rates of viral rebound among HIV-positive individuals of all ages in Canada and evidence regarding the heightened vulnerability of AYA to drop out of care (65,125), this study assumes the following hypothesis:

   Hypothesis 3: Among those who ever achieve virological suppression, AYA will be more likely than older people to experience viral rebound.

1.7. Study Setting and Design

The three aforementioned objectives are presented in Chapters 4, 5, and 6, respectively. These quantitative studies utilize clinical and laboratory data from the Canadian Observational Cohort Collaboration (CANOC)*,* Canada's largest HIV cohort study, which includes data from the year 2000 onward on a total of 10,044 people living in three of Canada's largest provinces—British Columbia, Ontario, and Quebec. All participants in CANOC are HIV-positive and were cART-naive prior to initiating antiretroviral treatment on or after January 1, 2000. The analyses in this dissertation were conducted in accordance with the international STROBE guidelines (126)—a set of recommendations to promote complete reporting of cohort data in a systematic manner.

Ethical approval for the overall CANOC study as well as the studies involved in this dissertation was obtained from Simon Fraser University and Providence Health Care / University of British Columbia Research Ethics Board. There are eight CANOC sites across Canada, and each site was responsible for obtaining ethical approval from the appropriate research ethics boards. Ethical approval for the studies described here was obtained from Simon Fraser University. To prevent repetition, CANOC is described in greater detail in Chapter 3.

1.8. Summary

This dissertation is divided into seven chapters. **Chapter 1** outlines the background, rationale, and objectives of the study. **Chapter 2** reviews the literature regarding the various stages of the HIV Cascade of Care among young people living with HIV in North America. **Chapter 3**, published in *The International Journal of Epidemiology* (127), presents a cohort profile of the CANOC study, the data source for subsequent analyses included in this thesis. **Chapter 4,** published in *Journal of the International Association of Providers of AIDS Care* (128), examines factors associated with late initiation to cART among young people in Canada (Objective 1). **Chapter 5** compares time to virological suppression among AYA and older people receiving cART (Objective 2). **Chapter 6** examines viral load rebound among AYA receiving cART who have ever achieved virological suppression (Objective 3). **Chapter 7** summarizes the findings and proposes future directions for research and policy implications. Together these chapters will enhance the understanding of treatment outcomes across the HIV Cascade of Care among young people on cART in Canada. This work highlights what adolescents and young adults living with HIV need, in terms of improvements to services and programs, to assist them in reaching their full health potential.

Chapter 2.

Engagement in the HIV Cascade of Care among Adolescents and Young Adults Living with HIV

2.1. Abstract

Introduction: Adolescents and young adults (AYA) living with HIV report poor clinical health outcomes compared with older adults. The purpose of this review is to examine clinical outcomes along the HIV Cascade of Care among AYA living with HIV in Canada and the United States

Methods: A comprehensive review was conducted by searching online peer-review databases and grey literature for both qualitative and quantitative articles related to AYA and the different steps of the Cascade of Care. The term AYA was extended to include ages 15-29 for the purpose on this review. Extracted information was categorized according to the relevant stage of the Cascade of Care: HIV Infected; HIV Diagnosed; Linked to HIV Care; Retained in HIV Care; Need Antiretroviral Therapy; On Antriretroviral Therapy; Adherent; Virologically Suppressed.

Results: AYA reported poorer outcomes at all stages of the Cascade of Care. Significant barriers exist to engaging and retaining AYA in the health care system, which is intricately linked to clinical success—adherence and virological suppression. Barriers can be organized into four categories: Health System Factors; Therapeutic Factors; Psycho-emotional Factors; and Social Factors. All of these factors have a significant impact on clinical outcomes.

Discussion: AYA are performing poorly throughout the HIV Cascade of Care. The Cascade of Care offers multiple points at which interventions would assist AYA to

remain in care and reach their full health potential. More research is required for a greater understanding of how to better meet the needs of AYA

2.2. Introduction

Modern combination antiretroviral treatment (cART), with fewer side effects and a lower pill burden than earlier antiretroviral treatments, has transformed HIV into a chronic, manageable disease for those with adequate access to care. For adolescents and young adults (AYA), cART enables them to live long healthy lives and increases their sexual and reproductive options with a reduced risk of sexual and perinatal transmission (30–32,36–38). This treatment of AYA is especially important as the global HIV epidemic is increasingly driven by new infections among young people aged 15 to 24 years, who account for more than half of all incident cases worldwide (6). As with all age groups, the success of cART among AYA depends on whether they engage in the health care system and are able to maintain a suppressed viral load (38). Unfortunately, AYA consistently report poor HIV-related health outcomes (6,56,60,64,65).

To optimize the potential benefits of cART, AYA have to achieve and maintain certain milestones concerning their engagement with HIV care, a process known as the HIV Cascade of Care (60,109,129). The different stages of the Cascade of Care designed by Gardner et al. (109) are: HIV Infected; HIV Diagnosed; Linked to HIV Care; Retained in HIV Care; Need Antiretroviral Therapy; On Antiretroviral Therapy; Adherent; and Virologically Suppressed (3). Barriers to the Cascade of Care are relevant to AYA not just because they are a unique demographic with specific personal and social challenges (47,130–132), but also because they will likely be on cART longer. As a result, they may be vulnerable to a greater number of treatment issues such as treatment fatigue, poor adherence, treatment interruptions, or resistance to certain medications (133–136).

Accessible HIV testing, initiating treatment in a timely manner, supporting optimal adherence, and assisting AYA to remain in care are critical for reducing health burdens, transmission risk, and comorbidities over the life course (35,41,50,51). In addition, for young people who are initiating and negotiating dating and new sexual relationships,

adhering to cART and maintaining virological suppression have the enormous potential to normalize sexuality of seropositive youth by significantly reducing the risk of transmission (105).

In the current clinical landscape of Treatment as Prevention (TasP), the focus is to get all persons living with HIV on treatment and to assist them in achieving virological suppression (105,137,138). Several studies have repeatedly highlighted the urgent need to prioritize young people in the HIV response; however, to date, little Canadian research has focused on cART uptake and use among young people living with HIV (28,56,71,76,77). The purpose of this review is to examine, at each stage of the Cascade of Care, differences in health outcomes between AYA and older adults living in North America who are receiving cART, in order to better inform future interventions.

2.3. Methods

2.3.1. Definition of adolescents and young adults

There is no standardized definition or set parameters for what constitutes the adolescents and young adult demographic. Age ranges typically fall between 10 and 29 years of age, but various reference age groups often overlap. The Convention on the Rights of the Child defines *children* as individuals under the age of 18 (139); the World Health Organization (WHO) defines *adolescents* as individuals between 10 and 19 years of age (140); the United Nations (UN) uses the term *youth* for persons between the ages of 15 and 24 (141); and the Public Health Agency of Canada (PHAC) defines *youth* as 15- to 24-year-olds (142). For the purpose of this review, the age range will span 15 to 29 years, and the term used will be adolescents and young adults (AYA). As one author states, “Universal definitions of adolescence should—at best—be restricted to describing adolescence as a ‘period of transition,’ in which ‘although no longer considered a child, the young person is not yet considered an adult’” (143).

2.3.2. Conceptual Framework

A literature review was performed to assess engagement in care among AYA receiving cART. The driving question of the review was. how are young people performing in the different stages of the Cascade of Care in comparison with older adults? This literature review was informed by the HIV Cascade of Care, as described above and shown below in **Figure 2.1**. In this study, the Cascade of Care will incorporate previous adjustments made by researchers, which recognize Adherent and Undetectable (Virologically Suppressed) as distinct and separate stages (110). By utilizing the Cascade of Care to describe and quantify the spectrum of engagement in HIV care, we can better understand how gaps in the continuum of care affect clinical outcomes and explore possible interventions to improve individuals' engagement in care (3).

Figure 2.1. The HIV Cascade of Care (based on Gardner et al., 2011)

2.3.3. Search terms

The literature search was performed using PubMed and Google Scholar and grey literature from relevant international and national organizations. The search terms used to extract information about adolescents and young adults were: "adolescents," "youth," "teenagers," "young people," and "young adults." The terms were cross-referenced with the following search terms related to the Cascade of Care: "HIV," "HAART (includes antiretroviral therapy, ART, cART)," "diagnosis," "testing," "linkage," "linkage to care," "retention," "retention-in-care," "late initiation," "viral suppression," "adherence," "virologic failure," and "treatment interruption." The bibliographies of identified studies were searched for additional articles of interest. The search was restricted to English-language publications from the United States and Canada. Articles were accessed via Simon Fraser Univeristy and the University of British Columbia's electronic libraries. Grey literature from organizations such as UNAIDS, UNICEF, and WHO was searched for relevant information, as were government agency documents from Canada and the United States. Relevant articles were then categorized thematically in accordance with the eight stages of Gardner's Cascade of Care in order

to gain a better understanding of AYA's engagement in care and successful use of cART.

2.4. Results

2.4.1. HIV infected (prevalence and incidence)

In Canada, adolescents and young adults (15-29 years of age) comprised nearly one-quarter of all of the HIV-positive tests in 2010 (144). In 2008, AYA made up 11.8% of all AIDS cases in Canada, an increase from 7.5% in 1999. Of all incident HIV cases among AYA in 2013, more than half (59%) were attributable to men who have sex with men (MSM), one-quarter (24%) to heterosexual sex, 10% to injection drug use, and 4% to a combined category of injection drug use and MSM (11). Further factors associated with an HIV-positive status among youth are a history of sex work, incarceration, and being of Aboriginal ancestry (15,145,146)

Aboriginal AYA are disproportionately affected by HIV/AIDS, making up 40.9% of all HIV-positive results among youth (26,147) while accounting for 5.9% of Canadians aged 15 to 24 (148). Aboriginal people are more likely to be diagnosed with HIV at a younger age with approximately one-third of HIV-positive Aboriginal people diagnosed between the ages of 15 and 29 years, compared with 20.5% among non-Aboriginal people (17). In recent years, young Aboriginal women in particular, have been overrepresented in the epidemic with a grow disparity among AYA. The HIV diagnosis rate among young Aboriginal men and women in Canada aged 15-19 years was 5.38 and 21.6 per 100,000 respectively compared with 0.38 and 0.7 per 100,000 among Caucasian men and women(149).

Overall, women made up 33.5% of all HIV-positive test results among AYA in Canada in 2011, representing the highest proportion of HIV-positive women in any age group (26). There has been an increase in the number of HIV cases attributed to heterosexual transmission among AYA since the beginning of the epidemic, although MSM still made up over 50% of HIV cases (144). At present, there are no data available regarding the geographic distribution of AYA living with HIV in Canada.

2.4.2. HIV testing and diagnosis

It is estimated that approximately 25% of HIV-positive Canadians do not know their HIV status (144). According to a study recently released by the U.S. Centers for Disease Control and Prevention (CDC), this lack of diagnosis is higher among young people (ages 13-24) in the United States with an estimated 50 to 60% of young people (13-24 years) are unaware of their HIV-positive status (150,151). In contrast, it is estimated that approximately 80% of people in the United States over the age of 30 know their status (152). Gay, lesbian, and bisexual AYA appear to be at high risk for HIV; however, they are the least likely of any age group to be tested (153,154).

AYA are less likely to seek HIV prevention information and HIV testing if they have inadequate knowledge of HIV, believe they are not at risk for HIV, and lack access to adolescent-friendly testing sites and clinical care (75,79,122,155–158). Ideally, regular STI screening programs would be in place for youth who practice behaviours that put them at risk for STIs and HIV (e.g., unprotected sex, multiple partners, drug use); however, in place of such programs, health care providers are the frontline workers (159). Regularly accessing a health care provider for issues related to sexual health is of great importance, as HIV testing is related to previously seeing a health care provider for sexual health issues and condom use. Many young people in Canada and the United States do not regularly access this type of care (160,161), though, which may have to do with perceived stigma from health care workers which presents barriers to sexual health education and STI testing (162).

Many AYA are not diagnosed with HIV until they are very ill or have poor HIV clinical outcomes (5,163). It is estimated that half of AYA in Canada and the United States have CD4 counts of less than 350 cells/mm^3 at the time of diagnosis (44,157,164,165) compared with 22 to 30% of adults in similar settings (3,166,167). AYA often learn their status through routine screening for pregnancy or employment-related health tests or tests in emergency rooms, as opposed to self-initiating an HIV test (168,169). Of the 6,000 to 7,000 annual births in the United States among HIV-positive women, approximately 30% were unaware of their HIV status prior to receiving antenatal care (170). Although the ages of these women are unknown, we can assume that a significant proportion of them are between the ages of 18 and 29.

Rapid testing and anonymous testing programs have proven to be important mechanisms for encouraging individuals to get tested; however, currently these methods are more popular among people 30 years of age and older (171–173). The likelihood of a person using a point-of-care test increases as age increases (173).

2.4.3. Linked to HIV care

Linking to the health care system is important for young people in order for them to be monitored and supported. In general, AYA report poor uptake of preventative health care and HIV prevention, a pattern of utilization that carries on after HIV diagnosis (34). Adolescents who test positive at a health care facility tend to link in to care in a timely manner (25 days vs. 108 days) in comparison to those who test positive in a non-health care facility such as military, immigration, or medical screening procedures (168). Among AYA testing positive for HIV in the United States, only 62% are linked to appropriate HIV care within 12 months of their HIV diagnosis (60). Many AYA do not have routine health care at the time of diagnosis and there is concern about navigating the health care system on their own in addition to apprehensions about missing school or work for health appointments (176). Unless AYA are symptomatic at the time of their diagnosis, they typically do not see health care as a priority. Until they get ill, it may be difficult for them to appreciate the seriousness of their illness (155,177).

Psychosocial factors such as depression, alcohol and drug use, perceived stigma, and previous traumatic events can negatively affect an individual's likelihood of accessing treatment and health care support (67,85,177–181). These factors can be mitigated by tailored support and care from family, friends, and health care workers who are trained in methods to work with this population (88,182,183). Education sessions and mentorship programs can provide a safe environment to engage AYA in discussions about HIV treatment and answer any questions they may have (184–187). Education and counseling interventions using a combined family group and peer counseling approach have been shown to be very effective (184–187).

2.4.4. Retained in care

Retention in care is vital in helping young people to achieve and maintain virological suppression. As age increases, the likelihood of regular care also increases (115,188). Retention is often measured by the number of visits missed (189). An American study showed that HIV-positive youth attended only 66% of their appointments over a three- to six-month period, which was described as high for the AYA population (59).

Retention in care is less likely among young people than older people, with one cohort showing viral rebound occurring at least once in 18 of 32 (56.3%) AYA, and 5 of 38 (13.2%) adult subjects (P= 0.002). Loss-to-follow-up rates were 20 of 46 (43.5%) among AYA and 5 of 46 (10.9%) among adults (P=0.001)(65). One study shows that of those AYA in the United States who do initiate care, only an estimated 43% of them are retained in care (60). Missed HIV care visits are associated with increased risk of HIV-related mortality for AYA. Mortality rates were 2.3 versus 1.0 per 100 patient-years of follow-up in the missed-visit versus no-missed-visit groups, respectively (P=0.02) (190).

Structural factors associated with poor retention are homelessness, child care responsibilities, addiction, appropriate available services, and geographic location (urban vs. rural) (44,52,56,115,176,191,192). Any one of these factors makes it difficult for the individual to prioritize their HIV care. AYA who are managing many different and stressful life demands may find it difficult to make time for clinic visits, prescription refills, and other HIV-related appointments.

In terms of attending medical appointments, many AYA have reported that they do not feel comfortable in the health care settings to which they are referred for care (186,193,194). The lack of adolescent-friendly health care services impedes their decision to attend regular medical appointments, and many report not wanting to attend pediatric clinics while not feeling comfortable in adult clinics (176,193,195). Retention in care requires a trusting and ongoing relationship between the patient and the health care provider; however, many AYA report not having this relationship (74).

Adolescence highlights an important transition time for young people who have remained with the same caregivers for a long time. The change from pediatric care to

adult care can be challenging for AYA who have developed a trusting relationship with their care team (54,87). Even if the individual remains in the same health care centre, many youth fall out of care or report poor outcomes during the transition process from pediatric care to adult care (193).

2.4.5. Need cART / on cART

In accordance with several cohort studies that demonstrated improved health outcomes and survival for individuals who begin cART at higher CD4 counts (196–198), the International AIDS Society(IAS)-USA 2012 guidelines recommended that all people living with HIV with a CD4 count of ≤500 cells/µl, as well as pregnant women and discordant couples, should be offered cART (199). It is unknown how many people across Canada are in need of cART, but in British Columbia 27% of individuals with a CD4 count of ≤500 cells/µl are not currently taking medication (200). Youth living with HIV are less likely to start medication when eligible for a myriad of reasons including: lack of family support; no primary caregiver; lack of access to adolescent-friendly services; substance use; and not feeling that they need it yet (55,75,122,130,177,201).

Generally, youth are less likely than adults to initiate cART in a timely manner (with a CD4 count of >500 cells/mm3) (55,60,130). Time to initiation among non-perinatally infected youth tends to be longer than perinatally infected youth, which is generally explained by being linked to care earlier and being under the guidance of a caregiver (55). A study of non-perinatally infected AYA from the United States showed that although 84% of youth were offered cART, 77% of them had ever taken cART, and only 53% of them remained on cART at the time of the study interview (130). For many youth, although they may meet the clinical guidelines for initiating cART, they may wait until they perceive their health to be failing before doing so—that is, they make their own decisions rather than relying on their physician's recommendations (201).

2.4.6. Adherent to cART

Adherence to cART is achieved through optimal compliance to therapy, commonly defined as ≥95% adherence of prescribed medication (33–35). Research in North

America shows young people living with HIV have poor rates of adherence to their prescribed medications (8,72–75). Rates of adherence among youth living with HIV are significantly poorer than adults, with studies reporting that 40 to 50% of adolescents are optimally adherent (56,57,124). In contrast, rates of optimal adherence among adults range from 55.8% to 97% (31,34,204,205).

There are several reasons for the sub-optimal adherence observed among AYA. AYA face unique barriers to treatment access, uptake, and retention and are at increased biological and sociological vulnerability due to structural barriers to power, financial security, and physical maturity (47,75,80). As well, medications carry with them sometimes harsh side effects and complicated directions-of-use that make them difficult to take as directed (44,73,177,206–208).

Perinatally infected youth who have been on cART for a number of years often report treatment fatigue to be a factor in not adhering to medications (183,209). Both perinatally and non-perinatally infected AYA report forgetting, not feeling like taking medication, and not wanting to be reminded of their HIV status as reasons for missing doses, although these reasons were most common among perinatally infected AYA (210).

Feelings of being different and less-than-ordinary have an effect on AYA's health. They are in a phase of life when belonging and conforming is often very important, and living with a highly stigmatized illness can be difficult to deal with (123,206). Self-perceived stigma and discrimination by family and friends are strongly associated with non-adherence to cART among youth, as are negative life events and economic instability (50,85,114,186,211,212). Depression has been linked to poor adherence practices (58,213), and AYA living with HIV disproportionately report depressive symptoms (214). This population is one that, given the new advances in antiretroviral therapies, can expect to live long lives. If treatment adherence is not addressed, they will bear a greater health burden, have more health worries, and have a higher possibility of viral transmission to partners.

2.4.7. Virological suppression

Sustained virological suppression is the final stage in the Cascade of Care; however, once on cART, AYA often have difficulty reaching virological suppression, even short-term suppression (215). The benefits of cART are achieved through optimal compliance to therapy, defined as ≥95% adherence of prescribed medication (33–35). Once virological suppression is achieved, it is important that an individual remains adherent. Poor adherence can result in viral rebound and treatment failure (31,42). When compared with older people on cART, AYA were significantly less likely to reach virological suppression within six months due to poor adherence and retention in care (65). Among those who do reach suppression, AYA are more likely than adults to experience viral rebound and to have higher lost to follow-up rates, reflecting poorer retention in care amongst AYA (65,216). Among AYA who initiate cART in the United States, 54% achieve virological suppression (60). In a three-year follow-up of AYA on cART, only 24% achieved and were able to maintain an undetectable viral load over three years (97). Of concern, the six-month virological suppression rate among pregnant AYA was low (65). There are many steps in the journey towards having a sustained viral load, and it is important that AYA are well supported at each step if sustained virological suppression is going to be achieved.

2.5. Discussion

The literature suggests that AYA experience poorer outcomes across all stages of the HIV Cascade of Care compared to adults. AYA experience poorer virological suppression compared to adults, which is determined by the other stages of the Cascade of Care including timing of treatment initiation, medication adherence, and retention in care (57,60,61,63–65). Significant barriers exist to engaging and retaining AYA in the Cascade of Care, which is intricately linked to clinical successes (31). It is imperative to better meet the needs of AYA living with HIV beginning from the HIV test through the stages to virological suppression. Johnson et al. outline four categories of barriers to health care utilization among AYA living with HIV: Health System Factors (schedules, cost, legal impediments, or inappropriate services); Therapeutic Factors

(issues related to cART regimens); Psycho-emotional Factors (adolescent development and psychosocial issues); and Social Factors (family and peer relationships) (194).

Health System Factors

Many of the barriers to engaging in care are related to health system factors. Accessible and anonymous testing can reduce an individual's fear of being identified; however, not all AYA live in urban centres where anonymous testing or rapid testing is offered. Point-of-care testing is one way to retain youth (173) as they do not have to return to the clinic for results. Flexible hours for testing facilities as well as youth-specific services may help to attract AYA to seek sexual health services. There has been promising research regarding the possibility of self-testing kits for home use. The acceptability of the tests is high; however, there are concerns from health care providers about HIV counseling and appropriate linkage to care (217–220). Should the home tests become available, it would be an option for HIV testing that would ensure confidentiality.

Linkage to care following an HIV-positive diagnosis often depends on the sensitivity demonstrated by the health care professional, as well as their ability to make the appropriate referrals to care (74). Many AYA, especially those living with addictions, those who are homeless, or those who have a history of traumatic events with institutions, may not trust health authorities (221–223). For many young Aboriginal people in Canada, especially women, testing positive for HIV and being linked into care can be a difficult and frightening experience (221,222). The lack of culturally appropriate health services can hinder their willingness to seek care. AYA have voiced their frustration with the lack of youth-friendly messaging and language and services available to them (97). There is a need to develop resources that engage AYA when they first start thinking about sexual health needs, as opposed to when they are already living with HIV and experiencing adverse health issues or poor adherence.

AYA who are transitioning from pediatric care to adults care face their own challenges. It is well documented that youth with chronic illness in general face challenges when transitioning from pediatric to adult care; often resulting in gaps in care continuity and resultant poor health outcomes (224,225). That the literature speaks about the transition from paediatric to adult phase (226,227), but it is often a false

dichotomy for AYA. The "transition" may actually be comprised of many little transitions that take place over a long period of time. Recommendations to improve transition to adult care for all adolescents with chronic diseases (224–226,228,229) may miss vital components of the HIV+ youth's lived experience – including isolation stemming from stigma or discrimination, the perceived or real inability to tell others of their diagnosis, and the complicating expectation that youth disclose their HIV status to partners (85,212,230,231). Even when transition is planned according to the recommendations of the American Academy of Pediatrics (227) gaps in continuity of care and adherence to medications frequently occur.

Therapeutic Factors

Antiretroviral therapy requires optimal adherence for life. This is something that can be daunting for newly diagnosed individuals. As well, due to the nature of HIV and the long asymptomatic period, some AYA may not think that they need to start cART when prescribed by their doctor. Even when knowing the long-term risks of not taking cART, AYA may perceive themselves invincible to the disease if they are not experiencing symptoms (44).

Once initiated on cART, many AYA stop due to the adverse effects of the drugs (206). Side effects such as nausea, diarrhea, and loss of appetite can be distressing for AYA trying to maintain a normal routine (207,208). Physicians and pharmacists should engage in ongoing consultation with AYA in order to resolve any treatment issues or modify regimens as needed such as discussing dosing (number of pills and number of pills/day) in detail with the individual. AYA who are prescribed less complicated regimens have a better likelihood of maintaining optimal adherence(133,232–234).

Psycho-emotional Factors

As AYA develop through adolescence and young adulthood and wrestle with issues around identity, other more pressing non-HIV-related issues may take precedence (56). Competing life priorities such as homelessness, abuse, child care, addictions, and geographic location have an effect on an individual's ability to remain in care (44,52,56,115,191,192). Multidisciplinary teams that work to improve case

management and remove structural barriers such as transportation have been shown to improve retention (188). AYA must be seen as a dynamic, ever-changing group, which requires a flexible and adaptable care approach that can meet their changing realities.

Social Factors

Given the strong relationship between adherence and virological suppression, it is important that AYA have access to support systems that will help them adhere to cART however, many AYA are not living with parents or caregivers and thus do not reap the benefits of family support (64,86). There is a need for more holistic, multi-faceted adolescent-friendly services to provide AYA with the necessary support. A pilot study involving 15- to 22-year-olds taking part in a 12-week educational program with family members or designated adult "buddies" appeared to be a useful adherence intervention for AYA living with HIV (185). This program included six weeks of family and youth education sessions and six weeks of youth-only education sessions, allowing youth to speak freely with their peers. Including a family/mentorship component was likely successful because of the relationships built. Feelings of being cared for and cared about (185) can help AYA battle issues of isolation and depression.

AYA who are unstably housed and/or have a a history of injection drug use (IDU) may have difficulties in maintaining ART adherence, in part due because treating their HIV is not a priority in the faces of other competing necessities such as food, housing and addiction (235–237). As well, many AYA may face stigma when attending health clinics, making them reluctant to follow up on their care (238–240). Treatment partnerships in which health providers work directly with the patient in order to tailor healthcare to the individuals' needs (culturally and medically) can increase feelings of support and levels of comfort communicating with health providers(241–243).

From beginning to end, the Cascade of Care maps out a complex treatment structure for individuals living with HIV. Modifiable and non-modifiable factors exist that may help or hinder a person's success in care. **Figure 2.2** illustrates that these factors may affect an individual's likelihood of starting treatment on time, achieving virological suppression, and maintaining treatment as prescribed. These clinical factors affect the person's ability to experience sustained viral load suppression, which in turn affects HIV

incidence, community viral load, and morbidity/mortality. In order to significantly improve the health of the overall population, an individual's entire journey from the very beginning, looking at risk factors, to the end goal of sustained viral load, must be considered.

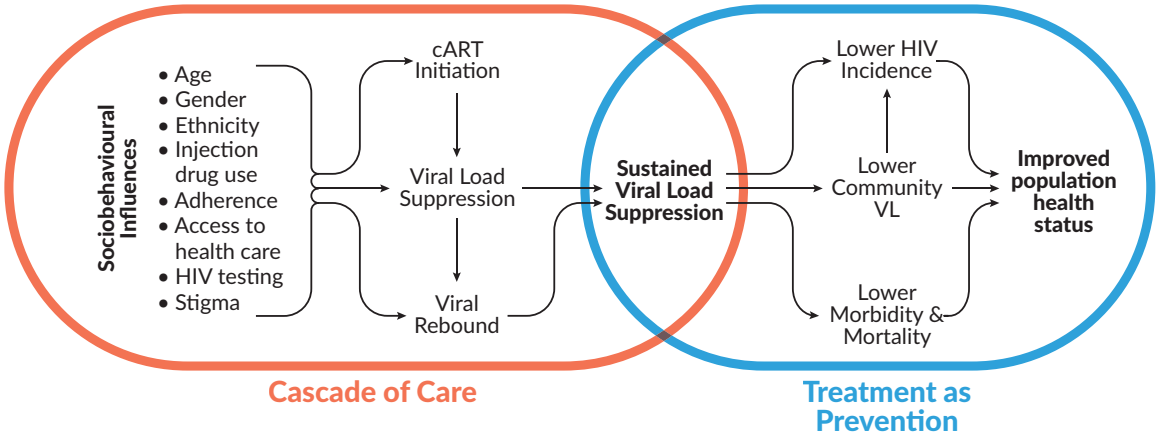

Figure 2.2. Adapted *Seek, Test, Treat, and Retain* framework

Readers should be cautious when interpreting the results of this review. Although the current literature highlights that AYA are doing poorly in clinical care, it is important to note that there is a limited amount of research available regarding AYA and their clinical outcomes. In particular, Canada has very few peer-reviewed manuscripts on this subject, making it difficult to gain a holistic understanding of how AYA are doing and where the gaps in care exist. As the topic is wide-ranging in scope and incorporates many different aspects of clinical care, some research may not have been captured here. Despite this, from the literature available it is clear to see that this is an important population to work with and support.

As cART is expanded globally, it is important for young people at risk of and living with HIV to have their needs met in order for them to reach the full benefit of treatment. As shown in the literature, there are many factors that must be in place for the Cascade of Care to be realized. Without support in the early stages of the Cascade, it is unlikely that an individual will proceed successfully through to reach virological suppression.

As background to the studies in this dissertation, this chapter reviewed current evidence and gaps in knowledge regarding AYA and HIV outcomes. Of relevance to this dissertation, this chapter described a growing body of evidence regarding the correlation of young age and adverse HIV outcomes. Findings from this review provide context to the pathways described in the adapted *Seek, Test, Treat, and Retain* conceptual framework (**Figure 2.2**), which will be applied in the following chapters and provide a knowledge-base from which to interpret and contextualize the following study results.

Chapter 3.

A Profile of the Canadian Observational Cohort Collaboration

Note: A version of this manuscript has been published in the *International Journal of Epidemiology*.

Palmer AK, Klein MB, Raboud J, Cooper C, Hosein S, Loutfy M, Machouf N, Montaner JSG, Rourke SB, Smieja M, Tsoukas C, Yip B, Milan D, Hogg RS; CANOC Collaboration. Cohort Profile: The Canadian Observational Cohort Collaboration. International Journal of Epidemiology. 2011;40(1):25-32.

3.1. Abstract

The Canadian Observational Cohort Collaboration (CANOC) is Canada's first interprovincial collaborative clinical cohort of HIV-positive individuals on antiretroviral therapy (ART). This collaboration of eight clinical cohorts from British Columbia, Ontario, and Quebec gives researchers the opportunity to conduct large and detailed analyses of HIV treatment outcomes that would not be possible within individual cohorts and to assess variations in patterns of access to treatment, patient management, and treatment outcomes across Canada. CANOC was funded from 2008 to 2013 by the Canadian Institutes of Health Research (CIHR) HIV/AIDS Research Initiative, which is supported by the Federal Initiative to Address HIV/AIDS in Canada.

3.2. An Introduction to CANOC

At the end of 2011, it was estimated that there were 71,300 HIV-positive individuals living in Canada and an estimated 3,175 infections occurring annually across the country (26). According to data collected and categorized by the Public Health Agency of Canada (PHAC), men who have sex with men (MSM) represent the largest affected population, making up almost half (46.7%) of all people living with HIV (PLWH) in Canada. Injection drug users are another key affected population and represent 16.9% of all HIV-positive individuals. Heterosexual individuals from HIV non-endemic and endemic areas represent 17.6% and 14.9% of all cases, respectively (26).

Aboriginal (First Nations, Inuit, and Métis) people are disproportionately represented; despite accounting for 3.8% of the Canadian population, they accounted for 8.9% of HIV-positive tests in 2011 (26). The number of women living with HIV in Canada also continues to grow, with 16,600 (23.3% of the national total) women living with HIV in 2011, which is a 12.6% increase from the estimated 14,740 women living with HIV in 2008 (26). The three provinces of British Columbia, Ontario, and Quebec represent the bulk of the epidemic—approximately 86% of the HIV-positive population—with the majority of PLWH in these provinces living in the cities of Vancouver, Toronto and Montreal (108) .

The delivery of antiretroviral therapy (ART) varies by province. Although health care is publicly funded in Canada, where medically necessary hospital and physician services are universally provided, medication coverage is provided though a combination of public and private mechanisms that differ between provinces. Of all PLWH in British Columbia in 2008, 45% were receiving combination antiretroviral therapy (cART), compared with 35% in Ontario and 37% in Quebec (108). Provincial and territorial programs for HIV antiretroviral treatment supply and distribution range from complete coverage for all PLWH within a given province (e.g., British Columbia) to special coverage categories or coverage through programs with income-based deductibles. Combined, these programs spent over $300 million on antiretroviral treatment in 2001/2002 (244). When exploring data pan-provincially, it is interesting to consider how

provincial payment plans and drug policies can potentially affect health differences. This comparison was not possible prior to the development of CANOC.

The Canadian Observational Cohort Collaboration (CANOC) is Canada's first interprovincial collaborative cohort of PLWH on antiretroviral therapy (ART). This collaboration of eight clinical cohorts from British Columbia, Ontario, and Quebec gives researchers the opportunity to conduct large and detailed analyses of HIV treatment outcomes that would not be possible within individual cohorts and to assess variations in patterns of access to treatment, patient management, and treatment outcomes across Canada. CANOC was funded from 2008 to 2013 by the Canadian Institutes of Health Research (CIHR) HIV/AIDS Research Initiative, which is supported by the Federal Initiative to Address HIV/AIDS in Canada (245). In 2014, CANOC was awarded an additional five years of CIHR funding through a Centres Grant (Centres for HIV/AIDS Population Health and Health Services Research) and two operating grants (HIV/AIDS Priority Announcement; Population and Public Health). CANOC is also supported by the CIHR Canadian HIV Trials Network (CTN242).

3.3. Inclusion in CANOC

Currently seven adult clinic-based HIV cohorts from research centres, universities, and clinics in Ontario and Quebec and one population-based cohort in British Columbia are participating in CANOC (**Table 3.1**). The initial collaboration has focused on a representative group of cohorts serving the largest population centres in Canada, but the collaboration is open to cohorts from other sites and provinces in the future. Clinical sites in Saskatchewan (Regina and Saskatoon) and Newfoundland have expressed interest in joining CANOC and will likely contribute data to the collaboration in the next one to three years. The eight cohorts currently participating in CANOC include a diversity of patients receiving a range of models of HIV care (from community-based clinics to tertiary care facilities).

CANOC is comprised of persons who initiated cART, defined as the use of three or more antiretroviral drugs, on or after January 1, 2000 with no prior antiretroviral experience (i.e., ART-naive). CANOC has focused on ART-naive patients initiating cART

because this patient group was considered of most clinical interest for the evaluation of modern cART regimens in Canada. As of December 31, 2012, 10,044 participants from CANOC sites met the study inclusion criteria. CANOC represents approximately 14% of the total HIV-positive population in Canada. Nearly half of the estimated 20,500 people receiving HIV treatment in the represented provinces are captured in this cohort (246), making CANOC the largest sample of HIV-positive people on antiretroviral therapy in Canada and one of the most representative samples in a high-income country.

3.4. Primary Objectives of CANOC

The primary aims of CANOC are: to develop a nationally and internationally recognized and policy relevant program of research in HIV therapeutics and population and public health in Canada; to establish mentoring, training, and research opportunities for graduate students, post-doctoral fellows, and clinicians interested in HIV cohort research in Canada; to improve research and dissemination to physicians and individuals living with HIV; and to improve knowledge translation of research regarding HIV therapeutics into provincial, national, and international HIV treatment guidelines. Ultimately, the goal of CANOC is to improve treatment quality, health outcomes, and engagement with evidence-based programs and services for people living and aging with HIV across Canada, prioritizing approaches to treatment and care that are sensitive to the health needs of key populations affected by HIV.

3.5. Recruitment and Attrition Rates

Since CANOC is based on electronic submission of patients' clinical records from each cohort, patients are not individually recruited into the study. Patients are lost to follow-up from CANOC when they are lost to follow-up from individual clinical cohorts. Currently, data for approximately 500 new ART-naive patients initiating cART is submitted to CANOC biannually. The median duration of follow-up is 52 months but is expected to increase with time. The loss to follow-up rate was 9.5% over the study period (2000-2012).

3.6. Data Collection and Management

Electronic data extraction of a predefined set of demographic, laboratory, and clinical variables is performed at the data centres of the participating sites and submitted annually to the BC Centre for Excellence in HIV/AIDS in Vancouver for pooling, data cleaning, and analysis. **Table 3.2** displays the structure of the variables collected (future data cuts may include a wider selection of data elements). All data are stripped of names and other personal identifiers prior to being sent to the Data Coordinating Site, and a unique CANOC study number is assigned to each participant. Overlap between cohorts is identified within provinces before data are sent to the Data Coordinating Site. A data dictionary has been developed by the CANOC data analysts and is shared among the investigators after each new data cut. All data are managed in a central relational database (at the British Columbia Centre for Excellence in HIV/AIDS), and an audit trail has been created for all data changes. Access to CANOC electronic data at the Data Coordinating Site is password protected and limited to essential study personnel.

All participating cohorts received research ethics board approval to contribute anonymous patient data to CANOC, adhering to established standards in data sharing/linkage and data security/residual disclosure. In the case of the Ontario HIV Treatment Network (OHTN) Cohort Study (OCS), additional approval was received from the OCS Governance Committee to release Ontario data to participate in CANOC. Data submitted to the Data Coordinating Site in Vancouver are used only to address specific research questions approved by the CANOC Scientific Steering Committee, and ownership of individual cohort data remains with the contributing cohort. Data elements used in any scientific publications are aggregated and de-identified.

3.7. Findings

As of December 2012, 10,044 individuals were included in CANOC. Almost half are from British Columbia (46.2%), 33.7% are from Ontario, and 20.1% are from Quebec. Men make up 81.4% of the CANOC participants, women make up 18.2%, and transgender individuals make up 0.4%. The median age at baseline is 40 years (IQR: 33-47 years). More than half of all participants (57%) reported a history of injection drug use (IDU).

Approximately one-third (31%) self-reported as men who have sex with men (MSM), 8.2% are from HIV-endemic countries, and 2% reported acquiring HIV from blood products. Baseline demographic and clinical characteristics of the CANOC participants are described in **Table 3.3**. In comparison with estimates from the Public Health Agency of Canada (PHAC), it appears that individuals with a history of IDU and men are over-represented in CANOC while women, MSM, and people from HIV-endemic countries are under-represented. **Table 3.4** shows the differences between the adolescents and young adults (AYA) in the different provinces. Significant differences exist in many variables, signifying the diversity of Canadian youth. Most notable are the differences regarding gender, ethnicity, and HIV risk factor. As noted above, a number of studies are being conducted on this cohort and the results of this work have been presented at conferences in Canada and internationally. As of November 2014, there have been 15 CANOC manuscripts published in peer-reviewed journals (61,113,127,128,247–257).

3.7.1. Main strengths and weaknesses

With eight sites, 10,044 participants, 15 Principal Investigators and 29 co-investigators with a broad spectrum of expertise, CANOC has a good representation of HIV-positive individuals in Canada who initiated cART after January 1, 2000 and a strong commitment from the HIV research community in Canada. The dataset will be enhanced bi-annually at each subsequent data cut by including more cohort members and a wider selection of data elements. Linkages with vital statistics, census tract databases, PopData^{BC}, the Institute for Clinical Evaluative Sciences (ICES) in Ontario, and Régie de l'assurance maladie du Quebec (RAMQ) will further enrich the CANOC dataset.

As with any cohort study, a number of inherent limitations exist. Most notably, patients were not randomly assigned or sampled so may not be representative of the Canadian population infected with HIV/AIDS. Patients who initiated cART prior to January 1, 2000 are not included in the cohort, so our findings will only be generalizable to individuals who have initiated therapy in the “modern cART era.” The cohorts involved in the collaboration are currently limited to three Canadian provinces (British Columbia, Ontario, and Quebec). While these provinces are representative of the largest HIV-positive populations in Canada, the collective cohort may not be fully representative of

the HIV-infected population in Canada. As stated above, however, it is anticipated that cohorts from Saskatchewan and Newfoundland will join CANOC in the next one to three years. As well, CANOC only includes individuals 18 years of age and older, so younger Canadians living with HIV (including perinatally infected AYA who started treatment as young children) are not captured in the dataset.

Differences in clinical outcomes among cohorts may be due to variations in the timing of follow-up visits and differential losses to follow-up between cohorts. It is important to note that British Columbia has population-level data of British Columbians on antiretroviral therapy whereas the data from Ontario and Quebec come from select clinic databases. Although there is considerable heterogeneity between the cohorts, these differences are more of a strength than a weakness, since this heterogeneity will allow us to better understand how various factors work together to influence the health of HIV-infected individuals. Since the data comes from cohorts that existed prior to the start of the collaboration, the reporting methods are not standardized across all cohorts. For example, ethnicity and adherence are not captured in all cohorts. For the variable regarding injection drug use, there is no distinction between participants who currently use injection drugs and those with a history of injection drug use. The data are completed by the clinician, not necessarily by the patient; therefore, there may be some misclassification in reports of HIV exposure risk and ethnicity. As well, CANOC does not collect socio-structural and psychosocial variables, limiting the investigative team to study mainly clinical outcomes, which prevents more nuanced assessments of predictors of HIV treatment outcomes. Despite these limitations, CANOC represents the largest cohort of adolescents and young adults (AYA) available in Canada.

3.8. Training Opportunities

Before the creation of CANOC, limited opportunities existed in Canada for training graduate students, post-doctoral fellows, medical trainees, and interested community members in the area of HIV cohort research. The team approach to training and knowledge translation creates unique opportunities for advanced multi-site and multi-investigator training. The CANOC team has a five-year history of great success in training students interested in pursuing research using the study database. Funding is

offered for fellowships at Masters, PhD, and post-doctoral levels and is awarded to the most qualified applicants at each level. Applicants submit a proposal for a CANOC research project and must be supervised by a CANOC investigator (www.canoc.ca). Training awards are for a one-year period with the possibility of renewal.

3.9. Knowledge Translation and Dissemination

Community researchers, representing HIV-affected communities, have been invited to sit on the CANOC Community Advisory Committee. The members of this committee contribute to the development of research questions, advise on and help build community partnerships, and assist with knowledge translation and the dissemination of research findings. Partnerships with non-governmental organizations such as the Canadian Aboriginal AIDS Network (CAAN), the Canadian AIDS Society (CAS), the Canadian AIDS Information and Exchange (CATIE), the Canadian Treatment Action Council, and the Canadian Working Group on HIV & Rehabilitation (CWGHR) allow the findings to be more readily available to individuals living with HIV/AIDS.

CANOC investigators are involved with policy-making and program development in their respective provinces. For example, the BC HIV/AIDS Therapeutic Guidelines are a consensus of the BC Centre for Excellence in HIV/AIDS' Therapeutic Guidelines Committee, which includes a number of CANOC investigators (258). This information represents the committee's interpretation of research findings relating to current treatment of HIV/AIDS. Through such mechanisms, the CANOC team has direct avenues for disseminating findings to health care practitioners and policy-makers at a provincial level. Relevant treatment-related results are also relayed to the appropriate therapeutic guideline committees across Canada, ensuring the knowledge obtained through research can be considered for the development and implementation of future guidelines.

CANOC encompasses a broad spectrum of expertise with individuals skilled in biomedical statistics, epidemiology, health services research, infectious diseases, population health, primary care, psychology, respiratory medicine, and virology. Team members have demonstrated track records in publishing research findings in high-

impact peer-reviewed scientific journals and presenting at academic conferences, and will continue to pursue these avenues as a means of promoting knowledge translation. While the team understands that publishing in academic journals should not be the sole means of knowledge translation, the CANOC team recognizes that adherence to the highest standard of peer-review is required to ensure widespread acceptance of research findings. Finally, the CANOC website (www.canoc.ca) is an important tool for communicating findings to other research groups in Canada and worldwide. Plain language summaries of all CANOC research findings are also posted on the website, ensuring the research is accessible to the general public.

3.10. Principles of collaboration

CANOC welcomes Canadian HIV treatment cohorts that are not members of CANOC to join their collaboration. The principles of collaboration are based on those principles approved and active in the ART Cohort Collaboration (259), the North American AIDS Cohort Collaboration on Research and Design (260), and the Ontario HIV Treatment Network Cohort Study (OCS) (261). The cohorts in the current collaboration were set up for various purposes and all existed prior to the development of CANOC. The majority are clinic-based populations except in British Columbia, where the study population is based on all people accessing therapy, and the OCS, which is a provincial multi-site research study. In addition, CANOC welcomes collaborations with other international HIV observational cohorts interested in pursuing joint or comparative analyses.

3.11. Discussion

Cohort collaborations provide the strongest level of evidence for research in areas such as disease progression, rare adverse events, and rare exposures (259,260). CANOC provides the largest database of current Canadian HIV patient information ever collected. Implementing research findings requires knowledge of important clinical issues—both population-level issues and issues likely to be of relevance to policy-makers at both the provincial and federal levels. CANOC aims to put Canadian HIV/AIDS research on par with other international collaborations in the field. Efforts to

improve research dissemination to physicians and persons living with HIV as well as to improve knowledge translation of research on HIV/AIDS therapeutics into provincial, national, and international HIV/AIDS treatment guidelines will contribute to global recognition of the Canadian HIV epidemic. The CANOC data will allow me to work with the largest cohort of adolescents and young adults (AYA) in Canada to better understand how to support these young people.

Table 3.1 Cohorts participating in CANOC

Site/Cohort	Cohort Type	Number of Participants N (%)	Province
BC Centre for Excellence in HIV/AIDS (BC-CfE)	Population-based	4,644	British Columbia
Maple Leaf Medical Clinic (MLMC)	Clinic-based	1,506	Ontario
Ontario HIV Treatment Network (OHTN)	Cohort-based	824	Ontario
Toronto General Hospital	Clinic-based	616	Ontario
Ottawa Hospital	Clinic-based	439	Ontario
Clinique Medicale L'Actuel	Clinic-based	1,301	Quebec
Montreal Chest Hospital Immunodeficiency	Clinic-based	560	Quebec
Electronic Antiretroviral therapy cohort (EARTH)	Clinic-based	154	Quebec
Total		**10,044**	

Table 3.2 Variables available in CANOC

	Variables
Demographics	Name of site or cohort
	Country of birth
	Province of origin
	Year of immigration/arrival in Canada
	Start date of cART
	Age
	Gender
	Risk factors MSM History of IDU Endemic country Blood products Heterosexual MTCT Other
	Ethnicity
	Postal code and/or census tract locator
	Census derived variables
	Date last seen in clinic (dd/mm/yy)
	Date of death (dd/mm/yy)
	Cause of death
Clinical Variables	Year of first HIV-positive test
	Year of entry into care
	HIV clade
	CD4 count
	CD4 percentage
	Viral load
	Assay type
	AIDS-defining illness
	HCV co-infection
	Year of first HCV-positive test
	HCV antibody positive
	HCV PCR positive

	Variables
	HEPB
	HPV
	Mortality
	Loss to follow-up
Antiretroviral Therapy	cART type
	cART start date (dd/mm/yy)
	cART stop date (dd/mm/yy)
	Combination product name
	Dose (only for ritonavir)
	Clinical trial (Y/N)
	cART type

HCV: Hepatitis C
MSM: Men who have sex with men
IDU: Injection drug use
MTCT: Mother-to-child transmission
cART: Combination antiretroviral therapy
HEPB: Hepatitis B
HPV: Human papilloma virus
PCR: Polymerase chain reaction

Table 3.3 Baseline demographic and clinical characteristics of CANOC participants

Variable	Number (%) or Median (IQR)
Initiated antiretrovirals	
2000-2002	1,667
2003-2005	1,886
2006-2008	2,468
2009-2012	3,279
Missing	744
Province	
British Columbia	4,644 (46.2)
Ontario	3,385 (33.7)
Quebec	2,015 (20.1)
Gender	
Female	1,832 (18.2)
Male	8,171 (81. 4)
Transgender	41 (0.4)
Age (years)	40 (33-47)
Baseline CD4 cell count (cells/mm3)	227 (124-332)
Baseline plasma viral load (log10 copies/mL)	67,261 (19,402-132,371)
AIDS at baseline	1,444 (14.4)
ADI	3,073 (29.4)
Risk known	8,049 (80.1)
History of IDU *Unknown = 2,161 (22)*	5,722 (57)
MSM *Unknown = 3,272 (33)*	3,120 (31)
HCV-positive *Unknown = 650 (6.5)*	2,435 (24.2)
Endemic country *Unknown = 5,768 (57.4)*	827 (8.2)
Acquired through blood products	203 (2.0)
Ethnicity *Unknown = 1,301*	
Black	867 (10)
Caucasian	2,683 (31)
Asian	51 (0.6)

Variable	Number (%) or Median (IQR)
South Asian	44 (0.5)
Aboriginal	478 (5.5)
Hispanic	203 (2.3)
Mixed	178 (2.9)
Other	63 (0.7)
Follow-up time (months)	52 (24-90)
Loss to follow-up	9.5%
Crude death rate	840 (8.4)

IDU: Injection drug use
MSM: Men who have sex with men
ADI: AIDS-defining illness
HCV: Hepatitis C

Table 3.4. Demographic information about AYA by province of residence (N=1,168)

Variable	Province						p-value
	BC (N=470)		ON (N=451)		PQ (N=247)		
	N	(%)	N	(%)	N	(%)	
Gender							
Male	299	(64)	310	(69)	186	(75)	0.006
Female	171	(36)	141	(31)	61	(25)	
Ethnicity							
Caucasian	99	(21)	166	(37)	30	(12)	<0.001
Black	15	(3)	83	(18)	40	(16)	
Aboriginal	56	(12)	9	(2)	1	(0)	
Other	43	(9)	55	(12)	7	(3)	
Unknown/Missing	257	(55)	138	(31)	169	(68)	
Aboriginal							
No	157	(33)	304	(67)	77	(31)	<0.001
Yes	56	(12)	9	(2)	<5	(0)	
Unknown	257	(55)	138	(31)	169	(68)	
HIV risk MSM							
No	200	(43)	69	(15)	96	(39)	<0.001
Yes	102	(22)	171	(38)	151	(61)	
Unknown	168	(36)	211	(47)			
HIV risk IDU							
No	204	(43)	291	(65)	224	(91)	<0.001
Yes	181	(39)	31	(7)	22	(9)	
Unknown	85	(18)	129	(29)	<5	(0)	
Hepatitis C							
Not co-infected	256	(54)	396	(88)	215	(87)	<0.001
Co-infected	168	(36)	52	(12)	21	(9)	
Unknown	46	(10)	3	(1)	11	(4)	
Baseline ADI							
None	426	(91)	406	(90)	178	(72)	<0.001
At least one	44	(9)	45	(10)	12	(5)	
None ever					57	(23)	

Variable	Province						p-value
Era of cART initiation							
2000-2003	135	(29)	90	(20)	59	(24)	0.033
2004-2007	126	(27)	145	(32)	69	(28)	
2008-2011	209	(44)	216	(48)	119	(48)	
Virological suppression							
No	80	(17)	58	(13)	23	(9)	0.013
Yes	390	(83)	393	(87)	224	(91)	
Classes of ARVs in first regimen							
NNRTI	213	(45)	225	(50)	102	(41)	<0.001
Unboosted PI	43	(9)	51	(11)	27	(11)	
Boosted PI	203	(43)	145	(32)	82	(33)	
Other	11	(2)	30	(7)	36	(15)	
Initial third drug							
Nevirapine	74	(16)	39	(9)	14	(6)	<0.001
Efavirenz	139	(30)	186	(41)	86	(35)	
Lopinavir	60	(13)	85	(19)	36	(15)	
Atazanavir	129	(27)	75	(17)	46	(19)	
Nelfinavir	40	(9)	29	(6)	18	(7)	
Other	28	(6)	37	(8)	47	(19)	
	Median (IQR_		Median (IQR)		Median (IQR)		P-value
Age at first cART initiation (years)	26 (24-28)		26 (24-28)		27 (24-28)		0.677
Baseline CD4 (cells/mm3)	240 (140-370)		256 (170-356)		273 (199-370)		0.03
Baseline viral load (log10 copies/mL)	5 (4-5)		5 (4-5)		5 (4-5)		<0.001
Time to virological suppression (months)	5 (3-16)		5(3-11)		5 (3-8)		0.008
Follow-up time (years)	4 (2-8)		4 (3-7)		4(2-7)		0.32

MSM: Men who have sex with men

IDU: Injection drug use

ARV: Antiretroviral

NNRTI: Non-nucleoside reverse transcriptase inhibitor

Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir

Unboosted PI: cART regimen consisting of a protease inhibitor

ADI: AIDS-defining illness

BC: British Columbia; ON: Ontario; PQ: Quebec

Chapter 4.

Factors associated with late initiation of highly active antiretroviral therapy among young HIV-positive men and women aged 18-29 years in Canada

Note: A version of this manuscript has been published in the *Journal of the International Association of Providers of AIDS Care.*

For the purpose of consistency between chapters, an amendment was added to Chapter 4 to incorporate a comparison between adolescents and young adults (AYA) and older adults. Previously, on the recommendation of the CANOC team, the analysis had focused solely on AYA.

Palmer AK, Cescon AM, Chan K, Cooper C, Raboud JM, Miller CL, Burchell AN, Klein MB, Machouf N, Montaner JSG, Tsoukas C, Hogg RS, Loutfy MR, and the CANOC Collaboration. Factors Associated with Late Initiation of Highly Active Antiretroviral Therapy among Young HIV-Positive Men and Women Aged 18 to 29 Years in Canada. *Journal of the International Association of Providers of AIDS Care (JIAPAC)* 2014; 13:56-62.

4.1. Abstract

Background: Initiating combination antiretroviral therapy (cART) when low CD4 counts are low or when an AIDS-defining illness (ADI) has already occurred increases the risk of treatment failure and death. This chapter examines factors associated with late initiation among 18- to 29-year-olds within the Canadian Observational Cohort Collaboration (CANOC), a multi-site study of HIV-positive persons who initiated cART on or after January 1, 2000.

Methods: Late initiation was defined as beginning cART with a CD4 count <200 cells/mm^3 and/or a baseline ADI. Multivariable logistic regression was used to identify independent correlates of late initiation.

Findings: In total, 1,026 individuals (422 from British Columbia, 400 from Ontario, and 204 from Quebec) met the age criteria. At cART initiation, the median age was 27 years (interquartile range [IQR]: 24-28 years). A total of 412 individuals (40%) identified as late initiators. Late initiation was associated with being female, being more than 25 years of age at initiation, initiating treatment in earlier years, and having a higher baseline viral load.

Conclusion: The high number of young adults in the cohort who started cART late indicates important target populations for specialized services, increased testing, and linkages to care.

4.2. Introduction

It is estimated that in 2011, there were approximately 71,300 people living with HIV/AIDS in Canada (26). From 1998 to 2008, young people (ages 15-29) made up 21 to 23% of HIV-positive diagnoses. The majority of these infections among young people are attributable to men who have sex with men (MSM) (53.9%), heterosexuals (22.9%), and injection drug users (IDU) (19.4%) (142). While combination antiretroviral therapy (cART) has improved health outcomes for people living with HIV, it is important for the medication to be started before the person develops an AIDS-defining illness (ADI) or has a low CD4 count (198,262). Understanding factors that support or undermine the initiation of cART among young people is essential to designing targeted programs that aim to optimize treatment outcomes.

Research has shown that starting antiretroviral medications while asymptomatic significantly delays illness (262). People who initiate cART with low CD4 counts or after an ADI develops are at greater risk for treatment failure (167,198,262–266). Also, for people who start late, immune recovery is less likely and the chance of experiencing treatment toxicity and death is greater (267). Immune Reconstitution Inflammatory

Syndrome (IRIS) and other opportunistic infections are also more likely in individuals who initiate treatment late (268).

It is also advantageous for people living with HIV to start cART in a timely manner in order to achieve a suppressed viral load for personal health as well as for public health reasons (30,38,103,269). The Treatment as Prevention (TasP) initiative is based on the premise that if a person maintains a suppressed viral load, they are significantly less likely to transmit HIV to sexual partners, IDU partners, and vertically to infants (30,104,196,270). At the population level, lower aggregate and community viral load has been shown to correlate with a reduction in new infections, which is a major accomplishment for public health (38,102,103,269).

First operationalized in British Columbia, TasP has now been endorsed by the World Health Organization (WHO) and is in the process of being implemented in a number of regions and countries worldwide, including China and France (2,137,138). TasP is the cornerstone of UNAIDS' ambitious 90-90-90 campaign that seeks to get 90% of all people living with HIV to know their HIV status; 90% of all people with diagnosed HIV infection to receive cART; and 90% of all people receiving cART to achieve virological suppression (7).

Following the findings of several cohort studies that demonstrated improved health outcomes and survival for individuals who began cART at higher CD4 counts (196–198), the International AIDS Society(IAS)-USA 2012 guidelines recommended that all people living with HIV with a CD4 cell count of ≤500 cells/μl should be offered cART (199). TasP promotes the notion that all people living with HIV should be offered cART regardless of CD4 count in order for them to maintain good health and lower transmission risk (138). Notably, this recommendation is also embraced in the 2013 WHO antiretroviral drug guidelines and the 2014 IAS-USA HIV treatment guidelines (271,272).

Previous research has shown that young people living with HIV are less likely to start medication earlier in the course of infection for a myriad or reasons including unstructured lifestyles, lack of family support, and engagement in high-risk activities such as substance use (55,75,122). However, little research has been done to date to

assess the prevalence and correlates of late initiation across provinces among Canadian young people.

Initiation of cART is an important component of the HIV Cascade of Care developed by Gardner et al. (109) (**Figure 4.1).** This spectrum of engagement in care represents an important framework for surveillance and evaluation for HIV treatment. The Cascade lays out the roadmap to achieving virological suppression and well-being, with each step representing numerous opportunities to engage with clients and to assist them in successfully moving to the next step. Each step is critical to achieving sustained virological suppression and optimizing TasP implementation efforts. As initiation of cART is a critical component in the Cascade, a better understanding of the barriers to timely treatment initiation will help to support young people living with HIV to experience the full benefits of cART. This study, therefore, seeks to examine factors associated with late initiation among Canadians 18 to 29 years of age who have access to a publicly funded universal health care system.

Figure 4.1. The HIV Cascade of Care (based on Gardner et al., 2011)

4.3. Methods

Study Methodology

The Canadian Observational Cohort Collaboration (CANOC) is a multi-site study of HIV-positive persons who initiated cART on or after January 1, 2000. The collaboration is open to all Canadian HIV treatment cohorts and currently includes eight participating cohorts from three provinces (British Columbia, Ontario, and Quebec). Eligibility criteria for inclusion were: documented HIV infection; residence in Canada; 18 years of age and over; initiation of a first antiretroviral regimen comprised of at least three individual agents; and at least one measurement of HIV-1 RNA viral load and CD4 cell count within six months of initiating cART (127).

Electronic data extraction of a predefined set of demographic, laboratory, and clinical variables is performed at the data centres of the participating sites and submitted annually to the BC Centre for Excellence in HIV/AIDS in Vancouver for pooling, data cleaning, and analysis. All data are stripped of names and other personal identifiers prior to being sent to the Data Coordinating Site, and a unique CANOC study number is assigned to each participant. Overlap between cohorts is identified within provinces before data are sent to the Data Coordinating Site. A data dictionary has been developed by the CANOC data analysts and is shared among the investigators after each new data cut. All data are managed in a central relational database (at the British Columbia Centre for Excellence in HIV/AIDS), and an audit trail has been created for all data changes. Access to CANOC electronic data at the Data Coordinating Site is password protected and limited to essential study personnel.

All participating cohorts received research ethics board approval to contribute anonymous patient data to CANOC, adhering to established standards in data sharing/linkage and data security/residual disclosure. In the case of the Ontario HIV Treatment Network (OHTN) Cohort Study (OCS), additional approval was received from the OCS Governance Committee to release Ontario data to participate in CANOC. Data submitted to the Data Coordinating Site in Vancouver are used only to address specific research questions approved by the CANOC Scientific Steering Committee, and ownership of individual cohort data remains with the contributing cohort. Data elements used in any scientific publications are aggregated and de-identified. The last date of follow-up in the cohort for the current analysis was September 30, 2011. This analysis was conducted in accordance with the international STROBE guidelines (126)—a set of recommendations to promote complete reporting of cohort data in a systematic manner.

Population

Our primary analysis was limited to CANOC participants who initiated cART between the ages of 18 and 29 during the period from January 1, 2000 to September 30, 2011. Our secondary analysis considered all CANOC participants who initiated cART during the same period.

Outcomes

The primary outcome of interest is late initiation among adolescents and young adults (AYA), defined as beginning cART with a CD4 count <200 cells/μL and/or having an AIDS-defining illness (ADI) prior to the start of therapy. The CD4 level of <200 cells/μL was selected to account for the evolving guidelines for treatment initiation since the CANOC study began in 2000 (273,274) and the fact that this level now represents a very late count at which to initiate cART.

A sub-analysis was performed using the entire CANOC cohort to compare late initiation between AYA and older adults. Covariates of interest for both analyses included: sex; province; hepatitis C co-infection; HIV risk factors; Aboriginal ancestry; baseline CD4 and viral load; composition of initial cART regimen; year starting cART; and follow-up time.

Statistical analysis

Baseline characteristics were summarized using medians and interquartile ranges (IQR) for continuous variables and frequencies and proportions for categorical variables. Late versus not late initiators were compared using the Pearson χ^2 or Fisher's exact, and Wilcoxon's Rank Sum tests, respectively.

Univariate logistic regression models were used to identify unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) for variables associated with late initiation. Variables with $p<0.05$ in the univariate analyses were candidates for inclusion in final possible multivariable logistic regression models for late initiation. Only the correlates with a significant effect ($p<0.05$) remained in the final multivariable model. When multiple covariates measured similar phenomena, the variable representing each construct with the higher effect size and most statistical significance was chosen. All analyses were performed using SAS software version 9.1 (SAS Institute, Cary, North Carolina, USA). Statistical methods were the same for both the AYA analysis and the sub-analysis that looked at the entire CANOC population.

4.4. Results

Study population and prevalence of late initiation

Of the 7,738 participants in CANOC, 1,026 (13.2%) individuals met the eligibility criteria of initiating cART between the ages of 18 and 29. As noted in **Table 4.1**, of these, 340 (33.1%) were female and 686 (66.9%) were male, and 422 (41.1%) were from British Columbia (BC), 400 (39.0%) from Ontario (ON), and 204 (19.9%) from Quebec (PQ). A total of 412 individuals (40%) in this sample initiated therapy with a CD4 count <200 cells/mm^3 and with baseline ADI.

Correlates of and temporal trends in late initiation

In the univariate analysis **(Table 4.2)**, late initiation was associated with: province of residence (BC, 48%; ON, 36%; PQ, 16%; p<0.001): having a positive hepatitis C test (27% vs. 19%; p=0.003); reporting a history of IDU (37% vs. 24%; p<0.001); having a baseline viral load of >100,000 copies/mL (54% vs. 23%; p<0.001); being between the ages of 25 and 30 at the time of cART initiation (67% vs. 60%, p=0.015); starting cART in an earlier calendar year (median year 2005 [IQR: 2002-2008] vs. 2007 [IQR: 2004-2009]; p<0.001); and longer follow-up time in years (median 4.6 [IQR: 2.2-7.0] vs 2.8 [IQR: 1.4-5.4]; p<0.001)**.**

In the multivariable analysis **(Table 4.3),** late initiation was independently associated with being female or transgender (aOR = 1.36; 95% CI: 1.00, 1.84); being older than 25 years of age at the time of cART initiation (aOR = 1.40; 95% CI: 1.05, 1.86); starting therapy earlier in terms of calendar year (aOR = 0.88; 95% CI: 0.84, 0.92); and having a higher baseline viral load (per log10) (aOR = 5.57; 95% CI: 3.71, 8.38).

The proportion of individuals starting cART late has declined since 2000. In that year, almost half (47.8%) of individuals initiating cART started with a baseline CD4 of <200 cells/μL. This proportion decreased to 17.5% in 2010 but increased to 25% in 2011 **(Figure 4.2).**

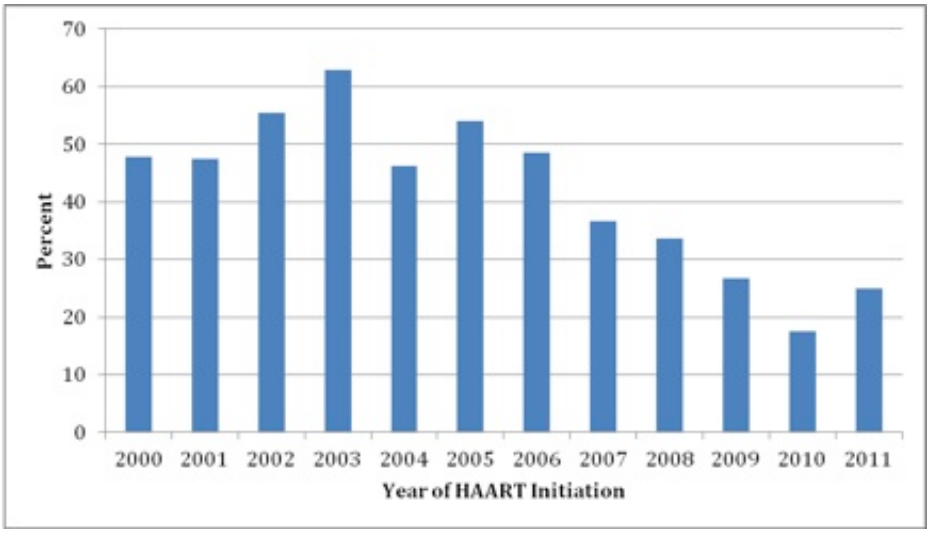

Figure 4.2. Proportion of late initiating AYA CANOC participants, by year (n=412)

4.4.1. Sub-analysis comparing AYA and older adults

Finally, in order to understand how AYA differed from older adults with respect to late initiation, we conducted the following sub-analysis. A total of 7,738 participants in CANOC met the eligibility criteria of initiating cART on or after January 1, 2000. Of the 7,738 participants in CANOC, 1,472 (19%) were female or transgender and 6,266 (81%) were male, and 3,588 (46.4%) were from British Columbia (BC), 2,675 (34.6%) from Ontario (ON), and 1,475 (19.1%) from Quebec (PQ). A total of 3,879 (50.1%) in this sample initiated therapy with CD4 counts <200 cells/μL and/or with a baseline ADI (i.e., late initiators). The average age of CANOC participants is 40 (IQR: 34-46).

Sub-analysis correlates of, and temporal trends in, late initiation

As shown in **Table 4.4,** older adults are more likely to be late initiators of cART (51.7% vs 40.2% p<0.001). AYA are more likely to be female or transgender (33.1% vs 16.9%, p<0.001), reside in Ontario (39% vs 33.9%, p<0.001), report Aboriginal ethnicity (16.6% vs 12.5%, p= 0.017), start cART with a lower viral load (22% vs 14.3%, p<0.001), and have a higher baseline CD4 count (24.9% vs 16.4%, p<0.001). Older adults are more likely to have tested positive for hepatitis C 27.4% vs 22.1%m p<0.001), report being

MSM (51.4% vs 46.7%, p= 0.018), and have had an AIDS-defining illness (ADI) prior to initiating cART (15.4% vs 8.2%, p<0.001).

In univariate analyses **(Table 4.5)**, late initiation was associated with province of residence (BC, 50.3%; ON, 33.2%; PQ, 16.5%; p<0.001), having a positive hepatitis C test (30.7% vs. 22.7%; p=0.001), reporting a history of IDU (36.9% vs 26.9%; p<0.001), not being MSM (45.3% vs. 56.7%, p=0.001), and reporting Aboriginal ethnicity (14.4% vs. 11.4%; p<0.012). Late initiation was also associated with initiating treatment with a boosted protease inhibitor (PI), having a baseline viral load >100,000 copies/mL (54.9% vs. 29.8%; p<0.001), and being 30 years of age or older (89.4% vs. 84.1%, p<0.001).

In the multivariable analysis **(Table 4.6)**, late initiation was independently associated with residing in British Columbia (aOR = 1.50; 95% CI: 1.30, 1.74) or Ontario (aOR = 1.30; 95% CI: 1.13, 1.49) and having a history of injection drug use (aOR = 1.34; 95% CI: 1.18, 1.53). Similar to the previous AYA analysis, starting therapy earlier in terms of calendar year (aOR = 0.87; 95% CI: 0.85, 0.88) was associated with late initiation of cART. Age (per decade) was associated with late initiation, with older people more likely to initiate cART late (aOR = 1.14; 95% CI: 1.09, 1.20).

4.5. Discussion

Contrary to our hypothesis, this analysis shows that older people in CANOC are more likely to be late initiators of cART (51.7% vs. 40.2%). Our multivariable analysis also shows that people who live in British Columbia or Ontario, who have a history of injection drug use, and who started treatment in an earlier calendar year were more likely to start cART with a CD4 count <200 cells/μL and/or when they had an AIDS-defining illness prior to the start of therapy. Note that this study was conducted in a setting with universal health care access, without the potential confounding effects of financial barriers to HIV treatment.

It is possible that the older individuals in our cohort have psychosocial and structural barriers to care that are not captured in this analysis. Irrespective of age, linkage to care following an HIV-positive diagnosis depends on many factors including

the sensitivity of care on the part of the health care team to make the appropriate referrals, in order for all those testing positive to receive care and treatment in a timely manner.

We found that late initiation was more likely among individuals initiating cART in earlier calendar years. This corresponds with temporal changes in the recommended CD4 count level for cART initiation over time. Treatment guidelines have changed as cART has evolved, and thus the definition of late initiation of therapy has also changed over our study period (199,273). However, the International AIDS Society(IAS)-USA guidelines from 2000-2011 have consistently recommended therapy for all patients with a CD4 count of ≤200 cells/ mm^3, thus rendering our definition appropriate for the entire study period. Of note, recently North American guidelines have converged in their recommendation that cART be offered to all people living with HIV irrespective of their CD4 count, with the exception of long-term non-progressors or elite controllers (199,275,276).

In this analysis people who have a history of injection drug use (IDU) are more likely to initiate treatment with a low CD4 count or at the point of being diagnosed with an AIDS-defining illness, which is consistent with other research in this area (277,278). Many injection drug users are dealing with competing life priorities such as incarceration, lack of adequate housing, food security, active addiction, and mental health conditions with personal health failing to be a priority (279–282). As well, many report feeling discriminated against in the health care system or fearing arrest/persecution and, therefore, avoid health services (240,279,283–286). Outreach can been helpful in connecting these individuals with health care services such as HIV testing, wound care, and adherence maintenance programs (287–289).

Individuals residing in British Columbia and Ontario are more likely to initiate cART at a later point than those living in Quebec, which may be related to the demographics in each province. For example, British Columbia has a higher proportion of people living with HIV with a history of injection drug users than the other provinces. The results are adjusted for IDU, but still the relationship with the province remains.

These pan-provincial differences require greater analysis and investigation to better understand the reasons for them.

Our study demonstrates that a large proportion (40%) of the HIV-positive young people in CANOC initiated cART at CD4 counts below 200 cells/mm^3. Although the proportion starting below 200 cells/mm^3 is decreasing, nearly a quarter continues to initiate cART late. We also discovered, in the multivariable analysis looking only at AYA, that being female, having a baseline age above 25 years, and starting therapy earlier in terms of calendar year.

The fact that our analysis showed women were more likely to be late initiators is consistent with other studies and could be related to late presentation and HIV testing due to lack of self-consideration of being at risk and fear of HIV testing due to stigma. Previous research from British Columbia has shown that women were more likely to die from HIV-related illnesses without ever accessing treatment (290).

Heterosexual men and women who were not involved in injection drug use were less likely to test, perhaps because their perceived risk is lower than in other populations. In Canada, HIV testing is highest among gay men and those who perceive themselves to be at greater risk for HIV (291). A Swiss study showed that gay men were more likely to have had a negative HIV test prior to seroconversion, suggesting that they were more risk-aware (167). The same study showed late presentation/diagnosis to be the major reason for late initiation of ART (167). This finding points to the importance of testing for HIV in women, sometimes a group considered to be at lower risk for HIV, especially in higher-income settings.

In the AYA analysis, individuals between the ages of 25 and 30 were more likely to start medications late compared to the younger young adults in the study. This may be due to 18-24 year olds accessing pediatric services prior to transitioning to adult health providers. As previously mentioned, findings related to age with young people showing more favourable outcomes are contrary to expectations, although similar results have been seen in other studies (292–294). However, the previous studies have been conducted within older adult populations where the average ages are higher; therefore, the populations are not necessarily comparable. It is possible that the older individuals in

our cohort have psychosocial and structural barriers to care that are not captured in this analysis.

Similar to previous findings with the larger CANOC group, we found late initiation to be more likely among young people initiating cART in earlier calendar years. The significant association of late initiation with higher baseline viral load among AYA is not surprising, given the well-established biological association between CD4 cell count and viral load. In accordance with the natural history of HIV infection, following the clinical latency period, CD4 cell counts decrease significantly and plasma viremia increases, approaching levels seen during acute infection (295). As HIV plasma viral load is a well-documented key correlate of HIV transmission risk (38,102,103,269), these findings allude to the importance of earlier cART initiation for both public and personal health.

Large international cohorts such as the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (198), Antiretroviral Therapy Cohort Collaboration (ART-CC) (296), the START trial (297), and the Swiss HIV Cohort Study (262) have demonstrated that initiation of cART at higher CD4 counts results in better health outcomes than initiation at lower CD4 counts. Thus, our findings have important clinical and public health implications. There is a demonstrated need to improve the stage at which young Canadians are initiating cART.

In the current context of HIV treatment in British Columbia, and increasingly in the rest of Canada, under the TasP initiative cART is promoted as the most promising tool in reducing HIV transmission, morbidity, and mortality (38,138,298). In order for TasP to be successful and for the more ambitious goal of the WHO's 90-90-90 campaign to be met in Canada, it is necessary for the Canadian health care system and service providers to address the disconnect between young people testing positive for HIV and subsequently initiating treatment in a timely manner. Further, expansion of the TasP program to other Canadian jurisdictions would be of value, as to date it has only been implemented in British Columbia.

TasP hinges on the ability of people to access treatment and remain engaged in care. Trusting relationships must be developed between AYA and service providers in order for AYA to initiate treatment, be retained in treatment, and reach sustained

virological suppression. Referring to the adapted *Seek, Test, Treat, and Retain* framework **(Figure 4.3),** it is clear to see how influences such as age, gender, drug use, and access to care play a role in an individual's ability to successfully move forward in the continuum and focus on things such as initiating cART. Before clinical outcomes such as initiation of cART, virological suppression, and viral rebound can be properly addressed, other influences must be taken into account.

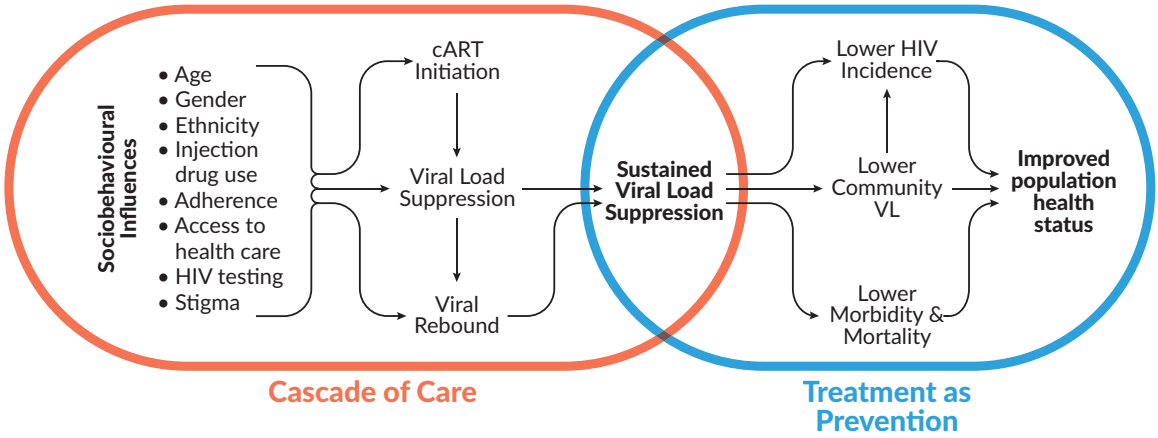

Figure 4.3. Adapted *Seek, Test, Treat, and Retain* framework

There are several limitations that readers of this work should consider. First, data were obtained from only three provinces and, therefore, our results cannot be generalized to all HIV-positive persons in Canada. Also, as with any cohort there is the potential for missing data as some clinics/databases collect different information. However, to our knowledge, this study includes the largest sample of HIV-positive young people in Canada analysed to date. We also acknowledge that young Canadians under the age of 18 were not included, due to CANOC's inclusion criteria. As CANOC is a clinical cohort collaboration, few socio-demographic variables are captured limiting our ability to analyze the impact of other influences. Future studies should consider the effect of socio-economic variables on timely initiation of cART.

4.6. Conclusions and Steps Forward

In conclusion, although we found AYA to be less likely than older adults to initiate cART with CD4 counts < 200 cells/mm^3 or when they have an ADI prior to the start of therapy

(i.e., less likely to be late initiators), we have nevertheless identified a high proportion of late initiators among AYA. The fact that 40% of young men and women accessed cART late in a universal health care setting is cause for concern regardless of how older adults are doing. Further efforts are clearly needed to improve earlier HIV testing and subsequent linkage to appropriate care, in order to maximize the benefits of modern treatments at the personal and public health levels. Seeing as young women are more likely to be late initiators, women-centered care services and messaging should be incorporated into all sexual health campaigns and health care development (285). We recommend the incorporation of HIV testing into routine discussions with primary care providers, in an effort to get all people living with HIV on treatment in a timely manner and reduce the prevalence of this key component of the HIV Cascade of Care (109).

Table 4.1. Demographic and clinical characteristics of AYA (N=1,026)

Characteristics	Category	N (%)
Gender	Female	340 (33.1)
	Male	686 (66.9)
Age	<25	383 (37.3)
	≥25	643 (62.7)
Province	British Columbia	422 (41.1)
	Ontario	400 (39.0)
	Quebec	204 (19.9)
Hepatitis C positive	Yes	212 (22.1)
	No	747 (77.9)
History of IDU	Yes	218 (29.3)
	No	525 (70.7)
MSM	Yes	347 (46.7)
	No	396 (53.3)
Aboriginal ancestry	Yes	76 (16.6)
	No	381 (83.4)
Initial third drug class	NNRTI	483 (47.1)
	Unboosted PI	155 (15.1)
	Boosted PI	369 (36.0)
	NUC x 3	19 (1.9)
Initial third drug	Nevirapine	133 (13.0)
	Efavirenz	350 (34.1)
	Lopinavir	171 (16.7)
	Atazanavir	208 (20.3)
	Other	164 (16.0)
Baseline viral load	<10,000	226 (22.0)
	10,000-99,999	451 (44.0)
	100,000+	349 (34.0)
ADI prior to starting cART	Yes	84 (8.2)
	No	942 (91.8)
Baseline CD4	<200	383 (37.3)
	200-349	388 (37.8)
	350+	255 (24.9)

Characteristics	Category	N (%)
Late initiation	Yes	412 (40.2)
	No	614 (59.8)
Late initiation as determined by:		
CD4 <200 cells/μL		328 (79.6)
ADI		29 (7.0)
CD4 <200 cells/μL and ADI		55 (13.3)

ADI: AIDS-defining illness
NNRTI: non-nucleoside reverse transcriptase inhibitor
NUC x 3: cART regimen consisting of three nucleosides
Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir
Unboosted PI: cART regimen consisting of a protease inhibitor
cART: combination antiretroviral therapy
IDU: Injection drug use
MSM: Men who have sex with men

Table 4.2. Comparison of late initiators vs. non-late initiators among AYA (N=1,026)

Characteristics	Category	Not Late, N (%) (N=614)	Late, N (%) (N=412)	p-value
Gender	Female	194 (31.6)	146 (35.4)	0.223
	Male	420 (68.4)	266 (64.5)	
Province	British Columbia	225 (36.6)	197 (47.8)	<0.001
	Ontario	251 (40.9)	149 (36.2)	
	Quebec	138 (22.5)	66 (16)	
Age	<25	248 (40.4)	135 (32.8)	0.015
	≥25	366 (59.6)	277 (67.2)	
HCV-positive	Yes	107 (18.7)	105 (27.1)	0.003
	No	465 (81.3)	282 (72.9)	
History of IDU	Yes	104 (24.1)	114 (36.5)	<0.001
	No	327 (75.9)	198 (63.5)	
MSM	Yes	222 (51.4)	125 (40.2)	0.003
	No	210 (48.6)	186 (59.8)	
Aboriginal ancestry	Yes	34 (13.5)	42 (20.5)	0.058
	No	218 (86.5)	163(79.5)	
Initial third drug class	NNRTI	304 (49.5)	179 (43.4)	0.046
	Unboosted PI	95 (15.5)	60 (14.6)	
	Boosted PI	201 (32.7)	168 (40.8)	
	NUC x 3	14 (2.3)	5 (1.2)	
Baseline Viral load copies/mL	<10,000	138(27.2)	40(10.8)	<0.001
	10,000-99,999	253(49.8)	131(35.5)	
	100,000+	117(23.0)	198(53.7)	
		Median (IQR)	**Median (IQR)**	
Year therapy started		2007 (2004-2009)	2005 (2002-2007)	<0.001
Baseline CD4 (cells/mm3)		310 (250-420)	120 (53-170)	<0.001
Baseline viral load (log10) copies/mL		4.6 (4.0-5.0)	5.0 (4.5-5.0)	<0.001
Total follow-up time (years)		2.8 (1.4-5.4)	4.6 (2.2-7.0)	<0.001

IDU: Injection drug use

MSM: Men who have sex with men

HCV: Hepatitis C

NNRTI: non-nucleoside reverse transcriptase inhibitor

Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir; Unboosted PI: cART regimen consisting of a protease inhibitor; NUC x 3: cART regimen consisting of 3 nucleosides

Table 4.3. Factors associated with late initiation of cART among AYA in CANOC

Variable	Unadjusted Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Gender				
Male	1.00	0.200	1.00	0.050
Female	1.19 (0.91, 1.55)		1.36 (1.00, 1.84)	
Province				
Quebec	1.00		1.00	
British Columbia	1.83 (1.29, 2.60)	<0.001	1.36 (0.93, 1.99)	0.108
Ontario	1.24 (0.87, 1.77)	0.235	1.19 (0.82, 1.74)	0.357
HCV-positive	1.62 (1.19, 2.20)	0.002		
History of IDU	1.81 (1.32, 2.49)	<0.001		
MSM	0.64 (0.47, 0.85)	0.003		
Age >25	1.39 (1.07, 1.81)	0.013	1.40 (1.05, 1.86)	0.020
Year therapy started	0.87 (0.83, 0.90)	<0.001	0.88 (0.84, 0.92)	<0.001
Baseline viral load (log10 copies/mL)	2.29 (1.83, 2.86)	<0.001		
Baseline viral load				
<10,000	1.00		1.00	
10,000-100,000	1.73 (1.20, 2.50)	0.004	1.91 (1.30, 2.80)	0.001
100,000+	5.18 (3.55, 7.57)	<0.001	5.57 (3.71, 8.38)	<0.001

HCV: Hepatitis C
IDU: History of injection drug use
MSM: Men who have sex with men
cART: Combination antiretroviral therapy

Table 4.4. Sub-analysis: Demographics of CANOC participants stratified by age group (AYA and older adults) (N=7,738)

Characteristics	Category	Total	<30, N (%)	≥30, N (%)	p-value
Gender	Female/ Transgender	1,472	340 (33.1)	1,132 (16.9)	<0.001
	Male	6,266	686 (66.9)	5,580 (83.1)	
	Total (N)	**7,738**	**1,026**	**6,712**	
Province	British Columbia	3,588	422 (41.1)	3,166 (47.2)	<0.001
	Ontario	2,675	400 (39)	2,275 (33.9)	
	Quebec	1,475	204 (19.9)	1,271 (18.9)	
	Total (N)	**7,738**	**1,026**	**6,712**	
HCV-positive	No	5,279	747(77.9)	4,532 (72.6)	<0.001
	Yes	1,926	212 (22. 1)	1,714 (27.4)	
	Total (N)	**7,205**	**959**	**6,246**	
History of IDU	No	3,715	525 (70.7)	3,190 (67.4)	0.083
	Yes	1,761	218 (29.3)	1,543 (32.6)	
	Total (N)	**5,476**	**743**	**4,733**	
MSM	No	2,666	396 (53.3)	2,270 (48.6)	0.018
	Yes	2,747	347 (46.7)	2,400 (51.4)	
	Total (N)	**5,413**	**743**	**4,670**	
Aboriginal ancestry	No	2,856	381 (83.4)	2,475 (87.5)	0.017
	Yes	429	76 (16.6)	353 (12.5)	
	Total (N)	**3,285**	**457**	**2,828**	
Initial third drug class	NNRTI	3,603	483 (47.1)	3,120 (46.5)	<0.001
	Unboosted PI	846	155 (15.1)	691 (10.3)	
	Boosted PI	3,159	369 (36)	2,790 (41.6)	
	NUC x 3	130	19 (1.9)	111 (1.7)	
	Total (N)	**7,738**	**1,026**	**6,712**	
Initial third drug	Nevirapine	895	133 (13)	762 (11.4)	0.002
	Efavirenz	2,692	350 (34.1)	2,342 (34.9)	

Characteristics	Category	Total	<30, N (%)	≥30, N (%)	p-value
	Lopinavir	1,479	171 (16.7)	1,308 (19.5)	
	Atazanavir	1,690	208 (20.3)	1,482 (22.1)	
	Other	982	164 (16)	818 (12.2)	
	Total (N)	**7,738**	**1,026**	**6,712**	
Baseline viral load	<10,000	1,184	226 (22)	958 (14.3)	<0.001
	10,000-99,999	3,277	451 (44)	2,826 (42.1)	
	100,000+	3,277	349 (34)	2,928 (43.6)	
	Total (N)	**7,738**	**1,026**	**6,712**	
ADI prior to starting cART	No	6,618	942 (91.8)	5,676 (84.6)	<0.001
	Yes	1,120	84 (8.2)	1,036 (15.4)	
	Total (N)	**7,738**	**1,026**	**6,712**	
Baseline CD4	<200	3,594	383 (37.3)	3,211 (47.8)	<0.001
	200-349	2,787	388 (37.8)	2,399 (35.7)	
	350+	1,357	255 (24.9)	1,102 (16.4)	
	Total (N)	**7,738**	**1,026**	**6,712**	
Late initiation	No	3,859	614 (59.8)	3,245 (48.3)	<0.001
	Yes	3,879	412 (40.2)	3,467 (51.7)	
	Total (N)	**7,738**	**1,026**	**6,712**	

IDU: Injection drug use
MSM: Men who have sex with men
NNRTI: Non-nucleoside reverse transcriptase inhibitor
Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir
Unboosted PI: cART regimen consisting of a protease inhibitor
NUC x 3: cART regimen consisting of 3 nucleosides
ADI: AIDS-defining illness
cART: Combination antiretrovital therapy
BC: British Columbia
ON: Ontario
PQ: Quebec
HCV: Hepatitis C

Table 4.5. Sub-analysis: Late initiators vs. non-late initiators among all CANOC participants (N=7,738)

Characteristics	Category	Not late, N (%) N=3,859	Late, N (%) N=3,859	p-value
Gender	Female/ Transgender	713 (18.5)	759 (19.6)	0.224
	Male	3,146 (81.5)	3,120 (80.4)	
Province	British Columbia	1,638 (42.4)	1,950 (50.3)	<0.001
	Ontario	1,387 (35.9)	1,288 (33.2)	
	Quebec	834 (21.6)	641 (16.5)	
HCV-positive	No	2,781 (77.3)	2,498 (69.3)	<0.001
	Yes	818 (22.7)	1,108 (30.7)	
History of IDU	No	1,898 (73.1)	1,817 (63.1)	<0.001
	Yes	700 (26.9)	1,061 (36.9)	
MSM	No	1,115 (43.3)	1,551 (54.7)	<0.001
	Yes	1,460 (56.7)	1,287 (45.3)	
Aboriginal ancestry	No	1,278 (88.6)	1,578 (85.6)	0.012
	Yes	164 (11.4)	265 (14.4)	
Initial third drug class	NNRTI	2,009 (52.1)	1,594 (41.1)	<0.001
	Unboosted PI	398 (10.3)	448 (11.5)	
	Boosted PI	1,380 (35.8)	1,779 (45.9)	
	NUC x 3	72 (1.9)	58 (1.5)	
Baseline viral load	<10,000	856 (22.2)	328 (8.5)	<0.001
	10,000-99,999	1,854 (48)	1,423 (36.7)	
	100,000+	1,149 (29.8)	2,128 (54.9)	
Age>=30	No	614 (15.9)	412 (10.6)	<0.001
	Yes	3,245 (84.1)	3,467 (89.4)	
Variable		**Median (IQR)**		**p-value**
Age (years)		41 (34-47)		<0.001
Year therapy started		2005 (2003-2007)		<0.001
Baseline CD4 (copies/ml)		113 (50-170)		<0.001
Baseline viral load (log10)		5.0 (4.6-5.0)		<0.001
Total follow-up time (years)		4.5 (2.3-7.2)		<0.001

IDU: Injection drug use

MSM" Men who have sex with men

NNRTI: Non-nucleoside reverse transcriptase inhibitor

Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir

Unboosted PI: cART regimen consisting of a protease inhibitor
BC: British Columbia
ON: Ontario
PQ: Quebec
NUC x 3: cART regimen consisting of 3 nucleosides
HCV: Hepatitis C

Table 4.6. Sub-analysis: Factors associated with late initiation among all CANOC participants (n=7,738)

Variable	Adjusted Odds Ratio (95% CI)	p-value
Province		
Quebec	1.00	<0.001
British Columbia	1.50 (1.30, 1.74)	
Ontario	1.30 (1.13, 1.49)	
Year therapy started	0.87 (0.85, 0.88)	<0.001
History of IDU yes vs. no	1.34 (1.18, 1.53)	<0.001
Age (per decade)	1.14 (1.09, 1.20)	<0.001

IDU: Injection drug use

Chapter 5.

Virological Suppression among Adolescents and Young Adults Living with HIV in Canada

5.1. Abstract

Background: Compared with older adults, adolescents and young adults (AYA) living with HIV often have poorer treatment and clinical outcomes. AYA are an important treatment population, yet information about clinical outcomes is not available in a Canadian context. The aims of this study are to assess time to virological suppression in the first year of combination antiretroviral therapy (cART) among AYA and to explore factors associated with suppression.

Methods: Participants are HIV-positive individuals from a multi-site Canadian cohort of cART-naive patients initiating cART on or after January 1, 2000. Virological suppression was defined as time to the first of at least two consecutive viral load measurements <50 HIV-1 RNA copies/mL in a one-year period, at least 30 days apart. Life tables were used to estimate probabilities of virological suppression. Univariate and multivariable Accelerated Time Failure models were constructed to explore factors associated with time to virological suppression among AYA aged 18 to 29.

Results: Of the 1,168 AYA (median age=27), 1,007 (86%) had ever experienced virological suppression compared with 6,670 (91%) of the older adults ($p<0.001$), and 73% of AYA compared with 80% of older adults suppressed within the first year of cART initiation ($p<0.001$). In the adjusted model restricted to AYA, AYA who suppressed were more likely to be men (Adjusted Hazard Ratio [aHR] = 1.68; 95% CI: 1.44, 1.95) to have started cART in later calendar years (aHR = 2 .46; 95% CI: 2.08, 2.92). They were less likely to have a higher viral load, to have a history of IDU (aHR = 0.46; 95% CI: 0.38,

0.55), to have started cART on an unboosted protease inhibitor (PI) (aHR = 0.55; 95% CI: 0.43, 0.70), and to be living in Ontario (aHR = 0.86; 95% CI: 0.74, 1.0,).

Conclusion: Over one-quarter of AYA are not reaching virological suppression within the first year of treatment. Our research shows it is imperative that evidence-based services be implemented to improve management programs for adolescents and young adults.

5.2. Introduction

Virological suppression among people living with HIV is the cornerstone and primary goal of antiretroviral treatment. It is well documented that virological suppression allows an individual living with HIV to maintain good health through the concomitant reconstitution of immune function, reducing illness and decreasing mortality with the potential to turn HIV into a chronic, manageable disease (29,41,48,299–301). Suppression dramatically decreases the likelihood of a person living with HIV of transmitting the virus horizontally or vertically as evidenced by the HPTN 052 trial and the Treatment as Prevention (TasP) initiative (2,30,37,38,138,269). For adolescents and young adults (AYA) living with HIV who can now expect a near-normal life expectancy (49), virological suppression is the key to long-term health and well-being. Unfortunately, AYA are consistently underperforming compared with older adults in regards to clinical outcomes, leaving them at risk for viral rebound, treatment failure, and mortality (55,65,302,303).

Previous research has shown AYA to be more likely to delay initiating therapy, and once on cART they often have difficulty reaching virological suppression, even short-term suppression contrary to what was found in the previous chapter (128,215,304). When compared with older people also on cART, AYA 17 to 24 years of age were significantly less likely to reach virological suppression within six months (60,65).

This disparity in health outcomes may be due to social and structural factors (such as access to age-appropriate health care, stigma, lack of adequate housing, and

addiction issues) that intersect to compromise AYA's agency and access to care (6,28,55,71,72). AYA with a history of injection drug use report poor virological suppression most likely due to poor adherence (57). However, little research has been done to date in Canada to address questions about virological suppression among this population.

Achievement and maintenance of virological suppression is the final stage in the HIV Cascade of Care, originally espoused by Gardner et al. (109) (**Figure 5.1**). This spectrum of engagement in care represents an important framework for surveillance and evaluation for HIV treatment. It lays out the roadmap to achievement of virological suppression with each step representing numerous opportunities to engage with clients and to assist them in successfully moving to the next step. Virological suppression, and ongoing sustained suppression, is the goal of the Cascade and is key to the Treatment as Prevention initiative, as previously discussed (138).

Figure 5.1. The HIV Cascade of Care (based on Gardner et al., 2011)

There is a clear need to study the efficacy of cART in terms of virological suppression, as it is an important factor to consider when supporting AYA living with HIV who are on treatment or thinking of initiating treatment. As the Interagency Working Group in Key Populations noted in their 2014 report, there is a particular need for more data regarding young people living with HIV who inject drugs. They call for an increase in research regarding this key population in order to coordinate a response (305). Young people are underrepresented in Canadian HIV research, and identifying factors associated with time to suppression will help to inform guidelines for engaging youth in care. The objective of this study is to examine the time to virological suppression and correlates of virological suppression among a national cohort of AYA on cART in Canada.

5.3. Methods

Study Methodology

The Canadian Observational Cohort Collaboration (CANOC) is a multi-site study of HIV-positive persons who initiated cART on or after January 1, 2000. The collaboration is open to all Canadian HIV treatment cohorts and currently includes eight participating cohorts from three provinces (British Columbia, Ontario, and Quebec). Eligibility criteria for inclusion were: documented HIV infection; residence in Canada; 18 years of age and over; initiation of a first antiretroviral regimen comprised of at least three individual agents; and at least one measurement of HIV-1 RNA viral load and CD4 cell count within six months of initiating cART (127).

Electronic data extraction of a predefined set of demographic, laboratory, and clinical variables is performed at the data centres of the participating sites and submitted annually to the BC Centre for Excellence in HIV/AIDS in Vancouver for pooling, data cleaning, and analysis. All data are stripped of names and other personal identifiers prior to being sent to the Data Coordinating Site, and a unique CANOC study number is assigned to each participant. Overlap between cohorts is identified within provinces before data are sent to the Data Coordinating Site. A data dictionary has been developed by the CANOC data analysts and is shared among the investigators after each new data cut. All data are managed in a central relational database (at the British Columbia Centre for Excellence in HIV/AIDS), and an audit trail has been created for all data changes. Access to CANOC electronic data at the Data Coordinating Site is password protected and limited to essential study personnel.

All participating cohorts received research ethics board approval to contribute anonymous patient data to CANOC, adhering to established standards in data sharing/linkage and data security/residual disclosure. In the case of the Ontario HIV Treatment Network (OHTN) Cohort Study (OCS), additional approval was received from the OCS Governance Committee to release Ontario data to participate in CANOC. Data submitted to the Data Coordinating Site in Vancouver are used only to address specific research questions approved by the CANOC Scientific Steering Committee, and ownership of individual cohort data remains with the contributing cohort. Data elements

used in any scientific publications are aggregated and de-identified. The last date of follow-up in the cohort for the current analysis was December 31, 2012. This analysis was conducted in accordance with the international STROBE guidelines (126)—a set of recommendations to promote complete reporting of cohort data in a systematic manner. Further details of the participating cohorts and the CANOC structure have been previously outlined in Chapter 3 and a previously published CANOC cohort profile (127).

Study population and design

CANOC eligibility criteria include: documented HIV infection; residence in Canada; 18 years of age and over; initiation of three or more antiretroviral drugs for the first time (i.e., antiretroviral-naive prior to initiating cART) on or after January 1, 2000; and a documented HIV-1 RNA measurement and CD4 T-cell count within six months of the start of therapy. To be included in this analysis, individuals had to have at least two viral load measurements after starting cART. Moreover, only individuals whose baseline viral loads were ≥50 copies/mL were included. Loss to follow-up among patients included in this analysis was defined as no contact for at least one year.

Outcomes

Virological suppression is defined as the time to the first of at least two consecutive HIV-1 plasma RNA measurements <50 HIV-1 RNA copies/mL, at least 30 days apart.

Covariates of interest for this analysis included: age, sex; province; ethnicity; Aboriginal ancestry; risk category (men who have sex with men (MSM), injecting drug use (IDU)), and clinical variables such as hepatitis C antibody seropositivity; baseline AIDS-defining illness (ADI); era of cART initiation baseline; composition of initial cART regimen (nucleoside reverse transcriptase inhibitor (NRTI) backbone and third drug in the regimen); baseline CD4 cell count and HIV plasma viral load (log10); time to virological suppression (months); and follow-up time (years).

Statistical analysis

Socio-demographic and patient characteristics were compared by age (≤29 vs. 30+ years old) and suppression status (yes vs. no) in bivariate tables using Chi-square tests for categorical variables and Wilcoxon's Rank Sum test for continuous variables. Viral load measurements were buffered to a minimum of 50 copies/mL and a maximum of 100,000 copies/mL to accommodate temporal changes in viral load assay sensitivities over the study period.

Kaplan-Meier methods and stratified life tables were used to compare time to virological suppression by age group (≤29 vs. 30+ years old). Because we wanted to explore variables associated with the outcome (VL suppression) an explanatory model selection process was used. Final multivariable models were selected using an exploratory model selection process based on Akaike Information Criterion (AIC) and Type III p-values. Based on the model diagnosis and the goodness-of-fit tests, we decided to use the Accelerated Failure Time (AFT) models (306) as it was the best fit. The goodness-of-fit was assessed by log-survivor plot. An AFT models with exponential distribution were used in univariate and multivariable analyses to explore the association between predictors and time to virological suppression. A two-sided P-value below 0.05 was considered statistically significant. A sub-analysis was then performed on the AYA population, using AFT models to identify significant covariates associated with time to virological suppression. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina, USA).

5.4. Results

A total of 8,471 individuals were included in this analysis. Of these, 1,168 (13.8%) were ≤29 years old at the time of cART initiation. The average age among AYA was 27 years (interquartile range [IQR]: 24-28 years) compared with 42 years (IQR: 36-48 years) among the older group.

Demographic and clinical characteristics of AYA and older adults were compared (**Table 5.1**). A higher proportion of AYA: were female (32% vs. 16%, p<0.001); were from Ontario (39% vs. 33%, p<0.001); started cART in later calendar years (2008-2011) (47% vs. 40%, p<0.001); started cART with an unboosted protease inhibitor (PI) (10%

vs. 5%, p<0.001); had a drug regimen with Nelfinavir in it (7% vs. 3%, p<0.001); and initiated cART with a higher baseline CD4 count (cells/mm3) (median= 256, IQR: 160-360 vs. 210, IQR: 116-310, p<0.001). A lower proportion of AYA: reported Caucasian ethnicity (25% vs. 29%, p<0.001); had a history of IDU (20% vs. 23%, p=0.012); had a hepatitis C co-infection (21% vs. 26%, p<0.001); and had an AIDS-defining illness (ADI) before or on their cART initiation date (9% vs. 16%, p<0.001). Importantly, a lower proportion of AYA had ever experienced virological suppression (86% vs. 91%, p<0.001); however, AYA were followed for a slightly shorter period of time than the older adults: median of four years (IQR: 2-8) compared with five years (IQR: 3-8) years (p<0.001).

Table 5.2 describes the predictors of virological suppression in the entire dataset (including AYA and older adults). As noted in this table, virological suppression is associated with: being over the age of 29 years (91% vs. 86%, p<0.001); being male (92% vs. 85%, p<0.001); living in Ontario or Quebec as opposed to British Columbia (93% vs. 92% vs 88%, p<0.001); being non-Aboriginal (93% vs. 79%, p<0.001); identifying as gay, bisexual, other men who have sex with men (MSM) (95% vs. 86%, p<0.001); not being co-infected with hepatitis C (94% vs. 83%, p<0.001); never reporting an AIDS-defining illness (ADI) (91% vs. 89%, p<0.001); and initiating cART between 2004 and 2007 (92% vs. 89% vs. 90%, p<0.001). Composition of baseline antiretroviral therapy regimens, including the class of the third drug and the specific third ARV agent, also differed significantly by suppression status (p<0.001). A higher baseline CD4 count (cells/mm3) was associated with virological suppression (median = 220, IQR: 125-319 vs. 181, IQR: 80-300, p<0.001).

Kaplan–Meier curves exploring differences in time to suppression overall and for subset populations indicated that age differences in suppression still existed when gender, a history of injection drug use, era of cART initiation, and province were examined exclusively (**Figures 5.3-5.6**).

Table 5.3 presents the findings from the multivariable analysis. Individuals in CANOC who suppressed their virus were less likely to: be younger in age (≤29 years) (aHR = 0.74; 95% CI: 0.69, 0.79, p<0.001); have a history of IDU (aHR = 0.52; 95% CI:

0.49, 0.55, p<0.001); be persons of Aboriginal ancestry (aHR = 0.73; 95% CI: 0.65, 0.83, p<0.001); be patients initiating cART on an unboosted PI (aHR = 0.75; 95% CI: 0.58, 0.98, p=0.024); be patients having Nelfinavir as the third drug in their regimen (aHR = 0.73; 95% CI: 0.54, 0.98, p<0.001); and have a higher baseline viral load (aHR = 0.77 per log10; 95% CI: 0.77, 0.8, p<0.001). They were more likely to have first started cART in the period from 2004 to 2007 or 2008 to 2011 than 2000 to 2003.

In the adjusted multivariable model among AYA only (**Table 5.4**), adolescents and young adults in CANOC who suppressed their virus were more likely to be men (aHR = 1.68; 95% CI: 1.4, 1.95, p<0.001) and to have started cART in later calendar years (aHR = 2.46; 95% CI: 2.08, 2.92, p<0.001). They were less likely to: have a higher baseline viral load (aHR = 0.72 per log10; 95% CI: 0.65, 0.8); have history of IDU (aHR = 0.46; 95% CI: 0.38, 0.55, p<0.001); have started cART on an unboosted PI (aHR = 0.55; 95% CI: 0.43, 0.70, p<0.001); and reside in Ontario (aHR = 0.86; 95% CI: 0.74, 1.0, p=0.043).

Table 5.5 illustrates the probability of achieving virological suppression 6, 12, 18, and 24 months after cART initiation, stratified by the two age groups. At six months there is no difference in suppression between AYA and older adults but as time goes on, older adults are more likely to suppress. After one year of first starting cART, 73% of AYA had experienced virological suppression compared to 80% of older adults (p<0.001); by two years, 81% of AYA had suppressed their virus compared with 89% of the older age group (p<0.001).

5.5. Discussion

In this large Canadian cohort of individuals who initiated cART since 2000, we found that AYA were less likely than older adults to have ever achieved virological suppression. Consistent with previous research studies showing AYA to be less likely to achieve virological suppression than older adults, (60,63,65) over one-quarter of AYA in CANOC did not achieve virological suppression within the first year of starting treatment. When focusing exclusively on AYA, women, those with a history of IDU, and those who started treatment in earlier calendar years were less likely to suppress. Finally, we found the

cART regimen that a person initiated treatment on had an effect on suppression with those starting treatment on an unboosted PI less likely to suppress than those who started treatment with a boosted PI or an NNRTI. In light of UNAIDS' 90-90-90 plan to have 90% of all people receiving cART being virologically suppressed, the data highlight the need for further population-based interventions to increase the proportion of AYA becoming suppressed on their initial treatment regimens.

In this analysis, women were less likely than men to achieve virological suppression. This is in contrast with some previous studies showing women to have similar or improved responses to treatment (307–309) and in accordance with other previous studies reporting women to have suboptimal treatment responses to cART when compared with men (61,113,310). Disparities in virological responses between men and women are likely largely influenced by context and have been found to be related to socio-economic and psychosocial factors such as poverty, housing, injection drug use, depression, other mental health concerns, and childcare responsibilities rather than biological factors, which may be the case with our cohort of young people (311–313). There is also the possibility that cART use in pregnancy to reduce the risk of vertical HIV transmission had an impact on the gender differences observed in this analysis. Indeed, a previous CANOC study found that gender differences in virological suppression were truncated among women without IDU history when 'presumed pregnancy' was adjusted for (113). Unfortunately, CANOC is not set up to capture detailed pregnancy, adherence data related to socio-economic factors that may have an influence on clinical outcomes. However, this analysis suggests that women are at risk for suboptimal treatment outcomes, identifying them as a priority group to work with.

The link between injection drug use and poor suppression is well established (57,239,314). AYA with a history of IDU may be managing competing priorities such as housing, food security, and active addictions. This likely impedes optimal access to care and adherence to cART, resulting in a need for increased supportive services to help them prioritize their health. Once barriers to medication are removed, people with a history of injection drug use have been shown to respond well to cART (120,239,315); therefore, it is imperative that we implement evidence-based and lower threshold services to improve management programs for the wider community, such as harm

reduction strategies, observed therapy programs, and other addiction services (such as methadone maintenance treatment) (316–318). Enrolment in Directly Observed Therapy (DOT) programs and Maximally Assisted Therapy (MAT) programs have been shown to have a positive effect on the adherence and clinical outcomes of people living with HIV (318,319). Adolescent and young adult-tailored MAT-DOT programs would likely be the most effective in meeting the needs of this population.

The era in which a person initiated cART has an effect on clinic outcomes, as shown by our data illustrating that virological suppression is more likely among individuals who initiated cART in the calendar years from 2008 to 2011. Since 2000, regimens have been improving and new drugs have been introduced that reduce dosing frequency, pill burden, and the level of toxicity, and also with improving degrees of efficacy, tolerability, and convenience (320,321).

The initial cART regimen prescribed has a significant impact on time to virological suppression (208,322). As shown here, individuals starting on ritonavir-boosted PI regimens or NNRTI regimens were more likely to achieve suppression than patients on unboosted PI regimens. The majority of AYA in this analysis were prescribed an NNRTI-based or ritonavir-boosted cART regimen. NNRTIs have vastly improved over the past 20 years, making them a first-line drug for many physicians (320). Ritonavir-boosted PIs have fewer pills, fewer side effects, and the dosing is more convenient than NNRTIs, older PIs, and single PIs—making the medication more appealing to young people and increasing their ability to achieve virological suppression (323,324).

Other important findings raised by our analyses indicate that AYA residing in the province of Ontario appear to be less likely to virologically suppress than in the other study provinces. Readers should interpret provincial differences cautiously, as in British Columbia data comes from a population-level cohort whereas the data from Quebec and Ontario are gathered from a selection of clinics or cohort studies. However, as demographic attributes of AYA in each province vary (See Table 3.4), significant differences exist between populations making exact comparison difficult.

Our analysis also demonstrates those who had a higher viral load at baseline were less likely to virologically suppress, a finding corroborating those of other studies

which concluded that time to suppression is a mathematical function corresponding to baseline viral load (325,326). Late initiators have a more difficult time controlling their viral load, reinforcing the importance of HIV testing and timely cART initiation (169,198,293,327). This supports the TasP goal to initiate all HIV-positive people on cART regardless of viral load in order to preserve health and decrease community viral load (105,138,328).

Initiating AYA on drug regimens with lower pill burden and greater tolerability can improve the likelihood that they will take the medications as prescribed (44) and that UNAIDS will reach its targets in this population group. The relationship between virological suppression and adherence is well established (31,32,35). Historically, rates of adherence among youth living with HIV are significantly poorer than adults, with some studies reporting that 50 to 60% of adolescents are suboptimally adherent (defined as taking less than 95% of their prescribed dose) (56,57,60,61,63,71,72). They may be navigating difficult issues such as self-identity and peer-relationships as well as employment, housing, and a myriad of other important topics, so health issues such as adhering to medication may not be a priority, especially when the medication comes with potentially difficult side effects (329–331).

Limitations

Readers should note that the findings from this study cannot be generalized to the entire Canadian HIV-positive population. However, the majority of HIV-positive individuals in Canada receive care in the three provinces where CANOC has cohort sites. In fact, CANOC contains over one-third of all patients on therapy and a much larger proportion of those who initiated treatment since 2000. Antiretroviral adherence, an important predictor of virological suppression, was not included in this analysis as some sites did not have these data (31). Missing data for MSM, Ethnicity and IDU was censored in order to be able to be more confident about results. Despite these limitations, important information regarding factors associated with virological suppression were identified.

5.6. Conclusions and Steps Forward

In light of the ambitious goals stated in UNAIDS' 90-90-90 plan (By 2020, 90% of all people will know their HIV status; 90% of all HIV-positive people will receive sustained antiretroviral therapy; 90% of all people receiving cART will be virologically suppressed), it is imperative that AYA are supported to reach virological suppression (7). This means supporting AYA in every stage of the Cascade of Care, from HIV testing to suppression. As illustrated in the adapted *Seek, Test, Treat, and Retain* framework (**Figure 5.3)**, factors such as gender, drug use behaviours, and other socio-demographic factors must be addressed while also treating the individual's HIV disease. Treatment must come to mean more than just prescribing cART and must encompass many aspects of health and life such as gender (285), addictions support (318), and multi-faceted service delivery (194) as well as discussions about different cART regimens and dosing (232). Treatment can come to mean many things; it may be linkage to a health care provider, referral to a specialized pharmacy, enrolling in a drug rehabilitation program for those who need it, as well as re-engagement in care for those who have dropped out.

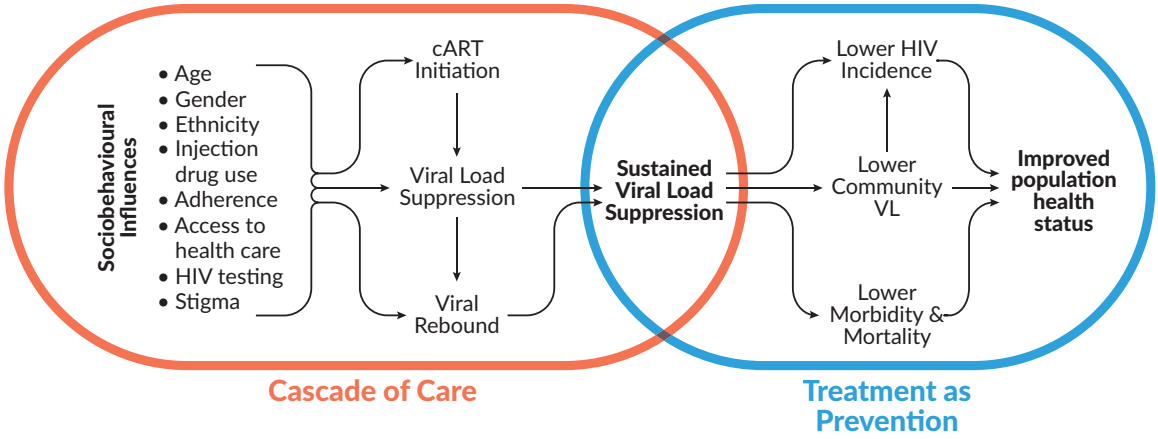

Figure 5.2. Adapted *Seek, Test, Treat, and Retain* framework

Table 5.1. CANOC participants by age at cART initiation (N=8,471)

Variable	Age at cART initiation				p-value
	≤29 years(N=1,168)		>29 years (N=7,303)		
	N	(%)	N	(%)	
Gender					
Male	795	(68)	6,117	(84)	<0.001
Female	373	(32)	1,186	(16)	
Province					
British Columbia	470	(40)	3,441	(47)	<0.001
Ontario	451	(39)	2,410	(33)	
Quebec	247	(21)	1,452	(20)	
Ethnicity					
Caucasian	295	(25)	2,090	(29)	<0.001
Black	138	(12)	605	(8)	
Aboriginal	66	(6)	340	(5)	
Other	105	(9)	545	(7)	
Unknown/Missing	564	(48)	3,723	(51)	
Aboriginal					
No	538	(46)	3,240	(44)	0.124
Yes	66	(6)	340	(5)	
Unknown	564	(48)	3,723	(51)	
HIV risk MSM					
No	365	(31)	2,355	(32)	0.502
Yes	424	(36)	2,702	(37)	
Unknown	379	(32)	2,246	(31)	
HIV risk IDU					
No	719	(62)	4,157	(57)	0.012
Yes	234	(20)	1,650	(23)	
Unknown	215	(18)	1,496	(20)	
Hepatitis C					
Not co-infected	867	(74)	5,014	(69)	0.001
Co-infected	241	(21)	1,866	(26)	
Unknown	60	(5)	423	(6)	
Baseline ADI					
None	1010	(86)	5,811	(80)	<0.001
At least one	101	(9)	1,164	(16)	
None ever	57	(5)	328	(4)	

Variable	Age at cART initiation				p-value
	≤29 years(N=1,168)		>29 years (N=7,303)		
	N	(%)	N	(%)	
Era of cART initiation					
2000-2003	284	(24)	1,907	(26)	<0.001
2004-2007	340	(29)	2,452	(34)	
2008-2011	544	(47)	2,944	(40)	
Virological suppression					
No	161	(14)	633	(9)	<0.001
Yes	1007	(86)	6,670	(91)	
Classes of ARVs in first regimen					
NNRTI	540	(46)	3,460	(47)	<0.001
Unboosted PI	121	(10)	384	(5)	
Boosted PI	430	(37)	2,979	(41)	
Other	77	(7)	480	(7)	
Initial third drug					
Nevirapine	127	(11)	719	(10)	<0.001
Efavirenz	411	(35)	2,657	(36)	
Lopinavir	181	(15)	1,261	(17)	
Atazanavir	250	(21)	1,619	(22)	
Nelfinavir	87	(7)	253	(3)	
Other	112	(10)	794	(11)	
	Median (IQR)		Median (IQR)		p-value
Age at first cART initiation (years)	27 (24-28)		42 (36-48)		<0.001
Baseline CD4 (cells/mm3)	256 (160-360)		210 (116-310)		<0.001
Baseline viral load (log10 copies/mL)	5 (4-5)		5 (4-5)		<0.001
Time to virological suppression (months)	5 (3-12)		5 (3-9)		0.747
Follow-up time (years)	4(2-8)		5 (3-8)		<0.001

IDU: Injection drug use

MSM: Men who have sex with men

ARV: Antiretroviral

FARVDT:

NNRTI: Non-nucleoside reverse transcriptase inhibitor

Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir

Unboosted PI: cART regimen consisting of a protease inhibitor

ADI: AIDS-defining illness

cART: Combination antiretroviral therapy

Table 5.2. Virological suppression in the entire CANOC cohort (N=8,471)

Variable	Virological suppression				p-value
	No (N=794)		Yes (N=7,677)		
	N	(%)	N	(%)	
Age at first cART initiation (years)					
<=29	161	(14)	1,007	(86)	<0.001
>29	633	(9)	6,670	(91)	
Gender					
Male	560	(8)	6,352	(92)	<0.001
Female	234	(15)	1,325	(85)	
Province					
British Columbia	462	(12)	3,449	(88)	<0.001
Ontario	198	(7)	2,663	(93)	
Quebec	134	(8)	1,565	(92)	
Ethnicity					
Caucasian	169	(7)	2,216	(93)	<0.001
Black	68	(9)	675	(91)	
Aboriginal	84	(21)	322	(79)	
Other	43	(7)	607	(93)	
Unknown/Missing	430	(10)	3,857	(90)	
Aboriginal					
No	280	(7)	3,498	(93)	<0.001
Yes	84	(21)	322	(79)	
Unknown	430	(10)	3,857	(90)	
HIV risk MSM					
No	390	(14)	2,330	(86)	<0.001
Yes	164	(5)	2,962	(95)	
Unknown	240	(9)	2,385	(91)	
HIV risk IDU					
No	313	(6)	4,563	(94)	<0.001
Yes	319	(17)	1,565	(83)	
Unknown	162	(9)	1,549	(91)	
Hepatitis C					
Not co-infected	368	(6)	5,513	(94)	<0.001
Co-infected	348	(17)	1,759	(83)	
Unknown	78	(16)	405	(84)	

Variable	Virological suppression				p-value
	No (N=794)		Yes (N=7,677)		
	N	(%)	N	(%)	
Baseline ADI					
None	614	(9)	6,207	(91)	0.054
At least one	140	(11)	1,125	(89)	
None ever	40	(10)	345	(90)	
Era of cART initiation					
2000-2003	244	(11)	1,947	(89)	<0.001
2004-2007	217	(8)	2,575	(92)	
2008-2011	333	(10)	3,155	(90)	
Classes of ARVs in first regimen					
NNRTI	302	(8)	3,698	(92)	<0.001
Unboosted PI	68	(13)	437	(87)	
Boosted PI	354	(10)	3,055	(90)	
Other	70	(13)	487	(87)	
Initial third drug					
Nevirapine	89	(11)	757	(89)	<0.001
Efavirenz	205	(7)	2,863	(93)	
Lopinavir	163	(11)	1,279	(89)	
Atazanavir	183	(10)	1,686	(90)	
Nelfinavir	52	(15)	288	(85)	
Other	102	(11)	804	(89)	
	Median (IQR)		Median (IQR)		p-value
Age at first cART initiation (years)	38 (31-45)		40 (33-46)		<0.001
Baseline CD4 (cells/mm3)	181 (80-300)		220 (125-319)		<0.001
Baseline viral load (log10 copies/mL)	5 (4-5)		5 (4-5)		<0.001
Time to virological suppression (months)	17 (7-38)		5 (3-8)		<0.001
Follow-up time (years)	2 (1-4)		5(3-8)		<0.001

IDU: Injection drug use
MSM: Men who have sex with men
NNRTI: Non-nucleoside reverse transcriptase inhibitor
Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir
Unboosted PI: cART regimen consisting of a protease inhibitor
ADI: AIDS-defining illness
cART: Combination antiretroviral therapy

Table 5.3. Factors associated with time to virological suppression among all CANOC participants (N=8,471)

	Unadjusted		Adjusted	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age at first cART initiation (years)				
>29	1.00 (-)	<0.001	1.00 (-)	<0.001
≤29	0.68 (0.64, 0.73)		0.74 (0.69, 0.79)	
Gender				
Female	1.00 (-)	<0.001	1.00 (-)	<0.001
Male	1.65 (1.56, 1.75)		1.28 (1.2, 1.36)	
HIV risk IDU				
No	1.00 (-)	<0.001	1.00 (-)	<0.001
Yes	0.46 (0.43, 0.49)		0.52 (0.49, 0.55)	
Unknown	1.02 (0.96, 1.08)		1 (0.93, 1.06)	
Aboriginal				
No	1.00 (-)	<0.001	1.00 (-)	<0.001
Yes	0.48 (0.43, 0.54)		0.73 (0.65, 0.83)	
Unknown/Missing	1.08 (1.03, 1.13)		0.96 (0.92, 1.01)	
Baseline ADI				
None	1.00 (-)	0.569	1.00 (-)	<0.001
At least one	1.06 (0.95, 1.18)		1.29 (1.14, 1.45)	
None ever	1.05 (0.93, 1.19)		1.35 (1.18, 1.54)	
Baseline CD4 (cells/mm3)				
<200	1.00 (-)	<0.001	1.00 (-)	0.150
>=200	1.23 (1.18, 1.29)		1.04 (0.99, 1.09)	
Classes of ARVs in first regimen				
NNRTI	1.00 (-)	<0.001	1.00 (-)	0.024
Unboosted PI	0.43 (0.39, 0.48)		0.75 (0.58, 0.98)	
Boosted PI	0.9 (0.86, 0.94)		0.93 (0.75, 1.15)	
Other	0.83 (0.75, 0.91)		1.01 (0.81, 1.25)	
Era of cART initiation				
2000-2003	1.00 (-)	<0.001	1.00 (-)	<0.001
2004-2007	1.56 (1.47, 1.66)		1.39 (1.3, 1.48)	
2008-2011	2.19 (2.07, 2.32)		1.66 (1.55, 1.78)	

	Unadjusted		Adjusted	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Province			Not selected	
British Columbia	1.00 (-)	<0.001		
Ontario	1.32 (1.25, 1.38)			
Quebec	1.27 (1.19, 1.35)			
Initial third drug				
Nevirapine	1.00 (-)	<0.001	1.00 (-)	<0.001
Efavirenz	1.99 (1.84, 2.16)		1.3 (1.19, 1.42)	
Lopinavir	1.36 (1.24, 1.49)		1.08 (0.86, 1.36)	
Atazanavir	1.65 (1.51, 1.79)		1.18 (0.93, 1.48)	
Nelfinavir	0.59 (0.52, 0.68)		0.73 (0.54, 0.98)	
Other	1.24 (1.12, 1.37)		1.01 (0.81, 1.25)	
Baseline viral load (log10 copies/mL)	0.84 (0.81, 0.87)	<0.001	0.77 (0.74, 0.8)	<0.001

IDU: Injection drug use
MSM: Men who have sex with men
NNRTI: Non-nucleoside reverse transcriptase inhibitor
Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir
Unboosted PI: cART regimen consisting of a protease inhibitor
ADI: AIDS-defining illness
cART: Combination antiretroviral therapy
ARV: Antiretroviral

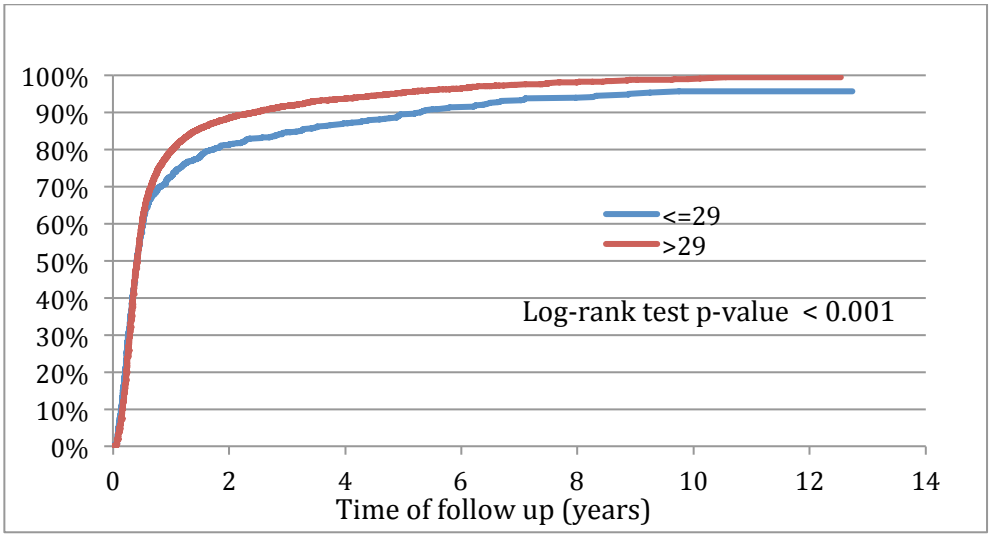

Figure 5.3 Probability of achieving virological suppression by age

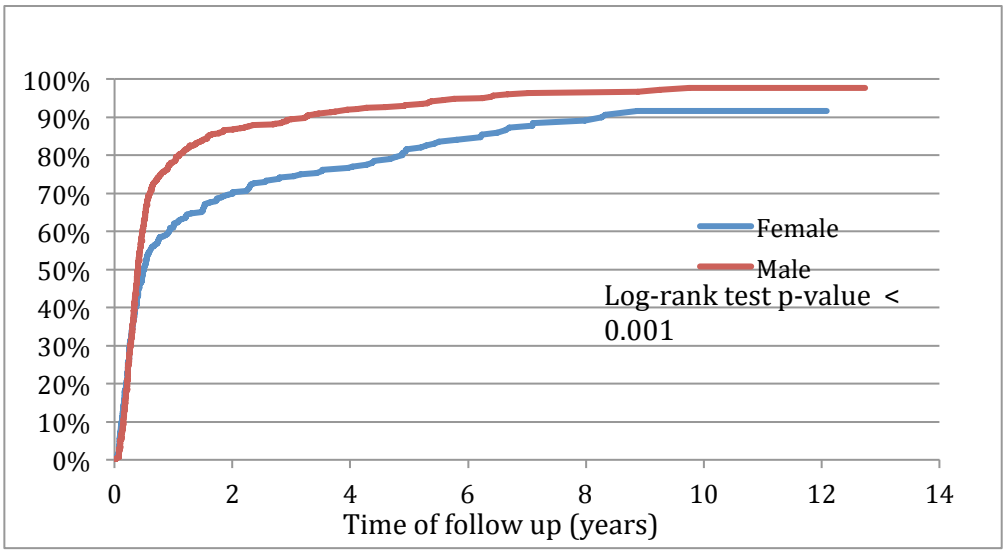

Figure 5.4. Probability of achieving virological suppression by gender

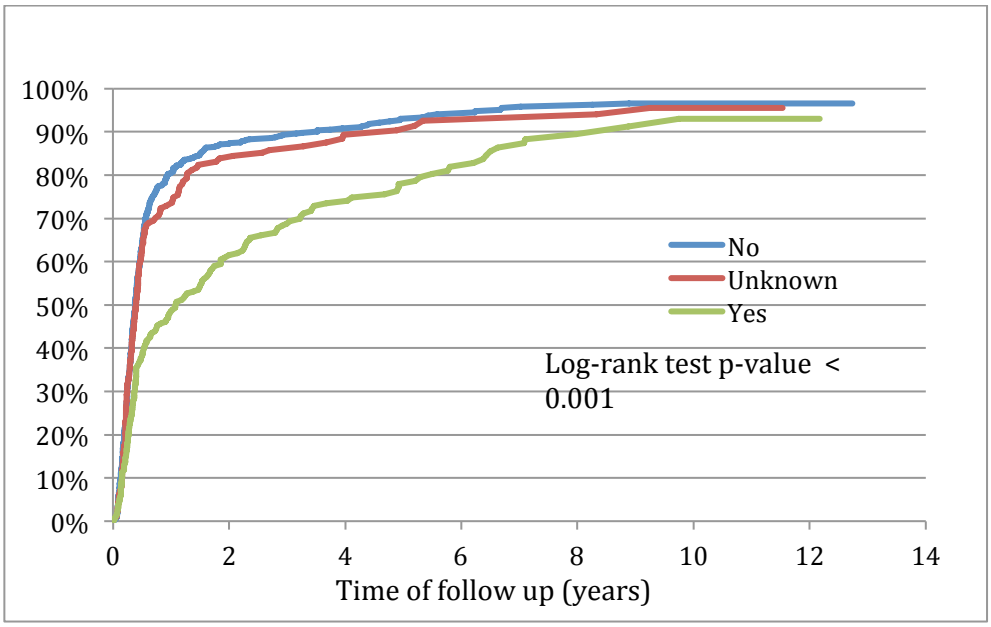

Figure 5.5. Probability of achieving virological suppression by IDU status

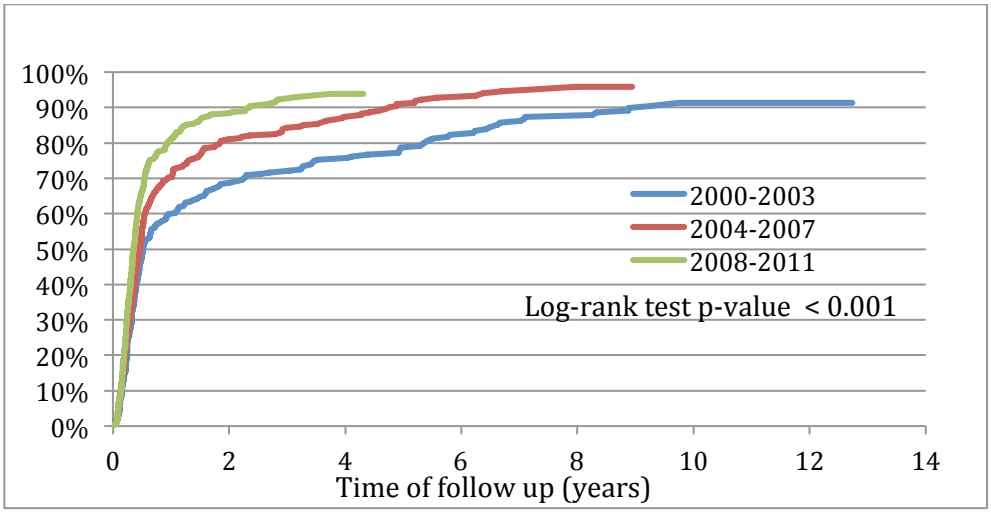

Figure 5.6. Probability of achieving virological suppression by era of cART initiation

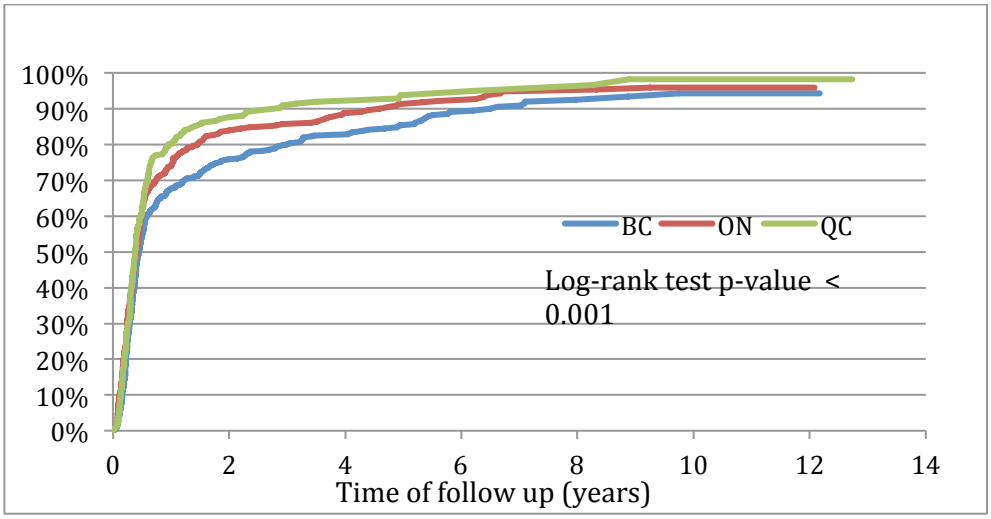

Figure 5.7. Probability of achieving virological suppression by province

Table 5.4. Factors associated with virological suppression among CANOC participants ≤29 years (N=1,168)

	Unadjusted		Adjusted	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Gender				
Female	1.00 (-)	<0.001	1.00 (-)	<0.001
Male	2.03 (1.77, 2.33)		1.68 (1.44, 1.95)	
HIV risk IDU				
No	1.00 (-)	<0.001	1.00 (-)	<0.001
Yes	0.38 (0.32, 0.45)		0.46 (0.38, 0.55)	
Unknown	0.84 (0.71, 0.99)		0.89 (0.75, 1.06)	
Aboriginal			Not selected	
No	1.00 (-)	<0.001		
Yes	0.47 (0.35, 0.62)			
Unknown/Missing	1.13 (1, 1.29)			
Baseline ADI			Not selected	
None	1.00 (-)	0.087		
At least one	1.01 (0.76, 1.35)			
None ever	0.78 (0.55, 1.11)			
Baseline CD4 (cells/mm3)			Not selected	
<200	1.00 (-)	<0.001		
>=200	1.2 (1.05, 1.37)			
Classes of ARVs in first regimen				
NNRTI	1.00 (-)	<0.001	1.00 (-)	<0.001
Unboosted PI	0.49 (0.4, 0.61)		0.55 (0.43, 0.7)	
Boosted PI	1.1 (0.96, 1.26)		0.89 (0.77, 1.03)	
Other	1.03 (0.79, 1.33)		1.08 (0.83, 1.41)	
Era of cART initiation				
2000-2003	1.00 (-)	<0.001	1.00 (-)	<0.001
2004-2007	1.82 (1.53, 2.16)		1.69 (1.42, 2.02)	
2008-2011	3.43 (2.93, 4.02)		2.46 (2.08, 2.92)	
Province				
British Columbia	1.00 (-)	<0.001	1.00 (-)	0.043
Ontario	1.38 (1.2, 1.58)		0.86 (0.74, 1)	
Quebec	1.71 (1.45, 2.01)		1.03 (0.86, 1.24)	
Baseline viral load (log10 copies/mL)	0.82 (0.74, 0.9)	<0.001	0.72 (0.65, 0.8)	<0.001

IDU: Injection drug use

MSM: Men who have sex with men

NNRTI: Non-nucleoside reverse transcriptase inhibitor
Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir
Unboosted PI: cART regimen consisting of a protease inhibitor
ADI: AIDS-defining illness
cART: Combination antiretroviral therapy
ARV: Antiretroviral

Table 5.5. The probability of virological suppression by months and age group

	Age		
Time (months)	**<=29**	**>29**	**p-value**
6	0.58 (0.61, 0.56)	0.6 (0.61, 0.59)	0.517
12	0.73 (0.75, 0.7)	0.8 (0.81, 0.79)	<0.001
18	0.78 (0.81, 0.76)	0.86 (0.86, 0.85)	<0.001
24	0.81 (0.83, 0.79)	0.89 (0.89, 0.88)	<0.001

Chapter 6.

Viral Load Rebound among Adolescents and Young Adults Living with HIV in Canada

6.1. Abstract

Background: Among HIV-positive men and women who achieve virological suppression, adolescents and young adults (AYA) are more likely to experience viral rebound than older adults. Viral rebound is associated with treatment failure, resistance to antiretroviral medications, and increased potential for HIV transmission making it an important phenomenon to understand. The objective of this study was to compare viral load rebound between AYA and older adults and to measure the prevalence and correlates of viral load rebound among AYA.

Methods: Data from the CANOC study were used to compare viral load rebound between AYA and older individuals. Multivariable models were constructed to explore factors associated with rebound. Viral load rebound was defined as the first of at least two consecutive viral load measurements above <50 HIV-1 RNA copies/mL, at least 30 days apart, after reaching virological suppression.

Results: AYA were more likely to experience viral load rebound than older adults (26% vs. 22%, p=0.009). In the adjusted multivariable model for AYA only, males were less likely than females to experience rebound (aHR = 0.5; 95% CI: 0.39, 0.65) as were individuals with a history of injection drug use (IDU) (aHR = 2.78; 95% CI: 2.13, 3.64). Those who initiated treatment in later calendar years were less likely to rebound than those who initiated earlier in the observation period (aHR = 0.68; 95% CI: 0.48, 0.95).

Discussion: AYA were significantly more likely to rebound as compared to older adults; however, rates of rebound for both groups were high. Supporting optimal adherence and

assisting AYA to remain in care will lead to lower rates of viral rebound, lowered transmission risk, and fewer comorbidities over their life course.

6.2. Introduction

Despite improvements in HIV treatment and care, adolescents and young adults (AYA) living with HIV in Canada face ongoing challenges with incomplete adherence to combination antiretroviral therapy (cART) and poor clinical outcomes including an inability to maintain a suppressed viral load (56,60). Suboptimal adherence can lead to viral rebound (69,332,333), which happens very quickly when a person stops treatment—the HIV-1 RNA viral load count increases and subsequently the CD4 cell counts decrease, making the person vulnerable to illness (333). Viral rebound is associated with treatment failure, resistance to antiretroviral medications, and increased potential for HIV transmission (2,31,32,136,300,334–337). If and when there is resumption of treatment, individuals can usually again achieve virological suppression; however, CD4 T-cell recovery is reduced in persons with treatment interruptions of more than six months (329,338).

When compared with older adults, AYA are less likely to achieve and maintain virological suppression (65,215,304). Among those who do reach suppression, they are more likely than older adults to have suboptimal adherence, higher loss to follow-up rates, and poorer retention in care, often leading to viral rebound (56,60,65,69,216). Viral rebound has been associated with younger age, pill burden, injection drug use, homelessness, and disruption in regular health care provision, but most importantly, with poor adherence (69,70,332,337,339–342). Failure to adhere to medications is strongly associated with progression to AIDS and mortality (205,343).

In the current clinical landscape of HIV Treatment as Prevention (TasP), there is a focus on offering antiretroviral treatment to all persons living with HIV immediately following diagnosis (regardless of CD4 T-cell count) and assisting them to achieve and sustain virological suppression (105,137,138). The understanding behind TasP is that those with suppressed viral loads will be healthier and, secondarily, are less likely to transmit HIV to partners, in turn lowering community viral load (138).

AYA comprise nearly one-quarter of all Canadian HIV-positive tests, and clinical outcomes tend to be worse among AYA than adults, making them a population of particular concern (11). Linking AYA to care is an important way to promote health and harm reduction particularly within this demographic. Supporting young people living with HIV to achieve optimal health is a priority; however, currently no information is available regarding rates of viral load rebound among this population. Further, in this setting viral load rebound has not yet been compared between younger and older adults. Using data from Canada's largest HIV treatment cohort study, we seek to measure the prevalence and correlates of viral load rebound among people living with HIV in Canada, in particular adolescents and young adults.

6.3. Methods

Study Methodology

The Canadian Observational Cohort Collaboration (CANOC) is a multi-site study of HIV-positive persons who initiated cART on or after January 1, 2000. The collaboration is open to all Canadian HIV treatment cohorts and currently includes eight participating cohorts from three provinces (British Columbia, Ontario, and Quebec). Eligibility criteria for inclusion were: documented HIV infection; residence in Canada; 18 years of age and over; initiation of a first antiretroviral regimen comprised of at least three individual agents; and at least one measurement of HIV-1 RNA viral load and CD4 cell count within six months of initiating cART (127).

Electronic data extraction of a predefined set of demographic, laboratory, and clinical variables is performed at the data centres of the participating sites and submitted annually to the BC Centre for Excellence in HIV/AIDS in Vancouver for pooling, data cleaning, and analysis. All data are stripped of names and other personal identifiers prior to being sent to the Data Coordinating Site, and a unique CANOC study number is assigned to each participant. Overlap between cohorts is identified within provinces before data are sent to the Data Coordinating Site. A data dictionary has been developed by the CANOC data analysts and is shared among the investigators after each new data cut. All data are managed in a central relational database (at the British

Columbia Centre for Excellence in HIV/AIDS), and an audit trail has been created for all data changes. Access to CANOC electronic data at the Data Coordinating Site is password protected and limited to essential study personnel.

All participating cohorts received research ethics board approval to contribute anonymous patient data to CANOC, adhering to established standards in data sharing/linkage and data security/residual disclosure. In the case of the Ontario HIV Treatment Network (OHTN) Cohort Study (OCS), additional approval was received from the OCS Governance Committee to release Ontario data to participate in CANOC. Data submitted to the Data Coordinating Site in Vancouver are used only to address specific research questions approved by the CANOC Scientific Steering Committee, and ownership of individual cohort data remains with the contributing cohort. Data elements used in any scientific publications are aggregated and de-identified. The last date of follow-up in the cohort for the current analysis was December 31, 2012. This analysis was conducted in accordance with the international STROBE guidelines (126)—a set of recommendations to promote complete reporting of cohort data in a systematic manner. Further details of the participating cohorts and the CANOC structure have been previously outlined in Chapter 3 and a previously published CANOC cohort profile (127)

Study design and population

CANOC eligibility criteria include: documented HIV infection; residence in Canada; 18 years of age and over; initiation of three or more antiretroviral drugs for the first time (i.e., antiretroviral-naive prior to initiating cART) on or after January 1, 2000; and a documented HIV-1 RNA measurement and CD4 T-cell count within six months of the start of therapy. To be included in this analysis, individuals had to have at least two viral load measurements after starting cART. Moreover, only individuals whose baseline viral loads were ≥50 copies/mL were included. Loss to follow-up among patients included in this analysis was defined as no contact for one year.

Outcomes

The primary outcome of interest in this analysis was viral rebound, defined as the first of at least two consecutive viral load measurements above 50 HIV-1 RNA

copies/mL, at least 30 days apart, after reaching virological suppression. Virological suppression was defined as the time to the first of at least two consecutive viral load measurements <50 HIV-1 RNA copies/mL, at least 30 days apart, in a one-year period.

Covariates of interest for this analysis included: age at cART initiation; gender; province; ethnicity; Aboriginal ancestry; risk category (men who have sex with men (MSM), injecting drug use (IDU)), and clinical variables such as hepatitis C antibody seropositivity; baseline AIDS-defining illness (ADI); era of cART initiation baseline; composition of initial cART regimen (nucleoside reverse transcriptase inhibitor (NRTI) backbone and third drug in the regimen); baseline CD4 cell count and HIV plasma viral load (log10); time to virological suppression (months); and follow-up time (years).

Statistical Analysis

Among those who achieved virological suppression, socio-demographic and clinical characteristics were compared by age (≤29 vs. 30+ years old) and viral rebound status in bivariate tables using Chi-square tests for categorical variables and Wilcoxon's Rank Sum test for continuous variables. Viral load measurements were buffered to a minimum of 50 copies/mL and a maximum of 100,000 copies/mL to accommodate temporal changes in viral load assay sensitivities over the study period.

Kaplan-Meier methods and stratified life tables were used to compare time to viral rebound by age group. Accelerated Failure Time (AFT) models were used in univariate and multivariable analyses to explore the association between variables and time to viral rebound.

Final multivariable models were selected using an exploratory model selection process based on Akaike Information Criterion (AIC) and Type III p-values. Based on the model diagnosis and the goodness-of-fit tests, we decided to use the Accelerated Failure Time (AFT) model (276) as it was the best fit. The goodness of fit test was assessed using a log-log survivor plot. AFT models with Weibull distribution were used in univariate and multivariable analyses to explore the association between variables and time to virological rebound among individuals who had previously achieved virological suppression. A two-sided P-value below 0.05 was considered statistically

significant. A sub-analysis restricted to AYA was then performed using AFT models to identify significant covariates associated with time to viral rebound. All analyses were performed using SAS software version 9.1 (SAS Institute, Cary, North Carolina, USA).

6.4. Results

A total of 8,471 individuals were included in this analysis. Among the 7,677 CANOC participants who achieved virological suppression, 1,720 (28.9%) experienced subsequent viral rebound. A greater proportion of AYA experienced viral rebound than older adults (26% vs. 22%, p=0.009).

Demographic and clinical characteristics of AYA and older adults were compared. **Table 6.1** illustrates the differences between these two groups, with 1,168 individuals (13.8%) aged ≤29 years old at the time of cART initiation. The average age among AYA was 27 years (interquartile range [IQR]: 24-28 years) compared with 42 years (IQR: 36-48 years) among the older age group. A higher proportion of AYA: were female (32% vs. 16%, p<0.001); were from Ontario (39% vs. 33%, p<0.001); started cART in later calendar years (2008-2011) (47% vs. 40%, p<0.001); started cART with an unboosted protease inhibitor (PI) (10% vs. 5%, p<0.001); and initiated cART with a higher median baseline CD4 count (cell/mm3) (median= 256, IQR: 160-360 vs. 210, IQR: 116-310, p<0.001). A lower proportion of AYA: reported Caucasian ethnicity (25% vs. 29%, p<0.001); had a a history of IDU (20% vs. 23%, p=0.012); had a hepatitis C (HCV) co-infection (21% vs. 26%, p<0.001); and had an AIDS-defining illness (ADI) before or on their cART initiation date (9% vs. 16%, p<0.001). Importantly, a lower proportion of AYA had ever achieved virological suppression (86% vs. 91%, p<0.001).

As shown in **Table 6.2**, in a bivariate analysis of the entire cohort viral rebound is associated with: being younger (26% vs. 22%, p=0.009); being female (34% vs. 20%, P<0.001); living in British Columbia rather than Ontario or Quebec (28% vs. 19% vs. 18%, p<0.001); identifying as Aboriginal (37% vs. 26%, p<0.001); not identifying as MSM (30% vs. 19%, p<0.001); having a history of IDU (35% vs. 20%, p<0.001); being co-infected with HCV (34% vs 19%, p<0.001); and beginning cART in an earlier calendar year (39% vs. 25% vs. 10%, p<0.001). Rebound was also associated with: initiating

cART with an unboosted PI as opposed to an NNRTI, a boosted PI, or "other" (39% vs. 20% vs. 23% vs. 24%, p<0.001); and having Nevirapine (35%) or Nelfinavir (44%) as the third drug in the regimen (p<0.001). Having a lower baseline CD4 T-cell count was also associated with viral rebound (230 vs. 190, p<0.001). Those who rebounded initially took longer to achieve virological suppression (5 months vs. 4 months, p<0.001).

In the adjusted multivariable model of all participants (**Table 6.3**), younger participants (≤29 years old) (adjusted hazard ratio [aHR] = 1.31; 95% confidence interval [CI]: 1.14, 1.5, p<0.001) and those with a history of IDU (aHR = 1.73; 95% CI: 1.55, 1.94, p<0.001) were more likely to rebound after achieving virological suppression. Men were less likely than women to rebound (aHR = 0.62; 95% CI: 0.56, 0.7, p<0.001). Individuals who initiated cART between 2004 and 2007 (aHR = 0.8; 95% CI: 0.71, 0.91) and between 2008 and 2011 (aHR = 0.67; 95% CI: 0.58, 0.78) were less likely to rebound than those who initiated cART in the earlier time period. Individuals receiving care in Ontario (aHR = 0.74; 95% CI: 0.66, 0.83) and Quebec (aHR = 0.68 95% CI: 0.59, 0.79) were less likely to rebound than those receiving care in British Columbia. Individuals on initial cART regimens containing atazanavir (aHR = 1.22; 95% CI: 1.01, 1.46) and nelfinavir (aHR = 1.34; 95% CI: 1.08, 1.66) were more likely to experience virological rebound than those whose first regimen contained nevirapine. Individuals whose first regimen contained efavirenz were less likely to experience viral rebound (aHR = 0.83; 95% CI: 0.7, 0.98).

In the adjusted multivariable model among AYA only (**Table 6.4**), male participants were less likely than females to experience viral rebound (aHR = 0.5; 95% CI: 0.39, 0.65). Individuals with a history of IDU (aHR = 2.78; 95% CI: 2.13, 3.64) and those who initiated treatment on a boosted PI (aHR = 1.35; 95% CI: 1.01, 1.8) were more likely to experience viral rebound. AYA who initiated treatment between 2004 and 2007 (aHR = 0.68; 95% CI: 0.51, 0.92) and between 2008 and 2011 (aHR = 0.68; 95% CI: 0.48, 0.95) were less likely to rebound than those who initiated cART in the earlier time period.

Life table analyses were used to further explore the relationship between age and viral load rebound. **Table 6.5** illustrates the probability of viral rebound 6, 12, 18,

and 24 months after suppression. While there is not a significant difference between AYA and older adults at 6 months (p=0.256), the probability of viral load rebound was significantly higher among AYA at 12 months (p=0.005), 18 months (p<0.001), and 24 months (p=0.001).

Kaplan-Meier curves exploring differences in viral rebound among subset populations indicated that significant differences still existed when age, gender, a history of injection drug use, and era of cART initiation were examined exclusively (**Figures 6.1-6.4**).

6.5. Discussion

This study sought to measure the prevalence and correlates of viral load rebound among people living with HIV in Canada in particular, adolescents and young adults. Our results show AYA to be significantly more likely to experience viral rebound than older adults with over a quarter of AYA experiencing viral rebound. Among AYA, women, those with a history of injection drug use, and those who initiated cART in earlier calendar years are more likely to rebound. These findings are in accordance with the hypothesis that younger people compared to older adults will have poorer clinical outcomes.

These findings were consistent with other large cohort studies. The UK Collaborative HIV Cohort Study (UK-CHIC) found that for every 10-year increase in age, the rate of viral rebound decreased by 28% (69). A large adolescent and young adult cohort in the United States (REACH) found that only 51% of AYA maintained a suppressed viral load for a year (339). Another study found that more than one-third of AYA drop out of care after 6 months, making sustained virological suppression extremely difficult(344). These, and other studies from the US have called for a more targeted approach to meet the needs of AYA living with HIV(60,65,227,344). As outlined in the US government's National HIV/AIDS Strategy, AYA are need of a seamless transition through the different aspects of HIV care(345).

AYA in Canada are in need of a targeted approach to retain them in care. Once initiated on cART, AYA struggle to virologically suppress and then, among those who

achieve suppression, one-quarter will experience viral rebound. Linking back to the adapted *Seek, Test, Treat, and Retain* framework, my work supports the notion that structural and socio-demographic factors such as gender and injection drug use must be addressed before clinical goals can be expected to be achieved.

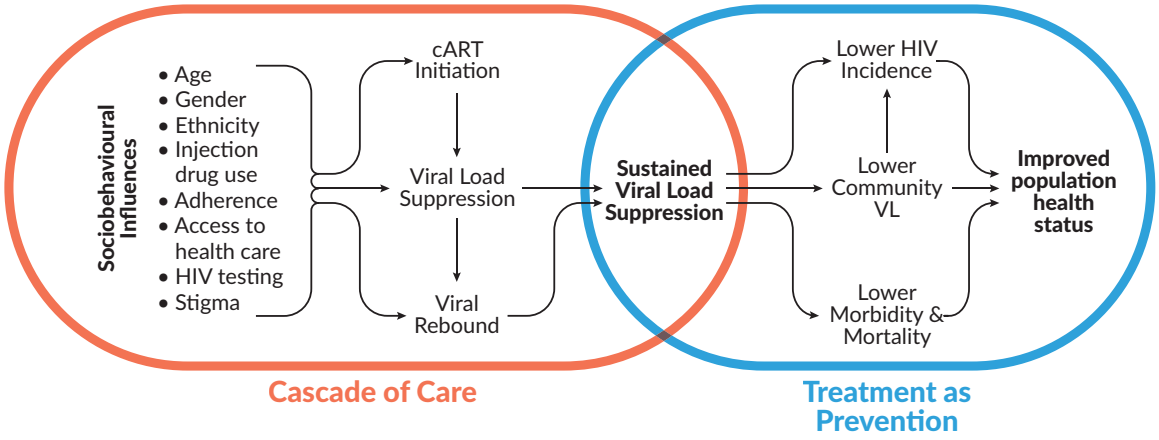

Figure 6.1. Adapted *Seek, Test, Treat, and Retain* framework

Young women were at greater risk of viral rebound than young men, which is most likely due to the fact that women have been shown to report poorer rates of adherence compared with men (313). Among women, young age, injection drug use, and regimen complexity were all associated with poor adherence (346). Many women are dealing with competing priorities, such as childcare, employment, and housing, which all affect one's ability to adhere to medications as directed (222,236,311,347,348). Women are also more likely to suffer from depressive symptoms that inhibit their ability to adhere to and take cART as prescribed (349,350). Access to services such as female-staffed clinics, medication support and onsite childcare may result in improved diagnosis and treatment, allowing the individual to focus on other health issues (285,351). In addition, gender sensitivity training is recommended for all health care workers to ensure that women receive complete care in a holistic and respective manner (285,352,353) and feel comfortable in the clinic environment.

AYA with a history of injection drug use (IDU) have significant difficulties in maintaining cART adherence, in part due to their often chaotic and irregular lives and

schedules. In this case, treating their HIV is not a priority in the face of other competing necessities such as food, housing, and addiction services (235–237). Many AYA with a history of IDU have also tested positive for hepatitis C (HCV) co-infection. Those who are co-infected with HCV may stop cART due to toxicities (331). As well, many young injection drug users may face stigma when attending health clinics, making them reluctant to follow up on their care (238–240). Low-threshold support programs such as directly observed therapy (DOT) and maximally assisted therapy (MAT) programs have been shown to improve adherence (318) for people on cART who use drugs. The development of such programs for AYA could assist those who are in need of low-threshold health care and support to remain on treatment as well as access other services that may be linked. Treatment partnerships in which health providers work directly with the patient in order to tailor health care to the individual's needs can increase feelings of support and levels of comfort when communicating with health providers (241–243) increasing the likelihood of the individuals being retained in care.

The finding that those who started treatment in earlier calendar years were more likely to experience viral rebound was expected, as those who have been on treatment longer have had greater opportunity to rebound. As well, earlier cART regimens often included drugs that carried with them greater side effects as well as greater regimen complexity, making adherence more challenging (208,211,354). More modern drug regimens have lower pill counts, dosages, and tend to have fewer side effects and toxicities, making adherence more manageable (211,354–356). As a World Health Organization (WHO) report states, the "main barriers to adherence, among chronic illnesses including HIV, related to regimen factors were dose frequency and side effects, and emphasized the need for the health systems to develop less frequent dosing and to mitigate side effects" (357). New, simpler and more effective drug regimens are being developed and have been approved making tolerability and adherence easier for AYA (358) and should be available as first line options for all AYA meeting the eligibility.

Pharmacological responses to issues with adherence to combat viral rebound are extremely valuable; however, the best clinical practice will incorporate comprehensive, multidisciplinary approaches to promote retention and adherence (242). A recent study from a large North American HIV cohort (NA-ACCORD) showed that

young people retained in care were more likely to remain virologically suppressed (359). The most promising strategies for improving retention among AYA use holistic approaches involving patient and caregiver education, self-monitoring, peer support, and telephone follow-up (159,185,191,213,360). Given that health literacy is often a barrier to adherence, education sessions and mentorship programs can provide a safe environment to discuss HIV treatment with AYA and to answer any questions they may have (361,362). Education and counselling interventions using a combined family group and peer psycho-education approach have been shown to be very effective (184–187). Previous adherence research has also shown the involvement of peers in developing a support network to be an important part of disease management (363).

In order for AYA to be retained in care, they must feel comfortable in their health care setting. Trusting in the government and in health care providers was associated with better health outcomes, fewer hospital visits, and a greater likelihood of adhering to prescribed medication (364). If AYA do not have a good relationship with or trust their care providers, they are less likely to remain in treatment, especially if they are symptom-free (177,365). AYA may not completely understand the gravity of staying on treatment and remaining adherent (177). It is up to the health care and social service providers to meet AYA where they are at, in a respectful and compassionate manner, in order to improve retention in care.

Limitations

Readers should be cautious when interpreting this data. Most notably, the data were obtained from only three provinces and thus the findings cannot be generalized to the entire Canadian HIV-positive population. However, the majority of HIV-positive individuals in Canada receive care in these three provinces. In fact, CANOC contains over one-third of all patients on therapy and a much larger proportion of those who initiated treatment since 2000. Importantly, it is possible that some women in the study may have experienced viral load rebound after halting therapy that was initiated solely for purposes of prevention of vertical HIV transmission; however, explicit pregnancy data are not available in the CANOC database. Additionally, the differences between provinces in viral load suppression may be due to the fact that the sample of participants

in British Columbia represents nearly everyone who initiated therapy during the study period, while the sample from Ontario and Quebec is based on a selection of clinics. Finally, we did not consider antiretroviral adherence, an important predictor of virological suppression and rebound, as some cohorts did not have these data (31). Despite these limitations, important information regarding factors associated with viral load rebound were identified. This information is of value in identifying AYA at risk for suboptimal therapeutic outcomes.

6.6. Conclusions and Steps Forward

Antiretroviral therapy adherence and retention in care is an important issue among HIV-positive adolescents and young adults. With over one-quarter of the AYA observed in this study experiencing viral load rebound, more attention in research and adherence support needs to be provided. Supporting optimal adherence and assisting AYA to remain in care will lead to lower health burdens, a lower transmission risk, and fewer comorbidities over their life course (35,41,50,51). Tailored approaches to engage young women and AYA who use drugs must be developed to assist them to reach their full health potential. Additionally, given that complex drug regimens are related to poor adherence among AYA, increasing the availability of once-daily regimens may increase adherence and retention in treatment (52,366,367).

In order to better understand the reasons behind viral rebound, it would be advantageous to conduct a qualitative study involving AYA from the various provinces. Given the diversity of the young population in Canada, teasing out the provincial and socio-demographic differences would give a regional context. The perspectives of the AYA would give greater depth and meaning to the data found in the CANOC database, although CANOC is a great starting point. Gathering data regarding adherence patterns among AYA would be beneficial to inform interventions targeted to improving AYA's health outcomes.

Table 6.1. CANOC participants by age at cART initiation (N=8,471)

Variable	Age at cART initiation (years)				p-value
	≤29 (N=1,168)		>29 (N=7,303)		
	N	(%)	N	(%)	
Gender					
Male	795	(68)	6,117	(84)	<0.001
Female	373	(32)	1,186	(16)	
Province					
British Columbia	470	(40)	3,441	(47)	<0.001
Ontario	451	(39)	2,410	(33)	
Quebec	247	(21)	1,452	(20)	
Ethnicity					
Caucasian	295	(25)	2,090	(29)	<0.001
Black	138	(12)	605	(8)	
Aboriginal	66	(6)	340	(5)	
Other	105	(9)	545	(7)	
Unknown/Missing	564	(48)	3,723	(51)	
Aboriginal					
No	538	(46)	3,240	(44)	0.124
Yes	66	(6)	340	(5)	
Unknown	564	(48)	3,723	(51)	
HIV risk MSM					
No	365	(31)	2,355	(32)	0.502
Yes	424	(36)	2,702	(37)	
Unknown	379	(32)	2,246	(31)	
HIV risk IDU					
No	719	(62)	4,157	(57)	0.012
Yes	234	(20)	1,650	(23)	
Unknown	215	(18)	1,496	(20)	
Hepatitis C					
Not co-infected	867	(74)	5,014	(69)	0.001
Co-infected	241	(21)	1,866	(26)	
Unknown	60	(5)	423	(6)	
Baseline ADI					
None	1,010	(86)	5,811	(80)	<0.001
At least one	101	(9)	1,164	(16)	
None ever	57	(5)	328	(4)	

Variable	Age at cART initiation (years)				p-value
	≤29 (N=1,168)		>29 (N=7,303)		
	N	(%)	N	(%)	
Era of cART initiation					
2000-2003	284	(24)	1,907	(26)	<0.001
2004-2007	340	(29)	2,452	(34)	
2008-2011	544	(47)	2,944	(40)	
Virological suppression					
No	161	(14)	633	(9)	<0.001
Yes	1,007	(86)	6,670	(91)	
Classes of ARVs in first regimen					
NNRTI	540	(46)	3,460	(47)	<0.001
Unboosted PI	121	(10)	384	(5)	
Boosted PI	430	(37)	2,979	(41)	
Other	77	(7)	480	(7)	
Initial third drug					
Nevirapine	127	(11)	719	(10)	<0.001
Efavirenz	411	(35)	2,657	(36)	
Lopinavir	181	(15)	1,261	(17)	
Atazanavir	250	(21)	1,619	(22)	
Nelfinavir	87	(7)	253	(3)	
Other	112	(10)	794	(11)	
	Median (IQR)		Median (IQR)		p-value
Age at first ARV initiation (years)	27 (24-28)		42 (36-48)		<0.001
Baseline CD4 (cells/mm3)	256 (160-360)		210 (116-310)		<0.001
Baseline viral lpad (log10 copies/mL)	5 (4-5)		5 (4-5)		<0.001
Time to virological suppression (months)	5 (3-12)		5 (3-9)		0.747
Follow-up time (years)	4 (2-8)		5 (3-8)		<0.001

IDU: Injection drug use

MSM: Men who have sex with men

FARVDT: First cART date

NNRTI: Non-nucleoside reverse transcriptase inhibitor

Boosted PI: cART regimen boosted with a protease inhibitor

ADI: AIDS-defining illness

Table 6.2. Viral rebound among CANOC participants who have ever achieved virological suppression (N=7,677)

Variable	Virological rebound				p-value
	No (N=5,957)		Yes (N=1,720)		
	N	(%)	N	(%)	
Age at first cART initiation (years)					
<=29	749	(74)	258	(26)	0.009
>29	5208	(78)	1462	(22)	
Gender					
Male	5076	(80)	1,276	(20)	<0.001
Female	881	(66)	444	(34)	
Province					
British Columbia	2,496	(72)	953	(28)	<0.001
Ontario	2,170	(81)	493	(19)	
Quebec	1,291	(82)	274	(18)	
Ethnicity					
Caucasian	1,636	(74)	580	(26)	<0.001
Black	501	(74)	174	(26)	
Aboriginal	202	(63)	120	(37)	
Other	459	(76)	148	(24)	
Unknown/Missing	3,159	(82)	698	(18)	
Aboriginal					
No	2,596	(74)	902	(26)	<0.001
Yes	202	(63)	120	(37)	
Unknown	3,159	(82)	698	(18)	
HIV risk MSM					
No	1,626	(70)	704	(30)	<0.001
Yes	2,404	(81)	558	(19)	
Unknown	1,927	(81)	458	(19)	
HIV risk IDU					
No	3,647	(80)	916	(20)	<0.001
Yes	1,014	(65)	551	(35)	
Unknown	1,296	(84)	253	(16)	
Hepatitis C					
Not co-infected	4,466	(81)	1,047	(19)	<0.001
Co-infected	1,153	(66)	606	(34)	
Unknown	338	(83)	67	(17)	

Variable	Virological rebound				p-value
	No (N=5,957)		Yes (N=1,720)		
	N	(%)	N	(%)	
Baseline ADI					
None	4,842	(78)	1,365	(22)	0.192
At least one	851	(76)	274	(24)	
None ever	264	(77)	81	(23)	
Era of cART initiation					
2000-2003	1,195	(61)	752	(39)	<0.001
2004-2007	1,938	(75)	637	(25)	
2008-2011	2,824	(90)	331	(10)	
Classes of ARVs in first regimen					
NNRTI	2,972	(80)	726	(20)	<0.001
Unboosted PI	266	(61)	171	(39)	
Boosted PI	2,350	(77)	705	(23)	
Other	369	(76)	118	(24)	
Initial third drug					
Nevirapine	494	(65)	263	(35)	<0.001
Efavirenz	2,417	(84)	446	(16)	
Lopinavir	967	(76)	312	(24)	
Atazanavir	1,324	(79)	362	(21)	
Nelfinavir	160	(56)	128	(44)	
Other	595	(74)	209	(26)	
	Median (IQR)		Median (IQR)		p-value
Age at first cART initiation (years)	40 (34-47)		39 (33-46)		<0.001
Baseline CD4 (cells/mm3)	230 (130-323)		190 (97-280)		<0.001
Baseline viral load (log10 copies/mL)	5 (4-5)		5 (4-5)		<0.001
Time to virological suppression (months)	4 (3-7)		5 (3-10)		<0.001
Follow-up time (years)	5 (3-7)		8 (5-10)		<0.001

IDU: Injection drug use
MSM" Men who have sex with men
FARVDT: First ARV date
NNRTI: Non-nucleoside reverse transcriptase inhibitor
Boosted PI: cART regimen boosted with a protease inhibitor
NUCx3: cART regimen consisting of 3 nucleosides
ADI: AIDS-defining illness

Table 6.3. Factors associated with viral rebound among all CANOC participants who have ever achieved virological suppression (N=7,677)

	Unadjusted		Adjusted	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age at first ARV initiation (years)				
>29	1.00 (-)	<0.001	1.00 (-)	<0.001
<=29	1.38 (1.21, 1.57)		1.31 (1.14, 1.5)	
Gender				
Female	1.00 (-)	<0.001	1.00 (-)	<0.001
Male	0.53 (0.48, 0.59)		0.62 (0.56, 0.7)	
HIV risk IDU				
No	1.00 (-)	<0.001	1.00 (-)	<0.001
Yes	2.13 (1.91, 2.36)		1.73 (1.55, 1.94)	
Unknown	0.87 (0.75, 1)		0.93 (0.81, 1.08)	
Aboriginal			-	
No	1.00 (-)	<0.001		
Yes	1.87 (1.54, 2.26)			
Unknown/Missing	0.82 (0.74, 0.91)			
Baseline ADI			-	
None	1.00 (-)	0.877		
At least one	1.06 (0.85, 1.33)			
None ever	1.06 (0.83, 1.36)			
Baseline CD4 (cells/mm3)			-	
<200	1.00 (-)	0.019		
>=200	0.89 (0.81, 0.98)			
Classes of ARVs in first regimen			-	
NNRTI	1.00 (-)	<0.001		
Unboosted PI	1.79 (1.52, 2.12)			
Boosted PI	1.25 (1.12, 1.38)			
Other	1.25 (1.03, 1.52)			
Era of cART initiation				
2000-2003	1.00 (-)	<0.001	1.00 (-)	<0.001
2004-2007	0.8 (0.72, 0.89)		0.8 (0.71, 0.91)	
2008-2011	0.63 (0.55, 0.72)		0.67 (0.58, 0.78)	

	Unadjusted		Adjusted	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Province				
British Columbia	1.00 (-)	<0.001	1.00 (-)	<0.001
Ontario	0.59 (0.53, 0.66)		0.74 (0.66, 0.83)	
Quebec	0.58 (0.51, 0.66)		0.68 (0.59, 0.79)	
Initial third drug				
Nevirapine	1.00 (-)	<0.001	1.00 (-)	<0.001
Efavirenz	0.59 (0.51, 0.69)		0.83 (0.7, 0.98)	
Lopinavir	0.8 (0.68, 0.94)		1.02 (0.86, 1.21)	
Atazanavir	0.94 (0.8, 1.1)		1.22 (1.01, 1.46)	
Nelfinavir	1.33 (1.08, 1.64)		1.34 (1.08, 1.66)	
Other	0.97 (0.81, 1.17)		1.17 (0.97, 1.4)	
Baseline viral load (log10 copies/mL)	1.04 (0.95, 1.13)	0.429	-	

IDU: Injection drug use
MSM: Men who have sex with men
NNRTI: Non-nucleoside reverse transcriptase inhibitor
Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir
Unboosted PI: cART regimen consisting of a protease inhibitor
cART: Combination antiretroviral therapy
NUCx3: cART regimen consisting of 3 nucleosides
ADI: AIDS-defining illness

Table 6.4. Factors associated with viral rebound among AYA in CANOC who have ever achieved virological suppression (N=1,007)

	Unadjusted		Adjusted	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Gender				
Female	1.00 (-)	<0.001	1.00 (-)	<0.001
Male	0.42 (0.33, 0.54)		0.5 (0.39, 0.65)	
HIV risk IDU				
No	1.00 (-)	<0.001	1.00 (-)	<0.001
Yes	3.06 (2.35, 3.98)		2.78 (2.13, 3.64)	
Unknown	0.74 (0.49, 1.11)		0.82 (0.54, 1.24)	
Aboriginal			Not selected	
No	1.00 (-)	<0.001		
Yes	3.05 (2.05, 4.54)			
Unknown/Missing	0.83 (0.64, 1.08)			
Baseline ADI				
None	1.00 (-)	0.257	1.00 (-)	0.132
At least one	1.5 (0.82, 2.75)		1.51 (0.8, 2.85)	
None ever	1.81 (0.89, 3.69)		2.06 (0.99, 4.29)	
Baseline CD4 (cells/mm3)				
<200	1.00 (-)	0.265	1.00 (-)	0.083
>=200	1.15 (0.9, 1.49)		1.27 (0.97, 1.68)	
Classes of ARVs in first regimen				
NNRTI	1.00 (-)	0.007	1.00 (-)	0.102
Unboosted PI	1.76 (1.24, 2.51)		1.21 (0.83, 1.76)	
Boosted PI	1.23 (0.93, 1.62)		1.35 (1.01, 1.8)	
Other	0.81 (0.45, 1.43)		0.74 (0.41, 1.34)	
Era of cART initiation				
2000-2003	1.00 (-)	0.019	1.00 (-)	0.018
2004-2007	0.73 (0.55, 0.97)		0.68 (0.51, 0.92)	
2008-2011	0.67 (0.49, 0.92)		0.68 (0.48, 0.95)	
Province			Not selected	
British Columbia	1.00 (-)	<0.001		
Ontario	0.66 (0.5, 0.86)			
Quebec	0.52 (0.37, 0.74)			
Baseline viral load (log10 copies/mL)	0.77 (0.64, 0.92)	0.004	0.82 (0.68, 1)	0.055

IDU: Injection drug use

MSM: Men who have sex with men

NNRTI: Non-nucleoside reverse transcriptase inhibitor

Boosted PI: cART regimen consisting of a protease inhibitor boosted with ritonavir
Unboosted PI: cART regimen consisting of a protease inhibitor
cART: Combination antiretroviral therapy
NUCx3: cART regimen consisting of 3 nucleosides
ADI: AIDS-defining illness

Table 6.5. The probability of viral rebound by months and age group

	Age		
Time (months)	**<=29**	**>29**	**p-value**
6	0.04 (0.05, 0.03)	0.03 (0.03, 0.02)	0.256
12	0.11 (0.13, 0.09)	0.08 (0.08, 0.07)	0.005
18	0.16 (0.18, 0.14)	0.11 (0.12, 0.1)	<0.001
24	0.19 (0.22, 0.17)	0.14 (0.15, 0.13)	0.001

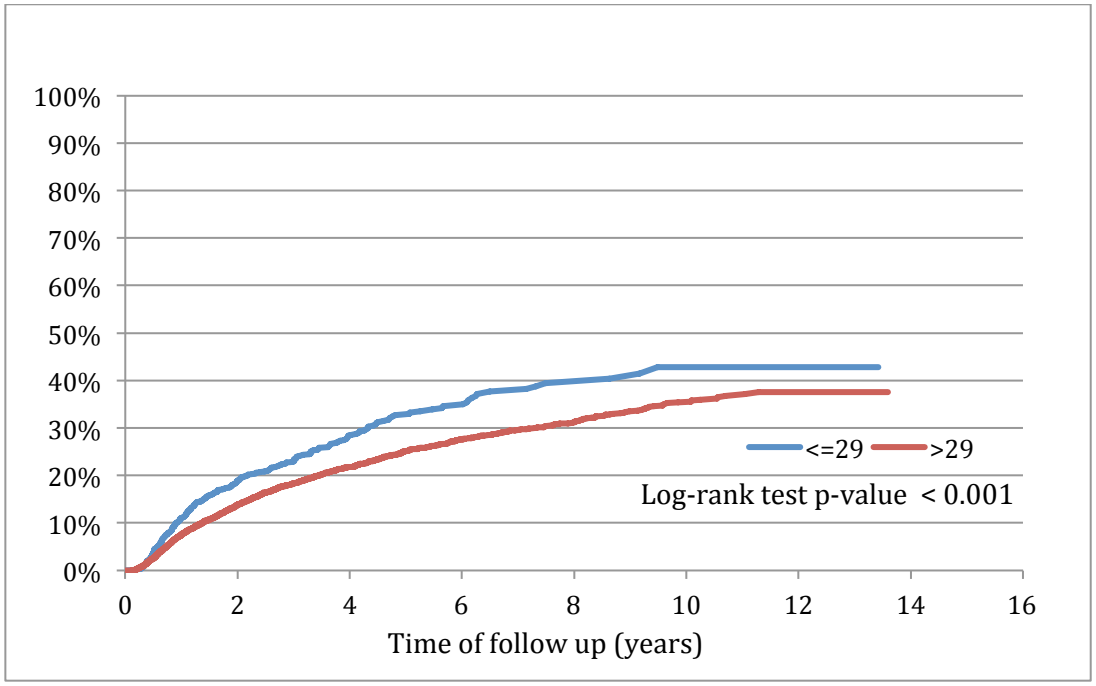

Figure 6.2. Probability of achieving viral rebound by age

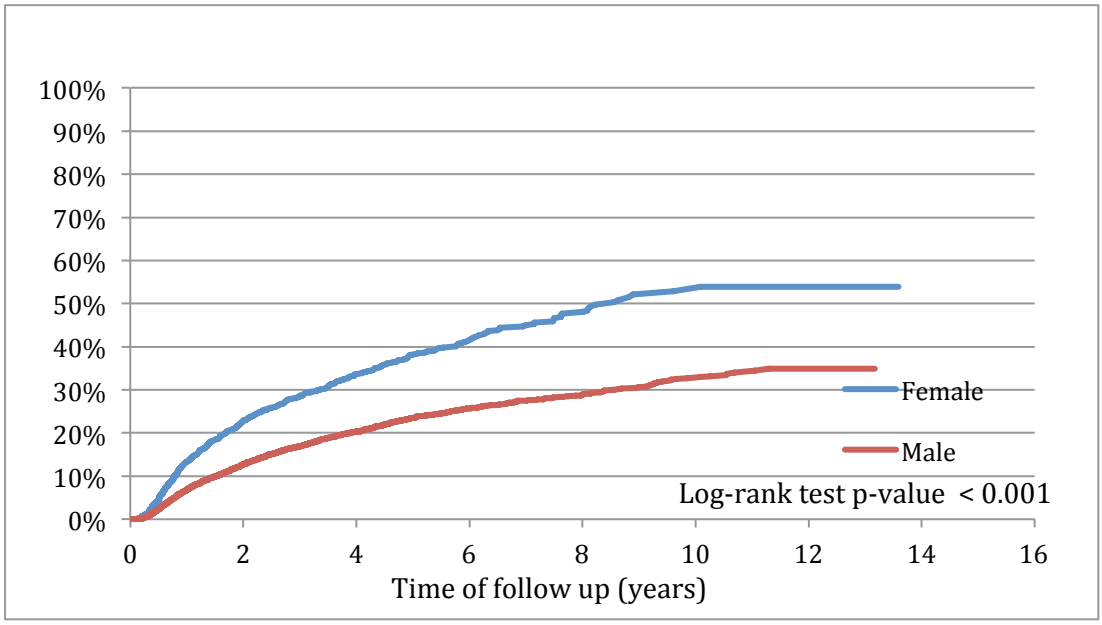

Figure 6.3. Probability of achieving viral rebound by gender

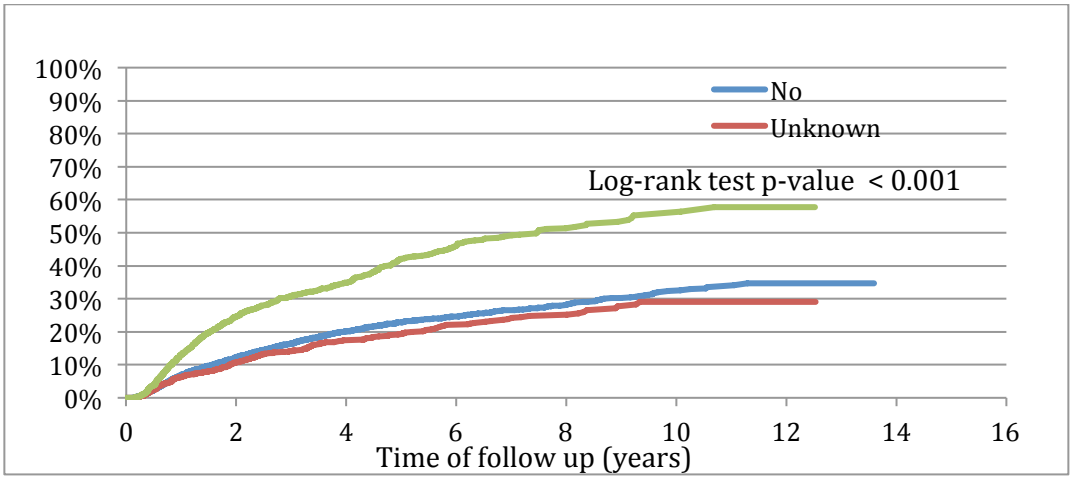

Figure 6.4. Probability of achieving viral rebound by IDU status

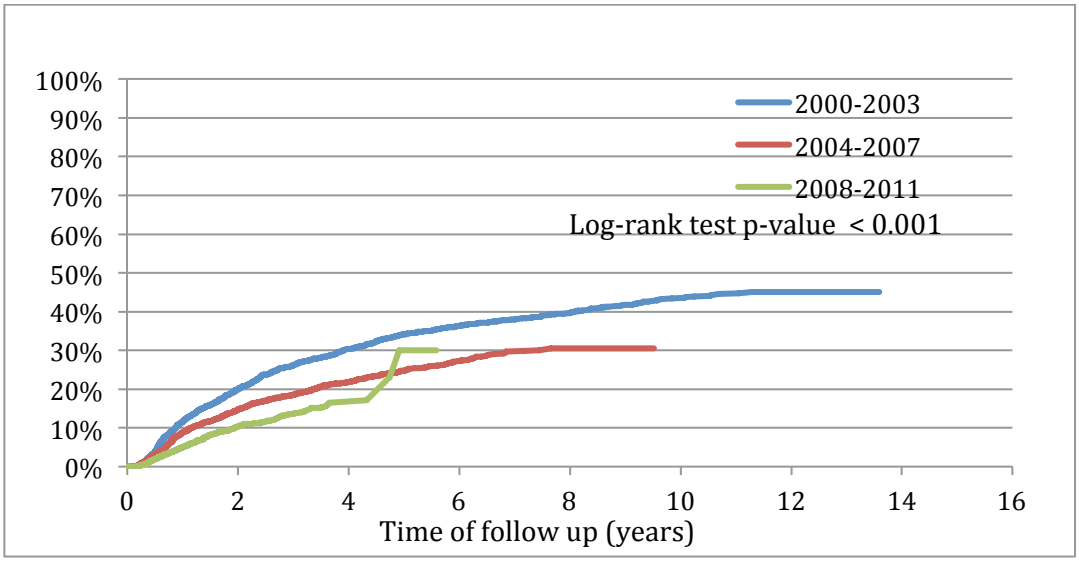

Figure 6.5. Probability of achieving viral rebound by year of cART initiation

Chapter 7.

Summary and Recommendations

7.1. Abstract

The main findings of my PhD dissertation research among adolescents and young adults (AYA) living with HIV in Canada are summarized in this chapter. In summary, I link the importance of clinical outcomes among AYA with the goals of the Treatment as Prevention (TasP) framework and the current political and treatment environment in Canada and discuss the strengths and limitations of the research and how they were mitigated. I also discuss how the research findings can be disseminated in order to inform and affect change at a health services and policy level. I conclude by recommending future research topics for potential studies and projects to address study limitations and knowledge gaps and by demonstrating that future work in this area needs to focus on qualitative, in-depth research with AYA in order to better understand what types of interventions could positively improve their treatment outcomes along the HIV Cascade of Care.

7.2. Summary of Findings

The purpose of this PhD dissertation was to examine key cART treatment outcomes along the HIV Cascade of Care among adolescents and young adults (AYA) living with HIV in Canada. The objectives of this dissertation were to: 1) compare the prevalence of late cART initiation among HIV-infected AYA (18-29 years) and older adults (30+ years) in Canada and identify factors associated with late initiation; 2) assess and compare virological suppression rates between HIV-infected AYA (18-29 years) and older adults (30+ years) in Canada and explore factors associated with time to virological

suppression; and 3) assess and compare the prevalence of viral load rebound among HIV-infected AYA (18-29 years) and older adults (30+ years) in Canada and characterize trends and determinants of viral load rebound.

Chapter 1 described the HIV epidemic in Canada among AYA as well as introduced the reader to the HIV Cascade of Care, Treatment as Prevention (TasP), and the importance of using a *Seek, Test, Treat, and Retain* model to frame the findings from this research. Within this Cascade of Care framework, an adapted *Seek, Test, Treat, and Retain* framework was used to try to understand the pathways from socio-structural factors (such as gender, injection drug use, mental health, access to services, and geographic location) to clinical outcomes. Gaps in research related to AYA and HIV were identified and the overall goal of this dissertation and the specific objectives were introduced. The HIV TasP concept was used to contextualize study objectives and frame the objectives within a public health lens.

Chapter 2 reviewed the literature pertaining to AYA research in North America focusing on topics related to the different stages of the HIV Cascade of Care: HIV infection; HIV diagnosis; Linked to care; Retained in care; cART indicated; On cART; Adherent; and Virologically suppressed. Using the term “Adolescents and Young Adults” to account for people 15 to 29 years of age, outcomes in all stages of the Cascade of Care were investigated. Among the studies available in the United States and Canada, it was apparent that significant barriers exist to engaging and retaining AYA in all of the stages of the HIV Cascade of Care. Retention in HIV care was intricately linked to clinical success, defined as adherence and virological suppression. Findings from the literature were themed into four categories of barriers: Health System Factors (schedules, cost, legal impediments, or inappropriate services); Therapeutic Factors (issues related to cART regimens); Psycho-emotional Factors (adolescent development and psychosocial issues); and Social Factors (family and peer relationships). There were just a few Canadian studies that were included in this review, leaving a gap in the understanding of how Canadian AYA are performing in comparison with those in the United States. Overall, this work demonstrated the need for further research and interventions to address the barriers outlined in the review and to ensure that the needs of AYA are met in the most efficient and appropriate manner possible.

Chapter 3 described the Canadian Observational Cohort Collaboration (CANOC) in detail and how AYA data generated from the collaboration was used in this dissertation. The collaboration of eight clinical cohorts from British Columbia, Ontario, and Quebec gives researchers the opportunity to conduct large and detailed analyses of HIV treatment outcomes that would not be possible within individual cohorts and to assess variations in patterns of access to treatment, patient management, and treatment outcomes across Canada. I was able to create the largest cohort of AYA available in Canada with the permission of the lead investigators from the collaborating cohorts.

Chapters 4 to 6, focused on objectives 1, 2, and 3, summarized the analyses I conducted using data from CANOC. Chapter 4 compared late initiation of cART between AYA and older adults (objective 1). Late initiation was defined as a CD4 count ≤200 cells/mm3 or having an AIDS-defining illness prior to initiating cART. The analyses showed that AYA were more likely than older adults to initiate treatment in a timely manner as recommended by the IAS-USA Treatment Guidelines group (199). This finding was contrary to expectations but rather than showing AYA to be doing well, it showed that Canadians in general were starting treatment with lower-than-expected clinical markers. With 40% of AYA initiating treatment late compared with 51% of older adults, a large number of participants, regardless of age, were starting treatment well below the threshold recommended by UNAIDS' 90-90-90 plan (7). CANOC participants who initiated treatment late were more likely to be women, to be ≥30 years of age at initiation, to have initiated treatment in earlier calendar years, and to have had higher baseline viral loads. These findings demonstrate a disconnect between AYA receiving a positive HIV diagnosis and remaining engaged in the health care system long enough to heed the advice of their medical team to initiate treatment when clinically indicated. AYA, as well as older adults, would benefit from greater engagement in care following an HIV-positive diagnosis to ensure that they are accessing the services necessary to meet their health care needs and progress through the Cascade of Care.

Chapter 5 examined the association between age and the likelihood of virological suppression across Canada and found 91% of older adults to have ever had a suppressed viral load compared with 86% of AYA which is very close the UNAIDS 90-90-90 target goals. When restricting my analyses to the first year of treatment, 73% of

AYA compared with 80% older adults suppressed within the first year of cART initiation. AYA who achieved virological suppression were more likely to be men and to have initiated cART in later calendar years. They were less likely to have a history of injection drug use (IDU), to have started cART on an unboosted protease inhibitor, to have started with a higher viral load, and to reside in Ontario. This work called for the need for pharmacological interventions among AYA, such as reduced pill burden and regimens with fewer side effects, in order to encourage optimal adherence and improve viral load suppression; and the need for the development of tailored structural interventions, such as the promotion of health care services that take into account the needs of young women and young people involved in injection drug use and interventions that factor in socio-demographic factors that would greatly inform current clinical practices and programming for AYA.

Chapter 6 investigated the association between age and the likelihood of viral load rebound among those who had ever achieved virological suppression. Approximately one-quarter of AYA experienced viral load rebound in comparison with 22% of older adults. Among AYA, this analysis found women and individuals with a history of IDU to be more likely to experience viral rebound. Individuals who initiated cART in earlier calendar years were more likely to experience viral rebound, which speaks to the improvement in treatments since 2000. Similar to the previous analysis, the discussion called for greater exploration of pharmacological regimens to assist with the maintenance of sustained virological suppression as well as greater examination of innovative methods to retain young women, AYA of Aboriginal descent, and injection drug users in care. Maximally assisted therapy (MAT) programs and directly observed therapy (DOT) programs should be explored as a possible intervention for AYA with a history of injection drug use. Overall, I argue the need for further in-depth research to better understand viral load rebound and consequently to design more effective programming.

As illustrated in **Figure 7.1,** AYA in my study were more likely to initiate cART in a timely manner; however, they were less likely to reach virological suppression (ever and/or within one year) and were more likely to experience viral rebound. There is an urgent need for strategies and interventions to address issues of retention.

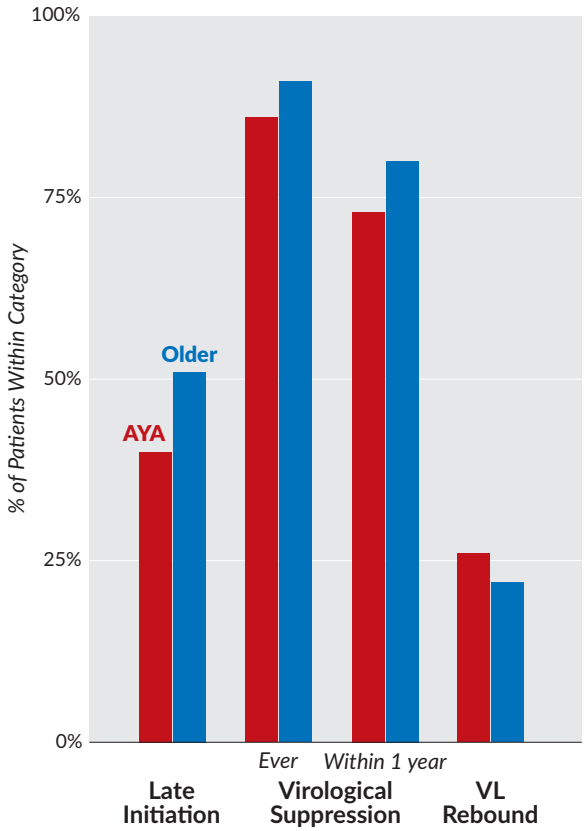

Figure 7.1. Differences in late initiation, virological suppression, and viral load rebound between AYA and older adults

As displayed in the adapted *Seek, Test, Treat, and Retain* framework in **Figure 7.2** below, without further examination of the socio-behavioural factors it is unlikely that the true roots of the causes of poor clinical outcomes will be determined—this is true for all three analyses. A strong foundation and consistent support is needed for AYA to be able to focus on their personal health care needs.

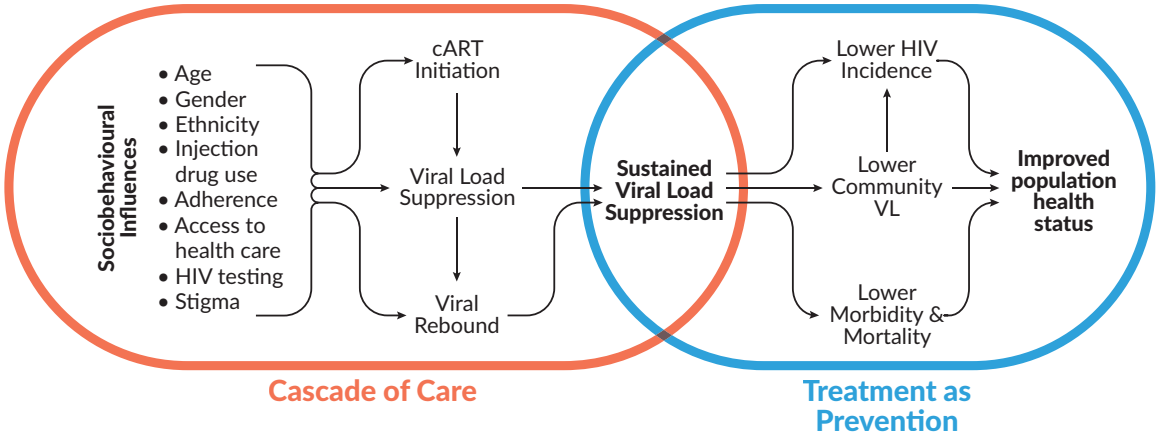

Figure 7.2. Adapted *Seek, Test, Treat, and Retain* framework

7.3. Unique Contributions

CANOC is Canada's largest HIV cohort collaboration and the only cohort to look at HIV outcomes pan-provincially. Many of Canada's foremost HIV researchers are involved in CANOC, making the collaboration a well-resourced, extremely knowledgeable team. This expertise and wealth of knowledge is beneficial to the work done in this dissertation. To date, this is the first work related to AYA that has been done pan-provincially in Canada. There have been previous collaborations among pediatric HIV-care providers, but as AYA are a unique population of their own, they require their own analyses and, as I argue in this dissertation, their own programming and services.

Prior to the development of CANOC, national analyses were not possible. The only national data available were through the Public Health Agency of Canada's surveillance program, which reports on only basic HIV indicators (10) or via national cohorts specializing in certain areas (e.g., co-infections, pediatrics) (368,369). The CANOC collaboration of databases offers the closest picture that we can get of a national cohort.

In the current context of TasP, there has been criticism that the response to HIV has been over-medicalized and that the socio-behavioural factors related to health have been overlooked in their importance (370). It was the intention of this dissertation to explore clinical outcomes while also taking into account as much socio-behavioural

information as possible. **Figure 7.2** illustrates an individual's pathway within a larger TasP framework to understand how socio-behavioural demographics play an important role in achieving the goals of more treatment-centered HIV care and prevention approaches. While this dissertation cannot speak directly to the underlying socio-behavioural issues related to clinical outcomes, I have tried as much as possible to acknowledge the importance that these factors play.

My hope is that this work will provide a starting point for working with AYA and will contribute to a greater understanding of clinical outcomes among AYA living with HIV across Canada within the current context of medical treatment for HIV. The HIV Cascade of Care, within the context of Treatment as Prevention (TasP), provides a framework to monitor how AYA are doing at each step in their journey from HIV testing through to sustained virological suppression (3). As illustrated in Chapter 2, there is an association between young age and poor clinical health outcomes among those living with HIV in Canada and the United States. Encouragingly, findings from Chapter 4 showed younger age to be associated with an increased likelihood of starting cART in a timely manner as recommended by international medical guidelines. Unfortunately, although AYA reported better uptake in terms of initiating treatment, there was still a large proportion (40%) of AYA initiating treatment with lower clinical markers than recommended showing that AYA are not engaging with the health care system and HIV-related services as health care providers would hope. Analyses in Chapters 5 and 6 found an independent association between young age and poor clinical health outcomes and poor retention in care across Canada. Together I believe these findings indicate an urgent need to explore the barriers to cART adherence and retention among AYA in order for young people to fully appreciate the benefits of cART and for public health strategies such as TasP and UNAIDS' 90-90-90 initiative to be successful.

7.4. Strengths and Limitations

The strengths and limitations have been described previously in each of the independent studies in this PhD dissertation (refer to Chapters 4, 5, and 6). However, in addition to what has already been stated, I comment on the strengths and limitations of my

measurement tools, sampling methodology and sample, and analytic techniques in this section.

7.4.1. Measurement tools

Readers should be cautious when interpreting the findings from this dissertation. Of note, data capture for some variables used in these analyses differs significantly between the cohorts in the collaboration. For example, ethnicity and adherence are not captured consistently in all cohorts and with variables, such as injection drug use, I was not able to distinguish between participants currently injecting drugs and those with a history of injection drug use. As well, CANOC does not collect socio-structural and psychosocial variables, limiting the investigative team to study mainly clinical outcomes, which prevented more nuanced assessments of predictors of HIV treatment outcomes in my dissertation. Despite these limitations, CANOC is a rich data source representing the largest available cohort of adolescents and young adults living with HIV in Canada.

7.4.2. Sampling methodology and study design

There are three major limitations to my AYA sample. First, AYA participants in CANOC are not representative of the Canadian AYA population as a whole living with HIV/AIDS. The cohorts involved in the collaboration are currently limited to British Columbia, and specific clinics in Ontario, and Quebec. While these provinces are representative of the largest HIV-positive populations in Canada (127), and nearly half of the estimated 20,500 people receiving HIV treatment in the represented provinces are captured in this cohort (246), the collective cohort may not be fully representative of the HIV-infected population in Canada. Cohorts from Saskatchewan and Newfoundland will likely join CANOC in the next one to three years, thus improving the reach of CANOC, but still it will not include individuals from all provinces and territories or be a random sample of all those on treatment. Second, AYA who initiated therapy prior to January 2000 were not included in the cohort; therefore, the findings are only be generalizable to individuals who initiated therapy in the modern cART era. Finally, CANOC only includes individuals 18 years and older who were cART-naïve when they initiated treatment, so younger Canadians living with HIV are not captured in the dataset (including those who were

perinatally infected and started treatment as young children). Further research outside of CANOC is proposed for AYA aged 14 to 29 years to better capture the population of young people living with HIV.

In regards to study design, differences in clinical outcomes among cohort participants may be due to variations in the timing of follow-up visits and differential losses to follow-up between cohorts. Furthermore, British Columbia's cohort is population-based and, therefore, includes the data of all people living in the province who are on antiretroviral therapy whereas the data from Ontario and Quebec come from select clinic databases that are more selective on how participants are chosen. Although there is considerable heterogeneity between the cohorts, these differences are more of a strength than a weakness since they allow researchers to better understand how various factors work together to influence the health of HIV-infected individuals. Despite limitations, CANOC is the largest sample of HIV-positive people on antiretroviral therapy in Canada and one of the most representative samples in a high-income country (246).

7.4.3. Analytic techniques

Participants were dichotomized by age in order to investigate differences between AYA and older individuals within CANOC. As AYA were the focus of this PhD dissertation, factors associated with the outcomes were then investigated in more detail among AYA only. The comparison between AYA and older adults helped to give perspective on the findings in Chapters 4, 5, and 6 and showed that significant differences exist between AYA and the older adults.

Co-linearity of variables was tested before the selection of the final model with all values having a Variance Inflation Factor <2. This allowed us to confidently examine associations between variables without the threat of confounders.

With respect to multivariable analyses, logistic regression was used in Chapter 4 to model factors associated with late initiationSurvival analyses were used to model the time to events in Chapters 5 and 6. Survival analyses were used as they take into account time (so that we were able to obtain a more complete picture), whereas logistic regression only looks at binary Yes/No outcomes without examining time. The

proportional hazards assumption was not valid so we could not use a Cox proportional hazard model. An Accelerated Failure Time (AFT) model was used instead. An AFT needs a distribution to be specified; therefore, for analyses in Chapters 5 and 6 Exponential and Weibull distributions were used, respectively. A limitation of the Accelerated Failure Time model is that the estimation of the models is carried out by assuming a distribution for the duration (371). Another limitation is that AFT models with Exponential/Weibull distributions assume the hazard function is monotonic. If the hazard function of the true data is not monotonic than our results are not valid, however, we checked the goodness-of-fit of the model and the test revealed that the assumption is valid.

Kaplan-Meier (KM) methods were used to examine time to virological suppression and rebound by key study variables. The KM curves used in Chapters 5 and 6 give a graphical representation of the estimated probability of not achieving virological suppression/rebound over time, allowing us to look at trends. Log tank tests were used to compare the KM curves between different groups. Life tables were used to compare the estimated probability of achieving certain clinical outcomes on selected time points. Despite limitations in the data, this dissertation provides important information regarding a vulnerable population that is often overlooked and is a launching point for future research studies here in Canada and elsewhere.

7.5. Application of Research Findings

7.5.1. Public health implications

From a public health perspective, the findings in this dissertation are of great importance. As discussed in previous chapters, the use of cART drastically reduces risk of vertical and sexual HIV transmission (36,37) and has been associated with population-level reductions in HIV incidence in what is referred to as “Treatment as Prevention” (TasP) (30,38). While sustained virological suppression is the determining factor of treatment success and the TasP paradigm, achieving and maintaining virological suppression remains a critical challenge (31,32,39–41). This can have negative consequences for individual health; as well, it increases the potential for HIV

transmission, which greatly undermines TasP strategies (2,43). As illustrated in Chapters 2, 4, 5, and 6, AYA are not doing well in terms of their clinical outcomes. They require additional support and appropriate interventions that are tailored to their needs.

In order for the TasP initiative to be successful and ambitious UNAIDS' 90-90-90 targets to be met, an increase in research into this unique cohort of young people is necessary in order to gain a better understanding of this population. Referring back to the adapted *Seek, Test, Treat, and Retain* framework, our analyses illustrate how socio-behavioural factors affect an individual's ability to progress through the continuum. Gender, injection drug use, region of residence, and prescribed drug regimen all affect a person's likelihood of continuing in care. Better support for adolescents and young adults living with HIV to mitigate these barriers will help them to achieve and maintain a suppressed viral load, which in turn will have a preventive impact on morbidity, mortality, and the transmission of HIV and should be seen as a critical public health priority across Canada.

7.5.2. Intervention and policy recommendations

Given that sustained virological suppression requires good adherence, interventions related to virological suppression need to address concerns of adherence. Despite the demand and potential positive impact, there is a lack of youth-accessible resources outlining treatment options and support services for AYA living with HIV (372). Tailored AYA services and clinics, or even just AYA-designated clinic hours, could help AYA feel more comfortable within the clinic setting and therefore more willing to return. Setting up low-threshold health care combined with services such as needle exchanges, wound care, and foot clinics could work as an entry point for connecting very marginalized AYA with the health care system.

As previously discussed, there are numerous structural barriers to be overcome in order for AYA to have the opportunity to improve engagement in care; however, there are some interventions at the individual level that have the potential to affect AYA's engagement and retention in care. Based on a pilot study in Ontario (97), it appears that AYA living with HIV would like an Internet-based one-stop shop for their HIV needs and

questions. Providing a virtual HIV resource removes the physical, financial, and social barriers to accessing clinics, doctor offices, and AIDS service organizations (ASOs). Previous research has shown an association between Internet health information seeking behaviour and improved adherence to cART (373). AYA-specific websites can appeal to varying degrees of literacy and can incorporate videos and online discussions monitored to ensure safety and oversee the accuracy of information provided (374).

Beyond offering accessible information, the Internet can act as a way to bring together AYA living with HIV, which may help to mitigate feelings of stigma and seclusion. Previous research found that AYA who were actively street-involved stressed the importance of using the Internet, particularly e-mail, as a vital communication mechanism (97). Among homeless and at-risk youth, social networking projects have been shown to be successful in promoting health messages and HIV prevention where other programs have failed (375). Many youth reported feelings of loneliness and isolation and thought that an online chat room or support group would be helpful as they navigate the health care system and confront challenges specific to their HIV status (3).

During adolescence and young adulthood, peers play a crucial role in individuals' development; therefore, peer-related interventions that develop support networks such as chat rooms and online forums and support groups may be appropriate, especially for AYA experiencing financial and physical barriers (84). Previous adherence research has shown the involvement of peers in developing a support network to be an important part of disease management (363).

The expansion and adoption of innovative communication methods provide new opportunities for delivering health promotion interventions. Two randomized control trials (RCTs) in Kenya (376,377) and one in the United States (356) showed mobile phone text messaging to be successful in enhancing adherence to ART, compared to standard care. One trial showed weekly mobile phone text messaging to be associated with improvements in clinical markers (377). Another pilot study testing the efficacy of a text-messaging adherence program found that personalized, daily text messaging significantly improved self-reported adherence from baseline to 12 and 24 weeks (378). A pilot study at a youth and family-centered HIV clinic in British Columbia has shown

mobile phone programs to be seen as valuable by both health care providers and patients (379). Given the uptake of mobile phones among AYA, this could be an effective adherence aid across Canada (380).

Text-messaging programs are able to adapt to the needs of the AYA, which indirectly includes them in their own health care planning. For instance, when setting up the text-messaging program, the facilitator along with the AYA can determine how interactive the messaging will be, the frequency of the messages, and the timing of the messages, and then can develop tailored messages that will be most appropriate for the individual (381). In this manner, the AYA may feel more connected to care; however, this intervention does not address the other barriers that the youth is experiencing. (382).

Despite the promise of new technologies to support AYA's positive health behaviours, there is still a need to focus on personal relationships, support systems, and clinical care. The best clinical practice will incorporate comprehensive, multidisciplinary, and low-threshold approaches to adherence and retention (242). AYA living with HIV are diverse and will respond differently to interventions; therefore, it is important that we meet AYA where they are at and in whatever capacity they require. For Aboriginal youth at risk of HIV, it is important for services and interventions to be designed and delivered in a culturally relevant and culturally safe manner (23).

7.5.3. Generalizability of the study

Although this dissertation is focused on AYA in Canada, the information gathered can be applied to AYA living in other regions of the world. This work shows a clear difference between AYA and older adults in terms of clinical outcomes highlighting the role that age plays in clinical success. In recent years, AYA have increasingly been recognized as a unique population – this work adds to the literature on this topic.

As well, CANOC consists of individuals who have access to universal health care coverage, which shows that even in an optimal setting, AYA living with HIV require a tailored response.

7.6. Future Research Directions

In Chapters 4, 5, and 6 I proposed a number of future research directions to be explored. Most importantly, there is an obvious need for greater understanding of AYA living with HIV in Canada. Based on my findings from the previous chapters and the recommendations from each of the chapters, this section puts forward potential research projects to address the gaps and limitations outlined in this dissertation. In particular, I believe there is a need for the development of a national youth cohort that includes in-depth qualitative research.

7.6.1. National AYA cohort

A longitudinal study would allow for temporal monitoring as well as the examination of individual-level trends while seeking answers to questions about social change (383,384). Given the relatively small number of AYA living with HIV across Canada, it is imperative to combine many small clinical databases to form one larger cohort, as CANOC has done. The pooling of data and resources would allow for greater power to investigate specific topics related to health outcomes and care. The development of a national AYA longitudinal cohort study of HIV-positive individuals 14 to 29 years of age would allow participants to be followed through time to see how transitions physically, emotionally, and structurally (e.g., clinics, schools, and families) affect one's health and well-being. Just as CANOC was developed as a collaboration, the same could be done with younger people.

Working in collaboration with provincial partners, greater socio-demographic information will be collected in order to gain a more complete picture of factors that may be affecting an individual's health status and outcomes. Although clinical information is extremely important, we know from the analyses in this dissertation that factors outside the medical realm often influence health outcomes—these factors require further investigation.

7.6.2. Qualitative study

Given the paucity of knowledge in the field of AYA and HIV, there is a pressing need to engage in a dialogue between young-adult community members and adult service providers to identify the gaps in research in an effort to better inform care and services. There are a number of national cohorts that could help recruit participants. CANOC-affiliated partners are the obvious choices as is the Canadian Pediatric AIDS Research Group (CPARG). Both groups are national and collaborative in nature and have shown interest in developing a national cohort.

Qualitative research would help to build a more comprehensive picture of how young people are doing in regards to their health. It is important to understand *why* AYA are or are not taking their medications and how contextual influences affect their behaviours. In order to develop a successful intervention and put in place appropriate support systems, we need to know how to best mitigate barriers/obstacles and support these individuals to reach their full health potential, which could be effectively explored through qualitative research methods (385).

In-depth qualitative research such as Focus Group Discussions (FGDs) and one-on-one interviews could be utilized to examine how and why these relationships unfold as they do. FGDs would allow participants to interact in a dialogue about issues around HIV and engagement in care. Such discussions give participants the opportunity to engage with their peers and take part in spontaneous discussions rather than fixed conversations with researchers (386,387). The in-depth interviews would allow researchers to probe more deeply into issues based on the themes that arise from the FGDs. Through interviews, context into the influences of social and environmental forces on a person's experience with cART could be explored.

The goal of this study would be to highlight the voices of AYA living with HIV in Canada and to help these voices resonate with other AYA experiencing similar experiences in other parts of Canada and globally. The advantage of this qualitative piece would be a more complete picture of individuals' barriers and facilitators to taking medications in order to make informed policy and practice recommendations. As requested, AYA would be represented by their own words.

7.7. Conclusion

In the current Canadian HIV landscape, Treatment as Prevention (TasP) is an overarching theme. Many parties are invested in making TasP a reality; for example, UNAIDS with their 90-90-90 campaign have welcomed TasP into their strategic framework for the elimination of AIDS. In order for TasP to be successful, however, a number of factors must be in place. Most of these factors are taken into account with the HIV Cascade of Care. This dissertation has generated evidence of the needs of adolescents and young adults (AYA) living with HIV in Canada. As illustrated in the previous chapters, AYA are an important population that must be respected when designing effective HIV programming related to TasP. As Figure 2.2 illustrates, factors other than clinical outcomes must be considered before an individual can move toward the end goals of the Cascade of Care and TasP. AYA are consistently underperforming in terms of clinic outcomes and require special consideration and tailored services in order to support them to achieve sustained virological suppression. Previous research as well as international bodies such as UNAIDS and UNICEF have called for greater involvement of young people in the HIV response. Expanding on these recommendations, this dissertation calls for longitudinal and AYA-driven qualitative studies to inform appropriate interventions. Studies in this dissertation have strengthened the understanding of young people living with HIV and have highlighted the importance of adolescents and young adults in making Treatment as Prevention, 90-90-90, and “the end of AIDS” a reality (388).

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Appendix A.

Acknowledgements

The **CANOC Collaborative Research Centre** members will be listed in the appendix of publications, grouped by role. Within each category, names will be alphabetized.

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